Clinical Investigations

Proton Pump Inhibitors for Patients with Coronary Artery Disease Associated with Reduced Chest Pain, Emergency Department Visits, and Hospitalizations

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Summary

Background: Patients with coronary artery disease (CAD) presenting to an emergency department (ED) with chest pain are likely to undergo hospitalization as clinicians attempt to elucidate the etiology.

Hypothesis: We hypothesized that proton pump inhibitor (PPI) therapy is associated with reduced chest pain events and evaluations in patients with CAD.

Methods: A patient population from a veterans medical center with documented CAD was identified retrospectively, and chest pain episodes, ED visits, and hospitalizations for chest pain were prospectively followed over 2 years. Comparison of patient outcomes between PPI (+PPI) and nonuse of PPI therapy (−PPI) was determined.

Results: Of 415 male patients, average age 73.4 years, 23% utilized a PPI and 77% did not. Proton pump inhibitor therapy was associated with reduced chest pain episodes (11.8 vs. 26.2%, $p = 0.002$), ED visits (12.3 vs. 24.3%, $p = 0.044$), and hospitalizations (12.8 vs. 23.9%, $p = 0.086$). Relative reductions were 55, 49, and 46%, respectively, after 2 years. Numbers of adverse events were also decreased in the +PPI group of patients: 70% fewer occurrences of chest pain ($p = 0.002$,

relative risk [RR] = 3.3), 55% fewer ED visits ($p = 0.049$, RR = 2.2), and 53% fewer hospitalizations ($p = 0.064$, RR = 2.1). By multivariate analysis, PPI therapy independently predicted reduced prevalence of patients experiencing chest pain, ED visits, or hospitalizations (odds ratio [OR] = 0.09 [0.04–0.21]; 0.15 [0.06–0.40]; 0.14 [0.05–0.40]; all $p < 0.001$).

Conclusions: Proton pump inhibitor therapy for male patients with CAD from a veterans medical center was associated with reduced prevalence of chest pain, ED visits, and hospitalizations for chest pain and reduced incidence of these events.

Key words: chest pain, hospitalization, emergency department, coronary disease, gastroesophageal reflux, proton pumps

Introduction

Chest pain experienced by patients may be related to myocardial ischemia or infarction. Yet, other causes of chest pain, for example, gastroesophageal reflux disease (GERD), can account for many of the episodes. In the U.S., approximately 5 million people annually present to an emergency department (ED) with a primary complaint of chest pain, resulting in 2 million hospital admissions at a cost of about 8 billion dollars.^{1,2} After appropriate evaluation, approximately 40% of patients admitted for potential acute coronary syndromes (ACS), for example, unstable angina, were determined not to have ischemic coronary artery disease (CAD).^{3–5} In the Emergency Room Assessment of Sestamibi for Evaluating Chest Pain Trial (ERASE) and a second study at a large hospital center in Philadelphia, 81–86% of all patients presenting to the ED with chest pain were shown not to have a final diagnosis of cardiac ischemia.^{6,7} Rapid, inexpensive, and safe diagnostic tests with high sensitivity and specificity to prove or disprove a noncoronary cause of chest pain would be ideal. A reasonable alternative approach is to reduce chest pain symptoms in patients with CAD caused by noncardiac etiologies.

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This could ultimately reduce the incidence of ED presentations and hospitalizations.

Noncardiac chest pain (NCCP) diagnoses are given to patients with episodes of retrosternal pain who lack cardiac abnormalities after they have undergone reasonable cardiac evaluations. However, patients with known CAD may also have concomitant NCCP, and after review of previous studies that utilize esophageal pH monitoring overall, about 50% of patients with CAD have concomitant GERD.⁸ Gastroesophageal reflux disease is a frequent cause of NCCP, and while many physicians, including cardiologists, prescribe acid-reducing therapy to patients with established CAD, no studies to date have evaluated such treatments to prevent chest pain in patients with CAD. We hypothesized that patients utilizing acid reducing therapy to alleviate potential GERD may reduce chest pain episodes experienced by patients with CAD, as well as ED presentations and hospital admissions for chest pain.

Methods

Patient Population

The patients in this study received medical care at a tertiary-care Veterans Affairs Medical Center (VAMC). The patients were identified by computerized search utilizing VA-developed File Manager software. Patients selected had an ICD-9 billing code for coronary atherosclerosis, coronary atherosclerosis of native coronary artery, or coronary atherosclerosis of autologous vein bypass graft. Permission to review patient charts was obtained from the Northport VAMC Institutional Review Board and Research & Development committees. Patient charts were in electronic format utilizing VA-developed CPRS software. A history of CAD was confirmed by the presence of documented myocardial infarction by ECG or cardiac enzymes; an abnormal stress test demonstrating ischemia or infarction; an angiogram with obstructive CAD defined as > 50 luminal narrowing; or revascularization by percutaneous coronary intervention or bypass surgery. If none of these was present, the patient was excluded.

