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# Proton Pump Inhibitor Use Is Not Associated With Cardiac Arrhythmia in Critically Ill Patients

**Kenneth P. Chen, MD[1], Joon Lee, PhD[2,3], Roger G. Mark, MD, PhD[3], Mengling Feng, PhD[3], Leo A. Celi, MD, MPH, MS[1,3], Brian E. Malley[4], and John Danziger, MD, MPhil[1]**

## Abstract

Hypomagnesemia can lead to cardiac arrythmias. Recently, observational data have linked chronic proton pump inhibitor (PPI) exposure to hypomagnesemia. Whether PPI exposure increases the risk for arrhythmias has not been well studied. Using a large, single-center inception cohort of critically ill patients, we examined whether PPI exposure was associated with admission electrocardiogram readings of a cardiac arrhythmia in more than 8000 patients. There were 25.4% PPI users, whereas 6% were taking a histamine 2 antagonist. In all, 14.0% had a cardiac arrhythmia. PPI use was associated with an unadjusted risk of arrhythmia of 1.15 (95% CI,1.00–1.32; $P = .04$) and an adjusted risk of arrhythmia of 0.91 (95% CI, 0.77–1.06; $P = .22$). Among diuretic users (n = 2476), PPI use was similarly not associated with an increased risk of cardiac arrhythmia. In summary, in a large cohort of critically ill patients, PPI exposure is not associated with an increased risk of cardiac arrhythmia.

## Keywords

arrhythmia, proton pump inhibitor, hypomagnesemia

Proton pump inhibitors (PPIs), used widely by prescription and over the counter, have recently been linked to hypomagnesemia,[1–9] although not consistently.[10–12] Risk factors for PPI-associated hypomagnesemia include long-term PPI use and diuretic exposure.[13,14] PPI may prevent the absorption of magnesium across the intestinal surface, leading to chronic magnesium deficiency.[15]

Whereas many observational studies have found significant associations between chronic PPI use and hypomagnesemia, there remain no conclusive data. Residual confounding because of decreased dietary magnesium intake remains in these studies. In addition, because magnesium is an intracellular ion, serum concentrations likely do not reflect magnesium homeostasis. Therefore, determining whether PPI use is associated with a known complication of magnesium depletion might clarify the relationship between PPI use and magnesium balance.

One of the most common adverse consequences of magnesium deficiency is cardiac arrhythmias. Low magnesium affects the modulation of the voltage-dependent L-type $Ca^{2+}$ channels and decreases the membrane-stabilizing action of $Mg^{2+}$.[16] A small study has found that PPI use is associated with an increased risk of arrhythmias (including ventricular fibrillation, ventricular tachycardia, nonsustained ventricular tachycardia, atrial fibrillation, and atrial tachycardia),[17] but has not been studied more comprehensively.

Using a large cohort of critically ill patients, we determined whether premorbid use of PPI was associated with the risk of arrhythmia. To account for confounding by indication, we also evaluated for a potential association between histamine 2 antagonist (H2RA) and arrhythmias. In addition, because concomitant diuretic use is considered a risk factor for PPI-associated hypomagnesemia, we evaluated whether diuretic exposure modified the association of PPI and arrhythmias.

## Methods

### Study Population

We used the Multiparameter Intelligent Monitoring in Intensive Care (MIMIC-II) research database, a joint

[1]Department of Medicine, Beth Israel Deaconess Medical Center, Boston, MA, USA
[2]School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario, Canada
[3]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA, USA
[4]Oakland University William Beaumont School of Medicine, Rochester, MI, USA

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**Corresponding Author:**
Kenneth P. Chen, 185 Pilgrim Road, Farr 8, Boston, MA 02215.
Email: kenneth.py.chen@gmail.com

venture of the Laboratory for Computational Physiology at Massachusetts Instituteof Technology (MIT) and the Department ofMedicine at the Beth Israel Deaconess Medical Center (BIDMC),[18] a large, urban academic medical center. The database contains data of high temporal resolution obtained from clinical computing systems, including lab results, electronic documentation, and bedside monitor trends and waveforms, for all patients admitted to the BIDMC intensive care units (ICUs) between 2001 and 2008. Use of the MIMIC II database has been approved by the institutional review boards of Beth Israel Deaconess Medical Center and MIT.

