

**UNIVERSITY OF KENTUCKY MARTIN SCHOOL OF PUBLIC POLICY  
AND ADMINISTRATION.**

The Incidence of Hip Fracture Associated with Proton Pump Inhibitor (PPI) and/or H<sub>2</sub> Receptor Antagonist (H<sub>2</sub>RA) Use in the Kentucky Medicaid Population.



Source: [www.fda.gov](http://www.fda.gov)

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**Objective:**

Proton pump inhibitors (PPIs) and histamine H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) rank in the top 5% of Kentucky Medicaid drug expenditures. These two classes of drugs are used to treat duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), active benign ulcer, and erosive esophagitis. They can also be used to treat heartburn, acid indigestion, and sour stomach. The FDA approved labeling for these medications recommend use for no longer than 8 weeks; however, a review of the literature shows that many patients take these classes of medications for much longer periods of time. There are also increasing concerns about the adverse effects (e.g., hip fractures) associated with these medications, especially the PPIs. An article featured in the Wall Street Journal (WSJ) on May 11<sup>th</sup> 2010 reported that more than 119 million prescriptions were written for PPIs in the U.S. in 2009 and some doctors believe these medications are over-prescribed for less severe ailments like indigestion or upset stomach.

The fact is that nearly everyone has seen commercials about heartburn and most people have experience with this condition. These agents are being consumed in large amounts and those who use them are probably unaware of the potential risk they are taking. Consumers have been led to believe for nearly two decades that these are 'benign' drugs although several studies have shown these medications are linked to infections, drug interactions, fracture and unnecessary drug expenditure. The Kentucky Medicaid spending is rising at twice the rate of the budget, hence a protocol (for example regarding length of therapy, or which patients are appropriate candidates for therapy) may help reduce expenditures for these medications and thus reduce the budget gap. The objective of this study is to determine the incidence of hip fracture associated with proton pump inhibitor (PPI) and/or H<sub>2</sub> receptor antagonist use in the Kentucky Medicaid population and to determine the total expenditures associated with treating these hip fractures.

**Background:**

The advent of medications such as proton pump inhibitors (PPI) and H<sub>2</sub> receptor antagonists (H<sub>2</sub>RA) have changed and revolutionized the management of acid-related diseases such as gastroesophageal reflux disease (GERD). There has been a great deal of interest in acid-suppressing medications because they are among the most commonly prescribed medications<sup>1</sup> in the United States. In fact global pharmaceutical sales for acid-suppressing therapies exceeded \$24 billion dollars in 2006.<sup>1</sup>

These agents carry an FDA labeled indication for short-term (4-8 weeks) therapy of duodenal ulcer, gastric ulcer, gastroesophageal reflux disease (GERD), active benign ulcer, and erosive esophagitis. In treatment of heartburn, acid indigestion, and sour stomach, the labeled indication is for 14 days of therapy, then repeat treatment after 4 months if needed<sup>2</sup>. Since most patients take these medications for periods greater than their indication<sup>21</sup>, there have been several reports about adverse effects associated with chronic use, one of them being hip fractures. Hip fractures are a major cause of morbidity and mortality; more than 329,000 persons are hospitalized annually with hip fractures in the United States and the mortality rate is 5-10% after one month and about 30% after one year<sup>3</sup>. The incidence and the economic consequences of hip fracture are substantial. Hence, the Kentucky Medicaid program may be able to institute some policies to control the use of these agents.

The table below shows the total drug expenditure of Kentucky Medicaid for PPIs and H2RAs and the cost associated with medical procedures for hip surgery from 2004 to 2009 (included in the drug costs are individuals' out-of-pocket payments and Medicaid costs; included in the hip surgery costs are individuals' out-of-pocket costs, Passport costs, Medicare and Medicaid costs)<sup>4</sup>. In other words, Kentucky Medicaid spends considerable tax dollars on the use of PPIs and H2RAs, hence if there is a causal effect between these medications and hip fracture, Medicaid should be encouraged to adopt a policy to ensure they are used appropriately thereby limiting Medicaid recipients' risk for these potentially costly adverse effects.