Measurement of Outcomes

Progress notes for outpatient visits in the electronic charts dated from November 1, 2000, to January 31, 2003 (average of 2.0 ± 0.25 patient years), and inpatient and hospital discharge summaries in the same study period were reviewed twice. Baseline demographic information such as age, gender, history of hypertension, diabetes mellitus, tobacco use (defined as current smoker or use within prior 1 year), GERD, peptic ulcer disease (PUD), and use of common cardiovascular and gastric acid-reducing medications taken concomitantly during the study period were recorded.

Measured outcomes included (1) chest pain as per the document patient chart, including events recorded at outpatient or emergency room visits and during inpatient hospitalizations; (2) an ED visitation for a primary complaint of chest pain;

and/or (3) hospitalization for chest pain. We excluded subsequent recordings of the same event appearing more than once. In addition, the number of chest pain events, ED visits, and/or hospitalizations for chest pain for each patient was recorded. A prior institutional study at the Northport VA demonstrated that 99% of all ER encounters were being recorded electronically as of November 2000, minimizing the possibility of missed ER encounters. If an episode of chest pain occurred during a hospitalization, but was not the primary reason for admission, it was considered a chest pain event but was not included as a hospitalization for chest pain. For the purpose of this investigation, patients with documented proton pump inhibitor (PPI) use were categorized as positive PPI (+PPI), whereas those not taking a PPI were classified as negative PPI (−PPI). Due to the VAMC formulary, the most common PPI prescribed was Aciphex® (Janssen Pharmaceutica Products, L.P., Titusville, N.J., USA) (rabeprazole) followed by Prevacid® (TAP Pharmaceuticals, Inc., Lake Forest, Ill., USA) (lansoprazole). A patient in whom PPI therapy was initiated or discontinued during the middle of the study period remained in the original group assigned to (intention to treat method).

Statistical and Data Analysis

The measured variables and outcomes for each patient were entered into Statistical Package for Social Sciences (SPSS) for Windows, Version 10.0.1 (SPSS Inc., Chicago, Ill., USA) for statistical analyses. Continuous variables are expressed as mean $\pm$ standard deviation of the mean (SD) and compared by unpaired Student's *t*-test. Nominal or dichotomous variables are expressed as proportions and compared by chi-square test. Two-tailed *p* values < 0.05 were considered statistically significant. Ordinal values such as the number of chest pain events, ED visits, and hospitalizations were analyzed using nonparametric testing based on rank sums using the Mann-Whitney and the Wilcoxon tests. *P* values < 0.05 were considered statistically significant. Risk ratio (relative fold increase) for chest pain events, ED visits, and hospitalizations were calculated using the number of events in the −PPI group divided by the number of events in the +PPI group, and then corrected by dividing by 3.4 since there were more −PPI than +PPI patients. Relative risk reduction for the +PPI group was calculated by the formula

$$\% \text{ Reduction} = \{ 1 - [3.4 \times (\# \text{ events in +PPI group} / \# \text{ events in -PPI group})] \times 100\% \}.$$

Univariate and multivariate binary logistic regression analysis was performed using forward selection to determine the final multivariate model. All variables with a *p* value of < 0.1 in the univariate analysis were included in the multivariate model. *P* values < 0.05 were considered statistically significant in the multivariate model. Multivariate binary logistic regression analysis for each of the outcome events was also performed utilizing models that either excluded solely GERD, PPI, or H₂-antagonist, or two of these three variables to evaluate the possibility of multiple colinearity.

TABLE I Patient baseline features comparing those who take and do not take proton pump inhibitor (PPI) therapy

Variable	– PPI % (n = 321)	+ PPI % (n = 94)	p Value
Age	73.5 ± 0.52	73.2 ± 0.90	0.75
Male sex	100	100	1.00
CAD	100	100	1.00
Hypertension	81.9	80.9	0.81
Diabetes mellitus	34.9	41.5	0.24
Smoker	16.2	11.7	0.29
GERD	15.0	76.7	<0.001 ^a
PUD	3.6	22.2	<0.001 ^a
Anticoagulant	88.5	83.0	0.16
Aspirin	66.0	58.5	0.18
Clopidogrel	17.4	22.3	0.28
Warfarin	17.8	14.9	0.52
Beta blocker	75.7	73.4	0.65
Ca ⁺⁺ blocker	29.3	29.8	0.93
ACE-I or ARB	65.1	67.0	0.73
ACE-I	52.6	52.1	0.93
ARB	12.1	17.0	0.22
Anticholesterol	76.0	71.3	0.20
Statin	73.5	68.1	0.30
Fibrate	4.7	5.3	0.80
Niacin	3.1	3.2	0.82
Nitrates	26.2	28.7	0.62
Digoxin	17.8	13.8	0.37
H ₂ blocker	18.7	5.3	0.002 ^a

^a p Values of <0.05 were statistically significant.