Of the 23,455 unique first-ICU admissions retrieved from the adult patients in the MIMIC-II database, 17,900 had an identifiable medication section of the discharge summary, indicating their premorbid medication exposure. Of these, 8567 did not have a documented electrocardiogram (ECG) rhythm, 267 had a paced rhythm, and 609 lacked clinical data and were further excluded (Figure 1). Eight thousand four hundred fifty-seven patients remained for analysis.

### Primary Exposure

PPI or H2RA exposure was defined as any PPI or H2RA listed as a preadmission medication. We evaluated medications on admission using Natural Language Processing (NLP) of discharge summaries. We used an NLP algorithm that searched for a discrete home medication section in the discharge summary and then

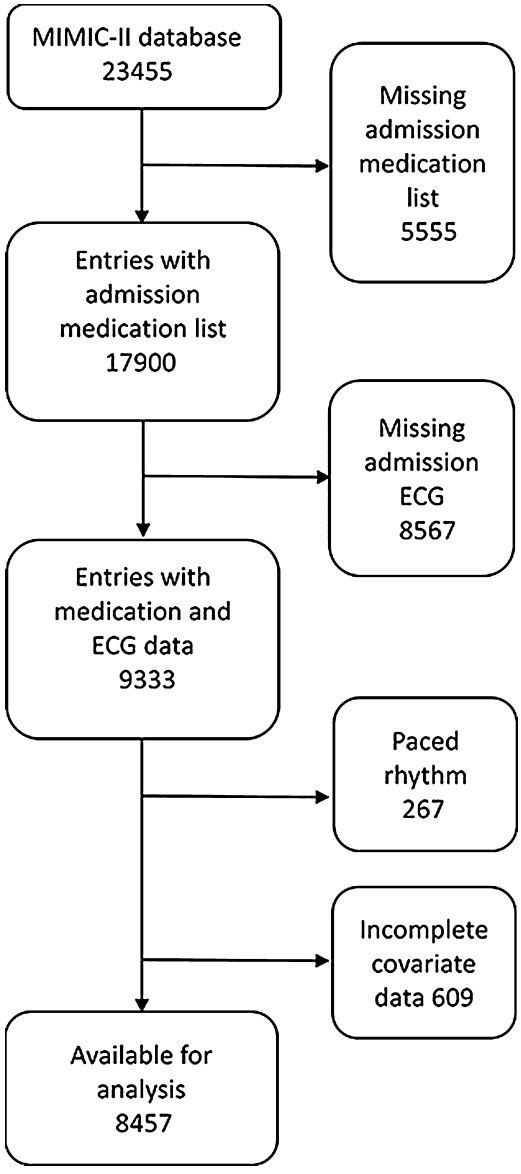


**Figure 1.** Selection of study population.

processed the medications to find individual entries of PPI, H2RA, diuretics, beta-blockers, and nondihydropyridine calcium channel blockers as described and previously validated.[13]

## Outcome

Electrocardiograms entered within 12 hours of a patient's admission to the ICU were used to document the presence of an arrhythmia. NLP was developed to read the automatic ECG rhythm interpretation and, on refinement, was manually tested by review of 200 randomly selected ECGs. From this sample, 98% of ECGs were interpreted accurately by the NLP code.

Any arrhythmia was considered the primary end point, but we also stratified by atrial and ventricular origin. Arrhythmias included 1 of the following rhythms: atrial bradycardia, atrial fibrillation, atrial flutter, premature atrial contraction, atrial rhythm, atrial tachycardia, atrial-ventricular dissociation, junctional rhythm, supraventricular bradycardia, ventricular rhythm, or ventricular tachycardia. Atrial arrhythmias included atrial bradycardia, atrial fibrillation, atrial flutter, premature atrial contraction, atrial rhythm, and atrial tachycardia. Ventricular arrhythmias included rhythms of ventricular rhythm and ventricular tachycardia.

