ORIGINAL ARTICLE

Lower GI bleeding is more common than upper among patients on dual antiplatelet therapy: long-term follow-up of a cohort of patients commonly using PPI co-therapy

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ABSTRACT

Objective Patients undergoing percutaneous coronary intervention require dual antiplatelet therapy. Proton-pump inhibitor (PPI) therapy is recommended for the prevention of upper GI complications. No study has determined the rate and type of GI bleeding events in such patients in routine clinical practice.

Design Observational study with a prospective follow-up to confirm medication use and occurrence of events, which were validated.

Patients and setting We have followed up a cohort of 1219 consecutive patients admitted for percutaneous coronary intervention in Zaragoza (Spain).

Main outcome measures Major GI bleeding and cardiovascular events.

Results At discharge, 96.7% of patients were on dual antiplatelet therapy and 76.6% on PPI therapy, which increased up to 87.9% during follow-up of 2107.6 patient (pt) s-years (1.72±1.07 years/patient). There were eight patients who developed GI bleeding during hospitalisation and 27 patients during follow-up, (1.52 bleeds per 100 pt-years). Most GI bleeding events (81.4%) occurred during the first year (mean time to bleeding event: 7.03±7.65 months) and 84.6% of patients were on long-term PPI at the time of the bleed. Lower GI bleeding occurred more frequently than upper GI bleeding (74% lower vs 26% upper). Peptic ulcer history and concomitant warfarin therapy were the only risk factors identified for upper or lower GI bleeding respectively.

Conclusions Among patients on dual antiplatelet therapy and PPI co-therapy, gastrointestinal bleeding episodes are more frequent in the lower GI tract. This changing pattern of bleeding may reflect the success of gastroprotection and focuses attention on research to address lower GI bleeding in this population.

INTRODUCTION

Dual antiplatelet therapy with aspirin (ASA) and clopidogrel (CLP) reduces recurrent cardiovascular events in acute coronary syndrome (ACS) among patients with established ischaemic heart disease, and reduces coronary stent thrombosis.[1 2] It is also well established that ASA is associated with twofold increased risk of upper GI bleeding (UGIB), which is further increased when combined with CLP therapy. The presence of age >70, previous ulcer history (complicated > uncomplicated), *Helicobacter Pylori* infection, and concomitant therapy with anticoagulants, NSAIDs or steroids are known risk factors for UGIB in ASA users. The risk of GI bleeding increases in relation to the number of risk factors.[3–7]

A recent consensus document,[8 9] concludes that proton pump inhibitor (PPI) should be considered in any person with risk factors for gastrointestinal bleeding receiving antiplatelet therapy. Although some recent data have been raised concerns that the co-administration of a PPI with CLP could pose a risk of drug interaction via cytochrome P450 2C19,[10 11] and therefore the potential to increase the risk of CV events,[10 12] the recommendations of the panel are based[13 14] upon the lack of firm evidence of a clinically important interaction leading to worsened CV outcomes and the inconsistently of the association between PPI use and increased CV events.[15] On the other hand, ASA may also damage the lower GI tract and promote bleeding. Epidemiological[16 17] and capsule endoscopy studies[18] have shown increased risk of lower GI complications and small bowel mucosal damage among low-dose ASA users. However, no studies have been carried out in patients on dual antiplatelet therapy examining specifically at the type and characteristics of GI bleeding events in this type of patients. We have previously reported high rates of prescription of PPI co-therapy at hospital discharge in patients receiving dual antiplatelet therapy after percutaneous coronary intervention (PCI),[19] but little is known on the outcomes of these patients after hospital discharge.

Therefore, the objectives of this study were to evaluate the rate and type of GI bleeding in routine clinical practice in at-risk patients on dual antiplatelet therapy after PCI, to determine whether PPIs were being used to reduce the risk of GI bleeding in such patients and the impact of that approach in the occurrence of GI complications.

METHODS

Study design and setting

The study was designed as an observational study of patients discharged from the Cardiology Service at the University Hospital Lozano Blesa in Zaragoza (Spain) with a prospective follow-up telephone interview and chart review validation for

all patients. In this way, a cohort of consecutive patients admitted for PCI due to coronary heart disease were studied from January 2006 to December 2009. All patients received low-dose ASA therapy (75–162 mg day) in addition to CLP 75 mg day.