Abbreviations: CAD = coronary artery disease, GERD = gastro-esophageal reflux disease, PUD = peptic ulcer disease, ACE-I = angiotensin-converting enzyme inhibitor, ARB = angiotensin-receptor blocker.

Results

Baseline features of the 415 patients with CAD, specifically the 321 –PI and the 94 +PPI patients, are shown in Table I. All patients had CAD; of these, 23% were and 78% were not taking a PPI. There were no differences in age, incidence of diabetes mellitus, hypertension, smoking, or use of cardiac medication between the –PPI and +PPI groups (Table I). However, a greater number of patients were receiving H₂-receptor antag-

TABLE II Prevalence of patients with coronary artery disease and chest pain events

Variable	– CP % (n = 313)	+ CP % (n = 102)	p Value
Hypertension	79.2	89.2	0.024 ^a
Diabetes	35.5	40.0	0.49
Smoker	14.7	16.7	0.63
GERD	24.1	45.2	<0.001 ^a
PUD	8.3	6.5	0.57
H ₂ blocker	10.5	31.4	<0.001 ^a
PPI	26.2	11.8	0.002 ^a

^a p Values of <0.05 were statistically significant.

Abbreviation: CP = chest pain, PPI = proton pump inhibitor. Other abbreviations as in Table I.

onist therapy in the –PPI group, indicating that H₂-receptor antagonist therapy may have precluded use of PPI therapy. In the +PPI group, 77% of patients had a diagnosis of GERD, versus only 28% in the –PPI group, demonstrating a correlation between this medical illness and use of PPI therapy.

There was a significantly higher prevalence of those without chest pain in the +PPI than in the –PPI group (26.2 vs. 11.8%, *p* = 0.002) (Table II), representing a 55% relative reduction (14.4/100 patients absolute reduction) in the number of patients with CAD who experienced chest pain events while on PPI therapy. Proton pump inhibitor therapy translated into a 15.2/100 patients absolute increase in symptom-free patients. It is interesting that among all the patients who had chest pain events, more than 88% did not use PPI therapy. The total number of chest pain events was also higher in patients without PPI therapy (Table III). There were 25 documented chest pain episodes among the 94 patients in the +PPI group, compared with 282 chest pain episodes among the 321 patients in the –PPI group. Correcting for the disparate number of patients between the two groups, this represented a 70% reduction in the number of chest pain episodes associated with +PPI therapy, and a risk ratio for chest pain of +3.3 in patients with CAD not receiving PPI therapy (Table III).

Emergency department visits for the primary reason of chest pain also decreased in the +PPI group (Table IV). Of the 102 patients with a chest pain episode, 57 visited an ED for the primary reason of chest pain. Compared with –PPI therapy,

TABLE III Number of chest pain episodes, emergency department (ED) visits, and hospitalizations in patients with coronary artery disease (CAD) who are and are not on proton pump inhibitor (PPI) therapy

Outcome	– PPI (n = 321)	+ PPI (n = 94)	p Value	Risk ratio	% Reduction
No. of chest pains	282	25	0.002 ^a	+ 3.3	70
No. of ER visits	90	12	0.049 ^a	+ 2.2	55
No. of hospitalizations	73	10	0.064	+ 2.1	53

^a p Values of <0.05 were statistically significant.

TABLE IV Prevalence of ED visits for chest pain in patients with coronary artery disease

Variable	– ED visit % (n = 358)	+ ED visit % (n = 57)	p Value
Hypertension	80.4	89.5	0.102
Diabetes	35.9	40.4	0.54
Smoker	14.9	17.0	0.71
GERD	26.3	52.4	<0.001 ^a
PUD	7.8	7.8	1.00
H ₂ blocker	12.6	35.1	<0.001 ^a
PPI	24.3	12.3	0.044 ^a

^ap Values of <0.05 were statistically significant.
Abbreviations as in Tables I and II.

