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Oral Bisphosphonates and Upper Gastrointestinal Toxicity: A Study of Cancer and Early Signals of Esophageal Injury

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Summary

We evaluated the association between bisphosphonate use and 1) upper-gastrointestinal cancer, 2) upper endoscopy, 3) incident Barrett's esophagus and 4) prescription antacid initiation among Medicare beneficiaries. We found no bisphosphonate-cancer association and negative bisphosphonate-Barrett's association.

Introduction—Bisphosphonates can irritate the esophagus; a cancer association has been suggested. Widespread bisphosphonates use compels continued investigation of upper-gastrointestinal toxicity.

Methods—Using a 40% Medicare random sample denominator, inpatient, outpatient (2003–2011) and prescription (2006–2011) claims, we studied patients age 68 and older with osteoporosis and/or oral bisphosphonate use. Inverse propensity weighting estimated marginal structural models for the effect of bisphosphonate intensity (pills per month) and cumulative bisphosphonate pills received on upper-gastrointestinal cancer risk. Secondary analyses of sub-cohorts without past bisphosphonates or upper endoscopy assessed bisphosphonate initiation and risk of (1) upper endoscopy (2) incident Barrett's esophagus, and (3) prescription antacid initiation.

Results—The cohort included 1.64 million beneficiaries: 87.9% women, mean age 76.8 (SD 9.3); mean follow up 39.6 months; 38.1% received oral bisphosphonates. Cumulative bisphosphonate receipt, among users, ranged from 4 to 252 pills (5th to 95th percentile). We identified 2,308 upper-gastrointestinal cancers (0.43/1000 person years). We found no association between cumulative bisphosphonates pills and cancer, odds ratio (OR) for each additional pill 1.00 (95% CI 0.99, 1.00). In sub-cohorts, compared to none, lowest cumulative bisphosphonate use (1–

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9 pills) was associated with higher risk of endoscopy (OR 1.11, 95% CI 1.08–1.14) and antacid initiation (OR 1.13, 95% CI 1.10–1.16); higher intensity conferred no increased risk. Higher intensity and higher cumulative bisphosphonate category were associated with lower Barrett's risk.

Conclusions—We found no bisphosphonate-cancer association and negative bisphosphonate-Barrett's association. Bisphosphonate initiation appears to identify patients susceptible to early irritating effects; clinicians might offer alternatives and delay endoscopy or antacids.

Keywords

Bisphosphonates; osteoporosis; osteopenia; Barrett's esophagus; Medicare Part D; Toxicity

Background

Studies to date on the association between oral bisphosphonates and esophageal cancer have drawn conflicting conclusions.[1–12] The divergent literature has been well summarized. [12–14] Case reports and studies have linked esophageal cancer cases to oral bisphosphonate use (especially nitrogen-containing alendronate) after relatively brief exposures.[2, 5, 6, 13] Others have found no such association.[1, 15, 16] A study of National Registers data from Denmark, found bisphosphonates protective against esophageal cancer; the authors reasoned that greater use of endoscopy before initiation of bisphosphonates may explain the apparent protective effect, by essentially pre-screening potential users.[17] In contrast some suggest esophageal irritation by bisphosphonates may prompt endoscopy and result in either earlier stage tumor diagnosis or cancer over-diagnosis, explaining reports of higher cancer risk associated with bisphosphonates.[2]

The unsettled relationship between oral bisphosphonates and cancer and the equally unsettled role of endoscopy in identifying treatment-appropriate patients or detecting cancer early compels further investigation of the effects of bisphosphonates on the esophagus. Guidelines and quality measures encourage use of bisphosphonates, and the target treatment population, largely the elderly, is growing. As a consequence, understanding risks associated with bisphosphonate use is increasingly important.

We aimed to advance understanding of the potential esophageal toxicity of bisphosphonates in four distinct ways. First, we assessed bisphosphonate exposure with greater precision than past observational studies; specifically, we quantified exposure by pill count rather than prescriptions received which permits examination of the most relevant, potential dose-response relationship. Cancer promotion by oral bisphosphonates is hypothesized to result from injury and inflammation arising from contact between pills and the esophageal mucosa. [18–25] For this class of medications, prescription count may be an especially imprecise measure of exposure. Dosing frequencies range from daily to monthly pills, or 12 to 365 pills per year for the perfectly adherent patient. The range of intended supply per prescription can vary substantially, from 30 to 90 days in general, so one prescription could represent as few as one and as many as ninety pills. Secondly, we assessed the association between bisphosphonate initiation and receipt of upper endoscopy to explore the relationship between this drug class and this test in the pathway of esophageal cancer diagnosis. Thirdly,

we assessed the relationship between bisphosphonate initiation and prescription antacid initiation (proton pump inhibitors and histamine two receptor antagonists PPI/H2RAs) as a proxy measure of esophageal symptoms and clinician tendency to treat those symptoms. Lastly, we assessed the relationship between bisphosphonate pills and incident diagnosis of Barrett's esophagus, a result of mucosal injury and a precursor to one type of esophageal cancer.

