Dual antiplatelet therapy and upper gastrointestinal bleeding risk: do PPIs make any difference?

Inamul Haq, Fazal-ur-Rehman Ali, Shakeel Ahmed, Steven Lindsay, Sudantha Bulugahapitiya

Authors

Inamul Haq
Specialist Registrar
Gastroenterology

Shakeel Ahmed
Specialty Doctor Elderly Medicine/
Stroke

Diana Princess of Wales Hospital, Grimsby, DN33 2BA

Fazal-ur-Rehman Ali
Specialist Registrar
Gastroenterology

Mid Staffordshire NHS Foundation Trust, Weston Road, Stafford, Staffordshire, ST16 3SA

Steven Lindsay
Consultant Cardiologist

Sudantha Bulugahapitiya
Consultant Cardiologist

Bradford Teaching Hospital, Bradford, West Yorkshire, BD9 6RJ

Correspondence to:
Dr I Haq
inamulhaq11@doctors.org.uk

Key words

acute coronary syndrome (ACS), CABG, dual antiplatelet therapy, gastrointestinal bleeding, NSTEMI, proton pump inhibitors, STEMI

First published online September 5th 2013

doi: 10.5837/bjc.2013.029

Br J Cardiol 2013;**20**:(4)

Dual antiplatelet therapy (DAT) with aspirin and clopidogrel is recommended for up to one year following acute coronary syndrome (ACS). Gastrointestinal bleeding is the main hazard of this treatment and proton pump inhibitors (PPIs) are often prescribed in selected patients to reduce this risk. The main purpose of this study was to analyse the effect of PPIs in reducing the subsequent risk of gastrointestinal bleeding.

The medical records of 177 consecutive patients treated with DAT following ACS, were specifically reviewed for the study parameters over a 12-month period.

The mean age was 66 years (range 24–96) with a median value of 68 years; 67% were males and 33% females, 74% Caucasians and 26% Asians. Patients were divided into two groups: the PPI group (patients on DAT and PPIs, n=91) and the control group (patients on DAT only, n=86). In the PPI group, 55% were on lansoprazole, 34% on pantoprazole and 11% on omeprazole.

Out of the 177 patients, evidence of upper gastrointestinal bleeding was found in 10 patients, with the mean age of these patients being 77 years in the PPI group and 53 years in the control group. In the PPI group, endoscopy findings from six patients (6.6%) revealed gastritis in four, bleeding angiodysplasia in one, and bleeding oesophagitis in one; while the findings for the four patients in the control group (4.6%) showed gastritis in two, gastric ulcer in one and Mallory Weiss tear in one (odds ratio: 1.45, 95% confidence interval 0.39–5.32, p=0.58). None of these patients had a previous history of gastrointestinal bleeding.

In conclusion, empirical prophylactic prescription of PPIs for patients on DAT following ACS is of no significant benefit in reducing their predisposition to upper gastrointestinal bleeding. However, studies utilising larger populations are warranted to confirm this conclusion.

Introduction

Dual antiplatelet therapy (DAT) with aspirin and clopidogrel is recommended for up to one year following acute coronary syndrome (ACS) in order to reduce the risk of further cardiac events.[1,2] Gastrointestinal bleeding is the main hazard of this treatment; however, although the incidence of bleeding is low, it results in significantly increased morbidity and mortality in these patients,[3-5] and proton pump inhibitors (PPIs) are often prescribed to selective patients to reduce this risk. PPIs act by reducing the secretion of gastric acid, neutralising gastric pH, increasing clot formation and decreasing the lysis of blood clots.

There are no formal guidelines concerning the initiation and continuation of PPIs for such patients. In addition, evidence regarding the treatment effect of this group of medications in lowering the risk of subsequent gastrointestinal bleeding is absent. Therefore, the main purpose of this study was to analyse the effect of PPIs in reducing the subsequent risk of gastrointestinal bleeding in patients on DAT with aspirin and clopidogrel following ACS.

Methods and materials

The medical records of 177 patients treated with DAT following ACS were specifically reviewed for the study parameters over a 12-month period of time. These patients were consecutive admissions following index myocardial infarction, admitted to the cardiology department of Bradford Teaching Hospital: 66 patients (37.3%) were admitted with

Table 1. Baseline demographics of the patients

Demographics	PPI group (n=91) N (%)	Control group (n=86) N (%)	p value
Mean age (± SD), years	69 (± 13)	63 (± 15)	0.01
Gender			
Male	53 (58%)	65 (76%)	0.02
Female	38 (42%)	21 (24%)	
Ethnicity			
Caucasian	69 (76%)	61 (71%)	0.50
Asian	21 (23%)	25 (29%)	
Afro-Caribbean	1 (1%)	0 (0%)	
Type of coronary event			
NSTEMI	64 (70%)	47 (55%)	0.04
STEMI	27 (30%)	39 (45%)	
Cardiac intervention			
PCI	39 (43%)	56 (65%)	0.006
CABG	4 (4%)	5 (6%)	
Conservative management	48 (53%)	25 (29%)	
Proton pump inhibitor			
Lansoprazole	50 (55%)		
Pantoprazole	31 (34%)		
Omeprazole	9 (10%)		
Esomeprazole	1 (1%)		

