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Proton Pump Inhibitors and Atrial Fibrillation

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PROTON PUMP INHIBITORS AND ATRIAL FIBRILLATION

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Abstract

Background

Proton pump inhibitors (PPIs) are widely used drugs in the United States. Atrial fibrillation (AF) affects 2.7 million people in this country and often leads to other serious medical conditions. There is a growing body of evidence suggesting that PPIs may be proarrhythmic. This study seeks to better appreciate the relationship between these popular drugs and the most common arrhythmia.

Methods

This is a nested case-control study using a large, nationally representative insurance database. Members with an incident AF diagnosis between 2007 and 2009 were identified. Each case was matched with one control member, using incidence density sampling, and both were assigned an index date of the case's date of AF diagnosis. PPI exposure was assessed through pharmacy claim records for both cases and controls prior to their assigned index date. Multivariable analysis was accomplished through conditional logistic regression as a means of comparing PPI exposure among cases and controls.

Results

The study included 40,484 eligible members (20,265 cases and 20,219 controls). Bivariate analyses revealed that cases were more likely to have each of the potentially confounding comorbidities of interest than controls. An unadjusted multivariable analysis suggested that cases were more likely to have redeemed a PPI prescription OR= 3.53

[3.12 – 3.99]. Following adjustment, the association diminished but remained significant OR= 1.98 [1.63 – 2.41]. A sensitivity analysis among cases and controls with redeemed prescriptions for PPIs and H2RAs failed to suggest that cases were significantly more likely to have been exposed to PPIs OR= 1.68 [0.88 – 3.19].

Conclusions

Exposure to PPI therapy was more likely among those with an incident AF diagnosis. This study is in agreement with similar findings that PPIs may cause arrhythmias. However, the insignificance of the sensitivity analysis weaken the study's ability to declare with more certainty that the observed association between PPIs and AF are independent of GERD, which has also been hypothesized as a causative condition of AF.

Literature Review

The following review of the literature is a summary of key concepts foundational to the understanding of proton pump inhibitors, atrial fibrillation, and their potential association. The works cited were located primarily using PubMed.gov and Web of Science™ through the University of Kentucky Medical Center Library website. PubMed searches used include: "atrial fibrillation and proton pump inhibitors" (atrial fibrillation plus each individual proton pump inhibitor e.g. "atrial fibrillation and omeprazole" were also conducted searches), "atrial fibrillation and hypomagnesaemia", and "hypomagnesaemia and proton pump inhibitors" as well as hypomagnesaemia plus individual proton pump inhibitors. Additional key references were recommended by instructors providing guidance. Works cited include predominantly observational studies, case reports, and clinical guidelines from the disciplines of gastroenterology, cardiology, and pharmacology.

An Introduction to PPIs

Proton pump inhibitors (PPIs) are widely prescribed drugs that suppress the secretion of gastric acid. Currently available PPIs in the United States include: omeprazole, esomeprazole, lansoprazole, dexlansoprazole, pantoprazole, and rabeprazole. They are all available by prescription, while omeprazole, esomeprazole, and lansoprazole are also available as non-prescription medications. PPIs are the most potent acid-suppressing drugs used to treat esophagitis and gastroesophageal reflux disease (GERD)[1,2] and they play an important role in managing both acute and chronic peptic ulcer disease.[1,3] In 2011, omeprazole was the sixth most dispensed prescription in the United States[4] and its

actual use may be underestimated due to its availability without a prescription since 2003. Indeed, the class as a whole remains popular and accessible as generic versions of omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole are now available.

