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**Underutilization of gastroprotection for at risk patients  
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(1) **Title page:**

**Underutilization of gastroprotection for at risk patients undergoing  
percutaneous coronary intervention: Spain compared with the USA**

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(2) **Abstract and Key words:**

Proton-pump inhibitors (PPIs) are the preferred agents for the prevention of aspirin-associated upper gastrointestinal (UGI) bleeding. Data are limited to determine whether PPIs are being used to reduce UGI bleeding risk. **Aim:** To evaluate the implementation of PPI treatment to reduce the GI risk in two cardiology centers from Europe and USA. **Methods:** Retrospective cross-sectional study carried out at the University of Michigan and University Hospital-Zaragoza in 429 consecutive patients hospitalized for PCI on dual antiplatelet therapy. **Results:** Admission PPI co-therapy was similar (34% vs. 30%) in both centers. At discharge, the proportion of high-risk patients receiving PPI therapy in the Spanish center (75.4%) was higher than their American peers (55.6%) (O.R: 2.5; 95% CI; 1.3-4.7). No differences in PPI prescription rates were found among Spanish patients with/without GI risk factors. The opportunity to initiate PPI co-therapy in high-risk patients was missed in 81.8% (36/44) of those not on PPI at admission in US patients vs. 24.1% (19/79) ( $p < 0.0001$ ) in Spanish patients. **Conclusions:** There are important differences concerning PPI prescription and risk stratification in the two centers when managing PCI patients. Efforts to stratify risks and utilize appropriate strategies for UGI bleeding prophylaxis in high-risk patients are warranted.

**Keywords:** revascularization, dual antiplatelet therapy, gastrointestinal haemorrhage.

### **(3) Introduction:**

Dual antiplatelet therapy with aspirin (ASA) in addition to clopidogrel (CLP) reduces recurrent cardiovascular events in acute coronary syndrome (ACS) among patients treated medically or with percutaneous coronary intervention (PCI)<sup>1, 2</sup>. It is also well established that ASA is associated with two fold increased risk of upper gastrointestinal bleeding (UGIB), which is further increased when combined with clopidogrel therapy. The presence of independent ulcer risk factors, which include age > 70, previous ulcer history (complicated > uncomplicated), H. Pylori infection, and concomitant therapy with anticoagulants, NSAIDs or steroids are well established<sup>3, 4, 5, 6, 7</sup>.

A recent consensus document published by the American College of Gastroenterology<sup>8</sup>, the American College of Cardiology Foundation and the American Heart Association, concludes that proton pump inhibitors (PPI) should be considered in any person with risk factors for gastrointestinal bleeding receiving antiplatelet therapy<sup>9</sup>. After PCI therapy, patients are prescribed dual antiplatelet therapy with ASA and CLP, putting these patients at GI risk, especially among those patients with additional risk factors. Therefore, physicians must evaluate the GI risk profile and adopt prevention therapies in an attempt to reduce GI complications<sup>10, 11</sup>. The consensus document was motivated, in part, by the hypothesis that non-GI physicians did not systematically consider UGI bleeding risk nor respond with appropriate gastroprotective strategies.

Although some concerns have been raised concerning that the co-administration of a PPI with CLP could pose a risk of drug interaction via cytochrome P450 2C19<sup>11, 12</sup>, and

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2  
3 therefore have the potential to increase the risk of CV events<sup>11, 13</sup> the recommendations  
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5 of the panel have not been changed based upon the lack of firm evidence of a clinically  
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7 important interaction leading to worsened CV outcomes. However, regulatory agencies  
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9 have proposed warnings that careful evaluations of the CV and GI risks should be  
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11 undertaken in the individual patient<sup>14, 15</sup>. Furthermore, as more recent data suggest that  
12  
13 the potential interaction between these two drugs may have no clinical impact on CV  
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15 events<sup>16</sup>, and since other therapeutic alternatives such as misoprostol, H2-blockers or *H.*  
16  
17 *pylori* eradication have still poor evidence of being effective as preventive strategies<sup>10</sup>,  
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19 PPI co-therapy still remains the main prevention therapy for those at risk **taking**  
20  
21 **antiplatelet therapy.**  
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27 No study has evaluated whether PPIs are being prescribed to reduce UGI bleeding risk in  
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29 at-risk patients on dual antiplatelet therapy after percutaneous coronary intervention (PCI).  
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31 We also sought to determine whether there are different prescription habits between  
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33 centers in different countries.  
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#### **(4) Methods:**