Methods

Data and Cohort

We used a 40% Medicare random sample Denominator file and corresponding Medicare claims from Parts A (inpatient insurance) and B (outpatient insurance) for 2003–2011 and Part D (prescription insurance) for 2006–2011, to identify osteoporosis/osteopenia patients. Patients were included in the study if they (1) received one or more inpatient or outpatient diagnosis of osteoporosis/osteopenia between 2003 and 2009 *or* (2) received one or more prescription fills for an oral bisphosphonate from 2006–2009. Patients meeting initial inclusion criteria were further required to: (1) be enrolled in the Medicare Part D prescription drug program for 12 or more consecutive months following achievement of above inclusion criteria (2) be 68 or older at the beginning of the 12 consecutive months of Part D enrollment, and (3) have at least 30 months of continuous fee-for-service Parts A and B enrollment immediately preceding the 12 months of the continuous Part D enrollment, to permit ascertainment of pre-observation co-morbidity and esophageal disease status. Patients with cancer diagnoses were excluded; this was defined as at least one inpatient or two outpatient diagnoses of cancer (other than non-melanoma skin) during the 30-month look-back or during the first 6 months of Part D observation (collectively 36 months total look back for morbidities). Patients diagnosed with Paget's disease were also excluded. See Appendix Table 1 for specific diagnosis codes and drugs.

From this main cohort, two sub-cohorts were created for secondary analyses: sub-cohort A: patients who were naïve to upper endoscopy, to serious gastrointestinal diagnoses (Barrett's esophagus or peptic ulcer disease) and to oral bisphosphonate use at the beginning of follow up and sub-cohort B: a sub-set of sub-cohort A also naïve to prescription PPI/H2RA use. Naïve status was based on the 36-month look back of non-prescription claims and on the first 6 months of prescription claim records for bisphosphonate and PPI/H2RA use. See Appendix Figure 1 for study framework and Appendix Table 1 for procedure codes used to identify upper endoscopy.

Exposure

Oral bisphosphonate exposure was measured from the Part D prescription fill records using the number of pills dispensed in each calendar quarter (3-month period). Number of pills was used rather than dose because this most closely estimates proposed mechanism of injury, namely pill-esophagus contact events. For each 90-day period, each patient was assigned a bisphosphonate intensity category based on pills received each quarter and a cumulative exposure count representing total observed bisphosphonate pills received up to that quarter. Prescription fills for the non-bisphosphonate anti-resorptive drug calcitonin

were also recorded for each 3-month period as an indicator of treatment-worthy low bone density. Initial exploratory analyses assessing the distinct bisphosphonate molecules received by patients revealed relatively low product loyalty, thus no product specific (e.g. alendronate) analyses were attempted. Overall, more than 99% of all bisphosphonate pills dispensed were, like alendronate, nitrogen containing, so findings reflect outcome associated with this group of bisphosphonates, the group previously associated cancer risk.[24, 25] Appendix table 2 displays the distribution of bisphosphonate use frequency by molecule (overall 67% alendronate, 32% risedronate).

Outcomes

The primary outcome of interest was incident esophageal cancer, specifically distal esophageal cancer, the type hypothesized to be associated with oral bisphosphonates. Administrative data, however, are not well suited to accurately distinguish precise anatomic location of esophageal cancer (e.g. distal from proximal) or even upper gastric from lower esophageal cancer. To address this limitation, and to maximize comparability of our study with others, we defined our principal outcome as the composite of incident esophageal or gastric cancer (included because upper gastric cancer may be poorly distinguished from lower esophageal). This was defined as one inpatient or two outpatient diagnoses of these cancer types (see Appendix Table 1 for ICD-9 codes). Sensitivity analyses examined esophageal cancer outcomes distinctly. Secondary analyses examined the association between oral bisphosphonate initiation and three distinct outcomes: (1) receipt of upper endoscopy (2) initiation of a prescription antacid (proton pump inhibitor or histamine-2 receptor antagonist (PPI/H2RA)), or (3) incident Barrett's esophagus disease, defined as one inpatient or two outpatient diagnoses (see Appendix Table 1).

