Concern for Myocardial Infarction Risk Associated with Proton Pump Inhibitor Use in Patients With No Underlying Cardiovascular Disease

Natasha K. Ludwig

Recommended Citation
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Abstract
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Methods: An exhausted search of available medical literature was performed using MEDLINE-Ovid, MEDLINE-Pubmed, Web of Science, and CINAHL using the keywords proton pump inhibitors, myocardial infarction, and epidemiology. Relevant articles were assessed for validity using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.

Results: Four articles met eligibility criteria and were included in this systematic review. Two of the articles were case-crossover analyses. The other two studies were a self-matched case-series design and data-mining analysis, respectively. There were some consistent results regarding an increased MI risk with PPI use in patients with no prior history of MI. Studies were limited with regards to the specific population in question, actual PPI dose and compliance, and failure to control confounding factors including obesity, smoking, and family history of coronary artery disease. Further research is warranted to address these concerns as well as the long-term risks associated with PPI therapy.

Conclusion: There were limited studies to evaluate the subsequent risk of MI with the lone use of PPIs in patients with no underlying cardiovascular disease. Thus far, they suggest that PPI use may be associated with an increased risk for MI. Pending further research however, the benefits of PPI use may outweigh the risks of adverse cardiovascular events.

Keywords: proton pump inhibitors, myocardial infarction, epidemiology

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Natasha Ludwig

A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR For the Masters of Science Degree, August 13, 2016 Faculty Advisor: Saje Davis-Risen, PA-C, MS Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted for privacy]
Abstract

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Conclusion: There were limited studies to evaluate the subsequent risk of MI with the lone use of PPIs in patients with no underlying cardiovascular disease. Thus far, they suggest that PPI use may be associated with an increased risk for MI. Pending further research however, the benefits of PPI use may outweigh the risks of adverse cardiovascular events.

Keywords: proton pump inhibitors, myocardial infarction, epidemiology
Acknowledgements

[Redacted for privacy]
Table of Contents

Table of Contents .............................................................................................................................................5
List of Tables ..................................................................................................................................................6
List of Abbreviations ....................................................................................................................................6
BACKGROUND ..............................................................................................................................................7
METHODS ....................................................................................................................................................8
RESULTS .......................................................................................................................................................9
  Shih et al .....................................................................................................................................................9
  Turkiewicz et al..........................................................................................................................................11
  Juurlink et al..............................................................................................................................................12
  Shah et al...................................................................................................................................................14
DISCUSSION ................................................................................................................................................16
CONCLUSION .................................................................................................................................................19
References ......................................................................................................................................................21
Table I: Quality Assessment of Reviewed Articles .....................................................................................23
Table II: Shih et al Summary of Findings\textsuperscript{9} .................................................................................24
Table III. Turkiewicz et al Summary of Findings\textsuperscript{11} .....................................................................24
Table IV. Juurlink et al Summary of Findings\textsuperscript{10} .........................................................................24
Table V. Shah et al Summary of Findings\textsuperscript{12} ................................................................................25
List of Tables

Table I: Characteristics of Reviewed Studies
Table II: Summary of Shih et al Findings
Table III: Summary of Turkiewicz et al Findings
Table IV: Summary of Juurlink et al Findings
Table V: Summary of Shah et al Findings

List of Abbreviations

GI..........................................................Gastrointestinal
GERD......................................................Gastroesophageal Reflux Disease
H2RA......................................................Histamine-2 Receptor Antagonists
HF........................................................Heart Failure
MI........................................................Myocardial Infarction
NNH......................................................Number Needed to Harm
NSAID...................................................Nonsteroidal Anti-Inflammatory
OR.........................................................Odds Ratio
PPI.......................................................Proton Pump Inhibitor
Concern for Myocardial Infarction Risk Associated with Proton Pump Inhibitor Use in Patients With No Underlying Cardiovascular Disease