##### **Study design and setting**

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45 The study was designed as a retrospective cross-sectional study of medical records at the  
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47 University Hospital Lozano Blesa in Zaragoza (Spain) and at the University of Michigan  
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49 Medical School (USA). Patients admitted to the hospital for PCI between January 2007  
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51 and December 2007 were eligible for inclusion. Data were obtained from charts after  
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53 discharge and included basic demographic information, date of hospitalization and  
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3 discharge, cause of hospitalization, presence of co-morbidities, cardiovascular events,  
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5 and GI bleeding during hospitalization. Medical treatment received by patients before,  
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7 during hospitalization, and prescription issued at discharge, were also recorded. The  
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9 ethics committee in both centers reviewed and approved the study protocol.  
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### 12 Patients:

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15 A total of 429 patients meet the inclusion criteria and were studied.  
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### 18 Interventions:

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21 None.  
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### 24 Main outcome measures:

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26 All patients included in the study were hospitalized to undergo PCI from coronary heart  
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28 disease (acute myocardial infarction, unstable or stable angina). Risk factors for UGI  
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30 bleeding were considered to be: age > 70, ulcer history, and concomitant therapy with  
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32 anticoagulants, NSAIDs or steroids<sup>3,4,6</sup>. Patients with  $\geq 1$  risk factor (in addition to dual  
33  
34 antiplatelet therapy) were defined as "high-risk" (HR) for UGI bleeding. The proportion  
35  
36 of patients at discharged on PPI therapy was calculated and stratified by GI bleeding risk.  
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38 All patients received low-dose aspirin therapy, (75 or 162 mg/day) in addition to  
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40 clopidogrel 75 mg/day. A loading dose (300 mg of Clopidogrel) was administered as  
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42 appropriate.  
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### 48 Statistics

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51 We assumed that the average rate of Spanish patients on PPI at discharge was 60% and  
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53 40% of the US patients. Therefore, we planned to enroll approximately 140 patients in  
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3 each study group who could be evaluated for the study to have 90% power to detect a  
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5 significant difference in the rates of patients discharged on PPI between the two centers  
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8 with a two-tailed significance level of 0.005 or less. Statistical differences and odds ratios  
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10 were calculated using Chi-square test for discrete variables and t-tests for continuous  
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12 variables (expressed as means and standard deviation). All statistical tests were  
13  
14 performed with the use of SPSS software. (SPSS v14, Chicago, IL)  
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18 **(5) Results:**  
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20 Table 1 defines the patient demographics and clinical characteristics of the study  
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22 population. Patients from the Spanish center were older than those from the USA,  
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24 translating to a higher proportion of patients at high GI risk in the Spanish population.  
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26 However, the Americans had significantly more cardiovascular co-morbidities  
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28 (hypertension, hypercholesterolemia and diabetes). American patients were also more  
29  
30 frequently on cardiovascular medications on admission. There were no differences  
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32 regarding GI ulcer history in the Americans. PPI treatment at admission was also similar  
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34 (Table 1). The two most frequent reasons for PPI at admission among Americans was  
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36 gastroesophageal reflux disease (GERD) in 22.6% (n=45) and past history of GI bleeding  
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38 in 4.5% (n=9). No reasons for PPI use was recorded among most Spanish patients in the  
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40 admission documents, and therefore these data are not reported here for the Spanish  
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42 cohort.  
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49 Of the Spanish patients not on PPI before admission {70% of the cohort (n=161)}, 49.7%  
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51 (n=80) had 1 or more GI risk factors and 50.3% (n=81) were low risk patients. Similarly,  
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3 for the Americans not on PPI before admission {68% of the cohort (n=131)}, 34.4%  
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5 (n=45) were high risk patients and 65.6% (n=86) were low risk patients.  
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8 During hospitalization (Table 2), 93% (n=185) of the American and 96.7% (n=223) of  
9  
10 the Spanish patients had a coronary stent placed. Two patients died during hospitalization  
11  
12 –one of complications with anoxic brain injury and another because of septic shock in the  
13  
14 Spanish center and two patients in the USA due to ventricular fibrillation and anoxic  
15  
16 brain injury. The proportion of patients who received PPI therapy during hospitalizations  
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18 was high, and increased when compared to those receiving PPI at admission, especially  
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20 in the Spanish cohort in both high and low risk GI patients, whereas that proportion was  
21  
22 much lower in the USA patients (Table 2). Three patients (2 from Spain and 1 from the  
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24 USA center), had a in-hospital GI bleeding after the interventional procedure; (the 3 were  
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26 on a PPI and two were HR patients)  
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35 At discharge, 419 (98.5%) out of the 425 patients of entire population were on dual  
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37 antiplatelet therapy; 2/197 (1%) of the USA patients and none of the Spanish were on  
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39 aspirin alone. Overall, in the Spanish center, 171/228 (75.0%) patients were prescribed  
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41 PPI therapy at discharge vs. 81/197 (41.1%) patients in the USA (O.R: 4.3; 95% CI: 2.8,  
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43 6.6; p < 0.0001). When patients discharged from hospital were stratified according to the  
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45 presence of risk factors (Figure 1), PPI rates were similar in patients with no risk factors  
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47 (83/114; 73%) or one or more risk factors (86/114; 75.4%) in the Spanish center (p =  
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49 0.679), whereas the Americans with no risk factors (36/116; 31.0%) differed from the  
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51 high risk cases (45/81; 55.6 %) (p = 0.0006)  
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4 Overall, high-risk American patients were more likely than low-risk patients to be  
5 discharged on a PPI (OR = 2.8, 95% CI: 1.5 – 5.2, p= 0.0007). In both centers the  
6 proportion of PPI therapy increased further for those patients with 1 or more risk factors  
7 (Figure 2).. Table 4, also includes PPI prescription rates according to individual risk  
8 factors. Figures were always higher for the Spanish cohort. Considering HR patients not  
9 on PPI at admission (80 out of 116 among the Spanish cohort and 45 out of 82 in the  
10 USA cohort; of the two Spanish patients who died during hospitalization both were HR  
11 and one was on PPI, whereas of the two Americans, one was HR and not on PPI), the  
12 opportunity to initiate PPI co-therapy following PCI and treatment with dual antiplatelet  
13 therapy at discharge in this population was missed in 81.8% (36/44) of the USA  
14 patients. In the Spanish cohort that proportion was 24.1% (19/79) (p < 0.001), but 7  
15 additional HR patients on PPI at admission were discharged with no PPI, which means  
16 that in this cohort, the overall opportunity was missed in 22.8% (26/114) of patients.  
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## **(6) Discussion**