Covariates

Covariates included age (at beginning of Part D prescription claims observation), gender, race (categorized as Black, Hispanic, other based on Medicare denominator file variable), and Medicare Part D low income subsidy (marker for income 150% or less of federal poverty level).[26] The following comorbidities, diagnosed once or more at any time in the 30 month look back were also included: Barrett's esophagus, other esophageal and gastrointestinal diseases, alcohol abuse, chronic obstructive lung disease and/or tobacco use (combined as "tobacco exposure" proxy variable), obesity and Charlson comorbidities not otherwise excluded or included.[27] We created indicator variables for one or more prescription fill of antacid (PPI or H2RA) in the 6-month prescription claims look back. We included the following variables in models as time-varying covariates due to their potential to influence bisphosphonate use: bone density testing, fragility fracture diagnosis, and receipt of institutional care (defined as 50% of fills dispensed by a long term care pharmacy in one or more quarter). For secondary analyses two additional time-varying, drug-use covariates were included due to their potential to influence receipt of upper endoscopy or prescription antacid initiation: (1) prescription non-selective non-steroidal anti-inflammatories (NSAIDs) and (2) Cox-II selective NSAIDs; use was based on Part D claims and classified dichotomously for each 3 month period.

Analysis

The risk of upper gastrointestinal cancer associated with oral bisphosphonate receipt was studied using a marginal structural model estimated with inverse propensity weights (IPW). [28] Propensities were derived for each 3-month period for each patient based on a logistic regression model for the effect of individual characteristics or events on bisphosphonate dose intensity category, (pills per 3-month period categorized based on natural data breaks as: no exposure, 1–3 pills, 4–12 pills, 13 or more pills). Time varying disease diagnosis covariates listed above was managed as irreversible states (i.e. once a fragility fracture patient, always a fragility fracture patient), whereas time varying drug use was permitted to flux for each patient in each 3-month period. In separate analyses, cancer risk was modeled on category of cumulative bisphosphonate pills received. This was done to test for a threshold effect of pills received and also to make our analyses comparable to other studies using thresholds of prescription fills as the exposure of interest. These secondary cancer models and all models on secondary outcomes were estimated using logistic regression with time varying exposure and disease state categories without IPW, because the principal exposure of interest was cumulative bisphosphonate pills for which a propensity weighting approach was not feasible. This approach of logistic regression, is sometimes referred to as pooled logistic regression and has an equivalence to hazard ratio estimation using Cox's model with time-dependent covariates.[29]. The odds ratio we estimate are a very close approximation of the cause specific hazard ratio of Cox's model. The Committee for the Protection of Human Subjects at Dartmouth College approved this study.

Results

Overall, 1.6 million patients met cohort inclusion criteria; mean age at time of cohort entry was 76.8 (standard deviation (SD) 9.3); 87.9% were women, 91.0% were non-Black/non-Hispanic and 40.6% received low income subsidy; follow-up time for main models was 39.6 months (SD 21.0). Preceding the start of observation, 23.9% received a prescription PPI, 6.0% an H2RA (based on 6 month look-back) and 17% had undergone upper endoscopy. The two sub-cohorts had similar characteristics. The endoscopy outcome sub-cohort (Sub-cohort A) included 880,205 patients (53.7% of full cohort); mean follow up was 38.5 months (SD 20.8). The prescription antacid (PPI/H2RA) initiation sub-cohort (sub-cohort B) included 682,289 patients (44.0% of full cohort); mean follow up was 39.0 months (SD 20.8), Table 1.

Crude outcomes and exposures are described in Table 2. Overall, 38.1% used some oral bisphosphonate; cumulative bisphosphonate receipt among users ranged from 4 to 252 pills; 20.2% of the cohort received more than 50 pills. We observed 2,308 incident gastric or esophageal cancer cases (0.43/1000 person years). Cancer rates in the clean-look-back sub-cohorts did not differ substantially from rates of the overall cohort. Among members of the clean-look-back endoscopy outcome sub-cohort A, 14.9% underwent at least one upper endoscopy. Among members of the PPI/H2RA initiation sub-cohort B, 28.8% initiated one or more of these prescription antacids.

Main Models on Cancer Outcomes

We found no association with cumulative bisphosphonate pills (as a continuous variable), OR associated with 1 additional pill 1.00 (95% CI 1.00, 1.00). Similarly, cancer risk associated with each bisphosphonate use intensity category (pills per 3-month period) was not different from no use. Cancer risk was higher in each older age stratum, and as expected, among those diagnosed with alcohol abuse, tobacco exposure, and among those with past upper endoscopy, Table 3. In models that were not weighted, compared to no bisphosphonate use, no category of cumulative bisphosphonate pills received was associated with an increased risk of upper gastrointestinal cancer, OR for the highest exposure group (50 or more pills) 1.11 (95% CI 0.88, 1.39), Table 4. A sensitivity analysis modeling bisphosphonate exposure and esophageal cancer cases only (rather than esophageal and gastric) revealed no significant association (data not shown).