Data were collected between September 2008 and June 2010 through chart review in all patients followed by a structured telephone interview, confirming the information provided by the medical records at the same time as the telephone call. Interviews consisted of questions regarding: demographics, past medical history, changes in health status, with specific questions on potential gastrointestinal bleeding and CV events requiring hospitalisation, medications during follow-up, and causes for changes in medication. The cut-off for the follow-up interval was considered either the telephone interview or the last visit registered in the hospital chart (as out patient or inpatient), whatever was the last.

The telephone interview and follow-up were conducted by the same cardiologist (RC) and nurse (MP) focused on medication use (PPI, antiplatelet therapy) and development of GI/CV events. Bleeding complication and CV events were identified during chart review and/or during the telephone interview. All potential bleeding and CV events were confirmed in medical records from the same hospital (most cases) or from records obtained from the other hospitals of the region. The ethics committee of our hospital approved the study, and all the patients gave oral informed consent before the telephone interview.

Main outcome measures

The primary endpoint of the study was the occurrence of a major GI bleeding event, defined as the presence of melena, haematochezia and/or haematemesis confirmed by hospital staff and requiring hospital admission. Adjudication of GI bleeding events was performed by an expert gastroenterologist (AL) using the clinical, endoscopic and/or angiographic findings. In the few cases where no lesions were found, the attribution of the bleeding event to either the upper or the lower GI tract was based on the clinical picture and endoscopic findings; for example, a rectal (bright red) bleeding or recent melena (black or red brown feces) with negative emergency upper GI endoscopy performed within 24 h of an emergency room visit or hospitalisation (if inpatient), was assumed to be a lower GI event (melena can be also a sign of small bowel bleeding); on the other hand a GI bleeding event with haematemesis was attributed as an UGIB event.

We considered the following as risk factors for GI bleeding: age ≥70; history of peptic ulcer disease; concurrent warfarin, corticosteroids ≥10 mg daily, or daily NSAIDs. The proportion of GI haemorrhage, Upper versus Lower was calculated and stratified according to age, lowest haemoglobin, death in follow-up, GI bleeding risk factors, PPI and dual antiplatelet therapy all at the time of the event. We also analysed cardiovascular outcomes after discharged as well as hospitalisation due to other medical events.

Statistical methods

Statistical differences and ORs were calculated using χ^2 test for discrete variables and t tests for continuous variables (expressed as mean values and SD). Logistic regression analysis was conducted to identify risk factors for bleeding events. All statistical tests were performed with the use of SPSS software (SPSS V.19). Although this study was exploratory in nature to find rates of GI bleeding in this specific population with high PPI use, we estimated to collect 1200 patients to potentially find differences (80% power, significance level of 0.05) between upper and lower GI bleeding based on expected higher rates of UGBI (2%) versus lower GI bleeding events (0.5%).

RESULTS

One thousand three hundred and six consecutive patients hospitalised in our center with coronary artery disease and PCI procedures from January 2006 to December 2009 were studied (figure 1). Eighty-seven patients were excluded because a PCI procedure was not performed and dual antiplatelet agents were not administered. Table 1 shows the demographic and clinical characteristics of the patients. Emergency revascularisation was performed in 27% of the patients (264/1219) and non-emergency revascularisation was performed in 73% (933/1219); 23% patients were revascularised because of unstable angina (276/1219), 24% because of stable angina (286/1219) and 22% due to myocardial infarction (268/1219). Patients were followed up for a total of 17 788 months (mean: 14.7±12.9 months). A total of 75 patients died, 26 during hospitalisation and 49 after discharge.

During hospitalisation gastroprotective agents were used in 78.7% of the patients (960/1219); (pantoprazole in 79.6% (765/960), and omeprazole in 15.6% (150/960) of patients) H2-RAs were prescribed in only 1.6% (16/1219) of the patients.

At discharge, 1156/1193 patients (96.9%) were on dual antiplatelet therapy and 916/1193 (76.7%) patients were on PPI therapy (table 1); 12% (24/202) of the high-risk patients admitted on PPI where discharged without any GI protection. Omeprazole (60%) and pantoprazole (34.2%) were the most frequently PPI prescribed, whereas H2-RAs were prescribed in only 1.6% of the patients. PPI co-therapy increased from 76.7% at discharge to 87.9% at the time of the last telephone interview or clinical contact.