According to current recommendations, patients at risk for upper gastrointestinal bleeding receiving dual anti-platelet therapy with ASA and CLP should receive PPI co-therapy<sup>8, 17, 18, 19, 20</sup>. Our study shows that the probability of receiving PPI therapy at hospital discharge varied significantly among the two centers studied. We found that the proportion of patients being prescribed PPI at discharge in the Spanish center was significantly higher than that observed in patients from the USA. The data should be of interest since no studies have reported transatlantic prescription habits in this type of patients.<sup>21, 22, 23</sup> Since the study collected information from patients records before concerns on the potential interaction of PPI with CLP were raised, the data reflects the awareness among the cardiologists in those centers on the necessity of risk assessment and response with co-prescription to reduce the risk of UGI bleeding. We suspect the more recent developments concerning the potential interaction of CLP with PPI, may have significantly reduced co-prescription rates.

It is unclear whether the data observed in these two centers reflect prescription habits among all cardiologists in other practice settings in their respective countries. However, we suggest it may well be the case, since data on GI bleeding and drug use, for example, from at least one of the centers [Zaragoza], has been often reproduced in other centers of the same country<sup>24, 25</sup>.

From the data reported here, it can be concluded that cardiologists in the Spanish center are more concerned of the UGI bleeding risk associated with dual antiplatelet therapy than their American peers, even before the recommendations of the consensus