## Statistical Analysis

Patients were separated into those with PPI exposure, those with H2RAexposure, and those with neither PPI nor H2RA exposure (Table 1). There were 47 patients on both PPI and H2RA, and they were included in the group of PPI exposure. To assess whether PPI exposure was related to arrhythmias, we developed sequential multivariable logistic regression models. PPI, H2RA, beta-blockers, and nondihydropyridine calcium channel blockers exposure were included as binary variables. Binary indicator variables were also created for all Elixhauser comorbidities (except for arrhythmia), ICU types, and ethnicity. Age and Simplified Acute Physiologic Score (SAPS) were included as continuous variables. Multivariable logistic regression was done separately for arrhythmia, atrial arrhythmia, and ventricular arrhythmia and adjusted for age, sex, race, ICU type, comorbidities, SAPS, and exposure to antiarrhythmic medications (beta- blockers and nondihydropyridine calcium channel blockers). To determine whether the association of PPI exposure and outcome was modified by premorbid diuretic exposure,

**Table 1.** Baseline Characteristics of Study Population Stratified by Acid Suppression Medication Exposure

| | Group | | | |
|---|---|---|---|---|
| Characteristics | Proton pump inhibitors (n = 2152)[a] | Histamine 2 receptor antagonists (n = 504) | None (n = 5801) | *P* value[*] |
| Age (mean ± Std) | 68.6 ± 14.5 | 68.7 ± 14.5 | 64.5 ± 16.9 | < .001[**] |
| Male | 54.7% | 57.9% | 58.8% | .005[**] |
| SAPS | 14.3 ± 5.3 | 14.0 ± 5.3 | 13.8 ± 5.5 | < .001[**] |
| Race | | | | |
| White | 71.8% | 68.3% | 68.9% | .034[**] |
| Black | 7.8% | 7.9% | 6.9% | .29 |
| Hispanic | 2.3% | 2.4% | 2.5% | .88 |
| Asian | 1.8% | 2.8% | 2.0% | .38 |
| Other | 1.9% | 1.6% | 2.9% | .016[**] |
| Comorbidities | | | | |
| Congestive heart failure | 26.2% | 22.4% | 17.4% | < .001[**] |
| Renal disease | 7.3% | 6.9% | 4.1% | < .001[**] |
| Hypertension | 33.8% | 33.5% | 33.4% | .93 |
| Diabetes mellitus | 35.6% | 35.3% | 27.8% | < .001[**] |
| ICU type | | | | |
| MICU | 44.4% | 36.3% | 32.1% | < .001[**] |
| CCU | 17.0% | 22.4% | 21.7% | < .001[**] |
| Cardiothoracic ICU | 22.6% | 26.4% | 28.4% | < .001[**] |
| SICU | 16.0% | 14.9% | 17.8% | .068 |
| Antiarrhythmia medication exposure | | | | |
| Beta-blocker | 54.1% | 49.4% | 39.7% | < .001[**] |
| Nondihydropyridine calcium channel blocker | 9.5% | 11.1% | 6.2% | < .001[**] |

Abbreviations: SAPS, Simplified Acute Physiologic Scor; MICU, medical intensive care unit; CCU, coronary care unit; SICU, surgical intensive care unit.
[*] *P* values reflect across-group differences.
[**] *P* values that are smaller than .05.
[a] Patients with both proton pump inhibitor use and histamine 2 receptor antagonist use (n = 47) are included in the proton pump inhibitor group.