+PPI therapy was associated with a 49% reduction in patients with ED visits for chest pain (12.3 vs. 24.3%, $p = 0.044$) (Table IV). Furthermore, the number of ED visits for chest pain in this population was increased in those not taking PPI therapy. There were 12 ED visits for chest pain in the +PPI group versus 90 in the –PPI group (Table III), representing a 55% reduction in ED visits for chest pain in the +PPI group, and correlating with a +2.2 risk ratio of an ED visit for chest pain among those not receiving PPI therapy.

Hospital admissions for chest pain were decreased in the group of patients utilizing PPI therapy (Table V). Of the 57 who presented to the ED with chest pain, 47 were hospitalized for further evaluation, representing a 46% reduction in the number of patients needing hospitalization for chest pain in the +PPI group (Table V). The total number of hospitalizations for chest pain was 73 in the –PPI group versus 10 in the +PPI group ($p = 0.064$), representing a 53% reduction in hospitalizations for chest pain in the +PPI group, and correlating with a +2.1 risk ratio toward hospitalization for chest pain in the –PPI group (Table III).

To test the validity of these findings, we constructed a multivariate model to evaluate the association of decreased outcome events with PPI therapy in the presence of the other 22 identified variables. The significant univariate predictors of these outcomes are shown in Table VI, and using logistic regression analysis, the only significant variable independently associated with reduced chest pain, ED visits, and hospitalization for chest pain in the multivariate model was PPI therapy (Table VI). Of interest is the fact that GERD and nitrate use became predictors of an increased number of patients experiencing chest pain, ED visits, and hospitalizations for chest pain.

Since PPI therapy and H₂-receptor antagonist therapy appeared to be clinically related—patients on –PPI therapy were more likely to be on an H₂-antagonist for the treatment of GERD and vice versa (Table I), we were concerned about possible collinearity. Utilizing models excluding H₂-antagonists from multivariate analysis produced identical results, as shown in Table VI. In models excluding GERD from analysis, PPI therapy was no longer a significant predictor, suggesting that these two variables are interrelated. When both GERD

TABLE V Prevalence of patients with coronary artery disease and hospitalizations for chest pain

Variable	– Hospitalization % (n = 368)	+ Hospitalization % (n = 47)	p Value
Hypertension	80.4	91.5	0.07
Diabetes	35.9	40.4	0.54
Smoker	14.9	17.0	0.71
GERD	26.3	52.4	<0.001 ^a
PUD	7.9	7.1	0.86
H ₂ blocker	13.0	36.2	<0.001 ^a
PPI	23.9	12.8	0.086

^ap Values of <0.05 were statistically significant.
Abbreviations as in Tables I and II.

and PPI therapy were removed from analysis, H₂-antagonists remained a significant predictor of increased adverse events.

Discussion

The results demonstrate that patients with CAD utilizing PPI therapy are less likely to have chest pain, ED visits, and hospitalization for chest pain than those not using PPI therapy. Over three-quarters of these patients had utilized PPI therapy for diagnosed GERD. This is the first report to associate a therapy for GERD with reduced chest pain for patients with CAD.

Recurring chest pain is an important clinical problem that induces anxiety in both patients and physicians and drives up health care costs.⁷ A cardiac evaluation ensues, and depending upon the patient's history and cardiac risk factors, ranges from noninvasive studies to invasive coronary angiograms. Hospital admissions for chest pain are more likely among patients with a history of obstructive CAD since this history alone allows for risk stratification to a diagnosis of unstable angina with a high likelihood that their symptoms represent an ACS secondary to CAD.^{9,10} It is interesting that 10 to 40% of patients initially diagnosed with unstable angina can have normal or insignificant coronary disease and a noncardiac cause of their chest pain.^{3,11,12}

Gastroesophageal reflux disease is a common cause of NCCP in patients with and without CAD.^{8,13} A recent study evaluating nonexertional chest pain at rest occurring despite cardiac medications in patients with known CAD found that 100% of nonischemic and 50% of ischemic patients had some kind of concomitant esophageal dysfunction.¹⁴ Specifically, the prevalence of GERD in nonischemic patients was 61% elicited by pH monitoring; in 45% of these chest pain symptoms correlated with reflux.¹⁴ Thus, a patient with CAD may have chest pain both cardiac and esophageal in origin, implying that acid-reducing therapy may be helpful. Two small, randomized prospective clinical trials have shown treatment benefit using omeprazole for secondary prevention of GERD-induced chest pain in patients in whom CAD had first been ruled out,^{15,16} suggesting that NCCP from GERD could effectively be treated with a PPI in patients without CAD.