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3 document were published <sup>5</sup>. However the data show that the PPI prescription observed in  
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5 the Spanish center was not guided by the assessment of the underlying UGI risk factors,  
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7 since the prescription of PPI is essentially independent of the presence and number of GI  
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9 risk factors. On the contrary, that was the case in the USA center, but the gap of risk  
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11 reducing co- therapy in high patients was much larger than in Spain, which reduces the  
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13 overall clinical impact, and still, a significant proportion of the group of high risk for UGI  
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15 bleeding were not started on PPI in both centers.  
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20 The reasons for the differences in PPI prescription rates found in both centers,  
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22 which could be generalized to other centers in the respective countries, are unclear.  
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24 Differences are unlikely to be driven by a patient's economic concerns, although the fact  
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26 that medications are widely subsidized by the health system in the European center may  
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28 facilitate prescription to patients, especially if CV safety is not of concern. More likely  
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30 the differences may be due to different perceptions on the intrinsic GI risk of antiplatelet  
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32 therapies, since PPIs are widely prescribed across Spain to patients receiving potential  
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34 gastro-toxic agents such as NSAIDs <sup>26</sup>. In any case, the lack of selectivity of PPI  
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36 prescription in the Spanish center and the wide gap of that in at-risk patients in the  
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38 American one, shows that there is a clear opportunity to better educate physicians on the  
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40 importance of gastroprotection in this group of patients and develop better educational  
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42 programs to disseminate the appropriate guidelines toward the goal of reducing UGIB.  
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49 The strengths of our study include the use of well defined risk factors and end  
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51 points as well as the use of structured data collection from hospital medical records  
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53 (electronic in USA and manual review of charts in Spain), which contained all the data  
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3 required for the study. There are also limitations of our study. The first is that our  
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5 analysis was based on medical and prescription records. A systematic assessment of  
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7 medication compliance was not possible due to the study design. While this is an  
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9 important consideration, it should be noted that the purpose of this study was to describe  
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11 prescription patterns of physicians in two different countries. Another weakness is that  
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13 GI bleeding risk may have been considered by the prescribers, but other aspects in the  
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15 decision-making process, including cost and insurance reimbursement policies are not or  
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17 may not be documented and however have a clear impact on the observed differences.  
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23 In summary, our data provide evidence that GI risk reduction strategies are not  
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25 considered routinely for at-risk patients on dual antiplatelet agents and co-therapy to  
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27 reduce risk varies widely across centers from two different countries. Our study also  
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29 demonstrates that prescription may not always be based on proper assessment of risk  
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31 factors. We conclude that future efforts be implemented to improve the rates of GI risk  
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33 assessment and of prevention strategies among the high-risk population as well as future  
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35 studies to assess the GI and CV impact of these strategies.  
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5 USA.  
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14  
15 James Scheiman has served as consultant to AstraZeneca as well as Takeda, Bayer, and  
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17 Pozen, Inc.  
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21 No other authors report any conflict of interest.  
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## (10) Text tables.

Table 1. Baseline Characteristics of Study Participants

	Spanish patients N = 230 patients	USA patients N = 199 patients	p-value
Age, mean (SD)	67.4 (8.9)	62.5 (11.7)	<0.0001
Male sex, N (%)	193 (83.9)	154 (77.4)	0.0877
Age > 70, N (%)	95 (41.3)	49 (24.6)	0.0003
NSAID use, N (%)	15 (6.5)	17 (8.5)	0.4308
Ulcer history, N (%)	13 (5.7)	17 (8.5)	0.2570
Steroids (>10 mg daily) use, N (%)	7 (3.0)	5 (2.5)	0.7529
Oral anticoagulants, N (%)	11 (4.8)	14 (7.0)	0.3318
High-risk GI patients (HR), N (%)	116 (50.4)	82 (41.2)	0.0566
Hypertension, N (%)	126 (54.8)	147 (73.9)	<0.0001
Hypercholesterolemia, N (%)	133 (57.8)	151 (75.9)	0.0001
Diabetes mellitus, N (%)	60 (26.1)	72 (36.2)	0.0238
Prior CABG, N (%)	5 (2.2)	38 (19.1)	<0.0001
Prior stroke or transient ischemic attack, N (%)	14 (6.1)	22 (11.0)	0.0677
At admission on:			

No antiplatelet agent, N (%)	120 (52.2)	64 (32.2)	<0.0001
ASA alone, N (%)	61 (26.5)	88 (44.2)	0.0001
Clopidogrel alone, N (%)	3(1.3)	4 (2)	0.5674
ASA and Clopidogrel, N (%)	45 (19.6)	43 (21.6)	0.6090
PPI, N (%)	69 (30)	68 (34.2)	0.3522
Statins, N (%)	89 (38.7)	114 (57.3)	0.0001

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Table 2. In-hospital Management.

	Spanish patients N = 230 patients	USA patients N = 199 patients	p-value
Stent placement, N (%)	224 (97.4)	185 (93.0)	0.0307
High-risk GI patients on PPI, N (%)	87/116 (75.0)	37/82 (45.1)	< 0.0001
Low-risk GI patients on PPI, N (%)	80/114 (70.1)	31/117 (26.5)	< 0.0001
In-hospital GI bleeding complications, N (%)	2 (0.9)	1 (0.5)	0.7724
In-hospital death, N (%)	2 (0.9)	2 (1.0)	0.9150
Length of hospitalization (days), mean (SD)	6.8 (6.78)	3.2 (4.52)	<0.0001

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Table 3. At Discharge Management.