Secondary models restricted to sub-cohort A

Models restricted to sub-cohort A assessed the relationship between bisphosphonate exposure and two distinct outcomes: 1) receipt of upper endoscopy and 2) Barrett's esophagus diagnosis. Models assessing endoscopy risk revealed no difference associated with increased intensity of pill receipt, Table 3, but a higher risk among patients in the lowest category of cumulative use (1 to 9 pills), OR 1.11 (95% CI 1.08, 1.14), Table 4. Models assessing risk of Barrett's esophagus diagnosis, revealed a negative association with pill use intensity, OR associated with 13 or more pills per quarter 0.38 (95% CI 0.18, 0.80), Table 3. Models assessing risk of Barrett's and category of cumulative exposure similarly revealed a negative association, OR associated with receiving 50 or more pills 0.56 (95% CI 0.39, 0.79), Table 4.

Secondary models restricted to sub-cohort B

Models assessing sub-cohort B and risk of prescription antacid initiation showed, compared to no use, no increased risk associated with higher pill intensity, OR associated with 13 or more pills per quarter 0.94 (95% CI 0.88, 1.01) Table 3. Models assessing category of cumulative exposure revealed the highest risk of prescription antacid initiation associated with the lowest cumulative exposure, OR associated with 1 to 9 pills, 1.13 (95% CI 1.10, 1.16), Table 4. In these sub-cohort models risk of antacid initiation associated with bisphosphonate use was dwarfed by risk associated with use of COX-2 selective and non-selective NSAIDs, Tables 3 and 4.

Discussion

Our study of an older American, predominantly female cohort found no association between oral bisphosphonates and upper gastrointestinal cancer. We find a negative association between bisphosphonate use and Barrett's esophagus. Our discovery that endoscopy and prescription antacid initiation were most likely among those with the lowest cumulative bisphosphonate exposure (compared to those with no exposure and relative to those with the most exposure) suggests early bisphosphonate use identifies patients susceptible to irritating pill effects; these findings have distinct clinical implications and expand current knowledge on toxicity of oral bisphosphonates.

Overall, the study cohort appears representative of the general, older, Medicare population; experiencing only modestly higher rates of each outcome measured. The rate of esophageal cancer we observed (17 per 100,000 person years) is similar to that reported for this age group by the Surveillance, Epidemiology, and End Results (SEER) Program which includes more clinically detailed data (11 to 17 per 100,000 person years for women).[30] The rate of prescription antacid initiation observed in sub-cohort B (25.3% for PPI and 7.4% for H2RA) was similar to the 2010 prevalence of the use of these medications in general fee-for-service, Medicare Part D population (25.8% PPI and 6.7% H2RA, authors' Medicare data analysis). [31]. The observed rates of upper endoscopy (5.0% per year) were modestly higher than that reported generally among Medicare enrollees 2004–2006, 12% over three years, or approximately 4% per year.[32]

Our finding of no relationship between upper gastrointestinal cancer and bisphosphonate receipt echoes the growing body of literature reassuring patients and clinicians on this aspect of bisphosphonate safety. [1, 4, 9, 15–17] The distinct features of our study advance the collective understanding of the impact of bisphosphonates on esophageal cancer risk. Our cohort had substantial bisphosphonate exposure (38% with some use), and we measured this exposure in pills dispensed, rather than prescription fills, which should closely reflect pill-esophageal contact events, the proposed mechanism of injury and cancer promotion. Our study controlled for receipt of upper endoscopy in the three years preceding start of observation and thus separated this factor from bisphosphonate exposure. Our cohort is older than that of other studies, but reflects the age group most commonly prescribed this class of medications. Our exposure time and follow-up time were similar to previous studies with both positive and negative findings.[1, 2, 9]

The higher risk of endoscopy or antacid prescription receipt among a subset of incident bisphosphonate users after relatively little cumulative exposure may have important clinical implications. We believe this reveals a group of patients especially susceptible to the esophageal side effects of oral bisphosphonates. After few pills they are more likely to get endoscopic evaluation and/or be treated for esophageal disease or symptoms. While this finding may result from scant bisphosphonate use unmasking gastro-esophageal pathology that prompts treatment discontinuation in some, our failure to find an association between bisphosphonate use and significant esophageal pathology instead suggests individual-level differences in ability to tolerate these pills and a tendency for these symptoms to trigger endoscopy and prescription antacid treatment by U.S. clinicians. Our findings parallel those of a Denmark registry study that found two-fold higher frequency of upper endoscopy among subjects in the year after beginning alendronate treatment (4.5% versus 2.1% in control ($p<0.001$)).[17]

