

Use of Proton Pump Inhibitors Increases Risk of Incident Kidney Stones

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BACKGROUND AND AIMS:

Proton pump inhibitors (PPIs) are widely prescribed and have effects on gut ion absorption and urinary ion concentrations. PPIs might therefore protect against or contribute to development of kidney stones. We investigated the association between PPI use and kidney stones.

METHODS:

We performed a retrospective study using data from the Women's Veteran's Cohort Study, which comprised men and women, from October 1, 1999 through September 30, 2017. We collected data from 465,891 patients on PPI usage over time, demographics, laboratory results, comorbidities, and medication usage. Time-varying Cox proportional hazards and propensity matching analyses determined risk of PPI use and incident development of kidney stones. Use of histamine-2 receptor antagonists (H2RAs) was measured and levothyroxine use was a negative control exposure.

RESULTS:

PPI use was associated with kidney stones in the unadjusted analysis, with PPI use as a time-varying variable (hazard ratio [HR], 1.74; 95% CI, 1.67–1.82), and persisted in the adjusted analysis (HR, 1.46; CI, 1.38–1.55). The association was maintained in a propensity score-matched subset of PPI users and nonusers (adjusted HR, 1.25; CI 1.19–1.33). Increased dosage of PPI was associated with increased risk of kidney stones (HR, 1.11; CI, 1.09–1.14 for each increase in 30 defined daily doses over a 3-month period). H2RAs were also associated with increased risk (adjusted HR, 1.47; CI 1.31–1.64). We found no association, in adjusted analysis, of levothyroxine use with kidney stones (adjusted HR, 1.06; CI 0.94–1.21).

CONCLUSIONS:

In a large cohort study of veterans, we found PPI use to be associated with a dose-dependent increase in risk of kidney stones. H2RA use also has an association with risk of kidney stones, so acid suppression might be an involved mechanism. The effect is small and should not change prescribing for most patients.

Keywords: Acid Suppression; Pharmacoepidemiology; Calcium; Nephrolithiasis.

Proton pump inhibitors (PPIs), a class of medications that reduce gastric acid production, are used to treat several conditions, including gastroesophageal reflux disease (GERD) and peptic ulcers.^{1,2} PPIs are among the most widely used medications in the United States and abroad, available by prescription and over the counter.^{3–5} While generally well tolerated, an increasing body of literature has found associations of PPI use with a variety of conditions including chronic kidney disease and enteric infections.^{6,7}

Decreased gastric acid secretion with PPIs is associated with gut absorptive effects including impaired absorption of calcium, iron, and magnesium.⁸ Additionally, PPIs are associated with decreased urinary excretion of calcium and magnesium.^{9–11} Given these effects, there is interest in understanding the effects of PPIs on

nephrolithiasis (kidney stones). Decreased calcium gut absorption and decreased urinary calcium excretion should protect against nephrolithiasis, specifically against calcium oxalate stones, the most common stone type.^{12,13} However, decreased urinary excretion of magnesium, an inhibitor of stone formation, could increase risk.^{14,15} Given conflicting mechanisms for a physiologic

Abbreviations used in this paper: CI, confidence interval; DDD, defined daily dose; GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; PPI, proton pump inhibitor; VHA, Veterans Health Administration; eGFR, estimated glomerular filtration rate.

effect of PPIs on stone formation, we performed a retrospective cohort analysis to clarify the relationship of PPI use and nephrolithiasis.

Materials and Methods

Setting

All data were from the Women's Veterans Cohort Study cohort, a national mixed male and female cohort of veterans within the Veterans Health Administration (VHA) who served in recent conflicts in Iraq and Afghanistan.¹⁶ We obtained patient encounter, medication prescribing, and outcomes data. Dispensing information for medications received outside the VHA, including over-the-counter medications, were limited to start and end dates of these medications as entered by providers.

Population

In this retrospective cohort study, we considered patients with at least 2 outpatient encounters between October 1, 1999, and September 30, 2017, for analysis. We defined preobservation as the time between the first primary care encounter to 1 year after and gathered baseline patient characteristics including demographics, comorbidities, and renal function.

The number of outpatient and inpatient encounters during preobservation were measured as a marker of health care utilization. Baseline creatinine was defined as the mean of outpatient creatinine values during preobservation with estimated glomerular filtration rate calculated using Chronic Kidney Disease Epidemiology Collaboration.¹⁷

Exclusions included <1 year of follow-up, diagnosis of nephrolithiasis during or before preobservation, PPI usage during or before preobservation, incomplete date of birth or sex, missing outpatient creatinine, and baseline estimated glomerular filtration rate <30 mL/min.

Observation endpoint was the earliest of the first episode of nephrolithiasis or the last primary care visit.

Outcome Measure and Covariates

We used the International Classification of Diseases–Ninth Revision and –Tenth Revision to identify nephrolithiasis and comorbidities. Comorbidities included diabetes, gout, gastroparesis, GERD, Barrett's esophagus, peptic ulcer disease, gastritis, functional dyspepsia, and gastrointestinal (GI) bleeding. Significant GI surgery was identified with Current Procedural Terminology codes. We utilized previously validated lists of diagnosis codes for nephrolithiasis, diabetes, gout, and GI bleeding.^{18–21} Relevant codes may be found in [Supplementary Table 1](#). Covariates included the number of inpatient and outpatient encounters during

What You Need to Know

Background

Proton pump inhibitors (PPIs) are widely prescribed and have effects on gut ion absorption and urinary ion concentrations, so they might protect against or contribute to development of kidney stones.

Findings

In a large cohort study of veterans, PPI use was associated with a dose-dependent increase in risk of kidney stones. Histamine-2 receptor antagonist use also has an association with risk of kidney stones, so acid suppression might contribute to kidney stone development.

Implications for patient care

The association between PPI use and kidney stone development is small and should not change prescribing patterns for most patients

preobservation and observation and outpatient creatinine values during observation.

We collected data for age, sex, and self-reported race. Medication utilization was measured for thiazide diuretics, loop diuretics, histamine-2 receptor antagonists (H2RAs), and gout-related medications. Both scheduled and as-needed prescriptions for H2RAs were included in H2RA use measurement. [Supplementary Table 2](#) contains a list of measured medications. Prescription data was collected with medication fill dates. The earliest date of PPI usage was defined as the PPI start time. Defined daily dosage (DDD) for PPIs was collected to measure an aggregate total of PPI exposure during a patient's observation period. One DDD was equal to omeprazole 20 mg, pantoprazole 40 mg, lansoprazole 30 mg, rabeprazole 20 mg, esomeprazole 30 mg, and dexlansoprazole 30 mg as per the World Health Organization Drug Statistics Methodology.²² Once-daily and twice-daily dosages could not be distinguished. Thiazide and loop diuretic, H2RA, and gout-related medication use were measured with usage start time equal to the first fill date. Patients were deemed to be continuously on a medication after it had been filled at least once, approximating the intention-to-treat principle in a clinical trial.

Survival Analysis Models

Given the large number of observational studies associating PPI usage with outcomes, 2 models were used to assess robustness of results.

Model 1: Time-Varying Cox Analysis. We developed a time-varying Cox proportional hazards model to study the PPI-nephrolithiasis association. This method performs an adjusted analysis with respect to time-varying covariates (eg, changes in clinical diagnoses or medication usage).²³ In our model, time-varying covariates

included initiation of any of the medications listed previously, diagnosis of the conditions listed previously, creatinine, and number of outpatient visits and hospitalizations in the preceding year. Most recent outpatient creatinine at time points when covariates changed estimated a patient's renal function.

Baseline covariates were included in this model as non-time-varying covariates. Unadjusted analysis measured events per patient time for individuals on and not on a PPI. Patients who start a PPI during observation period contribute non-PPI time before their first filled PPI prescription and contribute PPI time afterward.

Adjusted analysis was performed by sequentially adding covariates to the time-varying model in the order of baseline demographics, medications, comorbidities, laboratory studies, and inpatient and outpatient utilization. Separate adjusted analysis including cumulative DDD over the preceding 3 and 12 months of observation evaluated dose dependence. Hazard ratios (HRs) with 95% confidence intervals (CIs) are reported.

Model 2: Propensity Score Analysis. A randomized controlled study was emulated via matching patients at the start of PPI usage with a similar unexposed control. We performed a 1:1 matched analysis using a propensity score generated for each patient measuring the odds that the individual would be prescribed a PPI. Using the logarithm of the odds (logit) of being prescribed a PPI, a patient was selected randomly from the PPI-exposed group and matched to the individual from the nonexposed group with the closest logit value. Matches could differ by at most 0.2 SDs of the logit scores; otherwise, the PPI-exposed individual was excluded from matching as no close match could be found. To maintain the intention-to-treat principle, patients in the non-PPI group could initiate PPI therapy after the start date. These patients remained in the non-PPI group for analyses. Analyses were performed using R version 3.6.0 (R Foundation for Statistical Computing, Vienna, Austria).

Patients in the matched cohort were right-censored at the earlier of the last outpatient visit or nephrolithiasis episode. Unadjusted analysis in the propensity-matched cohort used the Kaplan-Meier estimator with log-rank testing. Adjusted analysis accounting for demographics, medications, comorbidities, laboratory studies, and healthcare utilization was performed via a Cox proportional hazards model over the matched cohort.