	Spanish patients N = 228 patients	USA patients N = 197 patients	p-value
Dual antiplatelet agents, N (%)	223 (97.8)	196 (99.5)	0.1385
PPI, N (%)	171 (75.0)	82 (41.2)	<0.0001
High risk GI patients on PPI at discharge, N (%)	86/114 (75.4)	45/81 (55.6)	0.0037
Low-risk GI patients on PPI at discharge, N (%)	83/114(72.8)	36/116 (31.0)	<0.0001
Bleeding in follow-up, N (%)	3 (1.3)	4 (2.0)	0.5692

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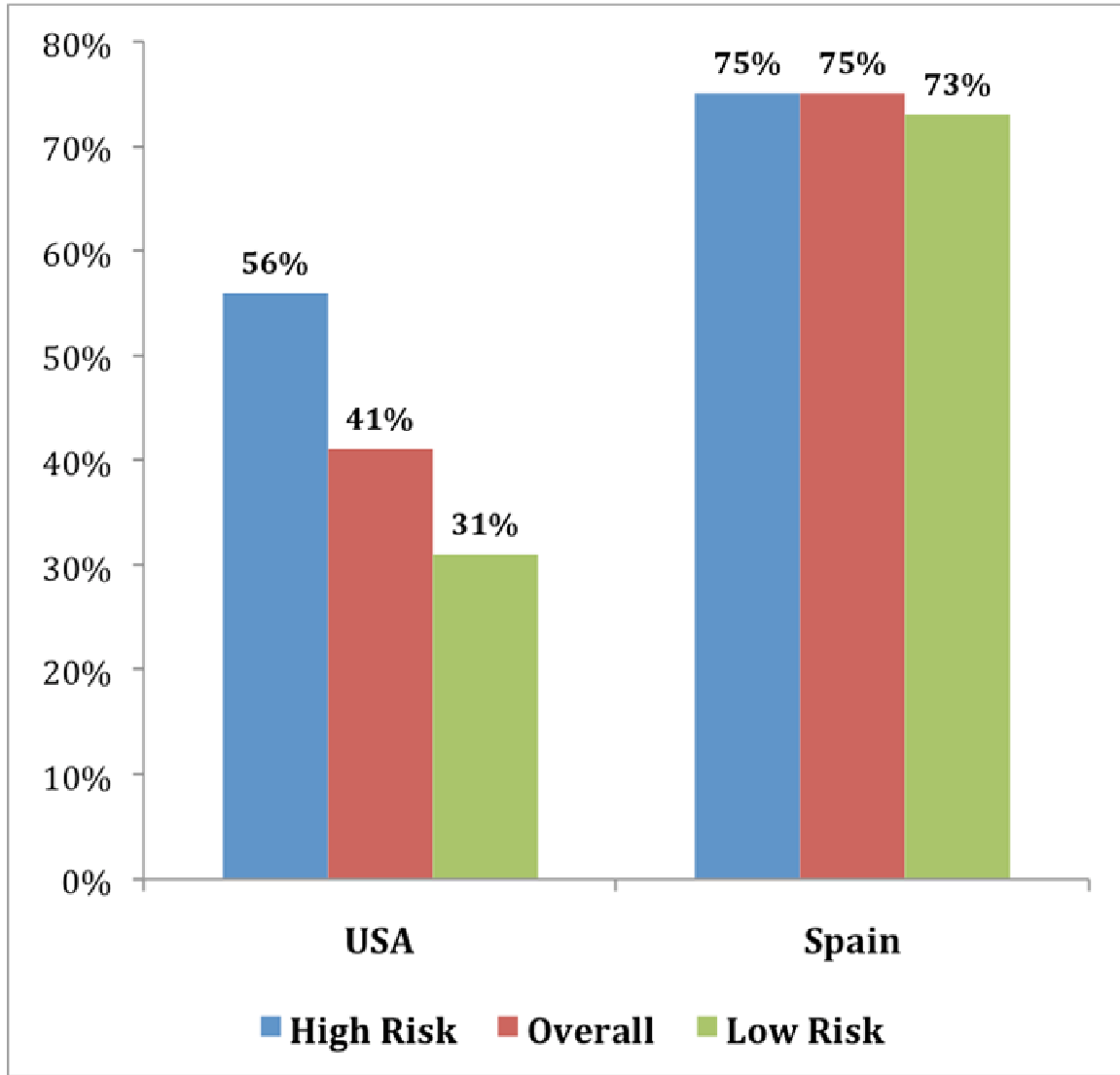
Table 4. PPI therapy at discharge according to GI risk factors.