Key: CABG = coronary artery bypass graft; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PPI = proton pump inhibitor; SD = standard deviation; STEMI = ST-segment elevation myocardial infarction

ST-elevation myocardial infarction (STEMI) and 111 (62.7%) with non-ST elevation myocardial infarction (NSTEMI). All the patients in the study were given 300 mg aspirin and 300 mg clopidogrel after index myocardial infarction followed by 75 mg aspirin and 75 mg clopidogrel daily. Records of re-admissions with gastrointestinal problems, particularly gastrointestinal bleeding, were retrieved from the medical records department.

Patients were divided in two groups: the PPI group (patients on DAT and PPIs, n=91) and the control group (patients on DAT only, n=86). At the time of data collection, there were no hospital guidelines in terms of prescribing PPIs for these patients. The database was analysed for re-admissions with upper gastrointestinal problems over one year while patients were receiving DAT. The unpaired *t*-test was used to compare age between the two groups, while Fisher's exact test was used for the remaining demographics, all of which were measured on a categorical scale. Subsequent analysis re-examined the difference adjusting for demographic factors found to significantly vary between groups. These analyses were performed using logistic regression. The end points were re-admissions with gastrointestinal bleeding or death.

Results

The mean age of patients was 66 years (range 24–96) with a median value of 68 years; 67% were males and 33% females, 74% Caucasians and 26% Asians. In the PPI group, 27 patients (29.7%) were admitted with STEMI and 64 patients (70.3%) with NSTEMI, while the corresponding values for the control group were 39 (45.3%) and 47 (54.7%), respectively. In the PPI group, 39 patients (42.9%) were treated with percutaneous coronary intervention (PCI), four (4.4%) with a coronary artery bypass graft (CABG) and 48 (52.7%) were managed conservatively, while the corresponding values for the control group were 11 (12.8%), five (5.8%) and 70 (81.4%), respectively. Baseline demographics are illustrated in **table 1**.

Out of the 177 patients, evidence of upper gastrointestinal bleeding was found in 10 patients, six in the PPI group and four in the control group (odds ratio 1.45, 95% confidence interval [CI] 0.39–5.32, p=0.58). In the PPI group (six patients, 6.6%), the endoscopy findings were as follows: gastritis in four, bleeding angiodysplasia in one and bleeding oesophagitis in one. The results for the control group (four patients, 4.6%) showed gastritis in two, gastric ulcer in one and Mallory Weiss tear in one. None of these patients had a previous history of gastrointestinal bleeding. **Table 2** explains these results in more detail.

Out of the six patients admitted with gastrointestinal bleeding, 4/50 (8%) were on lansoprazole, 1/31 (3.2%) on pantoprazole and 1/9 (11.1%) on omeprazole. Gastrointestinal bleeding was sufficiently severe to require a blood transfusion in two patients in the PPI group and one in the control group. In the PPI group, two patients required endoscopic intervention in the form of an adrenaline injection and diathermy, and only one patient was treated with heater probe coagulation and clips. In contrast, only one patient was treated with an adrenaline injection and haemostatic clips in the control group.

There was no statistically significant difference in gastrointestinal bleeding between the two groups, both unadjusted

and adjusted for potentially confounding variables. Although there were no significant differences, the differences in outcome between groups were reduced after adjusting for differences in demographics between groups. **Table 3** outlines the upper gastrointestinal bleeding episodes, both unadjusted and adjusted for variables.

There was no gastrointestinal bleeding related mortality in any of the study patients. Overall, 12 deaths were observed, seven in the PPI group (four ACS, one pulmonary embolism, one pneumonia, one heart failure) and five in the control group (three ACS, one metastatic disease with unknown primary, one pneumonia).

Discussion

Gastrointestinal bleeding is the main hazard identified for DAT with aspirin and clopidogrel following ACS. However, our study suggests that the co-prescription of PPIs with aspirin and clopidogrel does not alter the risk of gastrointestinal bleeding in these patients (odds ratio 1.45, p=0.58).