PPIs are often the drug of choice for the treatment of reflux symptoms. They are superior to other shorter-acting, acid-lowering therapies due to their ability to maintain intragastric pH <4 between 15 and 21 hours.[5] Their popularity in the United States is largely due to a high prevalence of GERD. It has been estimated that 23% to 27% of United States adults experience reflux symptoms at least weekly.[6] Estimates for the prevalence of regularly experienced heartburn, the most characteristic symptom of GERD, in western countries may be as high as 40%.[7] Initial GERD treatment recommendations focus on lifestyle modifications, including weight loss and tobacco cessation, but pharmacological therapy is frequently instituted.[8] Also adding to the popularity of PPIs is their use in hospitals. Admitted patients are frequently prescribed PPIs as a method of stress ulcer prophylaxis and often do not have the order discontinued at discharge.[8 9]

Hypomagnesaemia

While therapeutically useful, PPIs are not without the risk of adverse reactions. All PPI therapy poses the risk of common pharmaceutical adverse reactions such as headaches, dizziness, and gastrointestinal disturbances.[10] A more unique effect of long-term PPI therapy that has recently garnered more attention is hypomagnesaemia.

In response to increased reports of low serum magnesium levels during PPI therapy, the FDA notified healthcare professionals and the public in 2011 of the association between

hypomagnesaemia and PPI therapy of at least three months. The FDA recommended that clinicians consider obtaining serum magnesium levels prior to initiation of PPI therapy and periodically thereafter.[11] Case reports[12][13][14] and a systematic review[15] demonstrate that PPI-induced hypomagnesaemia, while relatively rare: is a class effect, resulted in severe symptoms due to magnesium deficiency, and was frequently resolved only by the removal of a PPI.

Atrial Fibrillation

Magnesium is required for more than 200 biochemical reactions in the human body. In addition to maintaining normal nerve and muscle function, supporting immune systems, and helping bones remain strong, it allows for a normal heart rhythm.[16] Hypomagnesaemia is known to be associated with cardiac arrhythmias[17] and was shown to be associated, specifically, with atrial fibrillation (AF) in Framingham offspring without cardiovascular disease.[18]

As the most common form of arrhythmias,[19] AF affects an estimated 2.7 million in the United States. It is a quivering or irregular heartbeat that may produce blood clots, strokes, and other cardiovascular complications.[20] There are more than 467,000 hospitalizations with AF as the primary diagnosis in the United States annually and it is estimated that AF contributes to more than 99,000 annual deaths.[21] The most concerning aspect of AF is that it often leads to other medical conditions. AF is associated with a five-fold increased stroke risk[22] and AF-related strokes are likely to be more severe than non-AF-related strokes.[23] Additionally, AF is associated with a three-fold increased risk

of heart failure,[24][25][26] a two-fold increased risk of dementia,[27] and an overall two-fold increased risk of mortality.[22]

GERD and AF

Given the popularity of PPIs, the pervasiveness of AF, and the intermediate hypomagnesaemia association- we seek to further examine the association between PPIs and AF. The theory that PPI therapy may increase the risk of AF has not been sufficiently investigated. This theory is further complicated by the most common indication of PPI therapy, GERD. There are studies suggesting that GERD, the condition itself, increases the risk of developing AF.

Multicenter questionnaire surveys have found significant correlations between AF and GERD among respondents.[28][29] Kunz, et al. published findings of a retrospective, epidemiologic study that investigated the association between GERD and AF diagnoses among 163,627 adult patients. They found that the presence of GERD significantly increased the relative risk (RR) of a diagnosis of AF after adjusting for cardiovascular disease risk factors (RR: 1.19, 95% CI: 1.13-1.25) and diagnoses known to be strongly associated with AF (RR: 1.08, 95% CI: 1.02-1.13).[30] It is worth noting that at least one large population-based study of patients surveyed for GERD did not find an association with the presence of GERD symptoms and AF. Long-term risk for AF was determined by a review of clinical evaluations and electrocardiographic database and found that 741 of the respondents developed AF. Following adjusting for confounders, the presence of GERD was not associated with risk of developing AF (HR: 0.81, 95% CI: 0.68-0.96, p=0.014).[31]

