Impact of Adherence to Concomitant Gastroprotective Therapy on Nonsteroidal-Related Gastroduodenal Ulcer Complications

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Background & Aims: The clinical impact of nonadherence to gastroprotective agents (GPAs) coprescribed with anti-inflammatory therapies has not been evaluated. In a large, commercial, managed-care database, we retrospectively characterized the use of GPAs among patients receiving nonselective nonsteroidal anti-inflammatory drugs (ns-NSAIDs) or cyclooxygenase-2–selective inhibitors (coxibs) and determined the impact of nonadherence on the likelihood of gastroduodenal ulcer complications. **Methods:** Analyses identified the populations of patients with concomitant histamine-2 receptor antagonist or proton pump inhibitor (PPI) therapy and determined adherence with the prescribed therapy with respect to the duration of anti-inflammatory treatment. Multivariate regression analyses modeled the association between adherence with concomitant protective therapy and the likelihood of upper gastrointestinal (GI) complications including peptic ulcer disease, ulcer, and/or upper-GI bleed. **Results:** Among 144,203 patients newly prescribed anti-inflammatory therapies, 1.8% received concomitant GPA treatment (ns-NSAIDs, 1.4% vs coxibs, 2.6%; $P < .0001$). The likelihood of GPA use increased with the presence of risk factors: age older than 65 years (odds ratio [OR], 1.40; 95% confidence interval [CI], 1.3–1.5) and prior history of peptic ulcer disease (OR, 2.5; 95% CI, 1.8–3.3), esophagitis/gastroesophageal reflux (OR, 3.8; 95% CI, 3.5–4.1), ulcer/upper-GI bleed (OR, 1.4; 95% CI, 1.2–1.5), or gastritis (OR, 2.5; 95% CI, 2.2–2.8). Of patients receiving concomitant PPI therapy, 68% had adherence rates of 80% or more. A significantly higher risk of upper-GI ulcers/complications was observed in ns-NSAID patients with adherence rates of less than 80% compared with adherence rates of 80% or more (OR, 2.4; 95% CI, 1.0–5.6), but no such relationship was observed among patients who took coxibs. **Conclusions:** Few patients receive concomitant GPA therapy when prescribed anti-inflammatory treatment, although use increased with the presence of risk factors. Adherence to concomitant therapy is paramount to reducing GI events among ns-NSAID users and educational efforts should be undertaken to promote use of and adherence to GPA therapy among these patients.

The management of arthritis and chronic pain syndromes often involves continued use of analgesic medications.[1,2] Because of their efficacy and relatively inexpensive cost, nonselective nonsteroidal anti-inflammatory drugs (ns-NSAIDs) continue to be the mainstay of arthritis and pain management despite their associated risk of gastrointestinal (GI) toxicity.[3–6] With the aim of circumventing the upper-GI toxicity associated with use of ns-NSAIDs, multiple studies have shown that co-administration of so-called *gastroprotective agents* (GPAs) such as misoprostol or proton pump inhibitors (PPIs), reduces the rate of endoscopic gastric and/or duodenal ulcers compared with ns-NSAIDs alone.[7–10] In the case of misoprostol, there is also evidence of a reduction in the rate of upper-GI complications.[11] Although a single prospective endoscopic clinical trial suggested high-dose famotidine (40 mg twice a day) reduces the rate of endoscopic gastroduodenal ulcers compared with ns-NSAIDs alone,[12] there is a paucity of evidence that histamine-2 receptor antagonists (H_2RAs) are effective in reducing ns-NSAID–related upper-GI ulcer complications.[3,13,14]

As an alternative to the use of coprescribed GPAs, cyclooxygenase-2–selective inhibitors (coxibs) are less likely to be associated with the development of endoscopic gastric and duodenal ulcers and upper-GI complications.[15–19] Recent studies also have suggested that PPIs co-administered with ns-NSAIDs are comparable with coxibs with respect to the rate of recurrent upper-GI ulcer bleeding in high-risk patients.[20–22]