In contrast, to these susceptible patients, greater cumulative use of bisphosphonates appears a marker of lower likelihood of endoscopy and antacid initiation, suggesting relatively tolerant a sub-population makes up the patients with the greatest use of these products. This may explain the “protective” effect of bisphosphonates observed by other studies assessing cancer outcome risks and the negative association we observed with Barrett's esophagus outcomes, namely a healthy user bias.[4, 16]

Clinically, patients susceptible to pill effects and early endoscopy and antacid prescription may be an important group to identify and to manage differently, either with especially judicious use of bisphosphonates, early consideration of intravenous bisphosphonates, or bisphosphonate alternatives. Importantly, our inability to identify significant esophageal pathology as a result of bisphosphonate exposure argues for a conservative approach to endoscopy and prescription therapy in the year following bisphosphonate initiation. A trial off of oral bisphosphonates and reassessment of symptoms may be the best initial approach. Identifying this population and optimal management of their low bone density as well as their bisphosphonate-associated esophageal symptoms will require robust risk benefits analysis.

Our claims-based study has important limitations. Osteopenia/osteoporosis has both known and unknown etiologies. Well-documented risk factors include tobacco use, poor nutrition, genetic predisposition, under weight, and hormone status. In this observational study, we are unable to ascertain many of these factors that may also be associated with esophageal cancer risk. We are equally unable to observe unknown risk factors. To address this limitation, we define our study cohort by disease state (osteopenia/osteoporosis diagnosis or bisphosphonate receipt). This approach creates a relatively homogeneous cohort of patients with relatively similar unobservable potential risk factors. While we believe this the best approach, it is possible however that untreated osteoporosis/osteopenia patients are substantially different from treated patients with the same diagnosis, creating a biased comparison.

The Medicare Part D program was initiated on January 1, 2006, we have no prescription use data preceding this date, thus our exposure measurement is left truncated and observed cumulative exposure may be underestimated in long-term bisphosphonate users. Bisphosphonates are administered intravenously but in our data use of this drug form was insufficient to permit study (< 1% of the cohort). Low product loyalty also made molecule-specific exposure modeling unfeasible; nearly all exposure (measured as pill count) was alendronate, but our models may miss differential effect of risedronate, which accounted for 32% of all pills received. We depend on diagnosis codes for identification of prevalent and incident disease as well as comorbidities. While researchers have validated use of diagnostic codes in other datasets for the ascertainment of incident esophageal cancer cases, we are aware of no such validation studies specific to Medicare claims.[33, 34] Our study thus is limited by the accuracy of the recorded codes. We also have only diagnosis-based data on key esophageal cancer risk factors, tobacco use and alcohol use. This is an important limitation. We also rely on diagnosis codes for the comorbidity obesity, a risk factor for reflux disease that might trigger endoscopy and/or prescription antacid initiation. Our exposure measurement reflects pills received rather than pills ingested and thus risks misclassifying exposure for patients not taking pills received, though financial incentives such as prescription co-payments should limit fills not consumed. Our mean follow up of 39.6 months for cancer outcomes, while comparable to some other studies, may be insufficient to detect a longer latency cancer related toxicity.

Conclusion

Our study adds to the literature reassuring patients and clinicians about the safety of bisphosphonates with respect to esophageal cancer risks. Our results also suggest reports by others of a protective effect of bisphosphonates likely stems from healthy user bias. Our findings of an especially susceptible sub-cohort likely to undergo endoscopy and/or prescription antacid initiation after relatively few pills, combined with the lack of association between oral bisphosphonates and significant esophageal disease suggests the need for careful oral treatment selection and a conservative approach to gastrointestinal symptoms that follow scant pill use. Future studies should seek to identify predictors of poor oral bisphosphonate tolerance so that these patients might be offered alternatives earlier. Additionally, studies aimed at quantifying the cost effectiveness of oral bisphosphonates should include the risk and cost associated with higher rates of upper endoscopy following initiation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Odds ratios for the association between cumulative bisphosphonate exposure and upper gastrointestinal cancer, receipt of upper endoscopy, Barrett's Esophagus and proton pump inhibitor initiation