Statistical Analyses

Baseline differences between PPI users and nonusers were compared via chi-square statistic for discrete variables and Kruskal-Wallis test by ranks for continuous variables.

Differences between PPI and non-PPI groups for propensity-matched samples were compared with standardized mean difference with 0.2 for small differences.²⁴ *P* values for propensity-matched samples were

calculated using paired statistics with McNemar's testing for categorical data and Wilcoxon signed rank testing for continuous variables.

Sensitivity Analysis

Several sensitivity analyses were performed to ensure validity. The first analysis included PPIs prescribed outside the VHA; these prescribing data rely on manual entry and self-report, and therefore have limited completeness and accuracy than VHA prescription data. We set a patient's date of first PPI as the earliest of the first VHA and non-VHA PPI.

Second, to assess potential protopathic bias we analyzed an alternate PPI usage definition where patients were considered PPI-exposed after 90 DDD were filled as well as evaluating the effects of introducing a 90-, 180-, and 365-day lag from study entry date to accrual of follow-up time.

A secondary analysis with respect to H2RA evaluated whether results were secondary to PPI usage or factors common to acid suppression medications. A cohort was developed in identical fashion to the PPI cohort except patients who previously took H2RAs during pre-observation or earlier were excluded. In the time-varying Cox model, patients who ever received PPIs during observation were excluded. In the propensity-matched model, matches were between H2RA users not on a PPI to control individuals on neither medication. To assess the potential for an additive/synergistic effect of concurrent PPI and H2RA use, we also compared those PPI patients on concurrent H2RAs (>1 H2RA prescription from 30 days before to 30 days after PPI prescription) in the primary PPI cohort to the control cohort.

Last, a negative control exposure tested the internal validity of our study. This method involves assessing a treatment which is expected to have no impact on the outcome.²⁵ We assessed the HR of levothyroxine, a hypothyroidism medication, for the development of incident nephrolithiasis. Literature review shows no established relationship between levothyroxine and nephrolithiasis.

The STROBE checklist was used to ensure reporting guidelines were followed. Approval for this study was obtained from the Human Studies Subcommittee from the Human Research Protection Program of the VA Connecticut Healthcare System.

Results

The Women's Veterans Cohort Study cohort contained a total of 1,065,962 initial patients for analysis. A total of 465,891 patients remained eligible for analysis after applying exclusion criteria (Figure 1). From this cohort, 89,329 (19.2%) were exposed to PPIs during observation. Baseline demographics for patients ever and never prescribed a PPI are displayed in Table 1.

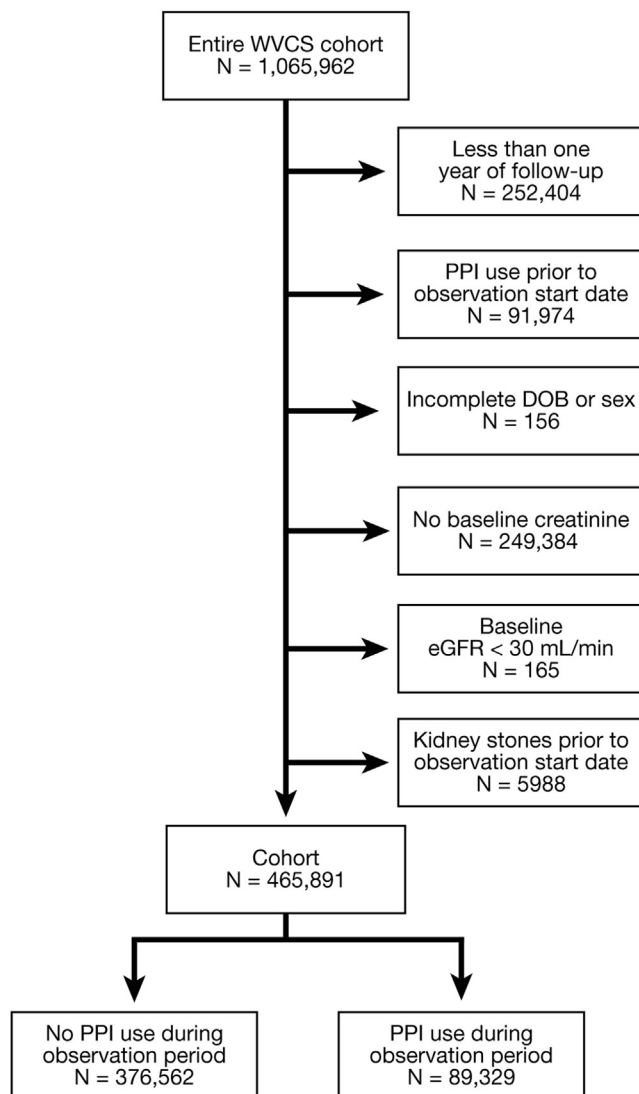


Figure 1. Cohort construction flow diagram with exclusion criteria and final cohort size. DOB, date of birth; eGFR, estimated glomerular filtration rate; WVCS, Women's Veteran's Cohort Study.

All baseline characteristics were statistically different between populations. Individuals ever prescribed PPIs were older at the start of observation, had more outpatient visits and hospitalizations, had more H2RA use, and had more GERD diagnoses. Patients who were ever prescribed a PPI had higher prevalence of all measured comorbidities.

Our cohort had 11,224 cases of nephrolithiasis over 2,544,638 patient-years of observation: 4219 cases in patients with PPI exposure and 7005 cases in those without exposure. PPIs carried an unadjusted incidence rate ratio of 1.74 (95% CI, 1.67–1.82). Based on these analyses, 365 (95% CI, 333–399) patients would need to be exposed to a PPI for 1 additional episode of nephrolithiasis in 1 year. The proximity of diagnosis of nephrolithiasis to prescription of a PPI was measured: 0.7% of cases were within 1 week of prescription, 3.3% within 1 month, and 26% within 1 year.

Table 1. Baseline Characteristics for Patients Who Did and Did Not Receive PPIs During Observation Period

	PPI-Unexposed group (n = 376,562)	PPI-Exposed group (n = 89,329)
Male	87.2	85.9
Race/ethnicity		
White	58.2	54.3
Black	15.3	15.7
Hispanic	10.9	12.3
Other	5.2	4.7
Unknown	10.4	13.1
Age, y	30.25 (26.20–40.12)	31.58 (26.52–41.85)
Baseline creatinine	1.00 (0.90–1.10)	1.00 (0.90–1.10)
H2RA	2.8	8
Thiazide diuretic	5	7.3
Loop diuretic	0.1	0.2
Gout medication	0.4	0.6
GERD	3.3	9.9
Peptic ulcer disease	0.1	0.3
Barrett's disease	0	0.1
GI bleed	1.7	2.5
Gastritis	0.3	0.7
Functional dyspepsia	0.4	1
GI surgery history	0	0
Diabetes	2.1	2.8
Gout	0.01 ± 0.08	0.01 ± 0.09
Outpatient encounters during preobservation	5.00 (3.00–9.00)	7.00 (4.00–11.00)
Inpatient encounters during preobservation	0.00 (0.00–0.00)	0.00 (0.00–0.00)

Values are %, median (interquartile range), or mean ± SD. The *P* value for comparison of all characteristics is <.001 with exception of GI surgery history, which carries a *P* value <.05.

GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

Sequential adjusted analysis was performed using the time-varying model with hazards listed in [Supplementary Table 3](#). Full multivariable adjustment revealed an adjusted HR of 1.46 (95% CI, 1.38–1.55) for PPIs and nephrolithiasis. Analysis restricted to those in the PPI cohort on concurrent H2RA (representing 3% of PPI users) revealed a similar adjusted hazard (1.41; 95% CI, 1.28–1.56), providing no evidence of an additive or synergistic effect of PPIs with H2RAs.

Additional adjusted analysis examined the effects of cumulative DDD on nephrolithiasis. Cumulative DDD measured in the preceding 3 months and 12 months for each patient time interval were used as covariates in the time-varying model. The 3-month cumulative DDD covariate had an adjusted HR of 1.11 (95% CI, 1.09–1.14) per 30-DDD change in cumulative dose. The 12-month cumulative DDD covariate had an adjusted HR of 1.04 (95% CI, 1.02–1.06) per 90-DDD change in cumulative dose.

For the propensity-matched model, the logistic regression model for propensity score had an area under the receiver-operating characteristic curve of 0.80;

Table 2. Characteristics of the Patients Who Did and Did Not Receive PPIs in the Propensity-Matched Cohorts

	PPI-Unexposed group (n = 86,264) ^a	PPI-Exposed group (n = 86,264)	Standardized mean difference ^b
Male	86	85.8	0.006
Race/ethnicity			0.019
White	54.7	54.1	
Black	15.8	15.8	
Hispanic	11.9	12.3	
Other	4.9	4.7	
Unknown	12.8	13.1	
Age, y	32.01 (26.81–42.49)	31.58 (26.52–41.84)	0.044
Most recent creatinine	1.00 (0.90–1.10)	1.00 (0.88–1.10)	<0.001
H2RA	19.8	17.4	0.061
Thiazide diuretic	1.9	1.5	0.034
Loop diuretic	14.7	13.8	0.025
Gout medication	1.2	0.9	0.03
GERD	40.9	40.9	<0.001
Peptic ulcer disease	1	1.3	0.029
Barrett's disease	0.4	0.4	0.005
GI bleed	9.1	8.4	0.024
Gastritis	5	5.7	0.031
Functional dyspepsia	3.6	3.7	0.006
GI surgery history	0.3	0.2	0.02
Diabetes	7.8	6.1	0.068
Gout	2.7	1.9	0.052
Outpatient encounters in preceding year	5.00 (3.00–10.00)	5.00 (2.00–10.00)	0.019
Inpatient encounters in preceding year	0.00 (0.00–0.00)	0.00 (0.00–0.00)	0.035

Values are % or median (interquartile range).

