Original Article

The Association between Proton Pump Inhibitors and Myocardial Infarction: What Do Food and Drug Administration Data Tell Us?

Jiun Ming Tan[1], Richard Parsons[1], Tin Fei Sim[1], Ya Ping Lee[1]

[1]School of Pharmacy and Biochemical Sciences, Faculty of Health Sciences, Curtin University, Western Australia

Abstract

Objective: There is limited and conflicting evidence on the association between proton pump inhibitors (PPIs) and myocardial infarction (MI). This study aims to examine the occurrence of MI associated with PPI use from the Food and Drug Administration (FDA) Adverse Event Reporting System database. **Methods:** This is a cross-sectional study using data from the FDA dated from December 2013 to April 2018. Standard descriptive statistics were used to describe demographic information. Logistic regression analyses were performed to investigate the association between the independent variables and MI. **Findings:** Among the 52,443 individuals who were taking a PPI and experienced an adverse event which was registered on the FDA database, 726 (1.38%) experienced MI. Of all the PPIs, esomeprazole had the largest proportion of users experiencing MI (1.81%). Compared to other PPIs, esomeprazole was associated with a significantly higher rate of MI (odds ratio [OR] =1.53, $P < 0.001$), whereas lansoprazole was associated with a lower rate of MI (OR = 0.74, $P = 0.03$). **Conclusion:** Among the PPIs, esomeprazole appeared to have the highest risk of MI. Although the observed associations do not infer causality, this study highlighted a need for further studies to determine if a PPI, especially esomeprazole, can indeed cause MI.

Keywords: *Adverse effects, cardiovascular, Food and Drug Administration, myocardial infarction, proton pump inhibitors*

Received: 10-02-2019.
Accepted: 19-04-2019.
Published: 16-10-2019.

Introduction

Proton pump inhibitors (PPIs) are widely used due to their prominent effectiveness in treating and preventing gastrointestinal (GI) diseases. More than 100 million prescriptions are dispensed for PPIs each year, contributing to the United States (US) $24 billion in annual expenditure worldwide.[1,2] Despite being on the US market for about two decades, esomeprazole was ranked ninth in the top 25 drugs by expenditures overall list in 2015.[3] At least one PPI is included in the top 10 drugs prescribed in Australia every year. In 2016–2017, esomeprazole was featured in the top 10 drugs by defined daily dose/thousand population/day and top 10 drugs by prescription counts.[4]

Overutilization of PPIs is the global norm in both inpatient and outpatient settings.[5] Inappropriate assessment and insufficient re-evaluation of the need for continued PPI therapy are believed to contribute to this issue.[6] In theory, PPIs, particularly omeprazole, may significantly attenuate the efficacy of clopidogrel, increasing the risk of platelet aggregation.[7] Omeprazole competitively inhibits the cytochrome P450 2C19-mediated metabolism of clopidogrel into its active metabolite, thereby reducing its antiplatelet effect.[7] In 2009, the US Food and Drug Administration (FDA) issued a warning statement to avoid the concurrent use of omeprazole or esomeprazole and clopidogrel.[8] However, the Clopidogrel and the Optimization of Gastrointestinal Events Trial and recent observational studies failed to prove the long-term clinical significance of the interaction between

Access this article online

Quick Response Code:

Website: www.jrpp.net

DOI: 10.4103/jrpp.JRPP_19_73

Address for correspondence:
Dr. Ya Ping Lee, E-mail: yaping.lee@curtin.edu.au

How to cite this article: Tan JM, Parsons R, Sim TF, Lee YP. The association between proton pump inhibitors and myocardial infarction: What do Food and Drug Administration data tell us?. J Res Pharm Pract 2019;8:123-8.

omeprazole and clopidogrel, and limited results were found with other PPIs.[9-11] These studies raised the concern that PPIs, as a group, might independently increase the risk of myocardial infarction (MI). The *post hoc* analysis of the Clopidogrel for the Reduction of Events During Observation trial showed an association between PPI use and cardiovascular events in the absence of clopidogrel.[12] In addition, a study by Goodman *et al*. revealed that the concomitant use of PPIs and ticagrelor has a similar association.[13] Limited observational studies also suggested that PPI use may increase the risk of MI in the general population, albeit confounding variables including adherence, over-the-counter use, and dosage of PPIs were not considered.[14,15] Various mechanisms have been postulated with respect to this association.[16] It is widely believed that PPIs interfere with nitric oxide synthesis by diminishing the vasoprotective effect of endothelial nitric oxide synthase.[16] Nevertheless, the clinical significance is questionable as the results from different studies were either statistically insignificant or invalid *in vivo*.[17,18]