Based on these data, clinical guidelines have been forwarded by expert panels and developed by several national professional societies addressing the appropriate use of preventive strategies for patients at high risk. These guidelines generally recommend the concomitant use of GPAs such as a PPI or misoprostol, or the use of a coxib alone in place of an ns-NSAID among patients at high risk for GI complications.[2,23–27] Well-recognized risk factors for upper-GI ulcer complications include advanced age, history of upper-GI ulcers or bleeding, and concomitant use of corticosteroids or anticoagulants.[3,11,28–33]

Despite the available data and the integrated guidelines, evidence suggests that significant proportions of high-risk patients are not receiving any protective strategies and, of those who do receive GPAs, many are treated inadequately with ineffective therapies.[34,35] For example, and despite the wealth of evidence supporting greater efficacy of PPIs compared with H_2RAs, it is unfortunately still relatively common for physicians in clinical practice to prescribe standard doses of H_2RAs (eg, ranitidine 150 mg twice a day) for prevention of ns-NSAID–induced GI adverse events.[35] The fact that various national

Abbreviations used in this paper: CI, confidence interval; GERD, gastroesophageal reflux disorder; GI, gastrointestinal; GPA, gastroprotective agents; H_2RA, histamine-2 receptor antagonist; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ns-NSAID, nonselective nonsteroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor; PUD, peptic ulcer disease.

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preventive guidelines for patients at high risk for NSAID-associated upper-GI toxicity are not applied uniformly in the clinical setting has been highlighted and quantified further. In a recent evaluation by Abraham et al[27] based on the use of a national Department of Veterans Affairs database, less than 30% of veterans considered to be at high risk for NSAID-associated upper-GI toxicity were found to receive appropriate therapies.

Patient adherence remains one of the important challenges of day-to-day clinical practice, and even when at-risk patients are identified and prescribed appropriate preventive strategies, nonadherence to the use of these medications may impact greatly on both short-term and long-term clinical outcomes.[36–38] Specific to anti-inflammatory treatment, Sturkenboom et al[35] determined that only 37% of patients newly receiving ns-NSAIDs had a greater than 75% adherence to their concomitant GPA therapy regimen. However, this study did not evaluate the clinical impact of this high level of nonadherence and, as such, leaves the issue of long-term GI safety and effectiveness of coprescription open to question. Therefore, this retrospective database study was undertaken to characterize the use of GPAs among patients receiving coxibs or ns-NSAIDs and to determine the impact of adherence to concomitant GPA therapy on the likelihood of coxib- and ns-NSAID–related gastroduodenal toxicity.

Patients and Methods

This retrospective study was based on the patient-level clinical, longitudinal PharMetrics Integrated Outcomes database (PharMetrics, Watertown, MA), which offers administrative claims information collected from approximately 75 commercial managed-care plans covering more than 43 million enrollees across the United States. The database includes inpatient and outpatient diagnoses, procedures, and prescriptions filled within the plans. All medical and pharmaceutical claims include dates of service, and prescription data include date filled/administered, days supplied, and quantity dispensed. Additional data elements include demographic variables (age, sex, geographic region), health plan type (eg, health maintenance organization, preferred provider organization), payer type (eg, commercial, self-pay), provider specialty, and start and stop dates for plan enrollment. For the purposes of this study, we accessed a subset of 35 commercial managed-care plans from the PharMetrics database in which access to coxibs and GPA therapies were known to be available. We restricted our analysis to commercial managed-care plans in which claims for the agents of interest were recorded during the time frame of this study as an indicator showing the ability of physicians to prescribe these medications.

Patient Sample

The study time frame spanned a 3-year period from January 1, 2000, to December 31, 2002. Patients were eligible for inclusion in the study if they had an index prescription claim for an ns-NSAID or coxib and at least 1 refill for the same medication during this time frame. Because this study intended to examine the effects of long-term therapy, patients were excluded if they had less than a 10-day supply for their index medication or gaps in therapy of 120 days or more. Inclusion criteria also required no prescription claims for ns-NSAIDs, coxibs, or GPAs (misoprostol, PPIs, or H_2RAs) during the 12 months before the index prescription date and 12 continuous months of enrollment in the plan both before and after the index prescription date. Patient data were analyzed during the 12-month preperiod to determine baseline demographic characteristics and the patients were followed-up for up to 12 months after the index prescription date to evaluate subsequent upper-GI outcomes related to ns-NSAID or coxib therapy.