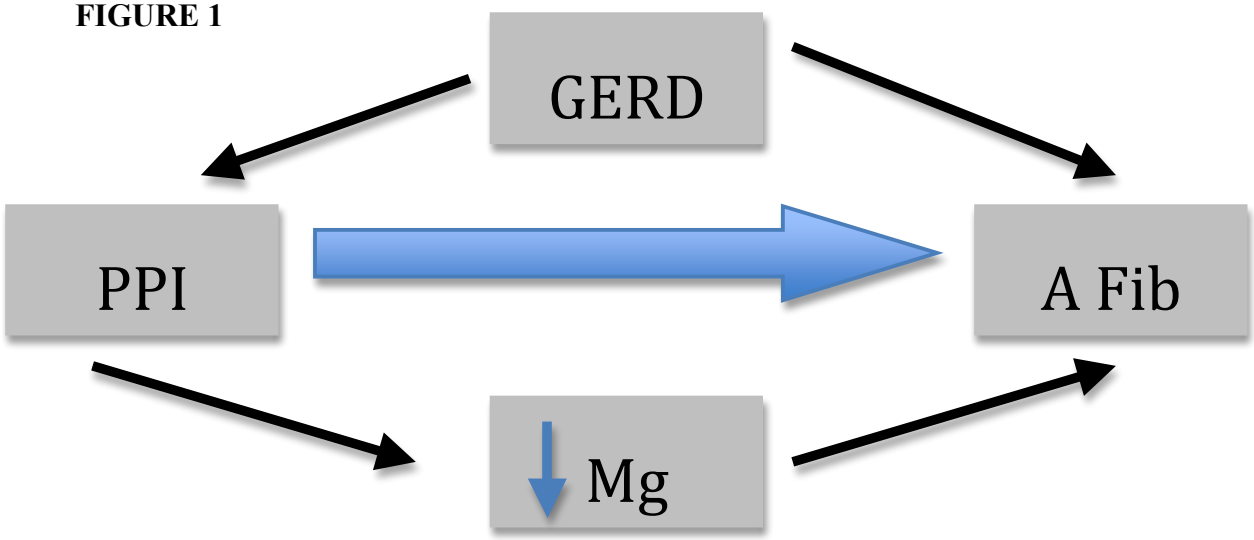
Huang, et al. conducted a prospective, epidemiologic study using Taiwanese national health insurance data that followed 29,688 newly diagnosed GERD patients and 29,597 controls. They observed that 184 patients (0.62%) with GERD experienced an occurrence of AF, while 167 patients (0.56%) non-GERD patients also received a diagnosis of AF. The investigators found that, following a Cox proportional-hazard model analysis, GERD was independently associated with an increased risk of developing AF (hazard ratio (HR): 1.31, 95% CI: 1.06-1.61, p=0.013).[32]

While the actual mechanism by which GERD may lead to AF is still undetermined, Huang, et al. detail several causal theories. GERD may induce vagal nerve stimulation,[3334] and animal and human studies have observed that vagal nerve overstimulation may be related to the induction of AF.[3536] There has also been an observed relationship between AF and cardiac inflammation.[37] The anatomical proximity between the atria and esophagus[38] and the local inflammatory process observed in GERD[39] provide another theoretical mechanism by which GERD induces AF. Another theory proffers that GERD may induce an autoimmune response that contributes to the development of AF.[40] Lastly, acidic stimulation of the lower esophagus has been shown to significantly reduce coronary blood flow within coronary artery disease patients[41]; chronic atrial ischemia has been suspected to predispose individuals to AF.[42]

The Taiwanese investigators also performed a sensitivity analysis for PPI administration for GERD. Among GERD patients, 12,862 received PPIs and 16,826 did not. GERD patients who received PPI therapy were found to have an increased risk of AF (HR: 1.46, 95% CI: 1.15-1.86, p=0.002) but GERD patients who were not prescribed a PPI were not found to have an increased risk of developing AF (HR: 1.14, 95% CI: 0.86-1.51,

p=0.378). The investigators suggested that GERD that produces significant enough symptoms to merit PPI therapy has a higher risk of AF. Huang, et al. admittedly point out that this interpretation could be flawed due to the availability of reports demonstrating that PPIs may be proarrhythmic.[32]