BACKGROUND

A substantial number of physician office visits can be attributed to dyspepsia,
\(^1\) defined as a chronic or recurrent pain or discomfort centered in the upper abdomen.\(^1\) Dyspepsia is a symptom of gastroesophageal reflux disease (GERD), which should be considered in patients with frequent heartburn or acid regurgitation symptoms.\(^1\) After their introduction in the 1980s,\(^3\) proton pump inhibitors (PPIs) have been the mainstay of GERD treatment by many medical providers and are available over the counter. The American College of Gastroenterology recommends empiric PPI therapy in patients where the presumptive diagnosis of GERD can be established in the setting of typical heartburn and regurgitation symptoms.\(^2\) PPIs are potent inhibitors of gastric acid. They work by irreversibly binding to the gastric parietal cell hydrogen-potassium ATPase pumps\(^4,5\) in the stomach decreasing the overall gastric acid production and thereby decreasing gastroesophageal reflux.\(^3\) PPIs are prodrugs, which means they require gastric acid for activation. This results in a delayed onset of acid secretion thus it is recommended that PPIs be taken 30 minutes prior to the first meal of the day for eight weeks.\(^4\)

In 2014, anti-ulcer agents were one of the top 20 classes of drugs prescribed globally, generating more than 28 billion dollars in revenue.\(^6\) Initially, they were considered to be a generally safe class of drugs however potentially adverse effects have been mentioned including nutritional deficiencies, bone fractures, and interstitial nephritis.\(^7\) Research regarding PPI safety has been evaluated over the last couple of years. Most recently, concern has been raised about the concomitant use of PPIs and clopidogrel. Clopidogrel is used in patients with a history of
coronary artery disease, cerebrovascular disease, and peripheral vascular disease to prevent further thromboembolic events from occurring. In January 2011, the US Food and Drug Administration issued a warning regarding the concomitant use of clopidogrel with omeprazole, a drug that interferes with CYP2C19 activity therefore decreasing the pharmacological activity of clopidogrel\(^7\) and increasing the risk of an acute thromboembolic event.

As the safety of PPI use in patients with underlying cardiovascular disease has prompted FDA warnings, the risk of adverse cardiac events connected with PPI use amongst the population with no prior history of myocardial infarction (MI) is unknown. Moreover, symptoms of GERD including dyspepsia, epigastric pain, and nausea can overlap with other conditions,\(^2\) including cardiac chest pain. With PPIs currently available over the counter, it is imperative that the symptoms of GERD be distinguished from that of an acute MI. The aim of this review is to find out if PPI use is associated with an increased MI risk in patients with no underlying cardiovascular disease.

**METHODS**

An exhaustive search of available medical literature was performed using MEDLINE-Ovid, MEDLINE-Pubmed, Web of Science, and CINAHL using the keywords *proton pump inhibitors, myocardial infarction, and epidemiology*. The search was narrowed to include studies published in the English language and conducted on humans. Studies examining cardiovascular and gastrointestinal bleeding risk with regards to aspirin and clopidogrel use were excluded. The bibliographies of the articles were reviewed for additional sources. Relevant articles were assessed for validity using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system.\(^8\)
RESULTS

A total of 201 articles were found in the initial search. For the purpose of this study, focus was drawn to the use of proton pump inhibitors and the risk of myocardial infarction in patients without underlying cardiovascular disease. After screening those articles using the search terms and exclusion criteria, four studies\textsuperscript{9-12} satisfied all the inclusion criteria and were included in this systematic review. See Table 1.

Shih et al

Shih et al\textsuperscript{9} conducted two different study designs. The first was a propensity-score matched analysis between PPI users and non-users to adjust for confounding factors such as age, sex, comorbidities and concomitant drug use. Patients included were 18-80 years of age with no prior history of MI, acquired immunodeficiency syndrome, human immunodeficiency virus, cancer prior to PPI prescription, or antecedent PPI prescription within 120 days of the study. All patients received a PPI prescription after diagnosis of peptic ulcer, duodenal ulcer, GERD by positive pan-endoscopy. Excluded were patients who received a PPI prescription within 60 days of an episode of severe upper GI bleeding requiring hospitalization, blood transfusion, or use of inotropic agent due to the presumed increase MI risk following these events.\textsuperscript{9}

The primary outcome was incidence of MI. A total of 126 367 PPI users were matched with 126 367 non-PPI users. Groups were homogenous with regards to age, gender, concomitant medications, and coexisting conditions. After the 120-day follow up period, 79 of the PPI users experienced an MI compared with 50 of the non-PPI users. MI risk was calculated as 1.58\% greater amongst PPI users (95\% CI = 1.11-2.25; P = 0.011). Interaction tests compared effects
across subgroups including age, gender, diabetes mellitus, use of antiplatelet agents, use of
clopidogrel specifically, and use of NSAIDs showing no statistically significant results.9