Treatment cohorts were defined by the index prescription claim during the study period. Ns-NSAIDs included ibuprofen, naproxen, nabumetone, diclofenac sodium, diclofenac potassium, etodolac, piroxicam, oxaprozen, sulindac, meloxicam, ketoprofen, flurbiprofen, and fenoprofen calcium. In these plans, aspirin use could not be measured objectively. Coxib products included celecoxib, rofecoxib, and valdecoxib. Patients were permitted to switch medications within their index cohort. For example, if a patient was initiated on celecoxib and had a subsequent prescription for a different coxib drug, they remained a coxib patient and were retained in the study. Similarly, a patient with an index claim for ibuprofen who switched to a different ns-NSAID treatment still was considered an ns-NSAID patient in the analyses. However, switching between treatment cohorts was not permitted; patients with any subsequent claims within 12 months after their index date for a medication listed in the alternative treatment group (ie, a coxib patient who had a subsequent claim for an ns-NSAID, or vice versa) were excluded from the analyses. In the case of patients switching between cohorts, the index time to the switch was not included in the analyses.

Demographic data were collected to describe treatment cohorts with respect to age, sex, and health status. Health status was determined by comorbid illness, measured by the most common 3-digit International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes recorded in secondary diagnosis positions on prior medical claims. Two standard measurement tools were used to evaluate patient health status further, the Charlson Comorbidity Index and the Chronic Disease Score.[39,40] In addition, analyses assessed the frequency of coded GI diagnoses during the 12 months before the index prescription. Diagnoses considered for this analysis included peptic ulcer disease (PUD), esophagitis/gastroesophageal reflux disease, ulcer/upper-GI bleed, and gastritis. These diagnoses were identified through medical claims containing the following ICD-9-CM codes: 533.xx (PUD); 530.xx (esophagitis/gastroesophageal reflux disease); 531.xx, 532.xx, 534.xx, and 578.xx (ulcer/upper-GI bleed); and 535.xx (gastritis).

Based on the available data, patients were grouped into 4 cohorts based on their use of ns-NSAIDs or coxibs with or without concomitant use of GPAs. Prescription claims were used to determine concomitant acid-suppressive GPA therapy, defined as initiation of PPI or H_2RA use up to 14 days after the ns-NSAID/coxib index prescription. In this analysis, H_2RAs were included in the GPA treatment definition because we assumed that it was a cognitive action taken by prescribers with the presumable intention of preventing subsequent GI events.

Analyses also determined the number and percentage of patients with GI diagnoses within 12 months before the index prescription date. Within the ns-NSAID and coxib cohorts, χ^2 analyses compared the proportion of concomitant and noncon-

Likelihood of Initiating Concomitant Gastroprotective Therapy

The χ^2 analyses first compared the proportion of concomitant PPI/H_2RA patients between ns-NSAID and coxib cohorts. Logistic regression analyses then modeled the likelihood of initiating concomitant therapy, with the index medication as the primary independent variable of interest and specific risk factors as predictors of secondary interest.[11,31,41] Three risk factors were of particular interest to this study because of their association with increased risk of GI events: patient age older than 65 years, previous ulcer diagnosis, and anticoagulant and/or steroid use. Results were adjusted for patient age and sex.

Impact of Adherence on Patient Outcomes

The effectiveness of adherence with concomitant GPA therapy on subsequent upper-GI complications was evaluated. These analyses only included PPIs as the appropriate GPA therapy because they are believed to be effective in reducing the incidence of upper-GI ulcers and complications compared with H_2RAs.[8,12,20,42,43]

Adherence to concomitant therapy was determined using a ratio of dispensed days' supply of PPI and ns-NSAIDs or coxibs. The duration of follow-up evaluation could extend for up to 12 months after the index ns-NSAID/coxib prescription date, given that there were no treatment gaps of greater than 120 days. Adherence rates were calculated by normalizing the total days' supply of PPI therapy by the total days' supply of ns-NSAID/coxib therapy as follows:

$$\text{Adherence}\,(\%) = \left(\frac{\sum \text{Dispensed PPI days' supply}}{\sum \text{Dispensed anti-inflammatory drug days' supply}}\right) \times 100$$

Adherence was capped at 100% because the intent was to identify PPI coverage over the course of ns-NSAID/coxib treatment. It was considered a continuous variable ranging from 0% to 100% and also as a categoric variable with 5 levels of adherence: 0%–20% to 80%–100%.