Reference exposure intensity is none. Models included the following variables: Race (Black, Hispanic, other), Part D low income subsidy status (an indicator of income $\geq 150\%$ of the federal poverty level), receipt of prescription non-selective, non-steroidal anti-inflammatory (NSAID), receipt of cyclooxygenase-2 selective anti-inflammatory, Charlson comorbidity count category, obesity diagnosis, gastroesophageal reflux peptic ulcer disease, and Barrett's Esophagus (for full cohort analysis only, top panel), based on inpatient and outpatient claims diagnosis codes appearing in the 36-month lookback period. Time-varying covariates included bone density testing, fragility fracture diagnosis, and receipt of institutional care (defined as $\geq 50\%$ of prescription fills dispensed by a long term care pharmacy in one or more 90 day period) and calcitonin use. Prescription antacids include proton pump inhibitors and histamine-2 receptor blockers.

Table 1

Characteristics of full cohort, analyzed for incident upper gastrointestinal cancer outcomes and two sub-cohorts studied for the distinct outcomes of upper endoscopy, Barrett's Esophagus and prescription antacid initiation

Cohort	Full Cohort	Sub-Cohort A	Sub-Cohort B
Outcome measured:	Upper gastrointestinal cancer	Upper endoscopy / Barrett's Esophagus	Proton pump inhibitor initiation
N (% total cohort)	1,637,992 (100%)	880,205 (53.7%)	682,289 (41.7%)
Follow up months: mean (SD)	39.6 (21.0)	38.5 (20.8)	39.0 (20.8)
Age mean (SD)	76.8 (9.3)	77.2 (9.6)	77.2 (9.4)
Female	87.9%	85.9%	85.9%
Part D low income subsidy (any)	40.6%	40.3%	37.0%
Race/ethnicity			
Black	6.2%	6.6%	6.3%
Hispanic	2.8%	2.4%	2.1%
Other	91.0%	91.0%	91.6%
Morbidities			
Charlson comorbidity counts			
0- to 1	71.6%	71.5%	75.7%
2 to 3	22.0%	22.4%	19.8%
4 or more	6.4%	6.1%	4.8%
Obesity diagnosis	3.7%	3.8%	4.5%
Peptic ulcer disease	2.2%	-	-
Gastroesophageal reflux	28.5%	23.6%	14.6%
Barretts Esophagus	0.6%	0.0%	-
Alcohol use diagnosis	0.5%	0.6%	0.5%
Tobacco use or history	7.0%	7.1%	6.6%
Prescription antacid use or procedure in look-back			
Upper endoscopy	17.0%		-
Proton pump inhibitor prescription	23.9%	18.0%	-
H2RA prescription	6.0%	5.4%	

The upper endoscopy outcome was measured in the subpopulation that was naive to upper endoscopy, peptic ulcer disease, and bisphosphonate use. The proton pump inhibitor initiation outcome was measured in a subpopulation that was naive to upper endoscopy, peptic ulcer diseases, bisphosphonate use, and prescription antacids. Mean follow up time for endoscopy events and for prescription antacid initiation were 2–3 months shorter than mean cancer model follow up times because achievement of these outcomes resulted in censoring. Age is at beginning of observation. Race is based on the Medicare denominator file race variable. Charlson Comorbidities from 1987 Journal of Chronic Disease -modified to exclude cancer (excluded from cohort), and tobacco use/tobacco-related lung disease included separately as "tobacco use/history" variable. Part D low-income subsidy is an indicator of poverty (< 150% of U.S. Federal Poverty Level). Morbidities are based on one or more diagnoses for each condition appearing in the 36-months preceding beginning of observation. Prescription antacid use is based on first 6 months of prescription claims observed; these months preceded observation for outcomes.

Table 2

Bisphosphonate use summary and crude outcomes: upper gastrointestinal cancer cases for the full cohort, and for sub-cohorts upper endoscopy, Barrett's Esophagus, and prescription antacid initiation

	Cancer	Upper Endoscopy & Barrett's	Proton Prescription Antacid Initiation
N	1,637,992	880,205	682,289
Cumulative pills at censor/end			
Total pills per user (range: 5th-95th percentile)			
None	4 to 252	3 to 180	3 to 184
1-9 pills	1,014,346	751,402	579,126
10-24 pills	91,654	35,984	28,312
25-49 pills	105,401	28,306	22,402
50+ pills	95,033	20,294	16,169
	331,558	44,219	36,280
Cancer Events			
Esophageal	935	0.06%	389
Gastric	1,373	0.08%	476
All upper gastrointestinal	2,308	0.14%	865
Cancer Rates			
Esophageal cancer cases/1000 person years	0.17	0.18	0.17
Gastric cancer cases / 1000 person years	0.25	0.23	0.21
All upper gastrointestinal cases / 1000 person years	0.43	0.41	0.39
Secondary Outcomes			
Incident upper endoscopy	-	130,916	90,419
Upper endoscopy events / 1000 person years	-	50.4	43.8
Prescription proton pump inhibitor initiation	-		172,338
Prescription H2RA initiation	-		50,136
Prescription antacid initiation	-		196,683
Barrett's Esophagus		2246	1,453
Time varying covariates hypothesized to affect likelihood of bisphosphonate use			
Incident bone density test or fragility fracture	1,049,633	64.1%	494,387
		56.2%	387,006
			56.7%