The second study design conducted was a case-crossover analysis to identify the association between PPI use and MI. This study design allowed for patients to serve as their own controls thereby reducing the effects of confounding elements such as race, body mass index, smoking status, and lifestyle. Calculations of MI risk were also performed in comparison to two drug controls. H2RA (Histamine-2 receptor antagonists) served as the negative control avoiding confounding by indication and NSAIDs served as the positive control. Index date was defined as the first day of hospitalization. The odds ratio (OR) for MI risk following drug exposure was estimated by the ratio of patients who were exposed to that drug 1-7 days before the index day to those who were only exposed to the drug 8-14 days before the index date.9

In the case-crossover analysis, 5430 patients 18-80 years of age who were hospitalized between 2000 and 2009 for an MI were identified. Those with a prior history of MI, those who were hospitalized within 60 days prior to the start of the study, and who had a history of severe acute GI bleeding were excluded. In the 7-day window, 109 PPI users experienced an MI compared to 75 in the control group. For the 14-day window, 114 PPI users experienced an MI in compared to 78 in the control group. Analysis revealed PPI use was associated with an increased MI risk for both the 7-day (Adjusted OR = 4.61, 95% CI = 1.76-12.07, P = 0.002) and 14-day (Adjusted OR= 3.47, 95% CI = 1.76-6.83, P < 0.001) periods.9 See Table II.

The authors concluded that both study designs performed demonstrate there is an increased MI risk amongst PPI users versus non-PPI users, even in those without a prior history of MI. An important limitation to consider is confounding by indication. The concern is that
more prescriptions for PPI are given to high-risk patients who would misinterpret abdominal pain as a sign of an MI. To minimize this, H2RA were examined as they are prescribed based on the same symptomatology and showed no increased MI risk. However, in this study, PPI prescriptions were prescribed to patients with GI diseases diagnosed per endoscopy. The propensity score analysis only observed patients for 120 days therefore further investigation of the long term cardiovascular effects of MI may be warranted. Despite using the case-crossover analysis to control for elements such as race, body mass index, smoking status, and lifestyle other potential confounding factors including obesity, smoking, alcohol, and family history of heart disease were not included in the analysis. Despite these inherent limitations, the authors thought it would unlikely change the risk during a short period of time and findings demonstrated that short-term PPI exposure was still associated with an increased risk of MI. However, with a calculated number needed to harm (NNH) of PPI users to be 4357, the authors state that the benefits of PPI therapy outweigh the risk of MI.9

Turkiewicz et al

Turkiewicz et al11 performed two case-crossover analyses. The first case-crossover analysis was to compare if the prescription of PPIs was more frequent during the 3-day period preceding the first day of the MI hospitalization, defined as the hazard period, compared to the thirty 3-day periods preceding the hazard period, defined as the control period. The second case-crossover analysis compared the dispensation of PPIs to the aforementioned hazard and control periods. The authors then repeated the analyses in a subgroup of patients with no history of prior MI.11
Utilizing the Swedish Population Register and Skåne Healthcare Register, 3490 patients 40-90 years of age with incident of acute MI between October 2005 and December 2006 were identified. The prescription of PPIs during the hazard period was not conclusively higher compared to that in the control periods with an OR of 1.36 (95% CI = 0.82-2.25). However, in patients with no history of acute MI, the risk of PPI prescriptions was conclusively elevated with an OR of 1.66 (95% CI = 1.00-2.76). When the dispensation date was used, the OR of having a PPI dispensed during the hazard period compared to the control in all cases of MI as well as those with no history of prior MI.11 See Table III.

To explain the observed increase in PPI prescriptions prior to MI, the authors discussed that MI symptoms may be misinterpreted as those of dyspetic conditions. This is supported by the diluted effect when dispensation date is used instead of prescription date. Authors discuss that their study maybe limited due to small sample size. In addition, they did not measure the actual exposure to the medication.11

Juurlink et al

Juurlink et al10 conducted a self-matched case-series method to analyze the association of PPI therapy initiation with MI and heart failure (HF). This study design allows patient to serve as their controls to reduce confounding by fixed patient factors. Included were Ontario residents 66 years of age and greater who were hospitalized within 12 weeks of initiating PPI therapy. Index date was defined as the first date of the PPI prescription. Excluded were patients discharged from the hospital after 3 days under the assumption that a true MI was unlikely. In the primary analysis, patients who were hospitalized for acute MI or HF within 1 year of the index date were included. A secondary analysis was performed and limited to patients who were alive at the end
of the 12-week follow up period. Additional analyses examined the risk of hospitalization in patients who were hospitalized for MI or HF 6-12 months preceding the initiation of PPI therapy.\textsuperscript{10}

