

ORIGINAL PAPERS

## Antiagregation and anticoagulation, relationship with upper gastrointestinal bleeding

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### ABSTRACT

**Introduction:** the high prevalence of cardiovascular diseases in the modern society brings a high prescription of platelet antiaggregation and anticoagulant medications. These treatments have been related to an increased incidence of upper gastrointestinal bleedings (UGB). Our aim was to estimate the fraction of UGB s presented to our hospital that was related to this kind of treatments and describe their clinical features in our environment.

**Material and methods:** a retrospective search was performed in the archives of our hospital of all the patients with diagnosis of UGB admitted during the period 2004-2007 both years inclusive. Patients on antiplatelet and/or anticoagulant treatment were included. We analyzed the information regarding the use of medication, the bleeding lesion, the severity of the bleeding, recurrences, mortality and their clinical features.

**Results:** we found 523 episodes of UGB. Of these 137 (26.1%) were patients receiving platelet antiaggregation or anticoagulant drugs. The patients were male 60.2%, and had a mean age of 75.6 ( $\pm$  10.8) years. The 65.5% (74) had HBP, 43.4% (49) diabetes mellitus and 37.2% (42) dislypemia and 13.3% (22) dementia.

The drug most frequently implicated was ASA in 36.3% (41), followed by acenocumarol in 27.4% (31), clopidogrel 18.6% (21), double therapy (ASA + clopidogrel) in 6.2% (7), triple therapy (ASA + clopidogrel + acenocumarol) in 0.9% (1), triflusal 4.4% (5), low molecular weight heparin 5.3% (5), and ticlopidine in one patient (0.9%). Only 36.3% (41) were on treatment with proton pump inhibitors. There were 24 recurrences and 4 deaths.

**Conclusions:** the 26.1% of the UGB attended in our environment were of iatrogenic origin. We also found a low use of proton pump inhibitors.

**Key words:** ASA. Clopidogrel. Upper gastrointestinal bleeding. Proton pump inhibitors.

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### BACKGROUND

The high prevalence of cardiovascular diseases brings a high quantity of antiplatelet and anticoagulant treatment prescriptions. These treatments have been related to an increase in the risk of upper gastrointestinal bleedings (UGB), with rates reported of up to 10% (1) and an annual risk of 1.5-4.5% (2,3). There are few data about the impact of these drugs in the daily clinical practice (3). Anyway these studies have been done in European or American population and have some limitations to be extrapolated to our environment. In Spain the most recent similar work, from the group of Lanás et al. (4), takes into account data from the year 2001, but they do not analyze exactly the same population, as they include patients on treatment with non-steroidal antiinflammatory drugs (NSAIDs).

The primary end-point of the study was to establish what proportion of the UGB were related to these drugs.

The secondary endpoints were: to describe the drugs most frequently implicated, the clinical characteristics, the adequacy of the treatment, the degree of prescription of proton pump (PPI) inhibitors, the bleeding lesion, the recurrences and the mortality.

### MATERIAL AND METHODS

A retrospective search was done in the archives of the hospital of the patients that were discharged with a diagnosis of UGB between the years 2004-2007, both inclusive. The computer program for the registry of discharge reports was

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**Table I. Clinical characteristics of the studied population (n = 113)**