GERD, gastroesophageal reflux disease; GI, gastrointestinal; H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

^a3.4% of PPI users were unmatched because no control individual meeting matching criteria was identified; these patients were excluded from analysis.

^bStandardized mean difference <0.2 suggests good matching with respect to the specific variable.

96.5% of patients in the PPI group were matched with 86,264 patients in both groups. Matched cohort characteristics are displayed in [Table 2](#).

In the propensity-matched cohort, there were 4735 episodes of nephrolithiasis over 765,154 patient-years of observation with median observation time of 4.01 (interquartile range, 1.92–6.52) years. The PPI group developed nephrolithiasis at a rate of 69.6 cases per 10,000 patient-years vs 55.3 cases per 10,000 patient-years in the non-PPI group. The unadjusted rate ratio in the propensity-matched cohort was 1.25 (95% CI, 1.19–1.33) and the Cox model adjusted HR was 1.28 (95% CI, 1.21–1.36). [Figure 2](#) displays the unadjusted survival per the Kaplan-Meier estimator.

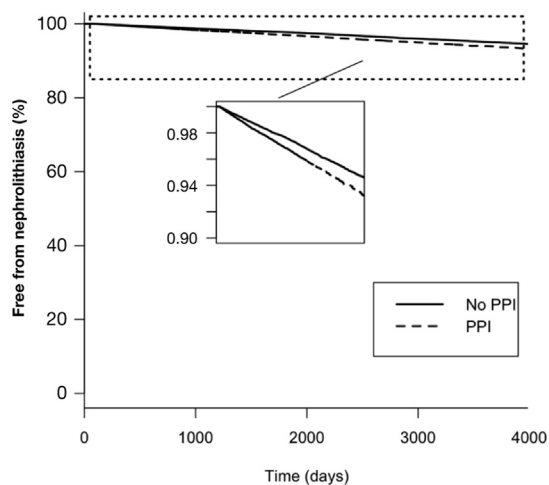
Sensitivity analysis including PPIs prescribed outside the VHA showed an unadjusted HR of 1.71 (95% CI, 1.63–1.79) and an adjusted HR of 1.42 (95% CI, 1.34–1.51). The sensitivity analysis in which individuals accrued at least 90 DDD to be defined as a PPI user showed an unadjusted HR of 1.62 (95% CI, 1.54–1.70) and an adjusted HR of 1.24 (95% CI, 1.17–1.33). Finally, analyses in which individuals needed to accrue 90, 180, and 365 days before the start of PPI observation time showed an unadjusted HRs of 1.66 (95% CI, 1.58–1.75), 1.63 (95% CI, 1.54–1.72), and 1.57 (95% CI, 1.48–1.66), respectively, and an adjusted HRs of 1.39 (95% CI, 1.30–1.48), 1.36 (95% CI, 1.27–1.45), and 1.30 (95% CI, 1.21–1.40), respectively.

Secondary analysis evaluating the H2RAs-nephrolithiasis relationship showed an unadjusted HR of 1.70 (95% CI, 1.53–1.89) and an adjusted HR of 1.47 (95% CI, 1.31–1.64). This H2RA cohort generally was older, had more women, had more Black/Hispanic patients, had a lower diagnosis of GERD or GI bleeding during preobservation, and had more outpatient visits than the PPI cohort. A propensity-matched cohort contained 21,907 patients with H2RA but not PPI exposure matched 1:1 to patients without exposure to either H2RAs or PPIs. Unadjusted and an adjusted analyses revealed an HR of 1.32 (95% CI, 1.17–1.50).

Negative control exposure analysis evaluating levothyroxine showed an unadjusted HR of 1.28 (95% CI, 1.13–1.46) and an adjusted HR of 1.06 (95% CI, 0.94–1.21). A propensity-matched cohort was developed in a similar fashion as with PPI and H2RA cohorts with 10,630 levothyroxine users matched 1:1 to nonusers. The unadjusted HR was 0.97 (95% CI, 0.82–1.16), with an adjusted HR of 1.02 (95% CI, 0.86–1.22). [Table 3](#) summarizes the unadjusted and adjusted HRs of these models.

Discussion

This study evaluated the relationship between PPIs and development of incident nephrolithiasis. Given



No. at Risk					
	0	1000	2000	3000	4000
PPI-Unexposed	74,787	56,553	33,313	15,767	5,057
PPI-Exposed	74,787	49,356	25,679	9,810	2,027

Figure 2. Kaplan-Meier curve for the PPI and non-PPI propensity-matched cohorts with respect to percentage free from nephrolithiasis (log-rank test $P < 1.0 \times 10^{-16}$).

numerous observational studies linking PPIs to various comorbidities, we used a rigorous approach using 2 survival analysis models. Both models found modest association of PPI use with nephrolithiasis, which was preserved after adjustment for pertinent covariates including demographics, laboratory studies, diagnoses, medications, and health care utilization. Furthermore, the effect was dose dependent, with modest increases in risk with increased PPI prescribing. Dose dependence was less pronounced when assessed over a longer time window of 12 vs 3 months.

This relationship was preserved across sensitivity analyses, including over-the-counter use. A small percentage of patients were found to be diagnosed with nephrolithiasis within 1 week and within 1 month of PPI prescribing. However, the relationship was maintained with modified start times for the observation date, ranging from 90 to 365 days after initial PPI prescription. These findings suggest against a protopathic bias (ie, the association is not primarily due to prescription of PPI for symptoms of nephrolithiasis preceding the diagnosis of the condition). A secondary analysis evaluating H2RA usage revealed an increased hazard for nephrolithiasis. These data suggest the possibility that the PPI-nephrolithiasis association is due to generalized acid suppression therapy. Though the hazard ratios for PPIs and H2RAs are similar, the populations used in the 2 analyses are very distinct; therefore, it is difficult to directly compare hazards between the populations. Levothyroxine, our negative control exposure, carried no association in adjusted or propensity-matched analysis, suggesting that important confounders were captured in this study.

A MEDLINE search through October 2019 found no studies evaluating the PPI-nephrolithiasis association. A

Table 3. HRs for Development of Nephrolithiasis With Medication Exposure vs No Medication Exposure in the Time-Varying Cox and Propensity-Matched Models

	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Model 1: Time-varying Cox		
PPI	1.74 (1.67–1.82)	1.46 (1.38–1.55)
PPI sensitivity analysis: non-VHA medication inclusion	1.71 (1.63–1.79)	1.42 (1.34–1.51)
PPI sensitivity analysis: at least 90-DDD definition of PPI use	1.62 (1.54–1.70)	1.24 (1.17–1.33)
H2RA	1.70 (1.53–1.89)	1.47 (1.31–1.64)
Negative control exposure: levothyroxine	1.28 (1.13–1.46)	1.06 (0.94–1.21)
Model 2: Propensity matching		
PPI	1.25 (1.19–1.33)	1.28 (1.21–1.36)
H2RA	1.32 (1.17–1.50)	1.32 (1.17–1.50)
Negative control exposure: levothyroxine	0.97 (0.82–1.16)	1.02 (0.86–1.22)

Covariates in adjusted analyses included: sex, race/ethnicity, age, most recent creatinine, use of the medications (H2RAs, thiazide diuretics, loop diuretics, gout medications), medical history (gastroesophageal reflux disease, peptic ulcer disease, Barrett's disease, gastrointestinal bleed, gastritis, functional dyspepsia, gastrointestinal surgical history, diabetes, gout) and total number of inpatient/outpatient encounters in the previous year.

CI, confidence interval; DDD, daily defined dose; H2RA, histamine-2 receptor antagonist; HR, hazard ratio; PPI, proton pump inhibitor; VHA, Veterans Health Administration.

study using the Food and Drug Administration Adverse Event Reporting System reported increased odds of nephrolithiasis in PPI users compared with H2RA users, but these are self-reported data that do not allow incidence estimates or adjusted analyses, and standard disproportionality methods were not used.²⁶ The only other report of this association is a conference abstract several years ago that reported an increased nephrolithiasis with acid suppression medications.²⁷

A mechanism to explain this increased risk is uncertain. PPIs decrease intestinal magnesium absorption and reduce urinary magnesium, a well-known nephrolithiasis inhibitor historically prescribed for patients with frequent stones.^{10,26,28} H2RA effects on urinary magnesium are less studied, with scant evidence available suggesting against an effect.¹⁰ The pathophysiology of stone formation is believed to be due to an imbalance in stone-forming and stone-inhibiting molecules within the urine.²⁹ In addition to magnesium, PPI use potentially might decrease urinary concentration of other inhibitory molecules or increase concentrations of stone-facilitating molecules.