To date, limited evidence exists to confirm the association between PPI use and MI. As PPIs are widely used at all levels of care and MI is a common cause of death, it is important that further studies are conducted to ascertain the association, if any, between PPI and MI. This study aimed to investigate whether there is any association between the use of different PPIs and MI by determining the proportion of all side effects attributable to each PPI which were MI.

Methods

This is a cross-sectional retrospective study of

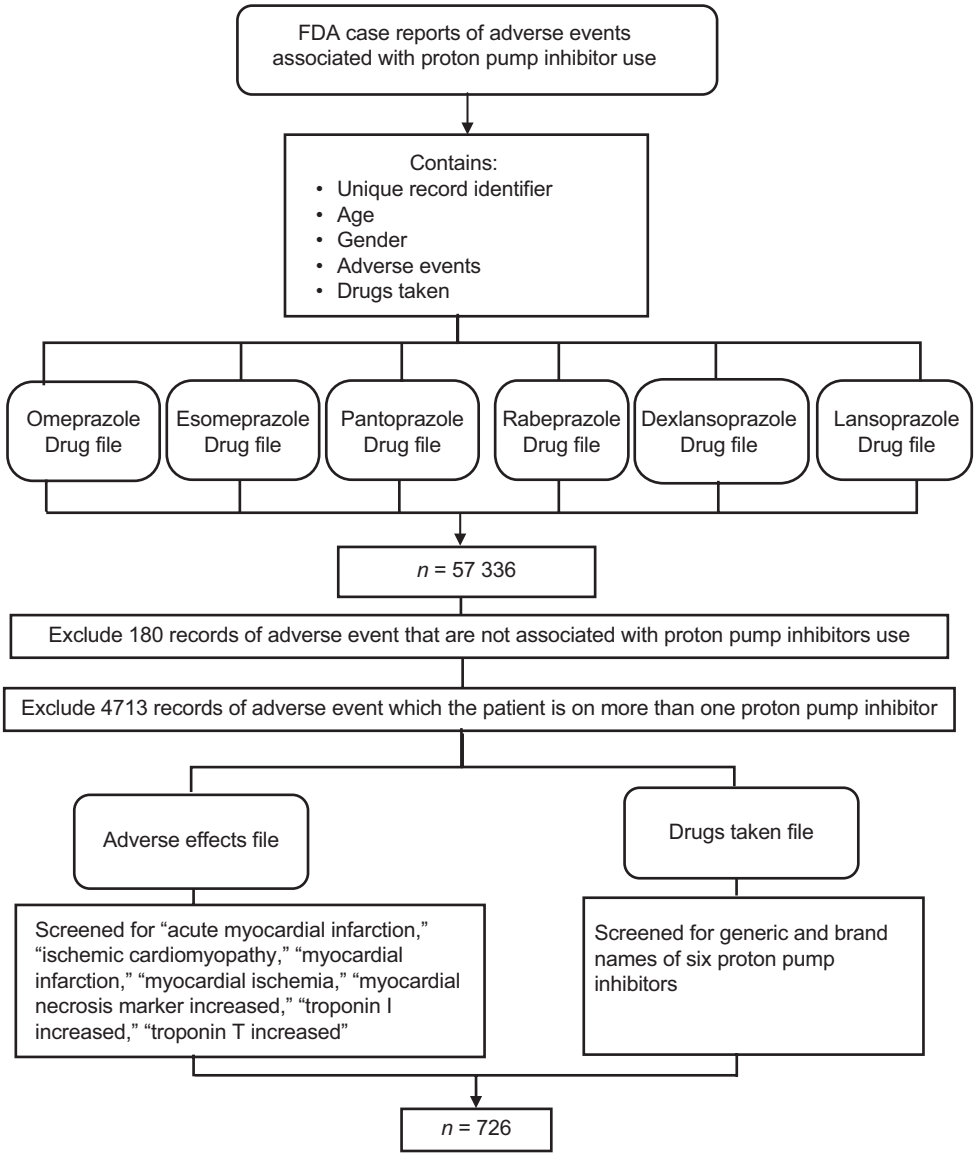

Figure 1: Schematic representation of the study methodology

cases of PPI-associated MI reported to the FDA. This study defines "elderly" as those 65 years old and above. The study methodology is illustrated in Figure 1. This study received ethics approval from the Curtin University Human Research Ethics Committee (HRE2018-0050).