		ASA n = 41	Acenocumarol n = 31	Clopidogrel n = 21	AAS + clopidogrel n = 7	Other n = 13
Age	75,6 ± 10,8 years	76.87 ± 10.6 y	74.96 ± 11.9 y	77.85 ± 9.1 y	69.42 ± 10.16 y	73.07 ± 11.6 y
Sex	60.2% men (n = 68)	61% (25) m	48.4% (15) m	66.7% (14) m	100% (7)	53.8% (7) m
HBP	65.5% (n = 74)	56.1% (23)	71% (22)	85.7% (18)	71.4% (5)	46.2% (6)
DM	43.4% (n = 49)	41.5% (17)	48.4% (15)	42.9% (9)	57.1% (4)	30.8% (5)
DLP	37.2% (n = 42)	34.1% (14)	35.5% (11)	52.4% (11)	42.9% (3)	23.1% (4)
Ischemic heart disease	35.4% (n = 40)	36.6% (15)	19.4% (6)	33.3% (7)	85.7% (6)	46.2% (6)
Heart failure	44.2% (n = 50)	41.5% (17)	41.9% (13)	33.3% (7)	85.7% (6)	53.8% (7)
Atrial fibrillation	33.6% (n = 38)	22% (9)	67.7% (21)	28.6% (6)	0% (0)	15.4% (2)
Chronic renal failure	11.5% (n = 13)	7.3% (3)	9.7% (3)	19% (4)	0% (0)	23.1% (3)
Dementia	13.3% (n = 15)	22% (9)	6.5% (2)	4.8% (1)	0% (0)	23.1% (3)
Hemoglobin at admission	9.2 g/dl ± 2.5	9 g/dl ± 2.5	9.2 g/dl ± 2.9	9.7 g/dl ± 2.4	7.84 g/dl ± 2.1	9.2 g/dl ± 2.4
Number of red blood cell concentrates transfused	1.69 ± 1.84	1.87 ± 2.1	1.9 ± 1.8	1.28 ± 1.45	2 ± 2	1.15 ± 1.14

HBP: high blood pressure; DM: diabetes mellitus; DLP: dyslipemia; ASA: acetylsalicylic acid. Other include: triple therapy (ASA + clopidogrel + acenocumarol) n = 1, triflusal n = 5, low molecular weight heparin n = 6, ticlopidine n = 1.

used to localize the cases and the medical record of each case was reviewed. UGB was defined as the bleeding of the upper gastrointestinal tract evidenced either by endoscopy or by direct visualization (hematemesis or melena). The patients receiving antiplatelet or anticoagulant drugs were included for analysis. Data collected were: the drugs received, the clinical characteristics, the disease that gave the indication for the antiplatelet/anticoagulation treatment, the bleeding lesion, the recurrences and the mortality. The adequacy of the treatment indication was analyzed according to the guidelines of the European society of Cardiology –atrial fibrillation (5), acute coronary syndrome without (6) and with (7) ST segment elevation and prevention of cardiovascular disease (8)–.

The statistical analysis was done with the program SPSS 15.0 (SPSS, Inc, Chicago, IL). Data are shown as mean ± standard deviation. The differences between quantitative variables were analyzed with Student's T test and the differences between qualitative variables were analyzed with Pearson's  $\chi^2$ . The multivariable analyses were done with a backwards binary logistic regression, including the variables that in the univariate analysis presented a  $p < 0.1$ , and those variables that because of biological plausibility could be influencing the results.

## RESULTS

### Patients

A total of 523 admission episodes discharged with the diagnosis of UGB were found. Of these, 137 (26.1%) were on treatment with some antiplatelet or anticoagulant drug. A total of 113 patients were included for the analysis as 24 episodes were recurrences. They were male in 60.2%

of the cases, with a mean age of 75.6 (± 10.8) years. The 65.5% (74) of the patients had high blood pressure (HBP), the 43.4% (49) type 2 diabetes mellitus (DM) and the 37.2% (42) dyslipemia. The 13.3% (15) had dementia. The rest of the characteristics are shown in table I. The most frequent disease that indicated the antiplatelet and/or anticoagulant treatment was ischemic heart disease in 20.4% (23) followed by atrial fibrillation in the 18.6% (21). The 16.8% of the patients (19) had more than one disease that indicated the received treatment (Table II). The indication of the prescription was not adequate according to the principal guidelines in 13.3% (15).