	Spanish Patients N = 228 N (%)	USA patients N = 197 N (%)	p-value
No risk factors	83/114 (72.8)	36/116 (31.0)	<0.0001
1 risk factor	68/94 (72.3)	34/63 (54.0)	0.0185
> 1 risk factor	18/20 (90.0)	11/18 (61.1)	0.0364
Age $\geq$ 70 years old	71 / 93 (76.3)	28 / 49 (57.1)	NS
Prior history of peptic ulcer disease	11 / 13 (84.6)	12 / 17 (70.6)	NS
Concurrent warfarin use	9 / 11 (81.8)	7 / 14 (50)	NS
Concurrent use of corticosteroids $\geq$ 10 mg daily	7 / 7 (100.0)	4 / 5 (80)	NS
Concurrent use of non-aspirin NSAIDs	13 / 15 (86.7)	7 / 17 (41.2)	0.0328



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Figure 1. PPI prescription at discharge: USA vs Spain.



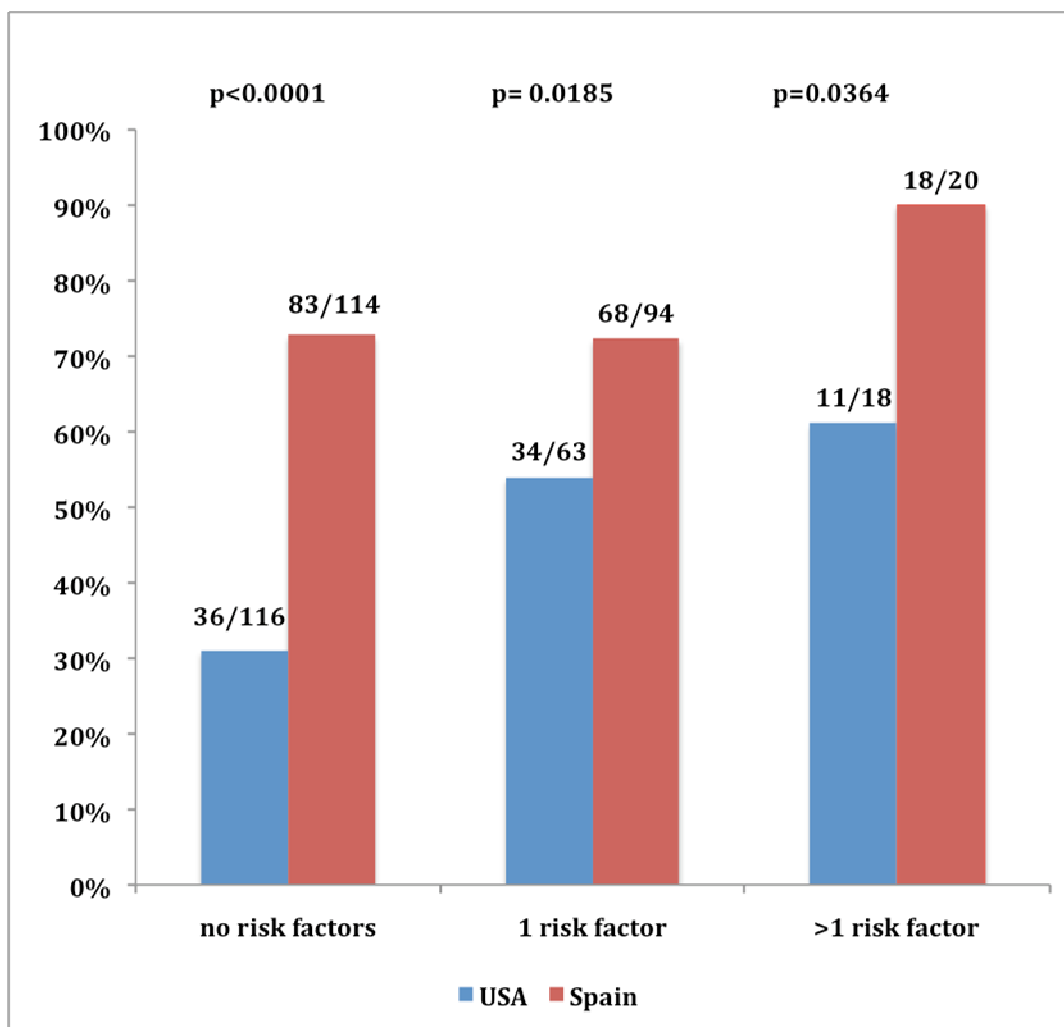


Fig 2. PPI therapy at discharge in relation to GI risk factors.