A request was made to the FDA for case reports between December 2013 and April 2018 of adverse events associated with the use of the six PPIs available in the US (omeprazole, esomeprazole, pantoprazole, rabeprazole, lansoprazole, and dexlansoprazole) from their Adverse Event Reporting System (AERS) database. From the list of adverse events , "acute MI," "ischemic cardiomyopathy," "MI," "myocardial ischemia," "myocardial necrosis marker increased," "troponin I increased," and "troponin T increased" were selected as indicating that an MI had occurred, and this formed the endpoint for analysis.

De-identified data were received from the FDA as a set of Microsoft Excel files, one for each PPI being taken, and each of which contained details including a unique record identifier, date of event, age, gender, all adverse events experienced, and all drugs being taken. A file of drug names associated with each event was assembled, with one record for each drug being taken, so that there were possibly several records per event.

The file of drugs was imported into a SAS dataset (SAS version 9.2, SAS Institute Inc., Cary, NC, USA, 2008). Each drug that a person was reported as taking at the time of the adverse event was classified as "suspicious" if the drug was suspected of causing the event or "concomitant" if it was not under suspicion. Records where the PPI was classified as "concomitant" or where more than one PPI was identified as contributing to the adverse event were removed from the file, as it was not possible to determine which PPI was being taken at the time of the adverse event. The records included in the analysis have a single PPI listed as the drug which was suspected of causing the adverse event.

The final logistic regression model was obtained using a backward elimination strategy, whereby all the PPIs were initially identified and included in the model as separate indicator variables along with age and gender. The reference PPI was taken to be pantoprazole, so that the odds ratios (OR) for MI for other PPIs were expressed relative to this drug. The least significant variable was dropped from the model (one at a time), until all variables remaining in the model were statistically significantly associated with the outcome ($P < 0.05$).

Results

There were 52,443 records that met the criteria for analysis. From these records, 726 individuals were taking a PPI which was suspected of causing the MI adverse event (1.38%). Among these individuals, 49.2% were female (n = 357) whereas 46.1% were male (n = 335). Gender was not recorded for the remaining 34 individuals (4.7%). Cases involving elderly and nonelderly patients made up almost the same proportion (41.9% and 40.2%, respectively), with age missing for the remaining records. Where age or gender was missing, these were classified as a separate category for each variable, so that these records could still be included for analysis.

Univariate analysis was carried out to determine the possible association between each type of PPI, gender, and age with MI [Table 1]. A Chi-square test was used to check if any difference in the rate of MI between those who were and were not taking a particular PPI was statistically significant. Age and gender were significantly associated with MI. Esomeprazole had the largest proportion of users experiencing MI (1.81%). Pantoprazole and omeprazole had similar percentages of MI cases (1.29% and 1.26%, respectively). This was followed by lansoprazole (0.91%), rabeprazole (0.85%), and dexlansoprazole (0.64%).

A binary logistic regression model was fitted to the data, with the occurrence of MI as the dependent

Table 1. Demographic characteristics of proton pump inhibitor users with adverse effects from the Food and Drug Administration Adverse Event Reporting System database

Variable	MI reported		*P*
	*n/N**	Percentage	
PPI			
Esomeprazole	324/17,918	1.81	<0.001
Lansoprazole	60/6622	0.91	<0.001
Omeprazole	209/16,561	1.26	0.103
Pantoprazole	114/8841	1.29	0.402
Rabeprazole	12/1409	0.85	0.083
Dexlansoprazole	7/1092	0.64	0.034
Gender			
Male	335/17,833	1.88	<0.001
Female	357/29,669	1.20	
Missing	34/4941	0.69	
Age			
<65	292/19,557	1.49	<0.001
≥65	304/17,286	1.76	
Missing	130/15,600	0.83	

