	Famotidine (n=204)	Placebo (n=200)	Total (N=404)	OR (95% CI)	P-value
All lesions	12 (5.9%)	66 (33%)	78 (19.3%)	0.13 (0.07-0.24)	P<0.0001
Esophagitis	9 (4.4%)	38 (19%)	47 (11.6%)	0.2 (0.09 - 0.4)	P<0.0001
Gastric ulcers	7 (3.4%)	30 (15%)	37 (9.2%)	0.2 (0.09 - 0.4)	P=0.00021
Duodenal ulcers	1 (0.5%)	17 (8.5%)	18 (4.5%)	0.05 (0.01- 0.4)	P=0.0045

407

Does High-Dose Famotidine Reduce Gastric and Duodenal Ulcers in NSAID Users? Two Double-Blind Six-Month Trials of Single-Tablet Combination Ibuprofen-Famotidine vs. Ibuprofen Alone (Reduce-1 and 2)

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Proton pump inhibitors are recommended to decrease NSAID-associated GI injury, while standard-dose histamine2-receptor antagonists (H2RAs) are not. However, a Cochrane review suggested that high-dose H2RAs provide significant benefit in NSAID users. Importantly, the benefit of antisecretory therapy in patients taking NSAIDs plus low-dose aspirin is uncertain. In addition, most NSAID users at increased risk for GI events do not receive or adhere to protective co-therapy, and decreased adherence is associated with an increased risk of ulcers and bleeding. We performed two 24-wk double-blind, randomized trials to determine if a single-tablet combination of ibuprofen (800mg) and famotidine (26.6mg) (HZT-501) given thrice daily (providing 80mg famotidine daily) will significantly decrease ulcers as compared to ibuprofen alone. **METHODS**: Patients 40-80 yrs expected to require daily NSAID therapy ≥6 mos with no history of ulcer complications, negative *H. pylori* stool test, and baseline endoscopy showing no ulcers and <5 erosions in the upper GI tract were randomly assigned in a 2:1 ratio to HZT-501 or identical-appearing ibuprofen 800 mg tablets thrice daily. Concomitant aspirin ≤325 mg daily and anticoagulant therapy were permitted. Randomization was stratified based on aspirin/anticoagulant therapy and prior ulcer history. Study endoscopies were done at 8, 16, and 24 wks of therapy. The predefined population for primary analyses of ulcers was all patients with ≥1 follow-up study endoscopy. **RESULTS**: The REDUCE-1 and REDUCE-2 studies included 812 and 570 patients in their primary analysis populations. Results are shown in the Table. The differences for HZT-501 vs. ibuprofen in the life table estimates of the proportion of patients developing ulcers over 24 wks were significant in both REDUCE-1 (14.7% vs. 29.1%, p=0.0002) and REDUCE-2 (13.8% vs. 22.6%, p=0.030). **CONCLUSIONS**: High-dose H2RA delivered in single-tablet combination ibuprofen-famotidine significantly reduces NSAID-associated gastric and duodenal ulcers. A reduction in ulcers also was seen in the subset of NSAID users taking low-dose aspirin.

Proportion of Patients with Ulcers at 24 Wks: Crude Proportions (n/N (%)); Life Table Estimates (%)

	REDUCE-1		REDUCE-2	
	HZT-501	Ibuprofen	HZT-501	Ibuprofen
Gastric or Duodenal (UGI) Ulcer	63/550 (11.5%)*; 14.7%*	61/262 (23.3%); 29.1%	40/380 (10.5%)*; 13.8%*	38/190 (20%); 22.6%
Gastric Ulcer	55/550 (10.0%)*; 12.9%*	52/262 (19.8%); 25.3%	37/380 (9.7%)*; 13.0%	34/190 (17.9%); 19.7%
Duodenal Ulcer	8/550 (1.5%)*; 2.1%*	14/262 (5.3%); 7.1%	3/380 (0.8%)*; 0.9%*	9/190 (4.7%); 6.6%
UGI Ulcer: Patients with Low-Dose Aspirin Use	11/89 (12.4%)*; 14.0%*	10/32 (31.3%); 33.3%	8/56 (14.3%); 14.9%	6/23 (26.1%); 27.5%
UGI Ulcer: Patients with Prior Ulcer	9/42 (21.4%); 17.8%	4/15 (26.7%); 27.3%	3/18 (16.7%); 23.5%	2/11 (18.2%); 20.0%