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For Peer Review

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3 Dear Editor:  
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5 Thank you for considering our article for resubmission and potential publication in  
6 the journal. We have revised the article and considered your comments and those of  
7 the reviewers. Below, please find our reply to those comments. The changes in the  
8 manuscript have been highlighted in yellow.  
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11 Subject: Manuscript APT-0197-2010.  
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13 Author comments to reviewers:  
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15 **Reviewer #1:**  
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17 **Comment:** *“One of the major flaws of this paper is that information of PPI*  
18 *prescription determinant were not captured in the databases. Thus authors have*  
19 *trouble to explain the differences across the Atlantic see. It is confusing to see that*  
20 *Spanish physician prescribe PPI to a vast majority of patients on dual therapy*  
21 *irrespective of risk factors whereas US physician miss a huge number of necessary*  
22 *prescription but seem to take risk factor into consideration”.*  
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25 **Reply:** As stated in the original manuscript, the only information, which was not  
26 included, or not fully captured (and therefore not reported), was the reason for PPI  
27 use in the cohort of Spanish patients **at admission**. The proportion of patients on  
28 PPI at admission was however similar in both the American and the Spanish  
29 cohorts, which could suggest similar patterns of use. Nevertheless, we believe that  
30 this aspect does not affect the actual objective of the study, which was to evaluate  
31 the proportion of patients on dual antiplatelet therapy and PPI prescription **at**  
32 **hospital discharge**, which should reflect the cardiologist’s concern regarding the GI  
33 risk of HR patients being treated with dual antiplatelet therapy.  
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37 The strong differences in PPI prescription rates observed in both cohorts at  
38 discharge are precisely the key findings of the study. Furthermore, we provide data  
39 that suggest that the higher proportion of PPI prescription in the Spanish cohort  
40 reflects a major concern for the GI risk of ASA-clopidogrel combination by the  
41 Spanish cardiologists, but their pattern of prescription does not seem to be driven  
42 by a decision process based on GI risk factors. On the contrary, the prescription rate  
43 of PPI at discharge was much lower in the American cohort, but the proportion of  
44 what was prescribed, in contrast, was somewhat based on the presence of risk  
45 factors. Still, many high-risk patients in this cohort did not receive prevention  
46 therapy. We have re-written some of the critical paragraphs for a better  
47 understanding of this message.  
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53 **Comment:** *“The discussion is of interest but only speculative”.*  
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55 **Reply:** We have rewritten some paragraphs of the discussion.  
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**Comment:** *"It would have been useful to have some follow-up data. US patients were less likely to receive a PPI, that is a fact, but what were their GI or cardiovascular outcomes with the year post discharge. In other words who was right, US or Spanish Physicians?"*

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**Reply:** What the reviewer suggests it is of interest but it was not the objective of this study. To have reliable data on that this important issue, the sample size needs to be much larger and the current study could not provide reliable data.

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**Comment:** *"I have trouble with the numbers. Indeed it is told page 6 that 131 American patients were not on PPI at admission, among which 42 were high risk patients, and then page 7 "The opportunity to initiate PPI co-therapy following PCI and treatment with dual antiplatelet therapy was missed in 80% (65/78) of the high risk patients who were not already on PPI therapy at admission in USA patients". Same remark is for Spanish patients. Please correct numbers or explain the apparent discrepancy"*

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**Reply:** The referee is right. We have revised all the numbers and found a few, minor, mistakes that although did not affect the findings and messages, they were not correct. We have clarified this issue and re-written the appropriate sentences.

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In the USA cohort, there were 82 HR at admission, 45 had no PPI, and 37 were on PPI. Of 81 HR patients at discharge (one HR patient died) , 36 had no PPI, and 45 were on PPI. All HR patients who were on PPI at admission were discharged on PPI, which means that 8 additional patients were put on PPI therapy at discharge; therefore 36 of 44 HR (81.80%) who did not have PPI at admission were sent home without PPI and lost the opportunity to start PPI therapy

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In the Spanish cohort, of 116 HR at admission, 80 had no PPI, and 36 were on PPI; Of 114 HR patients at discharge (2 died during hospitalization), 28 had no PPI, and 86 were on PPI. Of the 79 HR patients alive who had no PPI at admission 60 were started on PPI at discharge and therefore 19 lost the opportunity of initiate PPI therapy.- However, unlike the USA cohort, 7 additional HR patients on PPI at admission were discharged with no PPI, which means that in this cohort, the overall opportunity was missed in 21.9% (26/114) of patients.