FIGURE 1



PPI may be proarrhythmic

Marcus, et al. performed a case-control study reviewing 80 patients with focal tachycardias: 40 patients with focal atrial tachycardia (AT) and 40 patients with right ventricular outflow tract (RVOT) automaticity, designated as the cases. They used 80 patients with arrhythmias not attributable to increased automaticity as the control group. After adjustment for potential confounders, PPI use was found to be significantly associated with focal arrhythmias (OR: 5.2, 95% CI: 1.4-19.2, p=0.025).[43]

The investigators discussed potential PPI-induced proarrhythmic mechanisms to explain their findings including evidence of H+/K+-ATPase activity in cardiac muscle. Proton pump inhibitors function by irreversibly blocking this enzyme system (also referred to as the proton pump) and it has also been reported to be present in the myocardium of animals[4445] and humans.[46] However, the expression of the pump appears to be very low in myocardium compared with gastric tissue and no relevant changes in pH homeostasis were detected in the study from Schillinger, et al. that first reported the presence of the pump in human ventricular myocardium. The effects of PPIs on cardiac contractility, according to Schillinger, et al., involve intracellular mechanisms that are distinct from their effects in gastric tissue, and possibly related to increased intracellular calcium.[46] There has been a reported association between increased intracellular calcium and catecholaminergic polymorphic ventricular tachycardias.[47] Marcus, et al. point out, because intracellular calcium regulation is vital to normal myocardial automaticity, common forms of triggered and automatic arrhythmias like AT and RVOT could arise from abnormal intracellular concentrations.[4849]

While arrhythmias induced by calcium abnormalities are certainly not baseless, there is still much undetermined in the development of abnormal cardiac rhythms. Often, the interpretation and comparability of studies is difficult due to differences in many known arrhythmias and due to associated electrolyte abnormalities. For example, magnesium deficiencies are often accompanied by hypokalemia, hypophosphatemia, hyponatremia, and hypocalcemia.[50] Concomitant deficiencies of both magnesium and calcium have been well described and magnesium concentrations (intracellular and extracellular) also have an effect on the currents and transport capabilities of potassium and sodium[51], other

important electrophysiological determinants. As an established cofactor in the Na+/K+-ATPase enzyme system that manages sodium and potassium flux across cell membranes, magnesium plays a role in maintaining the potential required for the depolarization of cardiac muscle.

The proarrhythmic effects of PPIs remain controversial. In a two-year observational study of patients with paroxysmal, vagal AF who reported retrosternal and epigastric pain, Stöllberger, et al. followed 18 patients with PPI therapy. The investigators observed that patients' pain and inflammation were reduced and also that AF attacks either stopped completely or were decreased in frequency. They suggested PPIs in these patients may have facilitated cardioversion and a maintenance of normal sinus rhythm.[52] Similarly, another observational study from Weigl, et al. observed that not only GERD symptoms, but also paroxysmal AF symptoms were eliminated or decreased in 14 of 18 patients following PPI therapy. Five of the patients were even able to discontinue antiarrhythmic drugs.[53]

Conclusions

There is an insufficient amount of evidence to definitively elucidate the relationship between PPIs and AF. Despite the ubiquitous use of PPIs, the FDA's warning that PPIs may cause hypomagnesaemia, and the Framingham observation linking hypomagnesaemia and AF, there remains a dearth of relevant studies concerning the popular drug class and the most common arrhythmia, which is a major contributor to morbidity and mortality in the United States. Among the many post-market reports concerning PPI safety, several case reports have documented a newly diagnosed

arrhythmia with PPIs being the only plausible causative agent. These patients shared many laboratory abnormalities, including hypomagnesaemia, and saw a restoration of normal sinus rhythm following the discontinuation of the PPI.[545556]

This case-control study seeks to add to the body of evidence exploring the association between PPIs and AF. Although adverted by multiple case reports, we seek to appreciate this relationship on a population level. We anticipate that the findings of this large case-control study will provide a fair estimate of the relationship between PPIs and AF, adding to the small, but compelling study from Marcus, et al. on focal arrhythmias. Previous observational studies have been large, but focused upon the association between GERD and AF. While most of these studies have found that GERD is associated with an increased risk of developing AF, it is possible that these studies are capturing the effect of an established biochemical adverse event of the popular drugs used to treat GERD symptoms.