*p<0.05, HZT-501 vs. ibuprofen (separate comparisons for crude proportions and life table estimates)

408

Increased Aspirin Use and Upper Gastrointestinal Bleeding Rates in Socially Deprived Patients

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INTRODUCTION: Cardiovascular morbidity is associated with social deprivation but it is not clear whether this results in greater use of aspirin nor whether more aspirin associated gastro toxicity results. QRESEARCH is a new larger database that includes information on deprivation. AIMS & METHODS: We used QRESEARCH to investigate aspirin use in relation to the Townsend Index of deprivation and to co-morbidity and whether this was associated with a higher incidence of gastrointestinal bleeding. All patients aged 45-100 years with continuous aspirin use (definition: new prescription ≤8 weeks after previous) at any time during the period 1 April 2003 - 31 March 2007 were included. RESULTS: Four hundred and fifty nine practices met inclusion criteria to generate 4.87 million person years of observation. Over 99% of aspirin use was for ≤300mg per day. Aspirin use was higher at younger ages in men but similar between sexes by age 80. It increased from 9.9% in 2003 to 14% in 2007. Use was higher in deprived compared to affluent areas (11.8% in lowest quintile versus 8.6% in highest quintile in 2003, 15.9% and 12.5% in 2007). Of patients with coronary heart disease 55.2% were prescribed aspirin in 2003 and 59.1% in 2007, 50.8% and 54.2% for stroke, 33.7% and 44.1% for diabetes, 24.3% and 29.2% for hypertension. Coronary heart disease was more common in deprived than affluent areas (12.0% versus 8.8%). The incidence of upper gastrointestinal bleeding rose with age (from 44.3 per 100,000 at aged 60 to 325.2 per 100,000 at age 85 for women and 62.7 per 100,000 and 378.4 per 100,000 for men) but not over the four years of the study (80.1 per 100,000 in 2003/4, 72.3 per 100,000 in 2006/7) more men than women were affected and rates were higher in deprived than affluent areas (100.9 per 100,000 versus 58.3 per 100,000). Upper gastrointestinal bleeding was more common in patients with cardiovascular disease, diabetes or hypertension. Aspirin increased the risk of upper gastrointestinal bleeding, even after adjustment for age, sex, deprivation and co-morbidities (1.59, 1.47-1.73). CONCLUSION: Patients in deprived areas are prescribed more aspirin than in affluent areas and have higher rates of upper gastrointestinal bleeding. Aspirin may contribute to this. However, upper gastrointestinal bleeding appears not to be increasing despite increased use of aspirin.

409

Prescription Rates of PPI Therapy Are High in Patients On Dual Antiplatelet Therapy in Spain, Regardless of the Presence of Risk Factors