A priori, the study hypothesized that the likelihood of adherence to concomitant GPA therapy decreases as the days' supply of anti-inflammatory treatment increases. Because adherence might change over the duration of anti-inflammatory treatment with the possibility that patients on therapy for longer durations might have increased rates of nonadherence with time, we evaluated the proportion of patients with PPI adherence of 80% or greater according to the duration of anti-inflammatory therapy, measured by the number of index medication refills.

The likelihood of adherence was evaluated through multivariate logistic regression models. By using adherence as the dichotomous outcome, models controlled for patient age, hypertension, diabetes mellitus, prior cardiovascular conditions, previous PUD, previous ulcer/upper-GI bleed, number of concomitant medications, and the number of index medication refills.

After accounting for prior risk, concomitancy, and adherence, the primary end points of interest examined by the study were PUD (ICD-9-CM code 533.xx), ulcer, and/or upper-GI bleed (ICD-9-CM codes 531.xx, 532.xx, 534.xx, and 578.xx) occurring up to 12 months after the index prescription date. Descriptive analyses determined crude rates of predefined end points based on ICD-9-CM codes; univariate analyses examined the entire sample and χ^2 analyses compared the rates between ns-NSAID and coxib cohorts.

We also examined the predefined GI events for the ns-NSAID and coxib cohorts as a function of adherence. To do so, the number of GI events within each patient cohort was normalized by dividing the sum of events by the cumulative sum of total days' supply for the index medication; rates were expressed in patient-years. Rates of GI events per patient-year were plotted against levels of adherence for the ns-NSAID and coxib cohorts.

Finally, multivariate analyses modeled the impact of 80% or greater adherence on the likelihood of GI events. The dependent variable was occurrence of PUD, ulcer, and/or upper-GI bleed during the ns-NSAID/coxib treatment period. The ns-NSAID/coxib treatment period was defined as the duration between the initial and final index medication prescription plus days' supply for the last prescription or 12 months after the index prescription, whichever occurred first. Adherence was the independent variable of interest; the models also controlled for patient age, sex, and prior GI risk factors (previous PUD, esophagitis/gastroesophageal reflux disease, ulcer/upper-GI bleed, and gastritis) diagnosed within 12 months before the index ns-NSAID and coxib prescription. Logistic models evaluated ns-NSAID and coxib cohorts separately.

Based on data from other trials and reports, patients with prior diagnoses of cardiovascular ischemic events are likely to be given aspirin for secondary prophylaxis.[44–47] Because the data could not capture over-the-counter aspirin use reliably, we conducted an exploratory and post hoc analysis using coded cardiovascular diagnoses as a proxy measure for aspirin use to determine its impact on the likelihood of predefined GI outcomes. The analysis compared the rate of GI events among patients with cardiovascular disease diagnosed within 12 months before the index ns-NSAID/coxib date against the rate among patients without diagnosed cardiovascular disease. Cardiovascular conditions included ischemic heart disease (ICD-9-CM codes 410.xx and 411.xx, excluding 411.1x and 414.xx), angina (ICD-9-CM codes 411.1x and 413.xx), stroke (ICD-9-CM codes 430.xx–438.xx), and peripheral vascular disease (ICD-9-CM codes 443.8, 443.89, and 443.9). Multivariate logistic analyses modeled the likelihood of GI events in addition to the presence of cardiovascular disease; the model also controlled for patient age, the presence of hypertension and/or diabetes, prior PUD and/or ulcer, the number of concomitant medications during the anti-inflammatory treatment period, and the number of index product refills.