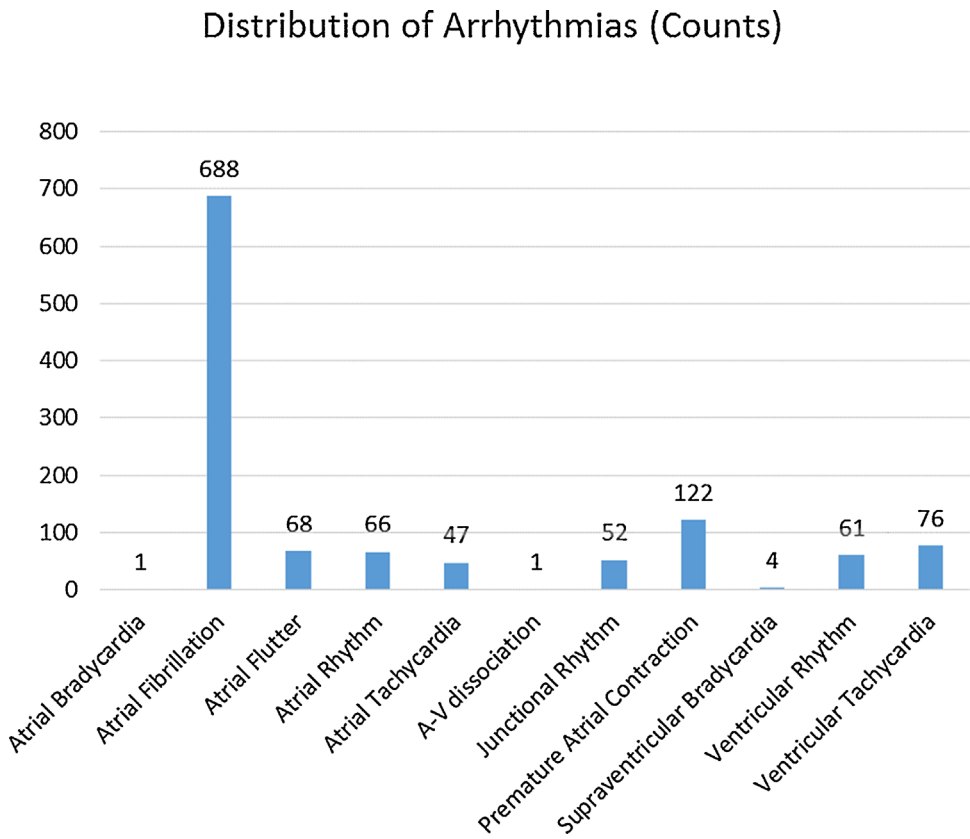


**Figure 2.** Types of cardiac arrhythmias.

we created an interaction term between premorbid diuretic exposure and PPI exposure and present the stratified results. Statistical analyses were done by JMP statistical software (Version 11 Pro). The statistical significance level was set at $P < .05$.

## Results

As seen in Table 1, PPI users tended to be older, with more comorbidities, and a higher level of illness acuity than non-PPI users. Of admission ECGs, 14.0% (n = 1186) had a nonsinus source of cardiac origin (Figure 2). Of these, 83.6% (n = 992) were atrial in origin, and11.6% (n = 137) were ventricular. The remaining 4.8% (n = 57) included atrial-ventricular dissociation, junctional rhythm, and supraventricular bradycardia (Figure 2).

Although PPI use was associated with an increased unadjusted risk of arrhythmia (OR, 1.15; 95% CI, 1.00–1.32; $P = .04$), adjustment for comorbidities and illness severity reduced this to nonsignificance (OR, 0.91; 95% CI, 0.77–1.06; $P = .22$). Similarly, PPI use was not associated with an increased risk of either atrial or ventricular arrhythmias. H2RA exposure was not associated with cardiac arrhythmias (Table 2).

Among the 2476 patients concurrently taking a PPI and a diuretic, PPI exposure was not a significant predictor of cardiac arrhythmia on admission to the ICU (Table 3).

A multiplicative interaction term between PPI and diuretics exposure in multivariable regression was not significant ($P = .91$). Multiplicative interaction terms between PPI and either beta-blockers or calcium channel blockers were not significant either ($P = .89$ and $P = .96$, respectively).

**Table 2.** Multivariable Analysis* of the Odds of Cardiac Arrhythmia on Admission ECG in Patients Who Received PPI or H2 Blocker

| | Odds ratio** | 95% CI | *P* value |
|---|---|---|---|
| Arrhythmia | | | |
| PPI | 0.91 | 0.77–1.06 | .22 |
| H2 blocker | 0.82 | 0.62–1.09 | .17 |
| Atrial arrhythmia | | | |
| PPI | 0.85 | 0.72–1.01 | .07 |
| H2 blocker | 0.88 | 0.66–1.18 | .40 |
| Ventricular arrhythmia | | | |
| PPI | 0.83 | 0.54–1.27 | .39 |
| H2 blocker | 0.74 | 0.34–1.61 | .45 |

*Adjusted for age, sex, race, ICU type, comorbidities, SAPS, and exposure to antiarrhythmic medications (beta-blockers and nondihydropyridine calcium channel blockers).

**Reference group is patients who received neither PPI nor H2 blocker.

**Table 3.** Multivariable Analysis* for the Odds of Cardiac Arrhythmia on Admission ECG in Patients Who Received PPI or H2 Blocker, Stratified by Diuretics Exposure