Methods

Introduction

The authors adapted methods similar to the nested case-control study conducted by Schmidt, et al.[57], which also investigated the association between drug exposure and atrial fibrillation.

Study Design

The authors conducted a nested case-control study using a large, nationally representative insurance database. The database contains medical claims from inpatient and outpatient encounters as well as pharmacy benefit utilization that include diagnoses and redeemed prescriptions. Claims were available for the years 2007 through 2009 and included approximately 22 million members for consideration.

Cases and Controls

Our outcome of interest was AF and patients with a first-time diagnosis of AF were identified and classified as cases. To be eligible for inclusion, members were required to have shown continuous enrollment in their health care plan from January 1, 2007 through December 31, 2009. Any members with documented AF within the first three months of continuous enrollment were excluded. The date of the AF diagnosis was considered the index date for each case. One control was selected for each identified case using incidence density sampling.[58] The controls were matched with each case and assigned the same index dates as their corresponding cases.

PPI use

In order to assess the exposure of interest (PPIs), prescription claim records were explored for both cases and controls. Medication exposure was identified through an NDC AHFS crosswalk. Cases and controls that had at least one prescription redeemed for a PPI up to 90 days prior to their index date were considered "exposed" to PPI therapy. This exposure requirement was used to capture both 30-day supply and 90-day supply prescriptions that are commonly redeemed.

Patient Characteristics

In order to account for potential confounding variables, demographic information including age, gender, and race were collected for cases and controls and categorized as presented in Table 1. Diagnoses and redeemed prescriptions known to be associated with AF or reduced magnesium levels were also obtained for cases and controls and presented in Table 1. The following ICD-9 were used to identify diagnoses of interest: congestive heart failure (398.91 and 428.0), myocardial infarction (410.xx, 412, 429.71, and 429.79), diabetes mellitus (249.xx and 250.xx), hypertension (401.0, 401.1, 401.9, 405.01, 405.09, 405.11, 405.19, 405.91, 405.99, 416.0, 459.30, 459.31, 459.32, 459.33, 459.39), valvular heart disease (093.20, 093.21, 093.22, 093.24, 394.9, 396.0, 396.2, 396.3, 396.8, 396.9, 397.0, 397.1, 397.9, 424.0, 424.1, 424.2, 424.3, 424.90, 424.99, 999.02, 999.71), hyperthyroidism (242.xx), alcoholism (291.xx, 303.xx, 357.5, 425.5, 535.30, 535.31, 571.xx), chronic kidney disease (403.xx, 404.xx, 585.xx), and overweight/obesity (278.00, 278.01, 278.02). Potential confounders were identified a priori through literature review and clinical expertise of investigators.

Statistical Analysis

Contingency tables were created to describe the relationship between the primary exposure of interest in cases and controls as well as potential confounders. From these, the frequency of cases and controls in categories of exposure and potential confounders of interest were calculated. First, univariate analyses were calculated to explore the overall population characteristics using means and standard deviations for continuous variables and percentages. Bivariate analyses were used to examine unadjusted differences between cases and controls using Pearson's chi-square test for categorical variables and t-tests for continuous variables. To examine the relationship between PPI exposure and AF in the presence of confounders, a multivariable analysis was conducted using conditional logistic regression to generate odds ratios and associated 95% confidence intervals. Conditional logistic regression is used to account for the incidence density sampling. All demographic and comorbidity categories displayed in Table 1 were considered for inclusion in the final model as all were shown to be associated significantly with both the outcome and exposure of interest. A final model was derived by examining the percent change in the estimated odds ratio natural log; variables were considered significant confounders and remained in the model if their absence generated a change in the natural log of the odds ratio estimate greater than ten percent.

All data analysis was performed in STATA 13, made available by the University of Kentucky.

Results

Table 1 presents descriptive data for the 40,484 members included in the study. The average age was 52 years (standard deviation: 22.61). More males (55%) were included than females. The largest racial group was white (79%). The most commonly documented co-morbidity of interest for all included members was hypertension (18.2%).