Results

Patient Sample

After all inclusion and exclusion criteria were applied, 144,203 patients were available for analysis (Table 1). Of these, 92,833 (64%) were treated with ns-NSAIDs and 51,370 (36%) were treated with coxibs. The most common ns-NSAID medications were naproxen and ibuprofen, comprising 37% and 32% of the patient sample, respectively. Other ns-NSAIDs included nabumetone (8%), diclofenac sodium (6%), etodolac (4%), piroxicam (4%), oxaprozen (3%), and sulindac (2%). All other ns-NSAID products were used by fewer than 2% of patients. Approximately 53% of coxib patients were prescribed celecoxib and 47% were treated with

Table 1. Patient Demographics by Index Prescription and Concomitant Therapy

	ns-NSAIDs (n = 92,833; 64%)		Coxibs (n = 51,370; 36%)		
	Concomitant	Nonconcomitant	Concomitant	Nonconcomitant	Total n = 144,203
Patients, n (%)	1312 (1.4[a])	91,521 (98.6)	1322 (2.6[a])	50,048 (97.4)	144,203 (1.8)
Mean age, *y* (SD)	48.40 (12.06)	47.04 (11.46)	50.24 (10.86)	50.59 (10.26)	48.32 (9.66)
Age, n (%)					
19–35 y	176 (13.41)	14,227 (15.55)	120 (9.08)	4080 (8.15)	18,603 (12.90)
36–45 y	332 (25.30)	25,368 (27.72)	278 (21.03)	10,576 (21.13)	36,554 (25.35)
46–55 y	453 (34.53)	31,089 (33.97)	515 (38.96)	19,323 (38.61)	51,380 (35.63)
56–65 y	271 (20.66)	17,184 (18.78)	343 (25.95)	13,449 (26.87)	31,247 (21.67)
>65 y	80 (6.10)	3653 (3.99)	66 (4.99)	2620 (5.23)	6419 (4.45)
Female, n (%)	815 (62.12)	53,777 (58.76)	833 (63.01)	30,936 (61.81)	86,361 (59.89)
Male, n (%)	497 (37.88)	37,737 (41.23)	489 (36.99)	19,110 (38.18)	57,833 (40.11)

[a]The difference in the proportion of concomitant patients between ns-NSAID and coxib cohorts is statistically significant with a *P* value of .003.

celecoxib. Less than 1% of the study population received valdecoxib. For details on health status by index prescription and concomitant therapy, see Supplemental Table 1 (supplementary material online at www.cghjournal.org).

Likelihood of Initiating Concomitant Gastroprotective Agent Therapy

Only 1.8% (n = 2634) of the total sample population initiated concomitant PPI or H_2RA therapy within 14 days of the index ns-NSAID/coxib prescription (Table 2). Interestingly, coxib patients were more likely to receive GPAs compared with ns-NSAID users. Rates of concomitancy were 2.6% among coxib-treated patients and 1.4% in NSAID-treated patients (odds ratio [OR], 1.82; 95% confidence interval [CI], 1.69–1.96). With respect to GPA therapy, 62% of patients received PPI therapy and 38% were treated with H_2RAs. Variations were noted based on the index treatment cohort: patients treated with coxibs were more likely to be prescribed PPIs than H_2RAs (74% vs 26%; $P < .0001$), whereas patients treated with ns-NSAIDs were equally as likely to be prescribed either therapy (50% each). Regression analysis further confirmed that patients treated with coxibs were more likely to initiate concomitant PPI/H_2RA treatment than patients treated with ns-NSAIDs (OR, 1.31; 95% CI, 1.26–1.35) (Table 3).