Our study has several strengths. We used a large cohort from a national dataset. Propensity matching was done to ensure the 2 study cohorts were similar in

characteristics other than use of PPIs. Analyses were adjusted for a variety of potential confounders including demographics, laboratory values, and medical comorbidities. We also adjusted for healthcare utilization. It has been suggested that PPI prescribing is related to interactions with the healthcare system; this is generally an unmeasured confounder and may contribute to the multitude of health conditions that are now associated with PPI use.^{30–32}

Additionally, we performed a sensitivity analysis accounting for PPI prescriptions obtained outside the VHA. Given that PPIs are commonly obtained over the counter, accounting for nonprescribed use is important. Finally, we performed analyses with a negative control exposure. If a medication not known to have an association with an outcome is found to be positively associated with that outcome, this may indicate bias. We show no association reducing the likelihood that residual confounding accounts for our findings with PPIs.

Our study should be viewed in light of several limitations. First, we acknowledge that our study is retrospective and unmeasured confounders may contribute to the association we observed between PPIs and nephrolithiasis; adjustment with numerous measured potential confounding factors reduced the HR compared with the unadjusted analysis, and inclusion of unmeasured confounders might further reduce the association. Such skepticism is important in light of a recent large randomized control trial in individuals randomized to receive PPI therapy or placebo, which showed increase in enteric infections but otherwise similar rates of commonly associated outcomes such as pneumonia, fracture, and chronic kidney disease.³³ This study did not evaluate nephrolithiasis and with the incidence we found in our analyses, and such a study would need to enroll around 40,000 patients to have sufficient power ($\alpha = 0.05$ and $\beta = 0.2$) to identify a difference; this study of around 18,000 participants is insufficient to evaluate this outcome. Additionally, this study evaluated patients with stable angina who otherwise did not meet criteria for PPI prescription. Our population was all-comers with incident prescription of a PPI, which improves the generalizability of our findings.

Other limitations include that daily dosage data was only obtained for PPI prescriptions within the VHA. Additionally, the study population was younger at the start of observation and mostly men, with over half being white. One should be careful when applying these results to significantly different populations.

Conclusions

We analyzed a large retrospective dataset with 2 robust survival analyses to evaluate the relationship between PPI use and nephrolithiasis. A modest increase in incident nephrolithiasis was seen in patients on PPI in both models with a dose-dependent response. The

mechanism may be related to acid suppression, given that H2RAs also showed an increase. The increased hazard is small; these findings should not alter prescribing of PPIs in the general population. However, these findings may be of interest for patients with history of nephrolithiasis. Further studies are needed to determine the direct effects of PPI use and nephrolithiasis.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <https://doi.org/10.1016/j.cgh.2020.02.053>.

References

1. Katz PO, Gerson LB, Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013;108:308–328; quiz 329.
2. Leontiadis GI, McIntyre L, Sharma VK, et al. Proton pump inhibitor treatment for acute peptic ulcer bleeding. *Cochrane Database Syst Rev* 2004;3:CD002094.
3. Forgacs I, Loganayagam A. Overprescribing proton pump inhibitors. *BMJ* 2008;336:2.
4. Heidelbaugh JJ, Kim AH, Chang R, et al. Overutilization of proton-pump inhibitors: what the clinician needs to know. *Therap Adv Gastroenterol* 2012;5:219–232.
5. Luo H, Fan Q, Xiao S, et al. Changes in proton pump inhibitor prescribing trend over the past decade and pharmacists' effect on prescribing practice at a tertiary hospital. *BMC Health Serv Res* 2018;18:537.
6. Yang YX, Lewis JD, Epstein S, et al. Long-term proton pump inhibitor therapy and risk of hip fracture. *JAMA* 2006; 296:2947–2953.
7. Trifan A, Stanciu C, Gîrleanu I, et al. Proton pump inhibitors therapy and risk of *Clostridium difficile* infection: systematic review and meta-analysis. *World J Gastroenterol* 2017; 23:6500–6515.
8. Ito T, Jensen RT. Association of long-term proton pump inhibitor therapy with bone fractures and effects on absorption of calcium, vitamin B12, iron, and magnesium. *Curr Gastroenterol Rep* 2010;12:448–457.
9. Mizunashi K, Furukawa Y, Katano K, et al. Effect of omeprazole, an inhibitor of H⁺,K(+)–ATPase, on bone resorption in humans. *Calcif Tissue Int* 1993;53:21–25.
10. William JH, Nelson R, Hayman N, et al. Proton-pump inhibitor use is associated with lower urinary magnesium excretion. *Nephrology (Carlton)* 2014;19:798–801.
11. Yang Y-X. Chronic proton pump inhibitor therapy and calcium metabolism. *Curr Gastroenterol Rep* 2012;14:473–479.
12. Curhan GC, Willett WC, Rimm EB, et al. A prospective study of dietary calcium and other nutrients and the risk of symptomatic kidney stones. *N Engl J Med* 1993;328:833–838.
13. Sorensen MD. Calcium intake and urinary stone disease. *Transl Androl Urol* 2014;3:235–240.
14. Su CJ, Shevock PN, Khan SR, et al. Effect of magnesium on calcium oxalate urolithiasis. *J Urol* 1991;145:1092–1095.
15. Fetner CD, Barilla DE, Townsend J, et al. Effects of magnesium oxide on the crystallization of calcium salts in urine in patients with recurrent nephrolithiasis. *J Urol* 1978;120:399–401.

16. Haskell SG, Mattocks K, Goulet JL, et al. The burden of illness in the first year home: do male and female VA users differ in health conditions and healthcare utilization. *Womens Health Issues* 2011;21:92–97.
17. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;150:604–612.
18. Harrold LR, Saag KG, Yood RA, et al. Validity of gout diagnoses in administrative data. *Arthritis Rheum* 2007;57:103–108.
19. Laine L, Yang H, Chang SC, et al. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. *Am J Gastroenterol* 2012;107:1190–1195; quiz 1196.
20. Miller DR, Safford MM, Pogach LM. Who has diabetes? Best estimates of diabetes prevalence in the Department of Veterans Affairs based on computerized patient data. *Diabetes Care* 2004;27(Suppl 2):B10–B21.
21. Tasian GE, Ross ME, Song L, et al. Annual incidence of nephrolithiasis among children and adults in South Carolina from 1997 to 2012. *Clin J Am Soc Nephrol* 2016;11:488–496.
22. World Health Organization Collaborating Centre for Drug Statistics Methodology. Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD). Available at: https://www.whocc.no/atc_ddd_index/?code=A02B. Accessed July 1, 2019.
23. Zhang Z, Reinikainen J, Adeleke KA, et al. Time-varying covariates and coefficients in Cox regression models. *Ann Transl Med* 2018;6:121.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28:3083–3107.
25. Dusetzina SB, Brookhart MA, Maciejewski ML. Control outcomes and exposures for improving internal validity of non-randomized studies. *Health Serv Res* 2015;50:1432–1451.
26. Massey L. Magnesium therapy for nephrolithiasis. *Magnes Res* 2005;18:123–126.
27. Ferraro P CG, Gambaro G, Taylor E. Proton pump inhibitors, histamine receptor-2 blockers and the risk of incident kidney stones. Presented at: American Society of Nephrology Kidney Week; November 17–20, 2016; Chicago, Illinois.
28. Ettinger B, Pak CY, Citron JT, et al. Potassium-magnesium citrate is an effective prophylaxis against recurrent calcium oxalate nephrolithiasis. *J Urol* 1997;158:2069–2073.
29. Han H, Segal AM, Seifter JL, et al. Nutritional management of kidney stones (nephrolithiasis). *Clin Nutr Res* 2015;4:137–152.
30. Moayyedi P. Making sense of the adverse effects of PPIs. *AGA Perspectives*. 2016. Available at: <http://agaperspectives.gastro.org/making-sense-adverse-effects-ppis/#.XPpyG9NKjOR>. Accessed July 1, 2019.
31. Targownik LE, Metge C, Roos L, et al. The prevalence of and the clinical and demographic characteristics associated with high-intensity proton pump inhibitor use. *Am J Gastroenterol* 2007;102:942–950.
32. Dublin S, Walker RL, Jackson ML, et al. Use of proton pump inhibitors and H2 blockers and risk of pneumonia in older adults: a population-based case-control study. *Pharmacoepidemiol Drug Saf* 2010;19:792–802.
33. Moayyedi P, Eikelboom JW, Bosch J, et al. Safety of proton pump inhibitors based on a large, multi-year, randomized trial of patients receiving rivaroxaban or aspirin. *Gastroenterology* 2019;157:682–691.e2.

Reprint requests

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Conflicts of Interest

These authors disclose the following: Francis P. Wilson has received consulting fees from a law firm that represented proton pump inhibitor manufacturers in litigation regarding chronic kidney disease and proton pump inhibitor use. Details of this report and activities surrounding the report were in no way communicated or discussed with that firm, who had no role in the funding, design, conduct, writing, editing, or decision to publish this paper. Loren Laine has served as a consultant for Phathom Pharmaceuticals. The remaining authors disclose no conflicts.