Table 2 displays the frequency of the demographic information and variables of interest among the 20,265 cases and 20,219 controls. Those with AF were more likely to be older, male, and white than controls without AF. The large sample size generated statistical significance between the two groups for all collected demographic information, comorbidities, and drug exposures of interest. All comorbidities of interest occurred more frequently in members with AF than in those without. Of note, the following comorbidities were observed to have occurred in cases in at least a 10-fold increase to the proportion of controls: congestive heart failure (8.1% vs. 0.09%), hypertension (33% vs. 3.2%), valvular disease (8.7 vs. 0.2%) and chronic kidney disease (2.6% vs. 0.2%).

Table 3 displays results from an unadjusted and adjusted conditional logistic regression. An unadjusted conditional logistic regression to explore PPI exposure among cases and controls yielded an odds ratio (OR) of 3.53 (95% CI: 3.12 – 3.99, $p<0.001$) i.e. the odds of exposure to PPIs were 3.53 times more likely among those with incident AF than those without AF. Following adjustment for confounding factors, a final model demonstrated a reduced OR of 1.98 (95% CI: 1.63 – 2.41, $p<0.001$).

A sensitivity analysis was performed among members exposed to PPIs and H2 receptor antagonists (H2RAs). H2RAs are another class of drugs used to treat GERD. Given the

body of evidence suggesting that GERD increases the risk of developing AF, the authors attempted to approximate a GERD variable (users of PPIs and H2RAs) and ascertain if there was a difference in PPI exposure among the cases and controls who were requiring acid suppression therapy. An unadjusted conditional logistic regression revealed a non-significant OR of 1.68 (95%CI: 0.88 – 3.19, p=0.12).

Discussion

This study found that members who had been diagnosed with AF were more likely to have redeemed a prescription for a PPI prior to their diagnosis than non-AF members prior to their assigned index date. In agreement with Marcus, et al., this significant association on a population level suggests that PPIs may indeed be proarrhythmic. This study is also in agreement with Huang, et al. who found that PPI users were more likely than non-PPI users to develop AF among GERD patients. However the authors' own sensitivity analysis among members receiving PPIs and H2RAs was not found to be significant. The small number of included members receiving H2RAs weakens the study's ability to propose that PPIs, instead of GERD, are causative of AF.

Strengths of this study include a large sample size. The large nationally represented database provided approximately 22 million members for consideration, of which 40,484 were eligible for inclusion. This large sample size provides for a more reliable reflection of the relationship between these popular drugs and a common condition among the population.

Another strength of this study is the use of incidence density sampling. Controls were selected from the members who were at risk at the time of an incident AF diagnosis. The use of incidence density sampling allows for the generation of an odds ratio that more closely approximates a risk ratio.

A sensitivity analysis was attempted following the primary analysis of interest. The use of an appropriate comparison group, such as users of H2RAs, was another strength of this study that tried to better understand the true relationship of PPIs and AF. So long as

GERD and PPI exposure remains clinically intertwined, future studies will require similar sensitivity analyses to separate the effects of the condition from adverse events of the drug.

One major limitation of this study was the absence of a minimal age requirement. The total sample of members was younger than anticipated. The youngest age group (0-49) included 40% of all cases and controls, while the mean age was 52 years. Of those belonging to the age group 0-49, 11.7% were cases and 88.3% served as controls. While age groups were accounted for in the final multivariable analysis, it cannot be ignored that many in the control group were children, as there was not a minimal age requirement. This channeling bias may have affected the findings of this study and should be avoided in future related studies. The absence of AF in these younger members rendered them eligible to serve as controls for the purpose of this study. However, for many, their youthful protection from the development of AF also afforded protection from many of the gastrointestinal conditions for which PPI therapy is indicated. This may have led to an overestimation of the association between AF and PPIs.