Impact of Gastrointestinal Risk Factors on Concomitant Gastroprotective Agent Therapy

As shown in Table 2, a significantly higher proportion of concomitant patients within both the ns-NSAID and coxib cohorts had prior GI diagnoses compared with nonconcomitant patients ($P < .0001$). Furthermore, prior GI diagnoses were more common among concomitant coxib users compared with concomitant ns-NSAID users (22.8% vs 12.3%; $P < .0001$). In general and consistent with these results, the multivariate analysis found that patients at increased risk of GI events were more likely to initiate concomitant therapy (Table 3). The probability of concomitancy was 38% higher for patients aged older than 65 years compared with those aged 36–45 years (OR, 1.38; 95% CI, 1.27–1.50), 36% higher for patients with a previous ulcer diagnosis (OR, 1.36; 95% CI, 1.20–1.54), 26% higher for patients with concomitant oral steroid use (OR, 1.26; 95% CI, 1.20–1.33), and 62% higher for patients undergoing concomitant anticoagulant therapy (OR, 1.62; 95% CI, 1.42–1.84).

Among ns-NSAID users, concomitancy rates did not vary significantly according to the presence of multiple GI risk factors and ranged from 1.4% among patients with no risk factors to 2.1% among patients with at least 2 risk factors. Similarly, concomitant therapy rates remained consistent across all levels of risk for patients treated with coxibs (no risk factors, 2.6%; 1 risk factor, 2.5%; 2 risk factors or more, 2.4%).

Table 2. Prior GI Diagnoses by Index Prescription and Concomitant Therapy

	ns-NSAIDs		Coxibs	
	Concomitant	Nonconcomitant	Concomitant	Nonconcomitant
Patients, n (%)	1312 (1.4)	91,521 (98.6)	1322 (2.6)	50,048 (97.4)
PPI prescription, n (%)	656 (50)	—	978 (74)	—
H_2RA prescription, n (%)	656 (50)	—	344 (26)	—
GI events during 12-month preperiod, n (%)				
PUD	9 (0.7)[a]	93 (0.1)	17 (1.3)[a]	96 (0.2)
Esophagitis	103 (7.9)[a]	1147 (1.3)	207 (15.7)[a]	1136 (2.3)
Ulcer/upper-GI bleed	23 (1.8)[a]	1035 (1.1)	50 (3.8)[a]	799 (1.6)
Gastritis	53 (4.0)[a]	713 (0.8)	70 (5.3)[a]	593 (1.2)
Any GI events, n (%)	161 (12.3)[a]	2774 (3.0)	302 (22.8)[a]	2355 (4.7)

Table 3. Logistic Regression Results: The Likelihood of Initiating Concomitant Therapy

Independent variable	Reference group	OR	95% CI
Coxibs	ns-NSAIDs	1.31	1.26–1.35
Age, *y*			
19–35	36–45 y	1.04	0.98–1.10
46–55	36–45 y	1.12	1.07–1.17
56–65	36–45 y	1.18	1.12–1.24
>65	36–45 y	1.38	1.27–1.50
Female	Male	1.25	1.21–1.30
Previous PUD	—	2.46	1.81–3.34
Previous esophagitis/GERD	—	3.78	3.47–4.12
Previous ulcer/upper-GI bleed	—	1.36	1.20–1.54
Previous gastritis	—	2.46	2.17–2.78
Previous oral steroid use	—	1.26	1.20–1.33
Pre-/postanticoagulant use	—	1.62	1.42–1.84

Table 4. Logistic Regression Results: Predicting Adherence With Concomitant PPI Therapy

Independent variable	Reference group	OR	95% CI
Age, *y*			
19–35	36–45 y	1.17	0.78–1.75
46–55	36–45 y	1.43	1.08–1.89
56–65	36–45 y	1.06	0.78–1.45
>65	36–45 y	0.81	0.48–1.36
Hypertension	—	0.87	0.67–1.14
Diabetes mellitus	—	1.20	0.83–1.75
Cardiovascular condition	—	1.02	0.67–1.55
Previous PUD	—	1.06	0.42–2.69
Previous ulcer/upper GI-bleed	—	1.62	0.84–3.12
Number of concomitant medications	—	0.90	0.87–0.94
Number of index medication refills	—	0.97	0.94–0.99

However, regardless of the level of risk, rates of coprescribed GPA therapy remained low.

Impact of Adherence on Patient Outcomes

For the purposes of evaluating the impact of adherence in reducing the occurrence of clinically significant upper-GI events, we limited our analysis to the concomitant use of PPIs only, resulting in a sample size of 1643 patients: 664 (40%) were treated with ns-NSAIDs and 979 (60%) were treated with coxibs.