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Supplementary Table 1. ICD and CPT Definitions for Comorbidities and Procedures Measured in Analyses

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
Nephrolithiasis	Calculus of kidney	592.0	9
	Calculus of ureter	592.1	9
	Urinary calculus, unspec	592.9	9
	Uric acid nephrolithiasis	274.11	9
	Calculus in diverticulum of bladder	594.0	9
	Other calculus in bladder	594.1	9
	Calculus in urethra	594.2	9
	Other lower urinary tract calculus	594.8	9
	Calculus of lower urinary tract, unspec	594.9	9
	Calculus of kidney	N20.0	10
	Calculus of ureter	N20.1	10
	Calculus of kidney with calculus of ureter	N20.2	10
	Urinary calculus, unspecified	N20.9	10
	Calculus in bladder	N21.0	10
	Calculus in urethra	N21.1	10
	Other lower urinary tract calculus	N21.8	10
	Calculus of lower urinary tract, unspecified	N21.9	10
	Calculus of urinary tract in diseases classified elsewhere	N22.	10
Gout	Gouty arthropathy	274.00	9
	Gouty nephropathy, unspecified	274.10	9
	Other gouty nephropathy	274.19	9
	Gouty tophi of ear	274.81	9
	Gouty tophi of other sites, except ear	274.82	9
	Gout with other specified manifestations	274.89	9
	Gout, unspecified	274.9	9
	Idiopathic gout, unspecified site	M10.00	10
	Idiopathic gout, right shoulder	M10.011	10
	Idiopathic gout, left shoulder	M10.012	10
	Idiopathic gout, unspecified shoulder	M10.019	10
	Idiopathic gout, right elbow	M10.021	10
	Idiopathic gout, left elbow	M10.022	10
	Idiopathic gout, unspecified elbow	M10.029	10
	Idiopathic gout, right wrist	M10.031	10
	Idiopathic gout, left wrist	M10.032	10
	Idiopathic gout, unspecified wrist	M10.039	10
	Idiopathic gout, right hand	M10.041	10
	Idiopathic gout, left hand	M10.042	10
	Idiopathic gout, unspecified hand	M10.049	10
	Idiopathic gout, right hip	M10.051	10
	Idiopathic gout, left hip	M10.052	10
	Idiopathic gout, unspecified hip	M10.059	10
	Idiopathic gout, right knee	M10.061	10
	Idiopathic gout, left knee	M10.062	10
	Idiopathic gout, unspecified knee	M10.069	10
	Idiopathic gout, right ankle and foot	M10.071	10
	Idiopathic gout, left ankle and foot	M10.072	10
	Idiopathic gout, unspecified ankle and foot	M10.079	10
	Idiopathic gout, vertebrae	M10.08	10
	Idiopathic gout, multiple sites	M10.09	10
	Lead-induced gout, unspecified site	M10.10	10
	Lead-induced gout, right shoulder	M10.111	10
	Lead-induced gout, left shoulder	M10.112	10
	Lead-induced gout, unspecified shoulder	M10.119	10
	Lead-induced gout, right elbow	M10.121	10
	Lead-induced gout, left elbow	M10.122	10
	Lead-induced gout, unspecified elbow	M10.129	10
	Lead-induced gout, right wrist	M10.131	10
	Lead-induced gout, left wrist	M10.132	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Lead-induced gout, unspecified wrist	M10.139	10
	Lead-induced gout, right hand	M10.141	10
	Lead-induced gout, left hand	M10.142	10
	Lead-induced gout, unspecified hand	M10.149	10
	Lead-induced gout, right hip	M10.151	10
	Lead-induced gout, left hip	M10.152	10
	Lead-induced gout, unspecified hip	M10.159	10
	Lead-induced gout, right knee	M10.161	10
	Lead-induced gout, left knee	M10.162	10
	Lead-induced gout, unspecified knee	M10.169	10
	Lead-induced gout, right ankle and foot	M10.171	10
	Lead-induced gout, left ankle and foot	M10.172	10
	Lead-induced gout, unspecified ankle and foot	M10.179	10
	Lead-induced gout, vertebrae	M10.18	10
	Lead-induced gout, multiple sites	M10.19	10
	Drug-induced gout, unspecified site	M10.20	10
	Drug-induced gout, right shoulder	M10.211	10
	Drug-induced gout, left shoulder	M10.212	10
	Drug-induced gout, unspecified shoulder	M10.219	10
	Drug-induced gout, right elbow	M10.221	10
	Drug-induced gout, left elbow	M10.222	10
	Drug-induced gout, unspecified elbow	M10.229	10
	Drug-induced gout, right wrist	M10.231	10
	Drug-induced gout, left wrist	M10.232	10
	Drug-induced gout, unspecified wrist	M10.239	10
	Drug-induced gout, right hand	M10.241	10
	Drug-induced gout, left hand	M10.242	10
	Drug-induced gout, unspecified hand	M10.249	10
	Drug-induced gout, right hip	M10.251	10
	Drug-induced gout, left hip	M10.252	10
	Drug-induced gout, unspecified hip	M10.259	10
	Drug-induced gout, right knee	M10.261	10
	Drug-induced gout, left knee	M10.262	10
	Drug-induced gout, unspecified knee	M10.269	10
	Drug-induced gout, right ankle and foot	M10.271	10
	Drug-induced gout, left ankle and foot	M10.272	10
	Drug-induced gout, unspecified ankle and foot	M10.279	10
	Drug-induced gout, vertebrae	M10.28	10
	Drug-induced gout, multiple sites	M10.29	10
	Gout due to renal impairment, unspecified site	M10.30	10
	Gout due to renal impairment, right shoulder	M10.311	10
	Gout due to renal impairment, left shoulder	M10.312	10
	Gout due to renal impairment, unspecified shoulder	M10.319	10
	Gout due to renal impairment, right elbow	M10.321	10
	Gout due to renal impairment, left elbow	M10.322	10
	Gout due to renal impairment, unspecified elbow	M10.329	10
	Gout due to renal impairment, right wrist	M10.331	10
	Gout due to renal impairment, left wrist	M10.332	10
	Gout due to renal impairment, unspecified wrist	M10.339	10
	Gout due to renal impairment, right hand	M10.341	10
	Gout due to renal impairment, left hand	M10.342	10
	Gout due to renal impairment, unspecified hand	M10.349	10
	Gout due to renal impairment, right hip	M10.351	10
	Gout due to renal impairment, left hip	M10.352	10
	Gout due to renal impairment, unspecified hip	M10.359	10
	Gout due to renal impairment, right knee	M10.361	10
	Gout due to renal impairment, left knee	M10.362	10
	Gout due to renal impairment, unspecified knee	M10.369	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Gout due to renal impairment, right ankle and foot	M10.371	10
	Gout due to renal impairment, left ankle and foot	M10.372	10
	Gout due to renal impairment, unspecified ankle and foot	M10.379	10
	Gout due to renal impairment, vertebrae	M10.38	10
	Gout due to renal impairment, multiple sites	M10.39	10
	Other secondary gout, unspecified site	M10.40	10
	Other secondary gout, right shoulder	M10.411	10
	Other secondary gout, left shoulder	M10.412	10
	Other secondary gout, unspecified shoulder	M10.419	10
	Other secondary gout, right elbow	M10.421	10
	Other secondary gout, left elbow	M10.422	10
	Other secondary gout, unspecified elbow	M10.429	10
	Other secondary gout, right wrist	M10.431	10
	Other secondary gout, left wrist	M10.432	10
	Other secondary gout, unspecified wrist	M10.439	10
	Other secondary gout, right hand	M10.441	10
	Other secondary gout, left hand	M10.442	10
	Other secondary gout, unspecified hand	M10.449	10
	Other secondary gout, right hip	M10.451	10
	Other secondary gout, left hip	M10.452	10
	Other secondary gout, unspecified hip	M10.459	10
	Other secondary gout, right knee	M10.461	10
	Other secondary gout, left knee	M10.462	10
	Other secondary gout, unspecified knee	M10.469	10
	Other secondary gout, right ankle and foot	M10.471	10
	Other secondary gout, left ankle and foot	M10.472	10
	Other secondary gout, unspecified ankle and foot	M10.479	10
	Other secondary gout, vertebrae	M10.48	10
	Other secondary gout, multiple sites	M10.49	10
	Gout, unspecified	M10.9	10
	Idiopathic chronic gout, unspecified site, without tophus (tophi)	M1A.00X0	10
	Idiopathic chronic gout, unspecified site, with tophus (tophi)	M1A.00X1	10
	Idiopathic chronic gout, right shoulder, without tophus (tophi)	M1A.0110	10
	Idiopathic chronic gout, right shoulder, with tophus (tophi)	M1A.0111	10
	Idiopathic chronic gout, left shoulder, without tophus (tophi)	M1A.0120	10
	Idiopathic chronic gout, left shoulder, with tophus (tophi)	M1A.0121	10
	Idiopathic chronic gout, unspecified shoulder, without tophus (tophi)	M1A.0190	10
	Idiopathic chronic gout, unspecified shoulder, with tophus (tophi)	M1A.0191	10
	Idiopathic chronic gout, right elbow, without tophus (tophi)	M1A.0210	10
	Idiopathic chronic gout, right elbow, with tophus (tophi)	M1A.0211	10
	Idiopathic chronic gout, left elbow, without tophus (tophi)	M1A.0220	10
	Idiopathic chronic gout, left elbow, with tophus (tophi)	M1A.0221	10
	Idiopathic chronic gout, unspecified elbow, without tophus (tophi)	M1A.0290	10
	Idiopathic chronic gout, unspecified elbow, with tophus (tophi)	M1A.0291	10
	Idiopathic chronic gout, right wrist, without tophus (tophi)	M1A.0310	10
	Idiopathic chronic gout, right wrist, with tophus (tophi)	M1A.0311	10
	Idiopathic chronic gout, left wrist, without tophus (tophi)	M1A.0320	10
	Idiopathic chronic gout, left wrist, with tophus (tophi)	M1A.0321	10
	Idiopathic chronic gout, unspecified wrist, without tophus (tophi)	M1A.0390	10
	Idiopathic chronic gout, unspecified wrist, with tophus (tophi)	M1A.0391	10
	Idiopathic chronic gout, right hand, without tophus (tophi)	M1A.0410	10
	Idiopathic chronic gout, right hand, with tophus (tophi)	M1A.0411	10
	Idiopathic chronic gout, left hand, without tophus (tophi)	M1A.0420	10
	Idiopathic chronic gout, left hand, with tophus (tophi)	M1A.0421	10
	Idiopathic chronic gout, unspecified hand, without tophus (tophi)	M1A.0490	10
	Idiopathic chronic gout, unspecified hand, with tophus (tophi)	M1A.0491	10
	Idiopathic chronic gout, right hip, without tophus (tophi)	M1A.0510	10