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Background: Dual antiplatelet therapy (aspirin and clopidogrel) potentiates the risk of gastrointestinal (GI) bleeding beyond the risk observed with the individual agents in cardiovascular patients. Proton pump inhibitors (PPI) reduce the risk of ulcer bleeding in high-risk patients treated with aspirin or clopidogrel. No studies have determined whether GI preventive therapy with PPIs is being prescribed in cardiovascular clinical practice. Methods: We performed a retrospective cross-sectional study of medical records at the University Hospital in Zaragoza (Spain). Patients admitted to the hospital Cardiology Unit undergoing percutaneous coronary intervention (PCI) between January and December 2007 were eligible for inclusion. Data were extracted on: (1) patient demographics; (2) medications used; (3) prescription drugs; and, (4) risk factors for GI bleeding (age ≥ 70; history of peptic ulcer disease; concurrent anticoagulant, corticosteroids ≥ 10mg daily, or daily/intermittent NSAID use). Patients with ≥ 1 risk factor were defined as "high-risk" for GI bleeding. The proportion of patients discharged on PPI therapy was calculated and stratified by GI bleeding risk. Statistical differences and Odds ratios were calculated using Chi-square tests Results: 230 patients were included in the study (3 died during hospitalization and no valuable information was available for 6 patients). The mean age was 66.9±8.9, and 16.1% were women. At admission, 69 patients (30.0%) were on PPI therapy and 110/230 patients (47.8%) were already on antiplatelet therapy. 112/230 patients (48.7%) were at high risk for GI bleeding (96/230 = 41.7% > 70 yrs old); 52% (34/112) of these high-risk patients were on a PPI at admission. At discharge, 220/221 patients (99.5%) were on dual antiplatelet therapy, and 171 (74.3%) patients were on PPI therapy. Among the high-risk patients not admitted on PPI therapy, the opportunity to initiate therapy was missed in 18 patients (23%) (95% CI: 13.7% - 32.4%). PPI therapy rates at discharge were similar in patients with no risk factors (73.5%), 1 risk factor (71.6%) or > 1 risk factor (90.9%) (p = 0.166). Conclusions: New prescription of PPI therapy is high among patients undergoing PCI on dual antiplatelet therapy in our center, regardless of the presence of risk factors. Still, almost a quarter of high-risk patients were not started on a PPI following initiation of dual antiplatelet therapy. Future efforts need to be implemented to further improve the rates of GI prevention strategies in the high-risk population. Studies to assess the GI and CV impact of these strategies in low and high risk patients are warranted.

410

Proton Pump Inhibitor Prescription in High-Risk Cardiac Patients: A Missed Opportunity?

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Background: Patients undergoing percutaneous coronary intervention (PCI) require therapy with aspirin and clopidogrel. Though such therapy decreases the risk of cardiac events, it also increases the risk of life-threatening gastrointestinal (GI) bleeding. No study has determined whether proton-pump inhibitors (PPIs) are being used appropriately to reduce GI bleeding risk in such patients. Methods: We performed a retrospective cross-sectional study of medical records at the University of Michigan Hospital. Patients admitted to the hospital status-post PCI between August 2007 and December 2007 were eligible for inclusion. Data were extracted on: (1) patient demographics; (2) medications used; (3) indication for PPI use; and, (4) risk factors for GI bleeding (age ≥ 70; history of peptic ulcer disease; concurrent warfarin, corticosteroids ≥ 10mg daily, or daily NSAIDs). Patients with ≥ 1 risk factor were defined as "high-risk" for GI bleeding. The proportion of patients discharged on PPI therapy was calculated and stratified by GI bleeding risk. The chi-squared test was used to assess for statistical significance. Results: 199 patients were included in the study. The mean age was 63 years, and 23% were women. The median length of hospital stay was 2 days. At admission, 68 patients (34%) were on PPI therapy (56% for heartburn). 79 patients (40%) were at high risk for GI bleeding; 48% of these high-risk patients were on a PPI at admission. High-risk patients were more likely than low-risk patients to be on PPI therapy at the time of admission (OR = 2.78, p<0.001, 95% CI 1.52-5.09). At discharge, 196 patients (98%) were on dual antiplatelet therapy, and 82 patients (41%) were on PPI therapy. Among the high-risk patients not admitted on PPI therapy, the opportunity to initiate therapy was missed in 80% (95% CI: 0.65-0.91). Overall, 42% of high-risk patients were discharged without PPI, though high-risk patients were more likely than low-risk patients to be discharged on a PPI (OR = 3.25, p<0.001, 95% CI: 1.80-5.89). Conclusions: While high-risk patients were significantly more likely to be discharged on PPI therapy than low risk patients, 80% of eligible high-risk patients were not started on a PPI following initiation of dual antiplatelet therapy. Such patients represent a "missed opportunity" for intervention. Future efforts to educate clinicians on the importance of utilizing PPIs for bleeding prophylaxis in high-risk patients are warranted.