### Drugs

The treatment regimen most frequently implicated was: acetylsalicylic acid (ASA) monotherapy in 36.3% (41) –9 of which received the dose of 300 mg/day and the rest 100 mg/day– followed by acenocumarol in 27.4% (31), clopi-

**Table II. Pathologies that indicated the antiplatelet/anticoagulant treatment**

Ischemic heart disease	20.4% (n = 23)
Atrial fibrillation	18.6% (n = 21)
Stroke	15% (n = 17)
Transient ischemic attack	2,7% (n = 3)
Prosthetic heart valve	4% (n = 3.5)
Diabetes mellitus	6.2% (n = 7)
Pulmonary thromboembolism	3.5% (n = 4)
Postsurgical prophylaxis	3.5% (n = 4)
More than one disease	18.6% (n = 19)
Others	3.5% (n = 4)

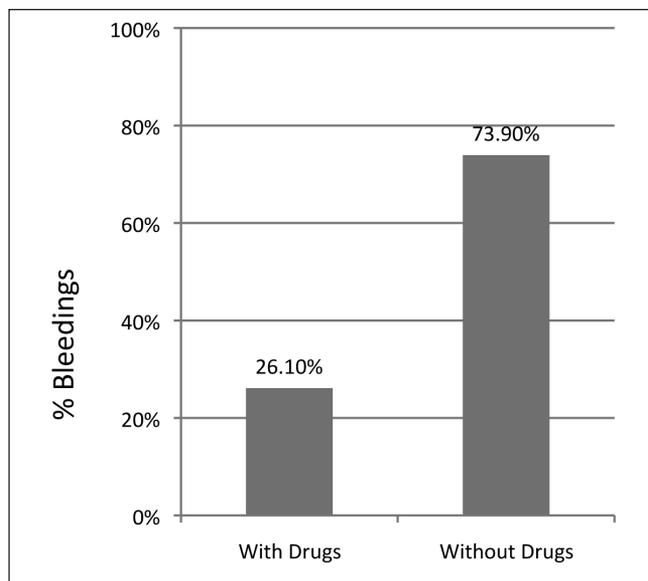


Fig. 1. Percentage of admissions due to upper gastrointestinal bleedings that received some kind of antiplatelet and/or anticoagulation treatment.

dogrel monotherapy in 18.6% (21), double antiplatelet treatment (ASA + clopidogrel) in 6.2% (7), triple therapy (ASA + clopidogrel + acenocumarol) in 1 (0.9%), triflusal in 4.4% (5), low molecular weight heparin (LMWH) in 5.3% (6) and ticlopidine in one patient (0.9%) (Fig. 2). The double therapy group was the one that required more transfusions (Table I) and lowest hemoglobin presented at admission,

but these differences did not reach statistical significance. There were no differences between both doses of ASA.

Regarding the prescription of PPI, of the patients with ASA monotherapy only 34.1% (14) received them, in the acenocumarol group 32.3% (10), in the clopidogrel group 47.6% (10), in the double antiplatelet group 28.6% (2), in the triple therapy group 100% (1), in the triflusal group 20% (1), in the LMWH 33.3% (2) and in the ticlopidine group the 100% (1).

### Endoscopic findings

The most frequent bleeding lesion was a gastric ulcer, followed by duodenal ulcer. The detailed description of the severity of the bleeding lesion and the drugs received is shown in table III. In 4.4% (5) of the cases, more than one lesion was found –gastric ulcer + esophagitis (3) duodenal ulcer + esophagitis (2)–. Infection by *Helicobacter pylori* was found in 23% (26), 11 were patients with a duodenal ulcer, 14 had a gastric ulcer and 1 patient acute lesions of the gastric mucosa.