Follow-up periods were divided into three 4-week intervals. The first 4-week period was considered the primary risk interval and followed the initiation of PPI prescription. The final 4-week interval was defined as the control interval. Tracer analyses for H2RA and benzodiazepines were performed. Neither of these drugs classes have a plausible link to adverse cardiac events therefore the authors reasoned a null finding with these drugs would enhance the argument for a cause-and-effect relationship with regards to the main analysis. Lastly, all analyses were replicated using risk and reference intervals of two-week duration rather than four, separated by a two-week washout period.\textsuperscript{10}

The 13-year study period revealed 5550 hospitalizations for an acute MI within 12 weeks initiation of PPI therapy. Patients had a mean age of 77 years, 49\% were female, and 956 died during the 12-week observation. The OR of hospitalization due to an MI during the risk interval versus the control interval was 1.8 (95\% CI = 1.7-1.9) for all MI cases. Amongst patients with no history of acute MI, the risk was slightly higher at an estimated OR 2.1 (95\% CI = 1.6-2.7). There were 6003 patients were hospitalized for HF within 12 weeks of the initiation of PPI therapy. Patients had a mean age of 80 years, 55\% were female, and 1235 died during follow-up. The OR of HF during the primary risk interval was 1.8 (95\% CI = 1.7-1.9). The risk was similar among patients with a history of HF. Similar results were found with regards to the risk of hospitalization for MI or HF in patients without history of the disease within 12 weeks of the initiation of H2RA (OR = 1.8, 95\% CI = 1.7-1.9) or benzodiazepines (OR =1.3, 95\% CI = 1.3-1.4).\textsuperscript{10} See Table IV for further clarification.
Since omeprazole is known to interfere with the bioactivation of clopidogrel, this study specifically focused on the association between omeprazole use and MI or HF. A calculated OR of 1.6 (95% CI = 1.6-2.0) was found. The study found this to be no different compared to pantoprazole, another PPI which does not affect the clopidogrel response. In patients taking clopidogrel at the initiation of PPI therapy, there was no increased risk of MI or HF found.\textsuperscript{10}

The authors discussed a higher risk of hospitalization for acute MI or HF was found in older subjects following the initiation of PPI therapy. A similar risk was also discovered with regards to H2RA and benzodiazepines, drugs with no plausible causal link to adverse cardiac effects. Together, these findings imply an unlikely cause-and-effect explanation for the observed association between PPIs and adverse cardiac events.\textsuperscript{10}

Jurrrlink et al\textsuperscript{10} concluded there to be an increased risk of acute MI or HF in the short term following the initiation of PPI therapy. However, similar risk was seen in other drugs without known cardiotoxicity. Limitations of this study include the concern for protopathic bias however it does not explain the associated between benzodiazepines and adverse cardiac events. The study also only examined the short-term effects of PPI therapy. Further investigation is warranted to exam the long-term effects. It should be considered that PPI therapy is often intermittent suggestive that long-term follow-up could be less reliable. There is also lack of information on drug dose, adherence, and risk factors for cardiac disease including obesity and smoking.\textsuperscript{10}

\textbf{Shah et al}

Shah et al\textsuperscript{12} conducted a data-mining design to screen if exposure to PPIs was associated with an elevated MI risk. This design used variables to predict the responses and should not be interpreted as a causal regression models, as is the goal with epidemiological studies.\textsuperscript{12} Data was
obtained from the Stanford Translational Research Integrated Database Environment from 1994-
2012 as well as Practice Fusion, Inc., an electronic based health record, from 2007-2012. Patients
included were 18 years of age and greater with GERD as defined by ICD-9 codes for
gastroesophageal reflux, heartburn, and the UMLS code for gastroesophageal reflux. Two study
groups were defined. The primary group was the defined by patients taking PPIs, including a
sub-group of patients who were not on clopidogrel. Six PPIs (omeprazole, lansoprazole,
pantoprazole, esomeprazole, rabeprazole, and dexlansoprazole) were studied as a class. Five of
the six were studied individually with the exception of dexlansoprazole from the individual
analysis due to lack of exposure. H2RA (cimetidine, famotidine, nizatidine, and ranitidine) were
examined as an alternative treatment for GERD in separate analysis. Controls were selected
using propensity score matching from the baseline population. The outcome of interest was MI
as defined by ICD-9 code for acute MI and more than 18 UMLS codes including myocardial
infarction and silent myocardial infarction. Excluded were patients less than 18 years of age at
the first mention of GERD.¹²