*The column headed *n/N* shows the number (*n*) of the total in each row (*N*) who experienced a MI, *P* values are for the univariate association between each independent variable and the occurrence of MI. PPI=Proton pump inhibitor; MI=Myocardial infarction

variable and different PPIs, age, and gender as independent variables [Table 2]. With pantoprazole as the reference PPI, and after adjusting for age and gender, the OR associated with omeprazole was not different from pantoprazole (OR = 1.00, 95% confidence interval [CI]: 0.80–1.26, P = 0.99). While the OR for dexlansoprazole (OR = 0.58, 95% CI: 0.27–1.24, P = 0.16) and rabeprazole (OR = 0.65, 95% CI: 0.36–1.18, P = 0.16) were both lower than one (lower likelihood of MI), neither were statistically significantly different from the reference. A number of users for both PPIs were very small in this study (2.08% and 2.69%, respectively). Following the backward elimination method, variables for these PPIs were removed from the model, implicitly collapsing these drugs, one by one, into the reference group.

Table 2: Binary logistic regression analysis for reporting of myocardial infarction (dependent variable)

Variable	OR	95% CI	*P*
PPI			
Pantoprazole	1 (reference)		
Esomeprazole	1.48	1.20-1.84	<0.001
Lansoprazole	0.72	0.52-0.98	0.038
Omeprazole	1.00	0.80-1.26	0.994
Rabeprazole	0.65	0.36-1.18	0.155
Dexlansoprazole	0.58	0.27-1.24	0.161
Age			
≥65	1 (reference)		
<65	0.82	0.70-0.97	0.020
Age missing	0.51	0.41-0.64	<0.001
Gender			
Male	1 (reference)		
Female	0.63	0.54-0.73	<0.001
Gender missing	0.55	0.38-0.81	0.003

Results are obtained from a multivariate analysis, so that all odds ratios are "after adjustment" for age and gender. OR=Odds ratio, CI=Confidence interval, PPI=Proton pump inhibitor

Table 3: Logistic regression analysis for reporting of myocardial infarction (dependent variable), following "backward elimination" of independent variables which showed no significant association

Variable	OR	95% CI	*P*
PPI			
Esomeprazole	1.53	1.31-1.79	<0.001
Lansoprazole	0.74	0.56-0.98	0.033
Other PPIs	1 (reference)		
Age			
≥65	1 (reference)		
<65	0.83	0.70-0.97	0.020
Age missing	0.51	0.41-0.64	<0.001
Gender			
Male	1 (reference)		
Female	0.63	0.54-0.73	<0.001
Gender missing	0.56	0.38-0.82	0.003

OR=Odds ratio, CI=Confidence interval, PPI=Proton pump inhibitor

In the final model [Table 3], after adjustment for age and gender, it appears that, compared to omeprazole, pantoprazole, rabeprazole, and dexlansoprazole as a single reference group, esomeprazole was associated with a significantly higher rate of MI (OR = 1.53, 95% CI: 1.31–1.79, P < 0.001), whereas lansoprazole was associated with a lower rate of MI (OR = 0.74, 95% CI: 0.56–0.98, P = 0.03). The association with esomeprazole is likely to be of greater clinical significance. The OR was estimated to lie within the range of 1.31–1.79, suggesting that esomeprazole was associated with at least 31% higher odds of MI compared to the other PPIs. The "protective effect" of lansoprazole was weaker, as the upper end of the 95% CI was close to the null value of one.

Discussion

The FDA data suggest that lansoprazole is associated with a significantly lower risk of MI than esomeprazole. Nevertheless, this does not necessarily imply that lansoprazole provides cardiovascular protective effect or that this PPI should always be preferred over esomeprazole, as there are other factors that need to be taken into consideration such as their potencies and therapeutic effects. A meta-analysis suggested that esomeprazole provides clinical benefits to patients who have severe GI diseases, such as better healing rate and greater symptomatic relief, when compared with equipotent doses of other PPIs.[19] In addition, it was estimated that esomeprazole appeared to be approximately twice as potent as lansoprazole in its acid suppression effect.[20] Therefore, esomeprazole could be the preferred PPI in patients who have complicated GI diseases or other comorbidities, which might be risk factors for MI.