	Transition to long term care pharmacy type	Cancer		Upper Endoscopy & Barrett's		Proton Prescription Antacid Initiation	
		340,469	20.8%	195,986	22.3%	134,318	19.7%

The upper endoscopy outcome was analysed only on a subpopulation naive to upper endoscopy, peptic ulcer disease, and bisphosphonate use. Prescription Antacid Initiation outcome was analysed only on a subpopulation that was naive to upper endoscopy, peptic ulcer diseases, bisphosphonate use, and prescription antacids. Total pill count is the sum of all oral bisphosphonate pills received during follow-up. Pill count categories are based on natural data breaks. Esophageal cancer includes all esophageal cancer locations; ICD-9 codes are listed in Appendix. Incident upper endoscopy is defined as an upper endoscopy during follow-up among those with no upper endoscopy in the 36-month look back. Prescription antacid initiation is defined as one or more fill of proton pump inhibitor or H2RA during observation among those in sub-cohort B with no such fills during the first six months Part D data look-back. Long term care pharmacy type is use an indicator of institutionalization or assisted living situation.

Table 3

Odds ratios for the association between bisphosphonate exposure intensity and outcomes: main model on incident upper gastrointestinal cancer, using inverse propensity weighted marginal structural models, and secondary analyses (not propensity weighted) of sub-cohorts on (1) receipt of upper endoscopy, (2) Barrett's Esophagus and (3) prescription antacid initiation

	Estimate	Lower CL	Upper CL	p
<i>Full cohort, inverse probability weighted models on upper gastrointestinal cancer N = 1,643,335</i>				
Quarterly Bisphosphonate Exposure intensity				
1 to 3 pills	0.89	0.63	1.26	0.52
4 to 12 pills	0.95	0.82	1.09	0.46
13 or more pills	0.86	0.61	1.21	0.39
Cumulative pills received				
	1.00	1.00	1.00	0.06
Age category				
50 to 64	0.77	0.57	1.04	0.08
70 to 74	1.12	0.92	1.36	0.28
75 to 79	1.39	1.14	1.69	0.00
80 to 84	1.61	1.32	1.95	<0.001
85 and older	1.63	1.33	2.00	<0.001
Alcohol abuse diagnosis	3.27	2.06	5.19	<0.001
Tobacco exposure	1.43	1.18	1.73	0.00
History of endoscopy	1.34	1.18	1.52	<0.001
<i>Sub-cohort A analysis, receipt of upper endoscopy, assessing association with quarterly exposure intensity, N = 882,996</i>				
Quarterly Bisphosphonate Exposure Intensity				
1 to 3 pills	1.05	0.99	1.11	0.104
4 to 12 pills	1.02	0.99	1.05	0.264
13 or more pills	0.93	0.86	1.02	0.107
Cumulative pills received				
	1.00	1.00	1.00	0.006
Cox II Selective NSAID fill in previous quarter	1.09	1.06	1.13	0.000
Non-selective NSAID fill in previous quarter	1.22	1.20	1.24	<0.001
<i>Sub-cohort A analysis, incident Barrett's Esophagus, assessing association with quarterly exposure intensity, N = 882,996</i>				
Quarterly Bisphosphonate Exposure Intensity				
1 to 3 pills	0.47	0.30	0.73	0.001
4 to 12 pills	0.51	0.39	0.67	0.000
13 or more pills	0.38	0.18	0.80	0.011

	Estimate	Lower CL	Upper CL	p
Cumulative pills received	1.00	1.00	1.00	0.538
Cox II Selective NSAID fill in previous quarter	0.54	0.38	0.75	0.000
Non-selective NSAID fill in previous quarter	0.70	0.59	0.82	0.000
Sub-cohort B analysis, prescription antacid initiation, assessing association with quarterly exposure intensity, N = 723,763				
Quarterly Bisphosphonate Exposure Intensity				
1 to 3 pills	1.03	0.98	1.09	0.241
4 to 12 pills	0.98	0.95	1.01	0.201
13 or more pills	0.94	0.88	1.01	0.095
Cumulative pills received	1.00	1.00	1.00	0.003
Cox II Selective NSAID fill in previous quarter	1.35	1.31	1.39	<0.001
Non-selective NSAID fill in previous quarter	1.55	1.52	1.57	<0.001