Authors reported a 97.5% specificity and 39% sensitivity in discerning a true association.
It provided an 89% accuracy with a positive predictive value of 81% when an equal number of
true and false associations are tested. Results demonstrated an adjusted OR of 1.16 (95% CI =
1.09-1.24) of PPIs as a class with MI. When clopidogrel was excluded, the association persisted
across the groups with an adjusted OR of 1.14 (95% CI = 1.06-1.24). H2RA on the other hand
had an adjusted OR of 0.93 (95% CI = 0.86-1.02).¹² See Table V.

Additionally, the authors prospectively examined the cardiovascular mortality in the
GENE PAD (the Genetic Determinants of Peripheral Arterial Disease) study with the association
of PPI use at enrollment. This study was independent of the text-mining approach. This cohort of
patients underwent an elective, non-emergent coronary angiogram secondary to angina, shortness of breath, or abnormal stress test. Within a median follow up period of 5.2 years, there were 58 cardiovascular mortalities. Cardiovascular mortality was defined as MI, cardiac arrest, stroke, heart failure, and aneurysm rupture. Unadjusted analysis using a Cox proportional hazard model showed a hazard ratio of 2.22 (95% CI 1.19–4.16; P = 0.013) with a 122% increased cardiovascular mortality risk among PPI users. When controlling for several cardiovascular comorbidities, the association persisted with a hazard ratio of 2.00 (95% CI = 1.07–3.78; P = 0.031). No association was found with H2RA in both the unadjusted and adjusted analysis.12

The authors concluded there to be an elevated MI risk in the general population whom take PPIs versus H2RA. This was association was independent of clopidogrel use and seen in non-elderly patients without an underlying history of acute coronary syndrome. As an observational study, data may be subject to confounding. Other limitations to their study were the unknown use of over the counter PPIs as well as differences in drug dosages. They were unable to control for factors such as obesity and insulin resistance. Additionally, the authors state that it is possible PPI use may reflect a generally sicker patient population.12

DISCUSSION

This review aimed to investigate the risk of MI in patients taking PPIs for treatment of GERD with no underlying cardiovascular disease. In the four reviewed studies,9-12 authors examined whether or not PPI use was associated with an MI risk. Shih et al9 and Juurlink et al10 matched PPI prescriptions with hospitalizations for MI and HF, respectively, while Turkiewicz et al11 explored the prescription date and medication dispensation with hospitalizations for MI, and Shah et al12 used a data-mining approach to screen if PPI exposure was associated with an MI. All studies concluded there to be an increased MI risk with PPI use, particularly in patients with
no underlying history of MI. For the Shih et al, the MI risk was 1.58-fold greater in PPI users versus non-users in the propensity-score analysis. In their case-crossover design, this risk persisted and PPI use 7-days prior to hospitalization for MI with an adjusted OR of 4.61 (95% CI = 1.76-12.07, P = 0.001). More notable was that this risk was also significant at 14-days prior to hospitalization at 3.47 (95% CI = 1.76-6.83, P < 0.001). Turkiewicz et al found there to be a slightly increased risk of MI after PPI prescription in patients with no history of prior MI. When dispensation date was used, there was no increased risk of MI in patients with and without a history of prior MI. Juurlink et al found an increase in cardiovascular events amongst PPI users with no history of prior cardiovascular events. They did note the risk for MI was slightly elevated in patients with a prior history or MI. Shah et al also found there to be an adjusted OR of 1.16 (95% CI = 1.09 – 1.24) for PPIs as a class with MI.