Another limitation stemming from patient characteristics is the under reporting of overweight and obese members. This study relied on ICD-9 coding to a health care plan, where height, weight, nor body mass index (BMI) were available for analysis. While in-clinic counseling may have occurred for weight loss, its treatment is not covered by insurance companies.[59] With little incentive to code a patient as overweight, it is likely that the proportion of overweight and obese members is severely underestimated. At the very least, the patient characteristics of this study sample fail to reach national CDC estimates that 69% of adults are at least overweight while obesity rates for children aged

2-5, 6-11, and 12-19 are 12.1%, 18.0%, and 18.4% respectively in the United States.[60] Obesity is a well-established risk factor for both AF[61] and GERD symptoms[62] and it could prove to be a greater confounding factor in related future studies.

This study did not account for any drug therapy occurring beyond prescription coverage. The large, nationally represented insurance database facilitated a large study, but was incapable of reporting any drugs that were purchased without a prescription or were dispensed without billing the insurance plan. This limitation certainly applies to the use of NSAIDs and it would be ideal to have a more complete picture of NSAID usage among cases and controls. More critically, this limitation applies to omeprazole, the most popular PPI, which has been available without a prescription since 2003.

We are unable to quantify with any certainty, the extent to which omeprazole was utilized beyond what pharmacy claims reveal. It is unknown if those purchasing omeprazole without a prescription are different than those who are having prescriptions filled, and billed, for the drug. It can be assumed that those who are more regular users of omeprazole would have prescription claims available for assessment as their co-pay would be more affordable than purchasing the drug without insurance. However, nothing is certain. The fact that omeprazole was available without a prescription for the duration of this study period means that omeprazole therapy was likely more common than the claims database suggests. This, likely, non-differential, misclassification may have lead to an underestimation of the association between AF and PPIs.

The lack of prescription claims for H2RAs also limited the authors' conclusions. The entire class of H2RAs (e.g. ranitidine, famotidine, etc) is relatively cheap and available

without a prescription. It is likely that their actual use has been under reported in the claims database. It is unknown how often they are truly prescribed, or at least, recommended by health care providers. H2RAs are used to address the symptoms of GERD, like PPIs. They are more rapid acting than PPIs, but ultimately do not possess the long-term acid-suppressing therapy provided by PPIs.

The authors undertook a sensitivity analysis among PPI and H2RA users to better appreciate the relationship between AF and PPIs. The argument can be made that PPI prescription claims may just be a proxy for a GERD diagnosis. The large population-based study of Huang et al. suggested that the presence of GERD increased the risk of developing AF. However, their sensitivity analysis among GERD patients treated with PPIs and those not treated with PPIs showed a significant association between PPIs and AF. There were not enough prescription claims for H2RAs from the database to support an effective analysis. Only 53 of the 40,484 members showed a paid prescription claim for an H2RA prior to their index date. When the relationship between PPIs and AF were assessed among only PPI and H2RA users, an OR of 1.68 [0.88 – 3.19] was calculated. This suggested a possible association, however in future studies, more than just 0.13% of the sample size would need to show H2RA exposure in order for a similar analysis to be worthwhile.

Related epidemiologic studies to come may find more definitive results by matching on the basis of age so that all included participants have the same chance of developing AF as well as needing PPI therapy for other age-related conditions. Another aspect for future consideration would be the length of PPI therapy. More conclusions may be drawn when investigating new vs. long-term users of PPI.

A large omission of this study was clinical information, namely, laboratory results. Though it was not possible on the large scale of this study, future assessments of electrolyte and electrocardiography laboratory values would demonstrate a more complete account of the AF/PPI relationship. As hypomagnesaemia has been an observed effect of PPI therapy and a known cause of AF, a more in-depth assessment of magnesium levels among participants would be especially valuable. Another significant omission here that may be improved in future studies is the record of non-prescription drug exposure.

Future settings where clinical values and a more comprehensive medication record may be available for future studies include Veterans Affairs Medical Centers and long-term care institutions. Both offer comprehensive medical care to patients and excel in documenting laboratory results and full medication regimens. Both have patient populations with comparable ages and risk factors. Medication records are typically reliable and complete due to either on-site administration or favorable co-pays.