### Bleeding recurrences

The bleeding recurrences were more frequent in the group of patients that received double therapy with ASA and clopidogrel (n = 3, 30%), followed by acenocumarol (n = 9, 22.5%) and clopidogrel monotherapy (n = 6, 22.2%) (Fig. 2). Nev-

Table III. Endoscopic description of the bleeding lesions

Bleeding lesion n = 113	ASA n = 41	Acenocumarol n = 31	Clopidogrel n = 21	ASA + clopidogrel n = 7	Other n = 13
Gastric ulcer	34.5% (n = 39)	25.8% (8)	33.3% (7)	28.6% (2)	46.2% (6)
Forrest clasification	IIa = 1 IIb = 2 IIc = 4 III = 9	IIa = 2 III = 6	IIa = 1 IIc = 2 III = 4	IIb = 1 IIc = 1	IIa = 2 III = 4
Duodenal ulcer	22% (9)	32.3% (10)	19% (4)	28.6% (2)	15.4% (2)
Forrest clasification	IIb = 1 III = 8	IIa = 1 III = 7	IIb = 1 III = 3	IIa = 1 III = 1	IIa = 1 III = 1
Esophagitis	7.3% (3)	3.2% (1)	14.3% (3)	28.6% (2)	15.4% (2)
Savary-Miller clasification	II = 1 III = 2	II = 1	II = 1 III = 2	II = 2	III = 1 IV = 1
ALGM	9.8% (4)	9.7% (3)	9.5% (2)	0% (0)	0% (0)
Gastric erosions	4.9% (2)	3.2% (1)	4.8% (1)	14.3% (1)	0% (0)
Gastric polyp	2.4% (1)	6.5% (2)	0% (0)	0% (0)	0% (0)
Erosive duodenitis	2.4% (1)	0% (0)	4.8% (1)	0% (0)	0% (0)
Gastric neoplasia	0% (0)	0% (0)	0% (0)	0% (0)	7.7% (1)
Unknown	12.2% (5)	19.4% (6)	14.3% (3)	0% (0)	15.4% (2)

The ulcers were clasified according to the clasification of Forrest, and the esophagitis according to the Savary-Miller clasification.

ALGM: acute lesions of the gastric mucosa; ASA: acetylsalicylic acid. Other includes: triple therapy (ASA + clopidogrel + acenocumarol) n = 1, triflusal n = 5, low molecular weight heparin n = 6, ticlopidine n = 1.

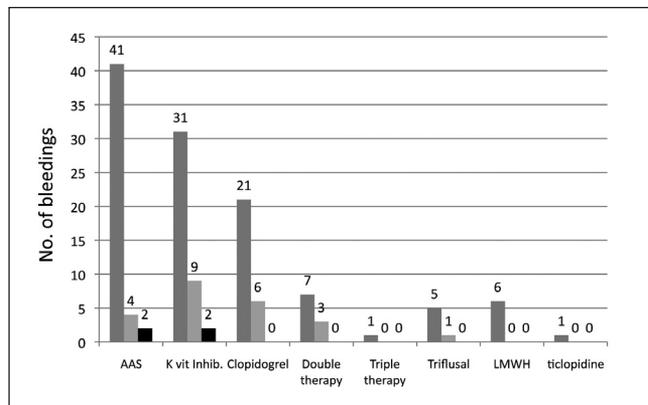


Fig. 2. Number of upper gastrointestinal bleedings (grey) according to the different treatment regimens, number of recurrences (lighter grey) and number of deaths (black). ASA: acetylsalicylic acid; double therapy: acetylsalicylic acid + clopidogrel; triple therapy: acetylsalicylic acid + clopidogrel + acenocumarol.

ertheless, there was no statistically significant association with any therapeutic regimen. In a univariate analysis an association was found between having a prosthetic heart valve and bleeding recurrence ( $p = 0.037$ ). A multivariate analysis was done with a binary logistic regression model introducing in the model those variables that had a  $p < 0.1$  in the univariate analysis, the age, the sex, the treatment regimens most frequently implicated and the treatment with a PPI. The association between having a prosthetic heart valve and recurrence maintained statistical significance (RR = 8,4; IC95% = 1,98-35,58) (Table IV).