The FDA warning in 2009 may have influenced trends in PPI use. Prescribers may have considered pantoprazole as the most appropriate PPI in patients with high cardiovascular risk because pantoprazole appeared to be associated with a lower risk of potential interaction with clopidogrel and therefore the risk of reinfarction.[21] Based on the results of the current study, the association between pantoprazole and the risk of MI was found to be similar to omeprazole, rabeprazole, and dexlansoprazole and intermediate between lansoprazole (lower) and esomeprazole (higher), indicating that the increased prescribing of pantoprazole in this group of patients with predisposed cardiovascular risk may have been wise.

Dose and duration of PPI use could have confounding effects on the association of PPI use and MI. Sehested *et al*. suggested that while all PPIs had a similar risk of MI at equivalent dose, high dose of pantoprazole appeared to be associated with the highest MI risk.[22] A recent meta-analysis suggested that long-term omeprazole use was associated with the highest risk of cardiovascular events among all the PPIs.[23] The highest risk of MI associated with esomeprazole use from the FDA data was inconsistent with the result of the recent meta-analysis. This warrants further studies to ascertain whether the high prevalence of esomeprazole-associated MI from the FDA data was due to the class effect or the duration of exposure.

There are several limitations in this study. The FDA data had a large number of records with missing information for age (29.7%) and gender (9.4%). Both of these missing categories were associated with a lower risk of MI. One possible explanation for this may be that the adverse event records were more likely to be incomplete when they were less serious. Nevertheless, when age and gender were omitted from the final model, the ORs associated with esomeprazole and lansoprazole, as well as their *P* values, were substantially unchanged. This suggests that age and gender, while significant themselves, had no material impact on the results as far as the PPIs are concerned.

Moreover, there is some uncertainty concerning the role of the PPI in causing the reported adverse event as the method of allocation of the "suspicious" code to each drug is not clear. It was impossible to verify the accuracy of the information as data are gathered by self-reports of adverse events from patients, health-care professionals, or manufacturers. Thus, the causal relationship between the drug and adverse event, while suggestive from these data, remains unproven.

In conclusion, esomeprazole appeared to have the highest risk of MI among all the PPIs. On the contrary, lansoprazole is suspected to be cardioprotective, albeit this benefit is likely to be mild and requires further investigation. Based on the findings of this study, esomeprazole should at least be avoided in patients at risk of MI. This study has highlighted a need for further research, especially those with a prospective design, to ascertain if a causal relationship between PPI use and MI exists.