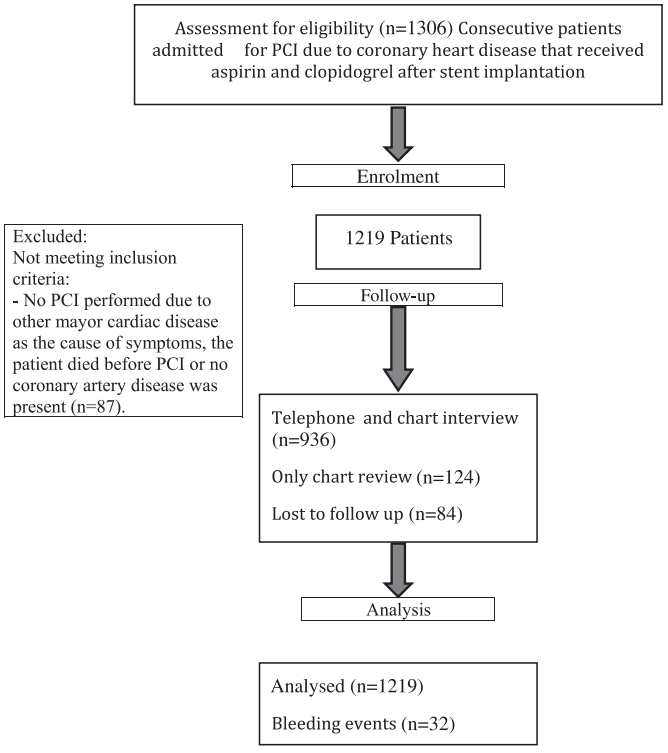

Figure 1 Flow diagram showing the process that leads to the final patient sample eligible for analysis.

Table 1 Characteristics of study participants

	GI bleeding (n, %) n=32	No GI bleeding (n, %) n=1187	p
Age ≥70-years-old	16 (50.0)	473 (39.8)	NS
Previous history of peptic ulcer disease	7 (21.9)	85 (7.2)	0.002
Concurrent previous warfarin use before hospitalisation	6 (18.8)	65 (5.5)	0.002
Concurrent warfarin use at telephone interview	5 (15.6)	46 (3.9)	0.001
Concurrent use of non-aspirin NSAIDs at discharge	2 (6.7)	29 (2.5)	NS
At discharge on			
No antiplatelet agent	0 (0.0)	1 (0.08)	NS
ASA alone	0 (0.0)	9 (0.8)	
CLP alone	0 (0.0)	21 (1.8)	
ASA and CLP	30 (100)	1126 (96.8)	
PPI	26 (81.3)	890 (75.0)	NS
Statins	18 (60)	849 (73)	NS
At admission GI risk			
No risk factor	13 (40.6)	616 (51.9)	<0.001
1 risk factor	9 (28.1)	462 (39.0)	
2 or more risk factors	10 (31.3)	108 (9.1)	
Number of blood units transfused (mean, SD)*	3.31 (1.32)	3.79 (3.60)	NS
Number of blood units transfused (mean, SD)—all cases	1.34 (1.84)	0.045 (0.56)	<0.001
Number of re-hospitalisations			
No	9 (40.9)	656 (71.7)	0.002
Yes	13 (59.1)	259 (28.3)	
Number of days from discharge to first re-hospitalisation	160.57 (187.9) 23 re-hospitalisations	294.34 (298.90) 232 re-hospitalisations	0.036
Cause of rehospitalisation			
Cardiovascular	3 (23.1)	114 (44.5)	<0.001
Digestive	6 (46.2)	12 (4.7)	
Other	4 (30.8)	130 (50.8)	

*transfused patients.

Outcomes

A total of 32 patients developed GI bleeding after PCI procedure on antiplatelet therapy (2.6%; 1.52 events per 100 patient-years) (tables 1 and 2); eight patients had a GI bleeding event during first hospitalisation and 27 in the follow-up period. Three patients bled during hospitalisation and again in the follow-up period due to LGIB.

GI bleeding events during index hospitalisation

Eight patients (0.6%) developed a GI bleed soon after the PCI procedure (web table 3); two patients UGIB (both on omeprazole 20 mg/day) and six LGIB (five on pantoprazole 40 mg/day, one on omeprazole 20 mg/day). Previous history of peptic ulcer disease was present in 37.5% (3/8) of the cases of GI bleeding, versus 7.3% (89/1211) in the non-bleeding group (p=0.018). Among those with bleeding from the lower GI tract, small bowel was the source in three cases (angiodysplasia, jejunal ulcer, and an active ileal arterial bleed), whereas the large bowel was the source in the other (rectal ulcer and diverticuli).