## Mortality

There were a total of 4 (3.5%) deaths between the patients included, 2 cases received ASA and 2 acenocumarol. A univariate analysis was done that showed an association between being diabetic ( $p = 0.033$ ) and having an atrial fibrillation ( $p = 0.011$ ) with the risk of death. A multivariate analysis was done with a binary logistic regression analysis, introducing in the model those variables with a  $p < 0.1$  in the univariate analysis, the age, the sex, to receive ASA or acenocumarol and the treatment with PPI. No variable remained statistically associated to death in this analysis (Table IV).

Of the four patients deceased, 2 were patients with a very advanced Alzheimer disease that were admitted with coffee grounds vomiting and melena. The therapeutic measures undertaken were limited in both cases. The third one was a patient that was admitted with a cardiac arrest due to ventricular fibrillation in the context of an acute myocardial infarction that required a long time cardiopulmonary resuscitation. Melenas, anemia and subsequently hypovolemic shock appeared, but because of a very severe anoxic encephalopathy the therapeutic measures were also limited. The fourth was a patient with a dilated ischemic myocar-

**Table IV. Factors associated to bleeding recurrences and death directly related to the bleeding**

<i>Recurrences</i>		
<i>Univariate analysis</i>	<i>% Recurrences</i>	<i>p-value</i>
Prosthetic heart valve (Yes/No)	41.7% (5)/15.2% (19)	$p = 0.037$
Dementia (Yes/No)	31.8% (7)/14.8% (17)	$p = 0.054$
Previous UGB (Yes/No)	33% (6)/15.1% (18)	$p = 0.09$
<i>Multivariate analysis</i>		
	<i>RR (IC95%)</i>	<i>p-value</i>
Prosthetic heart valve	8.4 (1.98-35.6)	$p = 0.004$
<i>Deaths</i>		
<i>Univariate analysis</i>	<i>% deaths</i>	<i>p-value</i>
DM (Yes/No)	8.2% (4)/0% (0)	$p = 0.033$
FA (Yes/No)	10.5% (4)/0% (0)	$p = 0.011$
Dementia (Yes/No)	13.3% (2)/2% (0)	$p = 0.085$
<i>Multivariate analysis</i>		
	<i>RR (IC95%)</i>	<i>p-value</i>
NS	NS	NS

In the univariate analysis all the clinical factors collected were introduced, but only those with a  $p < 0.1$  are shown. In the multivariate analysis of factors associated to recurrences the variables with a  $p < 0.1$  and the age, the sex, treatment with clopidogrel, acenocumarol double antiplatelet therapy and proton pump inhibitors were introduced. In the multivariate analysis of factors related to death the variables with a  $p < 0.1$  the age, sex, treatment with acenocumarol, acetylsalicylic acid or proton pump inhibitors were introduced. NS: not significative.

diopathy with severe mitral insufficiency that died of an acute pulmonary oedema because of a very intense fluid overload received for the bleeding.

## DISCUSSION

In this study we offer a detailed description of the UGB related to antiplatelet and/or anticoagulant treatments attended in a hospital in Spain during a 4 year period. In our series approximately 1 of each 4 UGB were related to these drugs.

The treatment with ASA at low doses has been related to a higher incidence of bleeding events. It doubles the risk of a major extracranial bleeding. This supposes 1-2 major bleedings for each 1,000 patient-years of treatment in adult patients (9). The number of cardiovascular events prevented for each 1,000 patient-years treated is 10-20 (9). Nevertheless, the increasing frequency of prescription of this drug carries an increase in the absolute number of UGB related to it. We can not forget that treatment with ASA is recommended in clinical guidelines to all patients with hypertension over 50 years of age (10) as to the diabetics (8). If we consider that

this supposes a 25% (11) and 10% (12) of the total of the adult population, we can see that the magnitude of the problem is considerable with high direct and indirect costs. A previous study with data of the year 2001 found a proportion of UGB related to this kind of drugs of 19% (4), but this study did not include exactly the same population as it included patients on NSAIDs. In the present work a proportion of 26.1% was obtained and patients on NSAIDs were not included. The difference probably reflects the increasing frequency of prescription of antiplatelet and anticoagulant drugs. In our series the 36.3% of the patients were receiving ASA, being indicated only in 75.6% of the cases and being the drug most frequently implicated. We can not evaluate if it is due to a higher gastric toxicity or due to a higher frequency of use because of the design of the study.