	Idiopathic chronic gout, right hip, with tophus (tophi)	M1A.0511	10
	Idiopathic chronic gout, left hip, without tophus (tophi)	M1A.0520	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Idiopathic chronic gout, left hip, with tophus (tophi)	M1A.0521	10
	Idiopathic chronic gout, unspecified hip, without tophus (tophi)	M1A.0590	10
	Idiopathic chronic gout, unspecified hip, with tophus (tophi)	M1A.0591	10
	Idiopathic chronic gout, right knee, without tophus (tophi)	M1A.0610	10
	Idiopathic chronic gout, right knee, with tophus (tophi)	M1A.0611	10
	Idiopathic chronic gout, left knee, without tophus (tophi)	M1A.0620	10
	Idiopathic chronic gout, left knee, with tophus (tophi)	M1A.0621	10
	Idiopathic chronic gout, unspecified knee, without tophus (tophi)	M1A.0690	10
	Idiopathic chronic gout, unspecified knee, with tophus (tophi)	M1A.0691	10
	Idiopathic chronic gout, right ankle and foot, without tophus (tophi)	M1A.0710	10
	Idiopathic chronic gout, right ankle and foot, with tophus (tophi)	M1A.0711	10
	Idiopathic chronic gout, left ankle and foot, without tophus (tophi)	M1A.0720	10
	Idiopathic chronic gout, left ankle and foot, with tophus (tophi)	M1A.0721	10
	Idiopathic chronic gout, unspecified ankle and foot, without tophus (tophi)	M1A.0790	10
	Idiopathic chronic gout, unspecified ankle and foot, with tophus (tophi)	M1A.0791	10
	Idiopathic chronic gout, vertebrae, without tophus (tophi)	M1A.08X0	10
	Idiopathic chronic gout, vertebrae, with tophus (tophi)	M1A.08X1	10
	Idiopathic chronic gout, multiple sites, without tophus (tophi)	M1A.09X0	10
	Idiopathic chronic gout, multiple sites, with tophus (tophi)	M1A.09X1	10
	Lead-induced chronic gout, unspecified site, without tophus (tophi)	M1A.10X0	10
	Lead-induced chronic gout, unspecified site, with tophus (tophi)	M1A.10X1	10
	Lead-induced chronic gout, right shoulder, without tophus (tophi)	M1A.1110	10
	Lead-induced chronic gout, right shoulder, with tophus (tophi)	M1A.1111	10
	Lead-induced chronic gout, left shoulder, without tophus (tophi)	M1A.1120	10
	Lead-induced chronic gout, left shoulder, with tophus (tophi)	M1A.1121	10
	Lead-induced chronic gout, unspecified shoulder, without tophus (tophi)	M1A.1190	10
	Lead-induced chronic gout, unspecified shoulder, with tophus (tophi)	M1A.1191	10
	Lead-induced chronic gout, right elbow, without tophus (tophi)	M1A.1210	10
	Lead-induced chronic gout, right elbow, with tophus (tophi)	M1A.1211	10
	Lead-induced chronic gout, left elbow, without tophus (tophi)	M1A.1220	10
	Lead-induced chronic gout, left elbow, with tophus (tophi)	M1A.1221	10
	Lead-induced chronic gout, unspecified elbow, without tophus (tophi)	M1A.1290	10
	Lead-induced chronic gout, unspecified elbow, with tophus (tophi)	M1A.1291	10
	Lead-induced chronic gout, right wrist, without tophus (tophi)	M1A.1310	10
	Lead-induced chronic gout, right wrist, with tophus (tophi)	M1A.1311	10
	Lead-induced chronic gout, left wrist, without tophus (tophi)	M1A.1320	10
	Lead-induced chronic gout, left wrist, with tophus (tophi)	M1A.1321	10
	Lead-induced chronic gout, unspecified wrist, without tophus (tophi)	M1A.1390	10
	Lead-induced chronic gout, unspecified wrist, with tophus (tophi)	M1A.1391	10
	Lead-induced chronic gout, right hand, without tophus (tophi)	M1A.1410	10
	Lead-induced chronic gout, right hand, with tophus (tophi)	M1A.1411	10
	Lead-induced chronic gout, left hand, without tophus (tophi)	M1A.1420	10
	Lead-induced chronic gout, left hand, with tophus (tophi)	M1A.1421	10
	Lead-induced chronic gout, unspecified hand, without tophus (tophi)	M1A.1490	10
	Lead-induced chronic gout, unspecified hand, with tophus (tophi)	M1A.1491	10
	Lead-induced chronic gout, right hip, without tophus (tophi)	M1A.1510	10
	Lead-induced chronic gout, right hip, with tophus (tophi)	M1A.1511	10
	Lead-induced chronic gout, left hip, without tophus (tophi)	M1A.1520	10
	Lead-induced chronic gout, left hip, with tophus (tophi)	M1A.1521	10
	Lead-induced chronic gout, unspecified hip, without tophus (tophi)	M1A.1590	10
	Lead-induced chronic gout, unspecified hip, with tophus (tophi)	M1A.1591	10
	Lead-induced chronic gout, right knee, without tophus (tophi)	M1A.1610	10
	Lead-induced chronic gout, right knee, with tophus (tophi)	M1A.1611	10
	Lead-induced chronic gout, left knee, without tophus (tophi)	M1A.1620	10
	Lead-induced chronic gout, left knee, with tophus (tophi)	M1A.1621	10
	Lead-induced chronic gout, unspecified knee, without tophus (tophi)	M1A.1690	10
	Lead-induced chronic gout, unspecified knee, with tophus (tophi)	M1A.1691	10
	Lead-induced chronic gout, right ankle and foot, without tophus (tophi)	M1A.1710	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Lead-induced chronic gout, right ankle and foot, with tophus (tophi)	M1A.1711	10
	Lead-induced chronic gout, left ankle and foot, without tophus (tophi)	M1A.1720	10
	Lead-induced chronic gout, left ankle and foot, with tophus (tophi)	M1A.1721	10
	Lead-induced chronic gout, unspecified ankle and foot, without tophus (tophi)	M1A.1790	10
	Lead-induced chronic gout, unspecified ankle and foot, with tophus (tophi)	M1A.1791	10
	Lead-induced chronic gout, vertebrae, without tophus (tophi)	M1A.18X0	10
	Lead-induced chronic gout, vertebrae, with tophus (tophi)	M1A.18X1	10
	Lead-induced chronic gout, multiple sites, without tophus (tophi)	M1A.19X0	10
	Lead-induced chronic gout, multiple sites, with tophus (tophi)	M1A.19X1	10
	Drug-induced chronic gout, unspecified site, without tophus (tophi)	M1A.20X0	10
	Drug-induced chronic gout, unspecified site, with tophus (tophi)	M1A.20X1	10
	Drug-induced chronic gout, right shoulder, without tophus (tophi)	M1A.2110	10
	Drug-induced chronic gout, right shoulder, with tophus (tophi)	M1A.2111	10
	Drug-induced chronic gout, left shoulder, without tophus (tophi)	M1A.2120	10
	Drug-induced chronic gout, left shoulder, with tophus (tophi)	M1A.2121	10
	Drug-induced chronic gout, unspecified shoulder, without tophus (tophi)	M1A.2190	10
	Drug-induced chronic gout, unspecified shoulder, with tophus (tophi)	M1A.2191	10
	Drug-induced chronic gout, right elbow, without tophus (tophi)	M1A.2210	10
	Drug-induced chronic gout, right elbow, with tophus (tophi)	M1A.2211	10
	Drug-induced chronic gout, left elbow, without tophus (tophi)	M1A.2220	10
	Drug-induced chronic gout, left elbow, with tophus (tophi)	M1A.2221	10
	Drug-induced chronic gout, unspecified elbow, without tophus (tophi)	M1A.2290	10
	Drug-induced chronic gout, unspecified elbow, with tophus (tophi)	M1A.2291	10
	Drug-induced chronic gout, right wrist, without tophus (tophi)	M1A.2310	10
	Drug-induced chronic gout, right wrist, with tophus (tophi)	M1A.2311	10
	Drug-induced chronic gout, left wrist, without tophus (tophi)	M1A.2320	10
	Drug-induced chronic gout, left wrist, with tophus (tophi)	M1A.2321	10
	Drug-induced chronic gout, unspecified wrist, without tophus (tophi)	M1A.2390	10
	Drug-induced chronic gout, unspecified wrist, with tophus (tophi)	M1A.2391	10
	Drug-induced chronic gout, right hand, without tophus (tophi)	M1A.2410	10
	Drug-induced chronic gout, right hand, with tophus (tophi)	M1A.2411	10
	Drug-induced chronic gout, left hand, without tophus (tophi)	M1A.2420	10
	Drug-induced chronic gout, left hand, with tophus (tophi)	M1A.2421	10
	Drug-induced chronic gout, unspecified hand, without tophus (tophi)	M1A.2490	10
	Drug-induced chronic gout, unspecified hand, with tophus (tophi)	M1A.2491	10
	Drug-induced chronic gout, right hip, without tophus (tophi)	M1A.2510	10
	Drug-induced chronic gout, right hip, with tophus (tophi)	M1A.2511	10
	Drug-induced chronic gout, left hip, without tophus (tophi)	M1A.2520	10
	Drug-induced chronic gout, left hip, with tophus (tophi)	M1A.2521	10
	Drug-induced chronic gout, unspecified hip, without tophus (tophi)	M1A.2590	10
	Drug-induced chronic gout, unspecified hip, with tophus (tophi)	M1A.2591	10
	Drug-induced chronic gout, right knee, without tophus (tophi)	M1A.2610	10
	Drug-induced chronic gout, right knee, with tophus (tophi)	M1A.2611	10
	Drug-induced chronic gout, left knee, without tophus (tophi)	M1A.2620	10
	Drug-induced chronic gout, left knee, with tophus (tophi)	M1A.2621	10
	Drug-induced chronic gout, unspecified knee, without tophus (tophi)	M1A.2690	10
	Drug-induced chronic gout, unspecified knee, with tophus (tophi)	M1A.2691	10
	Drug-induced chronic gout, right ankle and foot, without tophus (tophi)	M1A.2710	10
	Drug-induced chronic gout, right ankle and foot, with tophus (tophi)	M1A.2711	10
	Drug-induced chronic gout, left ankle and foot, without tophus (tophi)	M1A.2720	10
	Drug-induced chronic gout, left ankle and foot, with tophus (tophi)	M1A.2721	10
	Drug-induced chronic gout, unspecified ankle and foot, without tophus (tophi)	M1A.2790	10
	Drug-induced chronic gout, unspecified ankle and foot, with tophus (tophi)	M1A.2791	10
	Drug-induced chronic gout, vertebrae, without tophus (tophi)	M1A.28X0	10
	Drug-induced chronic gout, vertebrae, with tophus (tophi)	M1A.28X1	10
	Drug-induced chronic gout, multiple sites, without tophus (tophi)	M1A.29X0	10
	Drug-induced chronic gout, multiple sites, with tophus (tophi)	M1A.29X1	10