The use of anticoagulants (vitamin K antagonist) before hospitalisation was present in 25% (2/8) of the GI bleeding group versus 5.7% (69/1211) in the non-GI-bleeding group (p=0.07). Regarding GI risk factors for bleeding, 50% (4/8) of those cases who developed GI bleeding had two or more risk factors, versus only 9.4% (114/1211) in the group of patients with no GI bleeding events (p=0.0008). Patients with GI bleeding events had a mean hospitalisation of 24.4±26.7 days in comparison with the non-GI bleeding group of 7.6±7.5 days; p=0.0001. Other non-GI bleeding events occurred in 20 patients (14 related to femoral access, two to pericardial effusion during the procedure, two retroperitoneal bleeding, one urinary bleeding and one neck bleeding related to central venous access); 70% (14/20) of them received blood transfusion. The mean number of units transfused in these patients was lower than in those transfused with GI bleeding events (2.9±1.5 vs 5.4±4.3; p=0.008). The proportion of deaths during the index hospitalisation was also higher in the GI bleeding group (25%—2/8) when compared to the non-GI bleeding group (2%—24/1211) (p=0.011).

GI bleeding events after hospital discharge

A total of 27 patients developed ≥1 major GI bleeding event (web table 4). All were severe and required hospitalisation (figure 2). The mean time to bleeding event was 5.3±7.3 months and 84.6% of them were on long-term PPI at the time of the bleeding event. LGIB events occurred more frequently than UGIB (74% -20/27-lower vs 26% -7/27- upper) (p=0.012). Table 2 describes the characteristics of these bleeding events.

Table 2 Characteristics of the bleeding episodes

	Total n (%)	Lowest Hb mean (SD)	Units of blood transfused mean (SD)	Deaths n (%)	Ulcer Hx n (%)	Warfarin cotherapy n (%)	Dual antiplatelet therapy at time of the bleeding event n (%)	Number of GI risk factors mean (SD)
No bleeding event	1187 (97.4)	—	0.04 (0.6)	70 (5.9)	85 (7.2)	64 (5.5)	1126 (96.8)	0.6 (0.7)
Upper GI bleeding	9 (0.7)	9.7 (2.0)	2.0 (1.6)	1 (11.1)	3 (33.3)	1 (11.1)	9 (100.0)	0.8 (1.1)
Lower GI bleeding	23 (1.9)	7.6 (0.7)	1.1 (1.9)	4 (17.4)	4 (17.4)	5 (23.8)	21 (100.0)	1.1 (0.6)
Significance	—	—	<0.001	0.024	0.002	0.001	NS	0.020

Significance findings are between bleeding versus no bleeding events.

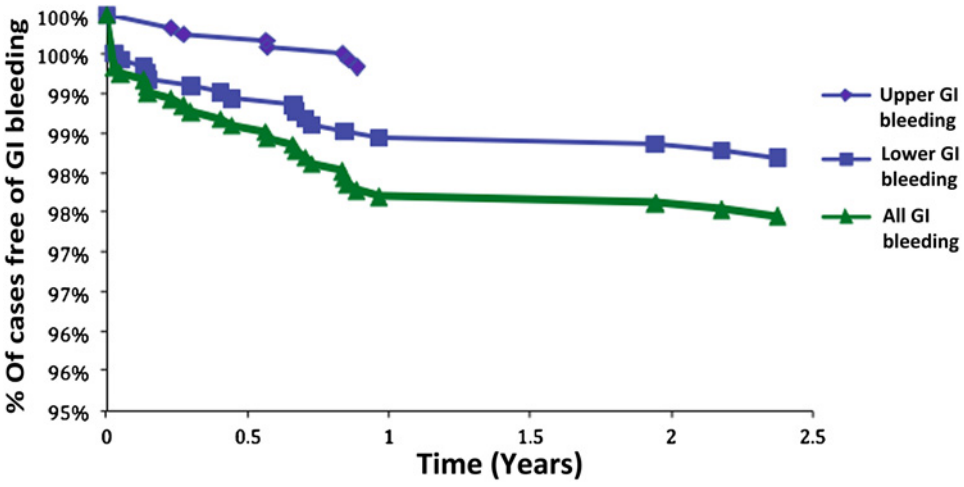

Figure 2 Time trends of upper, lower and all gastrointestinal bleeding events in the population studied.

Three of the cases with a GI bleeding event during the index hospitalisation had also a bleeding recurrence during the follow-up period; all were LGIB and one case was fatal. All three cases recurred from the same location, and in 2 of 3 the same cause was confirmed.