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**Comment:** *"Minor comments: I have trouble understanding the following sentence in the abstract "PPI prescription rates were found in the Spanish patients according to risk factors, whereas they were present among the Americans."*

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**Reply:** The referee is right; the sentence has been changed.

**Reviewer # 2**

**Comment:** *"In the Summary, there is a claim that this is the first such study... very unlikely, and immodest, even if true. The Summary needs writing in complete sentences, not staccato-style."*

**Reply:** Based on our review of the literature, we believe that this is the first study to determine differences between two cardiology centers in two continents providing data on PPI at discharge, but eventually we had followed the suggestion made by the referee.

**Comment:** *"Do the hospitals not have written protocols?"*

**Reply:** As stated in the manuscript, recommendations of PPI use and double anti-aggregation was stated in the consensus of the American College of Gastroenterology, the American College of Cardiology Foundation and the American Heart Association document was published in 2008 and our study collected data from 2007. In 2007, there were data suggesting the efficacy of PPI in the prevention of GI damage induced by ASA.

For collection of data in this study both hospitals followed the same protocol and IRB approval.

**Comment:** *"The under-treatment in the USA - is this just here or widespread? AP&T has recently published two possibly relevant studies / papers:*

1. *Meta-analysis: effects of proton pump inhibitors on cardiovascular events and mortality in patients receiving clopidogrel. Kwok CS, Loke YK. Aliment Pharmacol Ther. 2010 Jan 22. [Epub ahead of print]. PMID: 20102352 [PubMed - as supplied by publisher]*

2. *A randomized, placebo-controlled study of the effects of naproxen, aspirin, celecoxib or clopidogrel on gastroduodenal mucosal healing. Dikman A, Sanyal S, VON Althann C, Whitson M, Desai J, Bodian C, Brooks A, Bamji N, Cohen L, Miller K, Aisenberg J. Aliment Pharmacol Ther. 2009 Apr 1;29(7):781-91. Epub 2009 Jan 13"*

**Reply:** The article of Dr Kwok et al. is an interesting article, focused on outcomes but it does not report data on this specific aspect on PPI prescription rates at discharge. The authors also comments on the difficulties in obtaining reliable data, apart from RCTs, since many of the studies were in abstract form. The article by Dikman et al. is a clinical trial and does not report on these aspects either. As suggested in the article the data from these hospitals may well represent what happens in their respective countries, but no comparative data are available, at least in the USA.

**Reviewer # 3**

**Comment:** *"The "appropriateness" of a prescription practice is often difficult to be determined. Whether to administer PPI co-therapy is sometimes dictated by other issues such as cost and insurance reimbursement policies".*

**Reply:** We agree with the referee that reporting on prescription rates at discharges is not equivalent to reporting on the appropriateness of such a type of prescription, due to the multiple variables that may affect this clinical decision. Our intention was just to report rates and correlate that with the presence of risk factors. We have tempered some of the sentences in the manuscript. A sentence in this regard has been included at the end of the discussion section.

**Comment:** *"The incidence rate may be considered low by many patients. The study has no follow up data and therefore we do not really know if the underutilization translates to clinical adverse events in patients. In any case, the sample size accrued is unlikely to show a small difference. I am unsure if the variation in practice will have impact on current practice".*

**Reply:** As commented above to another referee, we believe that that is an issue of great interest, and agree that a follow-up of this cohort will not produce reliable data on the incidence of complications. Although we do believe that the lack of prevention therapy will be associated with an increased incidence of serious GI events as reported in abstract form by the still unpublished COGENT study, the sample size needed is much higher and out of the objective or scope of this study.

**Comment:** *"I would suggest to tabulate risk factors in tables - a previous ulcer complication e.g. bleeding carries a high GI risk than factors such as age > 70. The tabulation of these factors in tables will provide more clarity to their GI risks. Figures - the histograms. it is more informative to put actual no. of patients to each bar".*

**Reply:** For a better understanding and as suggested, we include data for additional and specific risk factors. We have also included actual numbers of patients to each bar in Figures.