Table 1: Drug expenditure of Kentucky Medicaid for PPIs and H2RAs and medical procedures costs for hip fracture (2004-2009)

Year	Total Spent (PPIs) [\$]	Total Spent (H2RAs) [\$]	Hip Fracture cost [\$]
2004	23,219,922	10,964,607	1,004,198
2005	22,405,920	6,638,345	956,855
2006	12,601,746	3,449,352	981,494
2007	13,804,347	3,059,668	1,015,387
2008	18,253,050	2,600,807	936,601
2009	28,620,537	2,027,572	886,589

H<sub>2</sub> receptor antagonists (H2RA) and PPIs effectively raise gastric pH. PPIs suppress acid secretion by gastric parietal cells which results in the inhibition of acid secretion from all physiologic stimuli.<sup>5</sup> H<sub>2</sub> receptor antagonists inhibit histamine stimulated acid secretion. H<sub>2</sub> receptors may be upregulated by H<sub>2</sub> receptor antagonist, which can result in tolerance over time.<sup>6</sup> Tolerance has not been shown with PPIs.<sup>5</sup> Several recent studies in human volunteers have suggested that short-term use of acid suppressing medications can decrease calcium absorption<sup>7-9</sup>, which may lead to calcium deficiency. Since calcium absorption is reduced in individuals taking acid suppression medications, the question arises about the long-term “maintenance” use of these therapies and the risk of bone fractures or osteoporosis. Decreased calcium absorption has been linked to increased risk of fracture, especially among older women with low calcium intake<sup>10,11</sup>.

Some H<sub>2</sub> receptor antagonists (H2RA) and PPIs can be found over-the-counter (OTC) and hence are easily accessible. As more patients self-medicate without consulting their physician and pharmacist, it further worsens the problems associated with the adverse effects and costs associated with these drugs.

In May 2010, the U.S Food and Drug Administration issued a warning about the use of PPIs and increased risk of bone fractures. The greatest risk for these fractures (hip, wrist and spine) were in patients who received high doses or used them for greater than 1 year. The majority of the patients in the epidemiologic studies were greater than 50 years of age with the risk of fractures being limited to this age group. To date, no randomized clinical trials of acid suppressing therapies have found an increased risk of hip, wrist or spine fractures.

#### **Literature review:**

A summary of the epidemiological studies that have evaluated fracture risk with PPIs and H2RAs use is presented in Table 2 below.

A retrospective case control study by Corley et al.<sup>12</sup> revealed that patients with hip fractures were more likely than controls to have previously received a greater than 2-year supply of PPIs or H2RA, odds ratio (OR) = 1.30 (95% CI, 1.21-1.39). Corley and colleagues concluded that use of drugs that inhibit gastric acid is associated with an increased risk of hip fracture; however, the association was only found among persons with at least one other risk factor for hip fracture. This study did not consider alcohol use, diet, physical activity, body mass index, smoking histories of the patients hence there is a possibility

of bias. In addition, some members who took over-the-counter PPIs and H2RAs may be classified as “unexposed” hence decreasing the strength of the association.

Another study by Yang et al.<sup>13</sup> concluded that there is an increased risk of hip fracture for PPI use greater than 1 year; adjusted odds ratio (aOR) = 1.44 (95% CI, 1.30–1.59). The risk of hip fracture increased with a high dose (>1.75 doses/day); aOR = 2.65 (95% CI, 1.80-3.90). The risk of hip fracture also increased with longer duration of PPI use: 1 year, aOR = 1.22 (95% CI, 1.15-1.30) and 4 year, aOR = 1.59 (95% CI, 1.39-1.80). Some of the limitations in this study were incomplete information about the BMI of 33% of the patients, inability to determine prior PPI use of patients enrolled in the database; hence there could have been an underestimation of the duration of exposure. There was no information on OTC calcium supplement use.

Vestergaard et al.<sup>14</sup> reported that use of PPIs was associated with an increased risk of fracture within the last year (OR = 1.18, 95% CI, 1.12-1.43) but no dose-response or duration-response relationships were present. H2RAs were associated with a decreased fracture risk if they had been used within the last year (OR = 0.88, 95% CI 0.82-0.95). During the study period, PPIs were available only on prescription and H2RAs were available as OTC. Hence this introduces a bias because the database does not contain information on drugs sold OTC. This may have underestimated the risk associated with these drugs.