The cause of UGIB events were: gastric ulcer (2), duodenal ulcer (2), acute gastric mucosal erosions (2), and bleeding related to portal hypertension (1). Four cases of LGIB were due to small bowel angiodysplasia. There were 12 cases of confirmed large bowel GI haemorrhage (four diverticular bleeding, two rectal cancer, two ischaemic colitis, one colonic cancer; one colonic polyp, one hemorrhoids and one ulcerative colitis). Probably most of these lesions were unmasked by the antiplatelet treatment (25/27 patients were on dual antiplatelet agents, one on ASA alone and one on warfarin and ASA, at the time of the bleeding event). Almost all GI bleeding patients were on PPI at the time of the bleeding event; 14/27 on pantoprazole, 9/27 on omeprazole and just 4/27 were without any gastroprotective therapy (two of these four patients had an UGIB event). Other non-GI bleeding events and subsequently transfusion occurred in 14 patients due to chronic renal insufficiency, haemoptysis due to lung cancer, pneumonia due to Pseudomonas, wound bleeding after implantation of a defibrillator among other aetiologies. The mean number of units transfused in these patients was similar to those transfused with GI bleeding events (3.79±3.6 vs 3.31±1.32; p=ns).

There were other 85 cases described as minor bleeding (no need for transfusion nor hospitalisation): 12 cases of epistaxis, 59 anorectal lesions (most haemorrhoids), three minor LGIB, eight urologic and three respiratory.

Determinants of GI bleeding events in the cohort

Overall, peptic ulcer history (OR=3.57; 95% CI 1.47 to 8.69) (7.2% vs 21.8%, p=0.002), and concomitant warfarin therapy (OR=3.82; 95% CI 1.48 to 9.84) (5.5% vs 18.7%, p=0.002), were the only risk factors for GI bleeding identified in this cohort. If we split the analysis into factors for lower and UGIB, peptic ulcer history was a risk factor for UGIB (OR=6.30; 95% CI 1.55 to 25.61, p=0.010,) but not for lower GI bleeding (OR=2.65; 95% CI 0.88 to 7.96; p=0.082). On the contrary, warfarin therapy was a risk factor for lower GI bleeding (OR=5.32; 95% CI 1.89 to 14.98, p=0.002), but not for UGIB (OR=2.02; 95% CI 0.25 to 16.38, p=0.510).

Non-bleeding patients were younger on average (66.0±10.5) than GI bleeding patients (70.0±11.4), although these differences were not statistically significant (p=0.056). There were also some gender differences. During the index hospitalisation males had more UGIB events events than females (80%, 6 males/2 females). At discharge there were 19 events in males and 8 in females. Mean age at the time of the lower GI bleeding event was higher in females (78.3 years) than in males (66.8 years), but the difference was not significant.

Deaths

After discharge, 49 patients died, 45% (22/49) due to cardiovascular events, 20% (10/49) due to oncological diseases, 8.1% (4/49) due to neurological diseases, 6.1% (3/49) due to sepsis, 4.1% (2/49) at time of the GI bleeding event (one case with concomitant respiratory sepsis, and another one with shock of unidentified origin, this last patient was receiving dual antiplatelet agents, ibuprofen and methylprednisolone before the episode GI bleeding). Other patient with GI bleeding died in the context of a GI cancer. The percentage of patients with gastrointestinal haemorrhage who died during the study was higher than non-GI bleeders (5/32 in the group of GI bleeding (15.6%) versus 70/1187 (5.9%) in the non-bleeding group (p=0.024) (figure 2).

One patient was hospitalised because of acute coronary ischaemia in the context of UGIB with very low haemoglobin levels (7 gr/dl), once stabilised the bleeding event, the cardiac catheterisationdid not show new coronary lesions.

DISCUSSION

The efficacy of low-dose ASA and CLP after coronary revascularisation in the prevention of new events is well established.[1 2 20] However, low-dose ASA may be injurious to the GI tract and the risk of developing upper GI complications is increased when combined with CLP.[3 4 21 22] Although the risk of a GI complication is low, given the prevalence of low-dose ASA use worldwide, the relevance of an appropriate assessment of the risk of complications in patients taking antiplatelet agents is clear. In this study we found that in patients on dual antiplatelet agents, LGIB is more common than UGIB when the percentage of PPI co-prescription use is high. This is the first study that reports a higher number of LGIB events when compared to UGIB events in this setting.