	Chronic gout due to renal impairment, unspecified site, without tophus (tophi)	M1A.30X0	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Chronic gout due to renal impairment, unspecified site, with tophus (tophi)	M1A.30X1	10
	Chronic gout due to renal impairment, right shoulder, without tophus (tophi)	M1A.3110	10
	Chronic gout due to renal impairment, right shoulder, with tophus (tophi)	M1A.3111	10
	Chronic gout due to renal impairment, left shoulder, without tophus (tophi)	M1A.3120	10
	Chronic gout due to renal impairment, left shoulder, with tophus (tophi)	M1A.3121	10
	Chronic gout due to renal impairment, unspecified shoulder, without tophus (tophi)	M1A.3190	10
	Chronic gout due to renal impairment, unspecified shoulder, with tophus (tophi)	M1A.3191	10
	Chronic gout due to renal impairment, right elbow, without tophus (tophi)	M1A.3210	10
	Chronic gout due to renal impairment, right elbow, with tophus (tophi)	M1A.3211	10
	Chronic gout due to renal impairment, left elbow, without tophus (tophi)	M1A.3220	10
	Chronic gout due to renal impairment, left elbow, with tophus (tophi)	M1A.3221	10
	Chronic gout due to renal impairment, unspecified elbow, without tophus (tophi)	M1A.3290	10
	Chronic gout due to renal impairment, unspecified elbow, with tophus (tophi)	M1A.3291	10
	Chronic gout due to renal impairment, right wrist, without tophus (tophi)	M1A.3310	10
	Chronic gout due to renal impairment, right wrist, with tophus (tophi)	M1A.3311	10
	Chronic gout due to renal impairment, left wrist, without tophus (tophi)	M1A.3320	10
	Chronic gout due to renal impairment, left wrist, with tophus (tophi)	M1A.3321	10
	Chronic gout due to renal impairment, unspecified wrist, without tophus (tophi)	M1A.3390	10
	Chronic gout due to renal impairment, unspecified wrist, with tophus (tophi)	M1A.3391	10
	Chronic gout due to renal impairment, right hand, without tophus (tophi)	M1A.3410	10
	Chronic gout due to renal impairment, right hand, with tophus (tophi)	M1A.3411	10
	Chronic gout due to renal impairment, left hand, without tophus (tophi)	M1A.3420	10
	Chronic gout due to renal impairment, left hand, with tophus (tophi)	M1A.3421	10
	Chronic gout due to renal impairment, unspecified hand, without tophus (tophi)	M1A.3490	10
	Chronic gout due to renal impairment, unspecified hand, with tophus (tophi)	M1A.3491	10
	Chronic gout due to renal impairment, right hip, without tophus (tophi)	M1A.3510	10
	Chronic gout due to renal impairment, right hip, with tophus (tophi)	M1A.3511	10
	Chronic gout due to renal impairment, left hip, without tophus (tophi)	M1A.3520	10
	Chronic gout due to renal impairment, left hip, with tophus (tophi)	M1A.3521	10
	Chronic gout due to renal impairment, unspecified hip, without tophus (tophi)	M1A.3590	10
	Chronic gout due to renal impairment, unspecified hip, with tophus (tophi)	M1A.3591	10
	Chronic gout due to renal impairment, right knee, without tophus (tophi)	M1A.3610	10
	Chronic gout due to renal impairment, right knee, with tophus (tophi)	M1A.3611	10
	Chronic gout due to renal impairment, left knee, without tophus (tophi)	M1A.3620	10
	Chronic gout due to renal impairment, left knee, with tophus (tophi)	M1A.3621	10
	Chronic gout due to renal impairment, unspecified knee, without tophus (tophi)	M1A.3690	10
	Chronic gout due to renal impairment, unspecified knee, with tophus (tophi)	M1A.3691	10
	Chronic gout due to renal impairment, right ankle and foot, without tophus (tophi)	M1A.3710	10
	Chronic gout due to renal impairment, right ankle and foot, with tophus (tophi)	M1A.3711	10
	Chronic gout due to renal impairment, left ankle and foot, without tophus (tophi)	M1A.3720	10
	Chronic gout due to renal impairment, left ankle and foot, with tophus (tophi)	M1A.3721	10
	Chronic gout due to renal impairment, unspecified ankle and foot, without tophus (tophi)	M1A.3790	10
	Chronic gout due to renal impairment, unspecified ankle and foot, with tophus (tophi)	M1A.3791	10
	Chronic gout due to renal impairment, vertebrae, without tophus (tophi)	M1A.38X0	10
	Chronic gout due to renal impairment, vertebrae, with tophus (tophi)	M1A.38X1	10
	Chronic gout due to renal impairment, multiple sites, without tophus (tophi)	M1A.39X0	10
	Chronic gout due to renal impairment, multiple sites, with tophus (tophi)	M1A.39X1	10
	Other secondary chronic gout, unspecified site, without tophus (tophi)	M1A.40X0	10
	Other secondary chronic gout, unspecified site, with tophus (tophi)	M1A.40X1	10
	Other secondary chronic gout, right shoulder, without tophus (tophi)	M1A.4110	10
	Other secondary chronic gout, right shoulder, with tophus (tophi)	M1A.4111	10
	Other secondary chronic gout, left shoulder, without tophus (tophi)	M1A.4120	10
	Other secondary chronic gout, left shoulder, with tophus (tophi)	M1A.4121	10
	Other secondary chronic gout, unspecified shoulder, without tophus (tophi)	M1A.4190	10
	Other secondary chronic gout, unspecified shoulder, with tophus (tophi)	M1A.4191	10
	Other secondary chronic gout, right elbow, without tophus (tophi)	M1A.4210	10
	Other secondary chronic gout, right elbow, with tophus (tophi)	M1A.4211	10
	Other secondary chronic gout, left elbow, without tophus (tophi)	M1A.4220	10
	Other secondary chronic gout, left elbow, with tophus (tophi)	M1A.4221	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Other secondary chronic gout, unspecified elbow, without tophus (tophi)	M1A.4290	10
	Other secondary chronic gout, unspecified elbow, with tophus (tophi)	M1A.4291	10
	Other secondary chronic gout, right wrist, without tophus (tophi)	M1A.4310	10
	Other secondary chronic gout, right wrist, with tophus (tophi)	M1A.4311	10
	Other secondary chronic gout, left wrist, without tophus (tophi)	M1A.4320	10
	Other secondary chronic gout, left wrist, with tophus (tophi)	M1A.4321	10
	Other secondary chronic gout, unspecified wrist, without tophus (tophi)	M1A.4390	10
	Other secondary chronic gout, unspecified wrist, with tophus (tophi)	M1A.4391	10
	Other secondary chronic gout, right hand, without tophus (tophi)	M1A.4410	10
	Other secondary chronic gout, right hand, with tophus (tophi)	M1A.4411	10
	Other secondary chronic gout, left hand, without tophus (tophi)	M1A.4420	10
	Other secondary chronic gout, left hand, with tophus (tophi)	M1A.4421	10
	Other secondary chronic gout, unspecified hand, without tophus (tophi)	M1A.4490	10
	Other secondary chronic gout, unspecified hand, with tophus (tophi)	M1A.4491	10
	Other secondary chronic gout, right hip, without tophus (tophi)	M1A.4510	10
	Other secondary chronic gout, right hip, with tophus (tophi)	M1A.4511	10
	Other secondary chronic gout, left hip, without tophus (tophi)	M1A.4520	10
	Other secondary chronic gout, left hip, with tophus (tophi)	M1A.4521	10
	Other secondary chronic gout, unspecified hip, without tophus (tophi)	M1A.4590	10
	Other secondary chronic gout, unspecified hip, with tophus (tophi)	M1A.4591	10
	Other secondary chronic gout, right knee, without tophus (tophi)	M1A.4610	10
	Other secondary chronic gout, right knee, with tophus (tophi)	M1A.4611	10
	Other secondary chronic gout, left knee, without tophus (tophi)	M1A.4620	10
	Other secondary chronic gout, left knee, with tophus (tophi)	M1A.4621	10
	Other secondary chronic gout, unspecified knee, without tophus (tophi)	M1A.4690	10
	Other secondary chronic gout, unspecified knee, with tophus (tophi)	M1A.4691	10
	Other secondary chronic gout, right ankle and foot, without tophus (tophi)	M1A.4710	10
	Other secondary chronic gout, right ankle and foot, with tophus (tophi)	M1A.4711	10
	Other secondary chronic gout, left ankle and foot, without tophus (tophi)	M1A.4720	10
	Other secondary chronic gout, left ankle and foot, with tophus (tophi)	M1A.4721	10
	Other secondary chronic gout, unspecified ankle and foot, without tophus (tophi)	M1A.4790	10
	Other secondary chronic gout, unspecified ankle and foot, with tophus (tophi)	M1A.4791	10
	Other secondary chronic gout, vertebrae, without tophus (tophi)	M1A.48X0	10
	Other secondary chronic gout, vertebrae, with tophus (tophi)	M1A.48X1	10
	Other secondary chronic gout, multiple sites, without tophus (tophi)	M1A.49X0	10
	Other secondary chronic gout, multiple sites, with tophus (tophi)	M1A.49X1	10
	Chronic gout, unspecified, without tophus (tophi)	M1A.9XX0	10
	Chronic gout, unspecified, with tophus (tophi)	M1A.9XX1	10
Gastroparesis	Gastroparesis	536.3	9
	Gastroparesis	K31.84	10
Diabetes	DM w/o complication – type 2 not uncontrolled	250.00	9
	Type 1 not uncontrolled	250.01	9
	Type 2 uncontrolled	250.02	9
	Type 1 uncontrolled	250.03	9
	Diabetes with ketoacidosis – type 2 not uncontrolled	250.10	9
	Type 1 not uncontrolled	250.11	9
	Type 2 uncontrolled	250.12	9
	Type 1 uncontrolled	250.13	9
	Diabetes with hyperosmolarity – type 2 not uncontrolled	250.20	9
	Type 1 not uncontrolled	250.21	9
	Type 2 uncontrolled	250.22	9
	Type 1 uncontrolled	250.23	9
	Diabetes with other coma	250.30	9
	Diabetes with other coma – t2 not uncon	250.30	9
	T1 not uncon	250.31	9
	T2 uncon	250.32	9
	T1 uncon	250.33	9
	W/ renal manifestations – t2 not uncon	250.40	9
	T1 not uncon	250.41	9