Targownik et al.<sup>15</sup> used a Canadian administrative claim database to determine if the use of PPIs has any association with an increased risk of hip fracture. They also explored if there is a relationship between duration of exposure to PPIs and osteoporosis-related fractures. They concluded that an exposure of 7 or more years was associated with increased risk of an osteoporosis-related fracture (adjusted OR 1.92, 95% CI, 1.16-3.16, p= 0.011). There was also an increased risk of hip fracture after 5 or more years of exposure (adjusted OR 1.62, 95% CI 1.02-2.58, p= 0.04). The study has some limitations such as lack of information about OTC calcium supplements, vitamin D supplements, tobacco and alcohol use.

Kaye et al.<sup>16</sup> estimated the relative risk of hip fracture associated with proton pump inhibitor (PPI) use in a population without major risk factors. This study was a 2-phase study. In phase 1, 4414 case patients (aged 50-79 yrs) with an incident hip fracture and at least 2 years of recorded history in the database were analyzed. Phase 2 (a sub population of phase 1) included 1098 case patients

identified as having no major medical risks for hip fracture. The results indicated that the relative risk (RR) for hip fracture among patients who received any PPI prescription was 0.9 (95% CI, 0.7–1.11) compared with those with no PPI prescription. In other words, they found no evidence of an increased risk of hip fracture with PPI use. One caveat for their research was that patients at risk for fracture were excluded from the analysis.

Yu et al.<sup>17</sup> used dual-energy X-ray absorptiometry and assessed baseline use of proton pump inhibitors (PPIs) and/or H2 receptor antagonists (H2RAs) in 5,755 men and 5,339 women. Medication use and bone mineral density (BMD) were assessed, and hip and other nonspine fractures were documented. On multivariate analysis, men using either PPIs or H2RAs had lower cross-sectional bone mass. No significant BMD differences were observed among women. However, there was an increased risk of nonspine fracture among women using PPIs (relative hazard [RH] = 1.34, 95% confidence interval [CI] 1.10-1.64). PPI use was also associated with an increased risk of nonspine fracture in men but only among those who were not taking calcium supplements (RH = 1.49, 95% CI 1.04-2.14). H2RA use was not associated with nonspine fractures, and neither H2RA use nor PPI use was associated with incident hip fractures in men or women. The use of PPIs in older women, and perhaps older men with low calcium intake, may be associated with a modestly increased risk of nonspine fracture.

Some of these studies have identified a possible correlation between acid suppressing therapies and bone fracture. A major shortcoming is the possibility of residual confounders unidentified by the administrative databases used to analyze this relationship. Some confounders are inability to track OTC use of these medications, and the fact that some of these databases do not report tobacco and alcohol use in the patients. These introduce a bias and decrease the validity and reliability of these studies. Another issue is that these studies are retrospective in nature and there are no randomized clinical studies that have been done to establish the relationship between the incidence of fracture and acid suppressive therapy use.

### **Methodology:**

This is a retrospective case-control study of pharmacy and medical claims from the Kentucky Medicaid database of patients on acid suppressing therapy with an incident diagnosis of hip fracture (ICD-9-CM) codes 820.0 to 821.20 (hip or femur fractures) between January 1, 2000 and December 31, 2009. The index date is the fracture date. Enrollment in Medicaid has to be continuous at least 18

months prior to the index date. For each case, matched controls were randomly selected from the Kentucky Medicaid Database. Controls were chosen from among eligible adult members who lacked a diagnosis of a hip fracture at the index date of the matched case. The controls also had 18 months of continuous membership before the index date. Pharmacy data were identified using the National Drug Code (NDC). Included in the pharmacy data were the drug dispensed, date the drug was dispensed, the frequency of refills, directions for use and amount paid. Medical claims were identified by using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes. Included in the medical claims data were date of service, and amount paid. In addition, data were available for age, gender, and plan enrollment time for each patient.