These data are in agreement with our recent epidemiological study where we showed a time trend decrease in the number of hospitalisations due to UGIB and an increase in the number of hospitalisations du to lower GI bleeding,[16] a trend that was attributed to an increase in the implementation of prevention strategies in NSAID/ASA-associated upper GI complications

(PPI and *H pylori* eradication). In the current study, we hypothesise that the main reason for the lower rate of UGIB events when compared to LGIB events in the studied population is likely to be the concomitant co-therapy with PPI. PPI co-therapy has been shown to reduce the incidence of peptic ulcers and peptic ulcers complications in patients taking ASA alone or combined with CLP, although it has the potential to alter the antiplatelet effect of these agents.[8 9 21–25] It is however of interest to note that in our study, 154 (12.8%) of patients not discharged on PPI were subsequently prescribed this drug because of the awareness of their medical practitioners on the effect of PPI lowering the risk of UGIB in ASA users.

The explanation for the relative proportion of lower GI events in this population may have different reasons, but it seems obvious that since low-dose ASA may induce damage in the lower GI tract and PPIs have no therapeutic effect beyond the duodenum, LGIB events may occur as a consequence of mucosal damage in the small and large bowel. Endoscopy capsule studies have shown that low-dose ASA induces erosions and ulcers in the small bowel.[18] It is also reasonable to assume that the antiplatelet effect of ASA and CLP may promote bleeding in patients with pre-existing mucosal damage or lesions in the lower GI tract. Epidemiological studies have shown that the use of low-dose ASA increases the risk of both upper GI complications and lower GI complications and that the RR increase is similar in magnitude for both conditions.[16]

In addition to the presence of pre-existent lesions, age is another factor noted in several studies as a risk factor for lower GI complications.[17 19 26] Our population with LGIB events showed a trend to be older and had a higher number of comorbitidies than those with no bleeding events or even those with UGIB events, which should be considered when assessing risk and benefits and the therapy in this population. Furthermore, LGIB events appear to be more severe, with higher mortality rate, a longer duration of hospitalisation, and greater economic costs due to an increased use of hospital resources, higher number of re-hospitalisations and visits to the emergency department.[16]

Studies reporting data from large databases linked to ASA use are focused on UGIB events, since the occurrence of LGIB events has not attracted as much interest so far and overall are not easy to characterise due to the difficulties to identify the lesions. Furthermore, diagnostic codes of UGIB events in widely used databases have been extensively validated, but this is not the case for LGIB events, which limits the interpretation of data of database studies for LGI bleeding.

One of the strengths of our study is that by reporting both upper and LGIB events, we have addressed a more comprehensive picture linked to GI complications associated with dual antiplatelet therapy in patients that for the most part have followed current recommendations in the prevention of UGIB. Among the limitations of our study, it should be pointed out that our analysis was based on medical and prescription records as well as on patient's report during the call and that a systematic assessment of medication compliance was not possible due to the study design. It is possible that any GI bleeding episodes have not been detected, but due to the fact that a high percentage of patients were contacted by telephone, it is quite unlikely.

In summary, our data provide the first evidence that the incidence of LGIB is higher than UGIB events in patients under dual antiplatelet agents when the prescription of PPI is high and consistent with international recommendations. The rate of gastrointestinal bleeding among patients on dual antiplatelet therapy after PCI with PPI co-therapy is 1.52 cases per 100 patient-years. In addition we have provided data on the source of GI bleeding among high risk cardiac patients, a critical unmet need in the literature mandated by the increased mortality associated with GI bleeding in this patient population. In this emerging field of LGIB complications associated with antiplatelet and anticoagulant therapy, efforts to identify and stratify high-risk patients for LGIB are warranted, given the increasing number of new agents for cardiac indications will continue to expand the at-risk patient population.

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Competing interests ICMJE conflicts of interest form for each author of this manuscript. Angel Lanas has served as consultant to AstraZeneca, Pfizer, and Bayer, and has received research funding from AstraZeneca and Pfizer for investigator-initiated research. James Scheiman has served as consultant to AstraZeneca as well as and Pozen, and Novartis Inc. Ruben Casado-Arroyo, Mónica Polo-Tomas and Maria P Roncales report no conflict of interest.

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

Ethics approval The ethics committee of Hospital Clínico Universitario Lozano Blesa approved the study.

Contributors Rubén Casado-Arroyo: data collection, telephone interview and follow-up, publication. Mónica Polo-Tomas: statistical analysis, review the data. Maria P Roncalés: telephone interview and follow-up. James Scheiman: desing the study, analysis the data, publication. Ángel Lanas: desing the study, analysis the data, publication.

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