Authors' Contribution

Ya Ping Lee contributed to the study conception, data acquisition and analysis, drafting and revising the manuscript. Jiun Ming Tan, Tin Fei Sim and Richard Parsons contributed to the design of the study, data analysis, drafting and revising the manuscript.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Durand C, Willett KC, Desilets AR. Proton pump inhibitor use in hospitalized patients: Is overutilization becoming a problem? Clin Med Insights Gastroenterol 2012;5:65-76.
2. Katz MH. Failing the acid test: Benefits of proton pump inhibitors may not justify the risks for many users. Arch Intern Med 2010;170:747-8.
3. Schumock GT, Li EC, Suda KJ, Wiest MD, Stubbings J, Matusiak LM, *et al.* National trends in prescription drug expenditures and projections for 2016. Am J Health Syst Pharm 2016;73:1058-75.
4. Top 10 drugs 2016-17. Aust Prescr 2017;40:237.
5. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. BMJ 2008;336:2-3.
6. Heidelbaugh JJ, Kim AH, Chang R, Walker PC. Overutilization of proton-pump inhibitors: What the clinician needs to know. Therap Adv Gastroenterol 2012;5:219-32.
7. Gilard M, Arnaud B, Cornily JC, Le Gal G, Lacut K, Le Calvez G, *et al.* Influence of omeprazole on the antiplatelet action of clopidogrel associated with aspirin: The randomized, double-blind OCLA (Omeprazole CLopidogrel aspirin) study. J Am Coll Cardiol 2008;51:256-60.
8. Prescribers' Digital Reference. Plavix (clopidogrel bisulfate) FDA Drug Safety Communication; c 2009. Availble from: https://www.pdr.net/fda-drug-safety-communication/plavix?druglabelid=525&id=5223. [Last accessed on 2019 Apr 19].
9. Bhatt DL, Cryer BL, Contant CF, Cohen M, Lanas A, Schnitzer TJ, *et al.* Clopidogrel with or without omeprazole in coronary artery disease. N Engl J Med 2010;363:1909-17.
10. Bundhun PK, Teeluck AR, Bhurtu A, Huang WQ. Is the concomitant use of clopidogrel and proton pump inhibitors still associated with increased adverse cardiovascular outcomes following coronary angioplasty?: A systematic review and meta-analysis of recently published studies (2012 – 2016). BMC Cardiovasc Disord 2017;17:3.
11. Bouziana SD, Tziomalos K. Clinical relevance of clopidogrel-proton pump inhibitors interaction. World J Gastrointest Pharmacol Ther 2015;6:17-21.
12. Dunn SP, Macaulay TE, Brennan DM, Campbell CL, Charnigo RJ, Smyth SS, *et al*. Abstract 3999: Baseline proton pump inhibitor use is associated with increased cardiovascular events with and without the use of clopidogrel in the CREDO trial. Circulation 2008;118:S-815. Available from: https://www.ahajournals.org/doi/abs/10.1161/circ.118.suppl_18.S_815-a. [Last accessed on 2018 Oct 16].
13. Goodman SG, Clare R, Pieper KS, Nicolau JC, Storey RF, Cantor WJ, *et al.* Association of proton pump inhibitor use on cardiovascular outcomes with clopidogrel and ticagrelor: Insights from the platelet inhibition and patient outcomes trial. Circulation 2012;125:978-86.
14. Shih CJ, Chen YT, Ou SM, Li SY, Chen TJ, Wang SJ. Proton pump inhibitor use represents an independent risk factor for myocardial infarction. Int J Cardiol 2014;177:292-7.
15. Shah NH, LePendu P, Bauer-Mehren A, Ghebremariam YT,

Iyer SV, Marcus J, *et al.* Proton pump inhibitor usage and the risk of myocardial infarction in the general population. PLoS One 2015;10:e0124653.

16. Sukhovershin RA, Cooke JP. How may proton pump inhibitors impair cardiovascular health? Am J Cardiovasc Drugs 2016;16:153-61.
17. Ghebremariam YT, Cooke JP, Khan F, Thakker RN, Chang P, Shah NH, *et al.* Proton pump inhibitors and vascular function: A prospective cross-over pilot study. Vasc Med 2015;20:309-16.
18. Tommasi S, Elliot DJ, Hulin JA, Lewis BC, McEvoy M, Mangoni AA. Human dimethylarginine dimethylaminohydrolase 1 inhibition by proton pump inhibitors and the cardiovascular risk marker asymmetric dimethylarginine: *In vitro* and *in vivo* significance. Sci Rep 2017;7:2871.
19. Gralnek IM, Dulai GS, Fennerty MB, Spiegel BM. Esomeprazole versus other proton pump inhibitors in erosive esophagitis: A meta-analysis of randomized clinical trials. Clin Gastroenterol Hepatol 2006;4:1452-8.
20. Kirchheiner J, Glatt S, Fuhr U, Klotz U, Meineke I, Seufferlein T, *et al.* Relative potency of proton-pump inhibitors-comparison of effects on intragastric pH. Eur J Clin Pharmacol 2009;65:19-31.
21. Juurlink DN, Gomes T, Ko DT, Szmitko PE, Austin PC, Tu JV, *et al.* A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. CMAJ 2009;180:713-8.
22. Sehested TS, Gerds TA, Fosbøl EL, Hansen PW, Charlot MG, Carlson N, *et al.* Long-term use of proton pump inhibitors, dose-response relationship and associated risk of ischemic stroke and myocardial infarction. J Intern Med 2018;283:268-81.
23. Sun S, Cui Z, Zhou M, Li R, Li H, Zhang S, *et al*. Proton pump inhibitor monotherapy and the risk of cardiovascular events in patients with gastro-esophageal reflux disease: A meta-analysis. Neurogastroenterol Motil 2017;29:e12926.