For comparisons of proportions, chi-square statistics were used. A conditional logistic regression model was used to estimate the relative magnitude in relation to the use of PPIs and H2RAs. The primary exposure for the analysis is acid suppressing therapy of more than one year before the index date. The one year duration was used because alterations in fracture risk due to the use of other medications, such as bisphosphonates, thiazide diuretics, and corticosteroids were apparent after 1 year of exposure.<sup>18,19</sup> Medication adherences for potential confounders will be measured by medication possession ratio (MPR). MPR of at least 80% is required for inclusion. Through retrospective drug claims analysis, MPR looks at medication refill history over a period of time and calculates how many doses of medication a patient obtained during the study period compared to how many doses should have been obtained.<sup>20</sup>

The primary outcome of the study is to determine if there is an association between acid inhibition and hip fractures. I also evaluated whether fracture risk is generally associated with other commonly used medications, which may suggest confounding. The study will utilize standard analytic techniques for evaluating case-control studies and conditional logistic regression. All definitions and modeling strategies were planned a priori. All statistical analyses were performed at a significance level of 0.05 in SAS statistical package version 9.2 SAS Institute Inc., Cary, North Carolina).

$MPR^{20} = \frac{\text{Sum of days supply of drugs}}{[\# \text{ of days between first and last fill plus days' supply of last fill}]}$

Table 2: Epidemiological Studies Evaluating Fracture Risk with Proton Pump Inhibitors (PPIs)

Study	Study time period	Study population	Finding related to PPIs
➤ Vestergaard 2006	1/1/2000 – 12/31/2000	<ul style="list-style-type: none"> <li>• 124,655 cases with fractures</li> <li>• 373,962 matched controls</li> <li>• All ages Data source: Denmark health database</li> </ul>	<p>PPI use within the last year</p> <ul style="list-style-type: none"> <li>• Overall fracture risk, Odds Ratio (OR) = 1.18 (95% CI, 1.12–1.43)</li> <li>• Risk of hip fracture, OR = 1.45 (95% CI, 1.28–1.65)</li> <li>• Risk of spine fracture, OR = 1.60 (95% CI, 1.25–2.04)</li> <li>• Risk of forearm fracture, OR = 0.95 (0.82-1.11)</li> <li>• No dose-response relationship seen with PPIs and fracture risk: <i>(DDD [defined daily doses] were the number of doses in a year)</i></li> </ul>
➤ Yang 2006	1987 - 2003	<ul style="list-style-type: none"> <li>• 13,556 cases with fractures</li> <li>• 135,386 matched controls</li> <li>• Ages ≥ 50 years</li> <li>• Data source: U.K./GPRD</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of hip fracture, PPI use &gt; 1 year adjusted Odds Ratio (aOR)<sub>±</sub> = 1.44 (95% CI, 1.30–1.59)</li> <li>• Risk of hip fracture increased with high-dose PPI use &gt; 1 year: <i>(dose defined as dose/day, &gt;1.75 doses/day)</i> aOR = 2.65 (95% CI, 1.80-3.90)</li> <li>• Risk of hip fracture increased with longer duration of PPI use <ul style="list-style-type: none"> <li>○ 1 yr, aOR = 1.22 (95% CI, 1.15-1.30)</li> <li>○ 4 yr, aOR = 1.59 (95% CI, 1.39-1.80)</li> </ul> </li> </ul>
➤ Targownik 2008	1996 – 2004	<ul style="list-style-type: none"> <li>• 15,792 cases with fractures</li> <li>• 47,289 matched controls</li> <li>• Ages ≥ 50 years</li> <li>• Data source: PHRDR/ Manitoba, Canada</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of hip, wrist, spine fractures with PPI use ≥ 7 years adjusted Odds Ratio (aOR) ¥ = 1.92 (95% CI, 1.16–3.18)</li> <li>• Risk of hip fracture increased with longer duration of use <ul style="list-style-type: none"> <li>○ PPI use ≥ 5 years, aOR = 1.62 (95% CI, 1.02–2.58)</li> <li>○ PPI use ≥ 6 years, aOR = 2.49 (95% CI, 1.33-4.67)</li> <li>○ PPI use ≥ 7 years, aOR = 4.55 (95% CI, 1.68–12.29)</li> </ul> </li> </ul>