| | | Odds ratio** | 95% CI | P value |
|---|---|---|---|---|
| Diuretics(n = 2476) | Arrhythmia | | | |
| | PPI | 0.93 | 0.72–1.18 | .55 |
| | H2 blocker | 0.93 | 0.60–1.43 | .76 |
| | Atrial arrhythmia | | | |
| | PPI | 0.86 | 0.66–1.12 | .28 |
| | H2 blocker | 1.04 | 0.65–1.63 | .86 |
| | Ventricular arrhythmia | | | |
| | PPI | 1.00 | 0.52–1.93 | 1.00 |
| | H2 blocker | 0.30 | 0.04–2.27 | .25 |
| No diuretics(n = 5981) | Arrhythmia | | | |
| | PPI | 0.87 | 0.00–1.07 | .20 |
| | H2 blocker | 0.76 | 0.52–1.09 | .14 |
| | Atrial arrhythmia | | | |
| | PPI | 0.83 | 0.65–1.04 | .11 |
| | H2 blocker | 0.79 | 0.53–1.17 | .23 |
| | Ventricular arrhythmia | | | |
| | PPI | 0.72 | 0.41–1.28 | .26 |
| | H2 blocker | 0.98 | 0.41–2.32 | .96 |

*Adjusted for age, sex, race, ICU type, comorbidities, SAPS, and exposure to antiarrhythmic medications (beta-blockers and nondihydropyridine calcium channel blockers).
**Reference group is patients who received neither PPI nor H2 blocker.

## Discussion

Because PPI exposure is potentially thought to decrease magnesium intestinal intake,[19] thereby leading to magnesium deficiency, and because magnesium deficiency is associated with the risk of arrhythmias, we hypothesized that PPI use would increase the risk of arrhythmias. However, in our large, single-center study of a cohort of critically ill patients, PPI use prior to hospital admission was not associated with the risk of arrhythmias. The results of our study differ from those of a smaller previously published study.[17]

Magnesium has well-described antiarrhythmic effects and is widely used for the prevention and treatment of cardiac arrhythmias. The electrophysiological effects of $Mg^{2+}$ include decreasing the automaticity of cardiomyocytes,[20] increasing atrial and atrioventricular (AV) nodal conduction time,[21] increasing atrial and AV nodal refractory periods,[21,22] blocking conduction via acc essory pathways,[23,24] decreasing early/delayed afterdepolarizations,[25,26] and prolonging His-ventricular conduction.[27] Hypomagnesemia is therefore an important arrhythmogenic factor.

The results of our negative study raise additional questions about the relationship between PPI use and magnesium homeostasis. Because magnesium is primarily intracellular, decreased magnesium intake, as might occur with prolonged PPI exposure, would hypothetically decrease intracellular magnesium stores. Assessing intracellular magnesium is not availably clinically, but case reports of intravenous magnesium loading, the gold standard in assessing magnesium balance, have suggested magnesium deficiency with prolonged PPI therapy,[1] which should make individuals more susceptible to arrhythmia development. Therefore, the negative results of our study should be interpreted with caution. It is possible that PPI therapy still causes intracellular magnesium depletion, yet such depletion is not arrhythmogenic. Additional studies evaluating other potential sequelae of intracellular magnesium depletion, such as lactic acidosis,[28] are necessary. In addition, it is also possible that PPI therapy causes hypomagnesemia without affecting intracellular stores. We did not examine magnesium concentrations in this analysis because arrhythmia is a strong determinant of renal function, thereby affecting serum concentrations. In a previous analysis of this same patient population, we showed PPI-associated hypomagnesemia.[13] Ultimately, our negative study suggests that better-designed studies evaluating a potential effect of PPI therapy on magnesium homeostasis are needed, particularly given the potential consequence of magnesium depletion and the prevalence of this class of medicine.

Interestingly, in our study, we found a nonsignificant trend toward protection from arrhythmias with acid suppressive therapies, as suggested previously by some studies.[29,30] PPIs have antioxidative[31] and anti-inflammatory[32] effects and potentially could decrease the damage and remodeling of cardiomyocytes from various causes, therefore decreasing the risk of developing arrhythmia. This remains speculative, however.

The limitations of this study include its retrospective and observational design. However, it is unlikely that arrhythmias would influence the decision to prescribe a PPI medication, and we accessed premorbid PPI use to separate exposure and outcome. The QTc interval information was not available by the NLP code interpretation of electrocardiograms. We were not able to include QTc interval analysis in multivariate analysis or stratification schema, and a difference of this parameter cannot be excluded. However, there is no reason to suspect a difference in baseline QTc interval between the groups based on the other criteria used in the analysis. In addition, because PPI and H2B can be obtained without a prescription, bias from unrecognized exposure is likely, and the length of premorbid medication use was not available.

## Conclusion

In summary, PPI exposure is not associated with an increased risk of arrhythmias in critically ill patients.

### Declaration of Conflicting Interests

The contributing authors declare no conflict of interest.

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