As shown in Figure 1, there was a tendency for patients to be less adherent with GPA therapy as the duration of anti-inflammatory treatment increased (as measured by the number of refills of their anti-inflammatory therapies). These results are confirmed in Table 4, which shows that adherence decreases significantly with increasing numbers of index prescription refills (OR, 0.97; 95% CI, 0.94–0.99). The likelihood of adherence also decreases as patients increase the number of any concomitant medications (OR, .90; 95% CI, 0.87–0.94). Recognized risk factors for ulcer complications did not influence the likelihood of adherence.

Collectively, 68% of ns-NSAID and coxib patients had adherence of 80% or greater over the entire duration of their days' supply of anti-inflammatory drugs. Figures 2 and 3 show the unadjusted rates of GI events per patient-year across increasing levels of adherence. Among ns-NSAID users, the likelihood of GI complications decreases as adherence increases (Figure 2, $R^2 = 0.3088$). In comparison, GI event rates remain relatively constant across all adherence levels for coxib patients (Figure 3, $R^2 = 0.0079$). Among ns-NSAID users, patients with less than 80% adherence were nearly 2.5-fold more likely to experience upper-GI events during therapy compared with patients with 80% or greater adherence (OR, 2.38; 95% CI, 1.02–5.56) (Table 5). Multivariate analyses confirmed that adherence to PPI therapy did not influence the likelihood of GI injury among the coxib cohort. Other factors found to influence the incidence of GI complications included previous PUD for ns-NSAID patients (OR, 19.62; 95% CI, 3.23–119.37) and previous ulcer/upper-GI bleed for coxib patients (OR, 6.22; 95% CI, 2.75–14.07).

The post hoc analysis using cardiovascular diagnoses as a possible proxy for aspirin use found that patients with a previous cardiovascular diagnosis had a significantly higher rate of

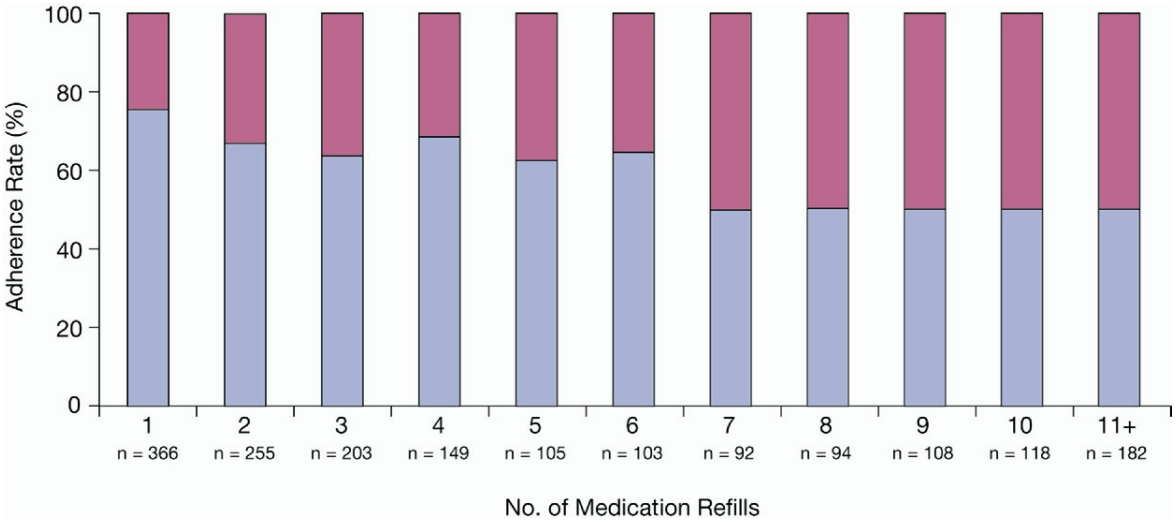

Figure 1. Percent adherence by number of index medication refills. ■, Adherence 80% or greater; ■, adherence less than 80%.

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