<ul style="list-style-type: none"> <li>➤ Kaye 2008</li> </ul>	<p>1995 - 2005</p>	<ul style="list-style-type: none"> <li>• 1,098 cases with fractures</li> <li>• 10,923 matched controls</li> <li>• Ages 50 – 70 years</li> <li>• Data source: U.K/GPRD</li> </ul>	<ul style="list-style-type: none"> <li>• Estimated Relative Risk (RR) of hip fracture = 0.9 (95% CI, 0.7–1.11) (<i>Patients at risk for fracture were excluded from the analysis</i>)</li> <li>• Risk of hip fracture not detected with increased number of PPI prescriptions</li> </ul>
<ul style="list-style-type: none"> <li>➤ Corley 2010</li> </ul>	<p>1995-2007</p>	<ul style="list-style-type: none"> <li>• 33,752 cases with fractures</li> <li>• 130,471 matched controls</li> <li>• Ages ≥ 18 years</li> <li>• Data source: KPNC/ California, USA</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of fracture with ≥ 2 years of PPI use and 1 other risk factor Odds Ratio (OR) = 1.30 (95% CI, 1.21–1.39) <ul style="list-style-type: none"> <li>○ Risk factors: alcohol abuse, arthritis, diabetes, kidney disease, glucocorticoids, cerebrovascular disease, dementia, epilepsy, gait disorder, hemiplegia, psychoses, smoking, visual impairment, anxiolytic use</li> </ul> </li> <li>• Risk of fracture increased with higher PPI dose: (<i>dose = number of pills per day &gt;1.5</i>) OR = 1.41 (95% CI, 1.21-1.64)</li> <li>• Risk of fracture did not consistently increase with longer duration of use</li> </ul>
<ul style="list-style-type: none"> <li>➤ Yu 2008</li> </ul>	<p>Women: 7.6 years mean follow-up  Men: 5.6 years mean follow-up</p>	<ul style="list-style-type: none"> <li>• Women (4,574 non-PPI users and 234 PPI users)</li> <li>• Men (4,920 non-PPI users and 487 PPI users) Ages ≥ 65 years</li> <li>• Data source:</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of hip fracture <ul style="list-style-type: none"> <li>○ Women: adjusted Relative Hazard (aRH)= 1.16 (95% CI, 0.80-1.67)</li> <li>○ Men: aRH = 0.62 (95% CI, 0.26-1.44)</li> </ul> </li> <li>• Risk of nonspine fracture <ul style="list-style-type: none"> <li>○ Women: aRH = 1.34 (95% CI, 1.10-1.64)</li> <li>○ Men: aRH = 1.21 (95% CI, 0.91-1.62)</li> </ul> </li> </ul>

		MrOS/SOF	
➤ Gray 2010	7.8 years, mean follow-up	<ul style="list-style-type: none"> <li>• 2,831 PPIs users</li> <li>• 127,756 non-PPIs users</li> <li>• Post-menopausal women ages 50 – 79 years</li> <li>• Data source: WHI OS/WHI CT</li> </ul>	<ul style="list-style-type: none"> <li>• Risk of total fractures adjusted Hazard Ratio (aHR) ≠ 1.25 (95% CI, 1.15-1.36)</li> <li>• Risk of hip fracture, aHR = 1.00 (95% CI, 0.71-1.40)</li> <li>• Risk of spine fracture, aHR = 1.47 (95% CI, 1.18-1.82)</li> <li>• Risk of wrist fracture, aHR = 1.26 (95% CI, 1.05-1.51)</li> <li>• No consistent trend for fracture risk with duration of use</li> </ul>

## Results:

Table 3 shows baseline characteristics of the hip fracture cases and controls. There were 500,910 patients without hip fracture and 2,634 patients with hip fracture; hence the baseline characteristics for the two populations were significantly different. The fracture cases more often were females. Fracture cases were prominent in individuals greater than 50 years and also residents of rural area. The comorbidity and use of drugs in general were higher among cases than controls. Hip fracture cases were also significantly more likely to have a medical diagnosis that had known associations with either hip fracture or the risk of falling which is consistent with findings from previous studies.<sup>13, 15</sup>