H2RA were explored as an alternative to PPI treatment by by Shih et al, Juurlink et al, and Shah et al. Both Shih et al and Shah et al found no increased MI risk with H2RA use. Juurlink et al however noted an increase in cardiovascular events with H2RA as well as benzodiazepines, another drug without known cardiotoxicity. With this finding, they concluded that their results of increased MI risk with PPI use could not represent a cause-and-effect relationship. In comparison to the two other studies, Juurlink et al had a smaller sample size and included patients 66 years of age and greater. Only those who had had an MI or HF within 1 year preceding the PPI prescription date were excluded. In these patients with a cardiovascular history occurring greater than 1 year prior to study date, they were found to have an increased risk of MI with PPI use. It is concerning that their subjects represent a sicker patient population.
The main limitations of these studies included in this systematic review of literature are analysis of drug dosage and compliance, long-term risk analysis, exploration of patients with no prior cardiovascular events, and controlling for confounding comorbid conditions including obesity, smoking, and family history of cardiovascular disease. No study specifically mentioned the PPI drug dose, frequency, and patient compliance therefore true drug exposure remains questionable. It remains unknown if the increase seen in PPI prescriptions prior to MI is due to misinterpretations of dyspeptic symptoms for acute coronary syndrome. With PPI prescriptions now available over the counter, it is crucial that medical providers educate patients on the signs and symptoms of GERD versus acute coronary symptoms.

While the systematic review demonstrated an increased MI risk with PPI use, the mechanism of action by which this occurs and conditions which may put a patient at risk for such adverse cardiac events remains unclear. Turkiewicz et al\textsuperscript{11} and Shah et al\textsuperscript{12} analyzed PPI use with MI however did not specifically mention whether or not patients had a prior history of MI. Juurlink et al\textsuperscript{10} on the other hand included patients with a history of MI or HF who were hospitalized for these conditions greater than a year from the index date. Further analysis is needed to evaluate MI risk in patients with no history of MI and controlling for confounding comorbid conditions including obesity, smoking, and family history of cardiovascular disease.

Future studies should explore the investigation of proinflammatory markers, such as dimethylarginine dimethylaminohydrolase (DDAH),\textsuperscript{12} and PPI use and whether or not pharmacological interactions exist. All studies also examined short-term effects of PPI use warranting further investigation as to the long-term cardiovascular events. In addition to further
examination of the cardiovascular effects of PPIs, further research should aim to evaluate the risk with alternative treatments such as H2RA.

Although evidence is limited with regards to this specific population in question, what is available suggests a possible relationship exists between PPI use and MI. The current collection of evidence is not strong enough to warrant a change in GERD treatment guidelines due to the aforementioned limitations in the reviewed studies. With a calculated NNH of 4357 per Shih et al, clinicians should consider the benefits of PPI treatment to outweigh the risk of adverse cardiac events.

CONCLUSION

There is some evidence presented in the case-crossover and data-mining analysis of an increased risk of MI with the use of PPI. With a calculated NNH of 4357, the current collection of evidence is not strong enough to warrant a change in GERD treatment guidelines due to limitations in the reviewed studies. Further studies should examine actual PPI use, dose of the medication, patient compliance, and outcome measurements for both short-term and long-term checkpoints.

Other factors warranting further investigation include comparison amongst subgroups known to be at a higher cardiovascular risk including those with obesity, diabetes, tobacco use, and family history of coronary artery disease. Comparisons should further investigate H2RA and whether there is a risk for cardiovascular events or if it is an acceptable alternative in patients who are at a higher risk for adverse cardiovascular events. However, as PPI use alone has been shown to have an increased MI risk in patients without prior MI, medical providers should take the time to properly educate patients of the early signs and symptoms of an MI, especially as this
medication is available over the counter. In addition, medical providers should also strongly consider whether or not to use PPIs in patients with a high risk for adverse cardiac event compared to other alternatives without shown adverse cardiotoxicity.
References


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<td>Serious⁴</td>
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⁴ Lack of addressing possible confounders
⁵ Lack of appropriate eligibility criteria (vague exclusion criteria)
⁶ Primary analysis excluded patients with previous hospitalization for AMI or HF within one year of the preceding index, all patients >66 years
### Table II: Shih et al Summary of Findings⁹

<table>
<thead>
<tr>
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<td>1.27-1.89</td>
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<tr>
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</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval

### Table III. Turkiewicz et al Summary of Findings¹¹

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### Table IV. Juurlink et al Summary of Findings¹⁰

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<th>History of Prior HF</th>
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<td>OR</td>
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Table V. Shah et al Summary of Findings$^{12}$

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