TABLE VI Univariate and multivariate predictors associated with decreased or increased outcomes of chest pain, emergency room visits, and hospitalizations

	Univariate OR (95% CI)	p Value	Multivariate OR (95% CI)	p Value
Chest pain				
PPI	0.38 (0.20–0.72)	0.003	0.09 (0.04–0.21)	<0.001 ^a
GERD	2.59 (1.60–4.22)	<0.001	8.47 (4.23–16.96)	<0.001 ^a
Nitrates	3.32 (2.06–5.35)	<0.001	3.87 (2.25–6.66)	<0.001 ^a
H ₂ blocker	3.88 (2.23–6.74)	<0.001	—	—
Niacin	2.73 (0.90–8.33)	0.077	—	—
HTN	2.17 (1.10–4.29)	0.026	—	—
Beta blockers	1.74 (0.99–3.07)	0.056	—	—
ED visits				
PPI	0.44 (0.19–0.99)	0.049	0.15 (0.06–0.40)	<0.001 ^a
GERD	2.72 (1.50–4.96)	0.001	5.89 (2.85–12.19)	<0.001 ^a
Nitrates	3.20 (1.80–5.68)	<0.001	3.47 (1.84–6.58)	<0.001 ^a
H ₂ blocker	3.76 (2.01–7.04)	<0.001	—	—
Hospitalizations				
PPI	0.47 (0.19–1.13)	0.092	0.14 (0.05–0.40)	<0.001 ^a
GERD	3.09 (1.61–5.91)	0.001	6.76 (3.07–14.89)	<0.001 ^a
Clopidogrel	2.31 (1.18–4.53)	0.014	2.98 (1.39–6.38)	0.005 ^a
Nitrates	3.05 (1.64–5.67)	<0.001	2.92 (1.45–5.89)	0.003 ^a
H ₂ blocker	3.78 (1.94–7.37)	<0.001	—	—
Beta blockers	2.02 (0.87–4.65)	0.100	—	—
HTN	2.61 (0.91–7.51)	0.075	—	—

^a p Values of <0.05 were statistically significant.

Abbreviations: HTN = hypertension, CI = confidence interval, OR = odds ratio. Other abbreviations as in Tables I and II.

Although prescribing a PPI is common among medical physicians, a study utilizing acid-reducing therapy for primary or secondary prevention of NCCP in patients with CAD has never been performed. The results of this retrospective study are the first to support the hypothesis that PPI therapy can reduce chest pain events, ED visits, and hospitalizations for chest pain in patients with CAD. It is believed that PPI therapy reduced chest pain caused by GERD. The multivariate model analyzing PPI therapy in the presence of all other variables demonstrated significantly reduced outcomes with PPI therapy, whereas nitrate therapy and GERD were associated with increased outcomes. The association of clopidogrel with increased hospitalization is complicated by lack of information regarding compliance, bleeding complications, and associated stents. The association of nitrates with increased chest pain is interesting since the use of these medications may represent a subset of patients with CAD who have more cardiac anginal events. Also, nitrates have been shown to reduce the muscular tone of the lower esophageal sphincter, a factor that can increase the incidence of GERD.¹⁷ The results of our study support further investigation to clarify this relationship between nitrates and GERD.

The limitations of this study are intrinsic to observational chart analyses. (1) Incomplete chart recording of chest pain episodes by practitioners may have occurred. Patients may not have recalled chest pains or may have been timid to disclose

events. Also, patients from the veterans medical center may have been admitted to other hospitals in an acute setting. These factors would have reduced the number of adverse events observed. (2) The population represented in this study is elderly, yet we believe it to be reflective of patients with CAD in the general population. (3) The CAD population studied consisted of all male veterans, although prior population studies of over 2,200 patients showed the prevalence of GERD among men and women to be similar among all age group.¹⁸ (4) Finally, multivariate analysis of significant univariate predictors that are clinically interrelated may cause their removal from the final model, as was the case for H₂-antagonists. This does not preclude H₂-antagonists as significant predictors of adverse events. We suspect that part of the reason for chest pain episodes, ER visits, and hospitalizations is that H₂-antagonist therapy did not effectively reduce NCCP in patients with known or undiagnosed GERD, and these medications had been prescribed for patients who actually needed PPI.

Conclusion

Our findings confirm that GERD-related NCCP is present in patients with CAD. Prescribed PPI therapy for such patients is significantly associated with a reduced number of important outcomes related to coronary disease, including chest pain,

ED visits, and hospitalizations for chest pain. These observations require confirmation by a prospective, randomized, double-blind, placebo-controlled study.

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