Table 3: Characteristics of hip fracture cases and controls

Variable	Cases (n = 2,634)	Controls (n = 500,910)	Adjusted OR (95% CI)
<b>Gender</b>			
Male	685 (26.01)	187,836 (37.50)	0.63 (0.58–0.69)
Female	1,949 (73.99)	313,074 (62.50)	Reference
<b>Region</b>			
Urban	1,010 (38.34)	196,196 (39.17)	1.06 (0.98–1.16)
Rural	1,624 (61.66)	304,714 (60.34)	Reference
<b>Age</b>			
≥50	2,157 (81.89)	199,913 (39.91)	3.92 (3.51–4.37)
<50	477 (18.11)	300,997 (60.09)	Reference
<b>Race</b>			
Black	178 (6.76)	55,177 (11.02)	0.72 (0.61–0.84)
White	2,308 (87.62)	416,844 (83.22)	Reference
Other	148 (5.62)	28,889 (5.77)	0.75 (0.63–0.89)
<b>Medication use</b>			
Thiazide	363 (13.78)	48,842 (9.75)	0.79 (0.70–0.89)
Corticosteroid	51 (1.94)	5,192 (1.04)	0.79 (0.59–1.05)
Estrogen	26 (0.99)	6,482 (1.99)	0.53 (0.36–0.78)
Antiparkinsonian	93 (3.53)	8,755 (1.75)	1.11 (0.90–1.37)
Antidepressants	817 (31.02)	150,314 (30.01)	0.64 (0.58–0.70)
NSAIDS	547 (20.77)	163,194 (32.58)	0.71 (0.64–0.79)
Statin	54 (2.05)	10,830 (2.16)	0.83 (0.72–0.97)
Thyroid	243 (9.23)	26,236 (5.24)	0.47 (0.36–0.62)
Bisphosphonates	55 (2.09)	2,161 (0.43)	1.84 (1.40–2.43)
Anticoagulants	207 (7.86)	13,632 (2.72)	1.17 (1.00–1.36)

Calcitonin	90 (3.42)	5,107 (1.02)	1.12 (0.90–1.39)
Sedatives	779 (29.57)	88,367 (17.64)	1.36 (1.24–1.49)
<b>Health Condition</b>			
Arthritis	15 (0.57)	1,256 (0.25)	1.38 (0.82–2.31)
Cerebrovascular disease	453 (17.20)	22,890 (4.57)	1.36 (1.21–1.52)
Hemiplegia	15 (0.57)	1,214 (0.24)	0.81 (0.48–1.36)
Asthma	159 (6.04)	28,197 (5.63)	0.78 (0.66–0.93)
Dementia psychoses	595 (22.59)	66,652 (13.31)	1.53 (1.39–1.69)
Diabetes Mellitus	673 (25.55)	56,174 (11.21)	1.05 (0.95–1.16)
Thyroid disease	156 (5.92)	18,938 (3.78)	1.15 (0.96–1.38)
Ischemic Heart Disease	450 (17.07)	36,585 (7.30)	1.04 (0.93–1.16)
Epilepsy	85 (3.23)	8,017 (1.60)	1.94 (1.55–2.43)
Gait disorder	123 (4.67)	4,871 (0.97)	2.23 (1.84–2.70)
Peptic ulcer disease	38 (1.44)	3,812 (0.76)	0.88 (0.63–1.21)
GERD	176 (6.68)	24,176 (4.83)	0.83 (0.71–0.97)
Visual Impairment	743 (28.21)	120,756 (24.11)	1.07 (0.98–1.17)
Chronic kidney disease	135 (5.13)	6,196 (1.24)	1.73 (1.45–2.08)
<b>Charlson Index</b>			
0	1,014 (38.50)	361,866 (72.24)	Reference
1	1,620 (61.50)	139,044 (27.76)	2.07 (1.87–2.29)

The relationship between use of PPIs, H2RAs and hip fractures is shown in Table 4. An MPR greater than 80% for PPIs and H2RAs use was statistically significantly associated with an increased OR for hip fracture. The multivariable adjusted OR for all potential confounders for hip fracture associated with PPI and H2RA therapies with more than one year use was 2.08 (95% CI, 1.85-2.34; P<.0001) and 3.08 (95% CI, 2.77-3.44; P<.0001) respectively.