Reference exposure intensity is none. Models also included the following variables: Race (Black, Hispanic, other), Part D low income subsidy status (an indicator of income 150% of the federal poverty level, Charlson comorbidity count category, obesity diagnosis, gastroesophageal reflux, peptic ulcer disease, and Barrette's Esophagus (for full cohort models), based on inpatient and outpatient claims diagnosis codes appearing in the 36-month look-back period. Time-varying covariates included bone density testing, fragility fracture diagnosis, and receipt of institutional care (defined as 50% of prescription fills dispensed by a long term care pharmacy in one or more 90 day period) and calcitonin use. NSAID is non-steroidal anti-inflammatory.

Odds ratios for the association between cumulative bisphosphonate exposure and outcomes: main model on incident upper gastrointestinal cancer and secondary analyses of sub-cohorts on (1) receipt of upper endoscopy, (2) Barrett's Esophagus and (3) prescription antacid initiation

Table 4

	Estimate	Lower CL	Upper CL	p
<i>Full cohort analysis, incident upper gastrointestinal cancer, assessing association with cumulative exposure category, N = 1,643,335</i>				
Bisphosphonate Cumulative Exposure Category				
1 to 9 pills	1.00	0.85	1.18	0.99
10 to 24 pills	0.95	0.80	1.13	0.53
25 to 49 pills	1.04	0.86	1.26	0.67
50 or more pills	1.11	0.88	1.39	0.37
Total treatment quarters	1.00	0.98	1.02	0.70
Cox II Selective NSAID fill in previous quarter	1.11	0.88	1.40	0.37
Non-selective NSAID fill in previous quarter	0.77	0.65	0.90	0.00
History of endoscopy	1.16	1.03	1.29	0.01
<i>Sub-cohort A analysis, receipt of upper endoscopy, assessing association with cumulative exposure category, N = 882,996</i>				
Bisphosphonate Cumulative Exposure Category				
1 to 9 pills	1.11	1.08	1.14	0.000
10 to 24 pills	1.05	1.01	1.09	0.011
25 to 49 pills	1.02	0.97	1.08	0.402
50 or more pills	0.95	0.89	1.01	0.106
Total treatment quarters	1.01	1.00	1.02	0.003
Cox II Selective NSAID fill in previous quarter	1.09	1.06	1.13	0.000
Non-selective NSAID fill in previous quarter	1.22	1.20	1.24	<0.001
<i>Sub-cohort A analysis, incident Barrett's Esophagus, assessing association with cumulative exposure category, N = 882,996</i>				
Bisphosphonate Cumulative Exposure Category				
1 to 9 pills	0.81	0.67	0.99	0.036
10 to 24 pills	0.80	0.63	1.01	0.056
25 to 49 pills	0.67	0.49	0.92	0.013
50 or more pills	0.56	0.39	0.79	0.001
Total treatment quarters	1.04	1.01	1.07	0.011
Cox II Selective NSAID Fill in previous quarter	0.53	0.38	0.75	0.000
Non-selective NSAID fill in previous quarter	0.69	0.59	0.81	0.000

	Estimate	Lower CL	Upper CL	p
Sub-cohort B analysis, prescription antacid initiation, assessing association with cumulative exposure category, N = 723, 763				
Bisphosphonate Cumulative Exposure Category	1 to 9 pills	1.13	1.10	1.16
	10 to 24 pills	1.06	1.02	1.09
	25 to 49 pills	1.04	0.99	1.09
	50 or more pills	0.99	0.94	1.05
Total treatment quarters		1.01	1.00	1.02
Cox II Selective NSAID fill in previous quarter		1.35	1.31	1.39
Non-selective NSAID fill in previous quarter		1.54	1.52	1.57

Reference exposure intensity is none. Models also included the following variables: Race (Black, Hispanic, other), Part D low income subsidy status (an indicator of income level, Charlson comorbidity count category, obesity diagnosis, gastroesophageal reflux, peptic ulcer disease, and Barrett's Esophagus (for full cohort models only), based on inpatient and outpatient claims diagnosis codes appearing in the 36-month look-back period. Time-varying covariates included bone density testing, fragility fracture diagnosis, and receipt of institutional care (defined as prescription fills dispensed by a long term care pharmacy in one or more 90 day period) and calcitonin use. NSAID is non-steroidal anti-inflammatory.