Conclusion

This nested case-control study found that exposure to PPI therapy was more likely in insurance members who were diagnosed with incident AF than in members without an AF diagnosis. This study is in agreement with case reports detailing first-time arrhythmia diagnoses following PPI therapy, the arrhythmia case-control study conducted by Marcus, et al, and with the sensitivity analysis from Huang, et al among patients with a GERD diagnosis. While this study adds to the body of evidence suggesting that PPIs may lead to AF, the meager number of members with a redeemed prescription for a

comparison drug limit its ability to declare with more certainty that the observed association between PPIs and AF are likely independent of GERD.

The strengths of this study include a large sample size, the use of incidence density sampling, and a sensitivity analysis with an appropriate comparator drug. The limitations of this study include not matching cases and controls based on age, a lack of clinical values such as BMI or laboratory tests, and the inability to account for the extent of non-prescription usage.

TABLE 1 PATIENT CHARACTERISTICS		
Characteristics	Entire Study Sample	
	Frequency	% of Total
Age		
0-49	16,017	39.56
50-59	7,890	19.49
60-69	6,502	16.06
70-79	5,288	13.06
≥80	4,787	11.82
Gender		
Male	22,122	54.64
Female	18,361	45.35
Race		
White	31,902	79.44
Black	1,887	4.70
Hispanic	2,274	5.66
Other	4,095	10.20
Overweight/Obese	415	1.03
Congestive Heart Failure	1,653	4.08
Myocardial Infarction	418	1.03
Diabetes Mellitus	2929	7.23
Hypertension	7334	18.12
Valvular Disease	1787	4.41
Hyperthyroidism	122	0.30
Chronic Kidney Disease	565	1.40
Alcoholism	118	0.29
Receiving NSAID therapy	1082	2.67
Receiving diuretic therapy	3,846	9.50

TABLE 2	**BIVARIATE ANALYSIS**		
Characteristics	Cases n=20,265 (%)	Controls n=20,219 (%)	P value
Age			<0.001
0-49	1,874 (9.2%)	14,143 (70%)	
50-59	4,046 (20%)	3,844 (19%)	
60-69	4,979 (24.6%)	1,523 (7.5%)	
70-79	4,828 (23.8%)	460 (2.3%)	
≥80	4,538 (22.4%)	249 (1.2%)	
Gender			<0.001
Male	12,371 (61%)	9,751 (48.2%)	
Female	7,894 (39%)	10,467 (51.8%)	
Race			<0.001
White	16,967 (83.7%)	14,935 (73.9%)	
Black	842 (4.2%)	1,045 (5.2%)	
Hispanic	571 (2.8%)	1,703 (8.4%)	
Other	1,742 (8.5%)	2,353 (11.6%)	
Overweight/Obese	341 (1.7%)	74 (0.4%)	<0.001
Congestive Heart Failure	1,634 (8.1%)	19 (0.09%)	<0.001
Myocardial Infarction	409 (2%)	9 (0.04%)	<0.001
Diabetes Mellitus	2,623 (12.9%)	306 (1.5%)	<0.001
Hypertension	6,691 (33%)	643 (3.2%)	<0.001
Valvular Disease	1,753 (8.7%)	34 (0.17%)	<0.001
Hyperthyroidism	108 (0.5%)	14 (0.07%)	<0.001
Chronic Kidney Disease	535 (2.6%)	30 (0.2%)	<0.001
Alcoholism	94 (0.5%)	24 (0.1%)	<0.001
Receiving NSAID therapy	707 (3.5%)	375 (1.9%)	<0.001
Receiving diuretic therapy	3205 (15.8%)	641 (3.2%)	<0.001

TABLE 3	**MULTIVARIABLE ANALYSIS**	
	Unadjusted OR [95% CI] *p-value*	Adjusted* OR [95% CI] *p-value*
PPI	3.53 [3.12 – 3.99] *p<0.001*	1.98 [1.63 – 2.41] *p<0.001*

*Adjusted for gender, age group, and diuretic use

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Biographical Sketch

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