In the CAPRIE study (13) the treatment with clopidogrel was related to a lower number of gastrointestinal bleeding adverse events compared to ASA. Clopidogrel showed an incidence rate of 1.99 vs. 2.66% for ASA after 3 years of follow-up. This difference hardly reached statistical significance ( $p = 0.05$ ) despite a total study population of 19,185 patients. Likewise, a higher efficacy in the prevention of recurrences of UGB due to gastric ulcer in patients on treatment with ASA adding a PPI than changing to clopidogrel (14). However, the benefit of clopidogrel has been widely proven, especially in patients with high cardiovascular risk (15). In our series it was the third drug most frequently implicated, probably because it is prescribed less frequently than ASA because of its higher cost.

The patients on treatment with K vitamin antagonists have a higher risk of gastrointestinal bleeding (16). To highlight of our results a high risk of recurrence, 22.5%. However, it was the combination treatment with ASA and clopidogrel that presented the highest risk of bleeding recurrence, 33.5%.

Omeprazol and H<sub>2</sub>-receptor inhibitors (ranitidine y famotidine) have been related with a lower number of bleeding events in patients on treatment with any kind of NSAIDs, low dose ASA included, in epidemiological studies (17,18). These results have been confirmed subsequently in clinical trials (19). Specifically, lansoprazol has a NNT of 32 to prevent the recurrence of an UGB in patients on treatment with antiplatelet drugs (19). At present, there is a controversy about the use of PPI in patients on treatment with clopidogrel because of pharmacological interactions (20), nevertheless this interaction could be clinically irrelevant (21). Even taking into account this fact, the underprescription of PPI is striking in our cohort, especially considering that this controversy is very recent and these benefits have been widely proven.

Our population had a mean age of 75 years. This is congruent with data published in the literature, that show the age as a risk factor for UGB in patients on treatment with antiplatelet/anticoagulation drugs (21).

Taking into account this fact, and that the studies on which clinical guidelines are based on, do not usually include old patients (22), we consider that these drugs

should be used with caution in this population as there is not a strong evidence about their efficacy and safety. Also, in our study the 13.3% of the patients had dementia, with important limitations for the basic activities of daily living. In this kind of patients probably the use of antiplatelet/anticoagulation drugs does not increase quality of life and increases significantly the bleeding risk. Moreover the benefit gets more doubtful as the use of these drugs showed a tendency in the univariate analysis, not statistically significant, towards an association with the risk of death and recurrences in this population.

The most frequent bleeding lesion was the gastric ulcer, contrasting with a recent publication that showed the duodenal ulcer as the principal lesion (23). This difference could be related to the subgroup of bleedings analyzed. Nevertheless in another work that analyzed the evolution of the UGB found a decrease in the incidence of duodenal ulcer as a cause of UGB in the last years (24).

In our series there were a total of 24 bleeding recurrences that was associated to have a prosthetic heart valve. Probably the need for intense anticoagulation in these patients is the determinant factor of this association.

The mortality was 3.5% (4). This proportion is similar to the findings of previous studies (4). In the univariate analysis it was associated with the presence of DM and atrial fibrillation, with a tendency towards an association with dementia. Nevertheless, no association was found in the multivariate analysis.

In conclusion, one of each four bleedings in our environment was related to antiplatelet and/or anticoagulant drugs prescribed for primary or secondary prevention of cardiovascular diseases. This should make us think about the benefits of these drugs, especially in certain groups of patients. We also believe that the use of gastroprotective drugs is very low.

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