Table 4. Association between PPIs and H2RAs Use and Hip Fracture Risk in a Population-Based Case-Control Study

Variable	Cases (n = 2,634)	Controls (n = 500,910)	Adjusted OR (95% CI)
<b>PPI ≥ 80% MPR</b>	420 (15.95)	29,514 (5.89)	2.08 (1.85–2.34)
<b>PPI &lt; 80% MPR</b>	2,214 (84.05)	471,396 (94.11)	Reference
<b>H2RA ≥ 80% MPR</b>	485 (18.41)	24,194 (4.83)	3.08 (2.77–3.44)
<b>H2RA &lt; 80% MPR</b>	2,149 (81.59)	476,716 (95.17)	Reference

**Discussion:**

In this population-based case-control study, I found a significant relationship between use of PPIs and H2RAs and the risk of hip fracture after controlling for potential confounders. This finding is consistent with previous studies.<sup>12, 13, 14, 15</sup> The risk of hip fracture was higher among subjects taking H2RAs compared with PPI. This is counterintuitive because PPIs are more potent acid suppressing therapy in comparison to H2RAs. Overall, the increased risk was confined to persons with certain other risk factors for hip fracture.

There are several mechanisms by which acid suppressing therapies may increase hip fracture risks. The increased risk may be as a result of a decrease in calcium absorption. An acidic environment in the gastrointestinal tract facilitates the release of ionized calcium from insoluble calcium salts<sup>22</sup>.

One of the strengths of this study was the use of a computerized database allowing for a large-scale population-based design and the use of data on exposure and confounders that are collected before the date of fracture. Thus recall bias did not influence data collection.

There are several potential limitations of this study; a number of possible confounding variables, including body mass index, physical activity, smoking, alcohol use, sun exposure and over-the-counter use of calcium/vitamin D supplements, which are associated with fracture were not available in the database. In addition some of the PPIs and H2RAs are over-the-counter (OTC) medications; hence some patients who took these OTC medications may have been classified as controls, which would have expected to decrease the strength of the association.

In summary, results of this study suggest that there is a significant relationship between PPIs and H2RAs use and hip fracture risk. Prospective randomized trial clinical studies are necessary to confirm my findings and an experimental study on the mechanism by which PPIs and H2RAs may increase hip fracture risk is necessary.

**Recommendations:**

A policy on appropriate acid-suppressing therapy use might be mandated by the Kentucky Medicaid program. This policy will essentially reduce cost by eliminating millions of dollars spent on unnecessary drug expenditure, thus closing the budget gap in Kentucky Medicaid program. The policy should be in accordance with the FDA approved labeling of this class of drug. Some policies that may improve appropriate use of these agents are:

1. Prior authorization protocol for patients taking this medication for more than 8 weeks. A requirement for endoscopic diagnosis should be mandated beyond 8 weeks.
2. Moving this drug class behind the counter just like pseudoephedrine containing products but not electronically monitoring these products. This will create an opportunity for patients to have a conversation with the pharmacist about appropriate drug use and most especially non-drug measures they can implement in avoiding heartburn and acid reflux.
3. When prescribing these agents, consider whether a lower dose or shorter duration of therapy would adequately treat the patient's condition.
4. Individuals at risk for osteoporosis should have their bone status managed according to current clinical practice, and should take adequate vitamin D and calcium supplementation.

Lifestyle changes should be advocated in order to reduce symptoms of GERD. These changes could be:

1. Avoid heart-burn triggering food such as orange juice, chocolate, tomato sauce, spicy foods, mint, garlic, and vinegar. These may vary from person to person.
2. Staying upright for a few hours after eating and abstaining from exercise after right after eating
3. Eating smaller meals, reducing caffeine and alcohol intake and avoiding cigarettes.
4. Weight loss and incorporating physical activity.
5. Wear looser-fitted clothes.
6. Bending with your knees instead bending over at the waist.
7. Elevate head of the bed.

## Appendix

Passport is a health care plan that uses federal and state funds, through a Medicaid waiver, to pay for in-home alternatives to nursing home care for low-income, Medicaid eligible seniors.

CPT codes used to determine the cost of hip fracture surgeries are: 27193, 27194, 27200, 27202, 27215, 27216, 27217, 27218, 27220, 27222, 27226, 27227, 27228, 27230, 27232, 27235, 27236, 27238, 27240, 27244, 27245, 27246, 27248, 27250, 27252, 27253, 27254, 27256, 27257, 27258, 27259, 27265, 27266, 27267, 27268, and 27269.

NDC is a unique 10 digit, 3-segment numeric identifier assigned to each medication intended for human use in the United States.

ICD-9-CM is used to code and classify morbidity data from the inpatient and outpatient records, physician offices, and most National Center for Health Statistics (NCHS) surveys.



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