The findings reported here are consistent with another retrospective study that was carried out to determine the efficacy of PPIs in lowering the risk of gastrointestinal bleeding for patients receiving DAT with aspirin and clopidogrel. In a retrospective study of 1,023 patients, no difference was found in the incidence of upper gastrointestinal bleeding between those patients receiving and those not receiving PPIs (0.7% *vs.* 0.6%, p=0.88).[6] A cohort analysis of a pharmacy database of 385 patients,[7] which assessed the role of PPIs in reducing the probability of gastrointestinal bleeding in patients who possessed additional risk factors for gastrointestinal bleeding, found that only those with an additional risk factor had a lower incidence of gastrointestinal bleeding with PPIs compared with those without PPIs (1.7% *vs.* 11.1%, p=0.05).[7] However, a retrospective study of 666 patients found a reduced risk of gastrointestinal bleeding with PPIs for patients receiving DAT.[8]

The benefits of prescribing PPIs should, therefore, be weighed in individual cases, and only patients with an increased risk of gastrointestinal bleeding should be considered for PPIs. Risk factors for gastrointestinal bleeding are not well characterised, but the most important are a prior history of peptic ulcers or gastrointestinal bleeding and advanced age.[4,9]

The limitations of our study include its retrospective nature and the small sample size.

In summary, empirical prophylactic prescription of PPIs in patients on DAT with aspirin and clopidogrel following ACS is of no significant benefit in reducing a predisposition to upper gastrointestinal bleeding; however, studies with larger population numbers are warranted in order to confirm this conclusion

Table 2. Results

Demographics	PPI group (n=91)	Control group (n=86)	Statistics
Re-admissions with GI bleeding	6 (6.6%)	4 (4.6%)	Odds ratio: 1.45, p=0.58
Mean age, years	77	53	
Gender			
Male	2	4	Odds ratio: 0.59, p=0.56
Female	4	0	Odds ratio: 5.60, p=0.25
Ethnicity			
Caucasian	5	2	Odds ratio: 2.34, p=0.32
Asian	1	2	Odds ratio: 0.54, p=0.63
Endoscopy findings			
Gastritis	4	2	
Gastric ulcer	0	1	
Bleeding angiodysplasia	1	0	
Bleeding oesophagitis	1	0	
Mallory-Weiss tear	0	1	

Key: GI = gastrointestinal; PPI = proton pump inhibitor

Table 3. Unadjusted and adjusted analyses

Adjustments	Odds ratio (95% CI)	p value
Unadjusted	1.45 (0.39, 5.32)	0.58
Age, sex	1.42 (0.37, 5.42)	0.61
Age, sex, type of event, intervention	1.15 (0.29, 4.57)	0.84

Key: CI = confidence interval

Conflict of interest

None declared.

Key messages

- Empirical prophylactic prescription of proton pump inhibitors in patients on dual antiplatelet therapy following acute coronary syndrome is of no significant benefit in reducing predisposition to upper gastrointestinal bleeding
- Studies with larger population numbers are warranted in order to confirm this conclusion

References

1. Yusuf S, Zhao F, Mehta SR *et al*. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* 2001;**345**:494–502. http://dx.doi.org/10.1056/NEJMoa010746

2. CAPRIE Steering Committee. A randomized, blinded, trial of Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE). *Lancet* 1996;**348**:1329–39. http://dx.doi.org/10.1016/S0140-6736(96)09457-3

3. Popławski C, Jakubczyk P, Jakubczyk M. Analysis of the upper gastrointestinal tract bleeding prevalence in patients treated due ischaemic heart disease. *Adv Med Sci* 2007;**52**:288–93.

4. Alli O, Smith C, Hoffman M *et al*. Incidence, predictors, and outcomes of gastrointestinal bleeding in patients on dual antiplatelet therapy with aspirin and clopidogrel. *J Clin Gastroenterol* 2011;**45**:410–14. http://dx.doi.org/10.1097/MCG.0b013e3181faec3c

5. Ng FH, Chan P, Kwanching CP *et al*. Management and outcome of peptic ulcers or erosions in patients receiving a combination of aspirin plus clopidogrel. *J Gastroenterol* 2008;**43**:679–86. http://dx.doi.org/10.1007/s00535-008-2215-4

6. Barada K, Karrowni W, Abdullah M *et al*. Upper gastrointestinal bleeding in patients with acute coronary syndromes: clinical predictors and prophylactic role of proton pump inhibitors. *J Clin Gastroenterol* 2008;**42**:368–72. http://dx.doi.org/10.1097/MCG.0b013e31802e63ff

7. Luinstra M, Naunton M, Peterson GM *et al*. PPI use in patients commenced on clopidogrel: a retrospective cross-sectional evaluation. *J Clin Pharm Ther* 2010;**35**:213–17. http://dx.doi.org/10.1111/j.1365-2710.2009.01089.x

8. Ng FH, Wong SY, Lam KF *et al*. Gastrointestinal bleeding in patients receiving a combination of aspirin, clopidogrel and enoxaparin in acute coronary syndrome. *Am J Gastroenterol* 2008;**103**:865–71. http://dx.doi.org/10.1111/j.1572-0241.2007.01715.x

9. Nikolsky E, Stone GW, Kirtane AJ *et al*. Gastrointestinal bleeding in patients with acute coronary syndromes: incidence, predictors, and clinical implications: analysis from the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial. *J Am Coll Cardiol* 2009;**54**:1293–302. http://dx.doi.org/10.1016/j.jacc.2009.07.019