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	T2 uncon	250.42	9
	T1 uncon	250.43	9
	W/ ophthalmic manifestations – t2 not uncon	250.50	9
	T1 not uncon	250.51	9
	T2 uncon	250.52	9
	T1 uncon	250.53	9
	With neurological manifestations	250.60	9
	W/neurological man – t2 not uncon	250.60	9
	T1 not uncon	250.61	9
	T2 uncon	250.62	9
	T1 uncon	250.63	9
	With peripheral circulatory disorder	250.70	9
	W/peripheral circulatory disorder – t2 not uncon	250.70	9
	T1 not uncon	250.71	9
	T2 uncon	250.72	9
	T1 uncon	250.73	9
	Diabetes with other specified manifestations	250.80	9
	T2 not uncontrolled	250.80	9
	T1 not uncon	250.81	9
	T2 uncon	250.82	9
	T1 uncon	250.83	9
	Diabetes w/ unspecified complication – t2 not uncon	250.90	9
	T1 not uncon	250.91	9
	T2 uncon	250.92	9
	T1 uncon	250.93	9
	Neuropathy in diabetes	357.2	9
	Background diabetic retinopathy	362.01	9
	Proliferative diabetic retinopathy	362.02	9
	Nonproliferative diabetic retinopathy NOS	362.03	9
	Mild nonproliferative diabetic retinopathy	362.04	9
	Moderate nonproliferative diabetic retinopathy	362.05	9
	Severe nonproliferative diabetic retinopathy	362.06	9
	Diabetic macular edema	362.07	9
	Diabetic cataract	366.41	9
	Type 2 diabetes mellitus with unspecified diabetic retinopathy without	E11.319	10
	Proliferative diabetic retinopathy	E11.3591	10
	Proliferative diabetic retinopathy	E11.3592	10
	Proliferative diabetic retinopathy	E11.3593	10
	Proliferative diabetic retinopathy	E11.3599	10
	Nonproliferative diabetic retinopathy NOS	E11.3291	10
	Nonproliferative diabetic retinopathy NOS	E11.3292	10
	Nonproliferative diabetic retinopathy NOS	E11.3293	10
	Nonproliferative diabetic retinopathy NOS	E11.3299	10
	Mild nonproliferative diabetic retinopathy	E11.3291	10
	Mild nonproliferative diabetic retinopathy	E11.3292	10
	Mild nonproliferative diabetic retinopathy	E11.3293	10
	Mild nonproliferative diabetic retinopathy	E11.3299	10
	Moderate nonproliferative diabetic retinopathy	E11.3391	10
	Moderate nonproliferative diabetic retinopathy	E11.3392	10
	Moderate nonproliferative diabetic retinopathy	E11.3393	10
	Moderate nonproliferative diabetic retinopathy	E11.3399	10
	Severe nonproliferative diabetic retinopathy	E11.3491	10
	Severe nonproliferative diabetic retinopathy	E11.3492	10
	Severe nonproliferative diabetic retinopathy	E11.3493	10
	Severe nonproliferative diabetic retinopathy	E11.3499	10
	Diabetic macular edema	E11.311	10
	Drug or chemical induced diabetes mellitus with diabetic cataract	E09.36	10
	Diabetes mellitus due to underlying condition	E08.	10
	Diabetes due to underlying condition w hyperosmolality	E08.0	10
	Diab d/t undrl cond w hyposm w/o nonket hyprgly-hypros coma	E08.00	10
	Diabetes due to underlying condition w hyposm w coma	E08.01	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Diabetes mellitus due to underlying condition w ketoacidosis	E08.1	10
	Diabetes due to underlying condition w ketoacidosis w/o coma	E08.10	10
	Diabetes due to underlying condition w ketoacidosis w coma	E08.11	10
	Diabetes due to underlying condition w kidney complications	E08.2	10
	Diabetes due to underlying condition w diabetic nephropathy	E08.21	10
	Diabetes due to undrl cond w diabetic chronic kidney disease	E08.22	10
	Diabetes due to undrl condition w oth diabetic kidney comp	E08.29	10
	Diabetes due to underlying condition w ophthalmic comp	E08.3	10
	Diabetes due to underlying condition w unsp diabetic rtnop	E08.31	10
	Diab due to undrl cond w unsp diabetic rtnop w macular edema	E08.311	10
	Diab due to undrl cond w unsp diab rtnop w/o macular edema	E08.319	10
	Diabetes due to undrl cond w mild nonprlf diabetic rtnop	E08.32	10
	Diab d/t undrl cond w mild nonprlf diab rtnop w mclr edema	E08.321	10
	Diab d/t undrl cond w mild nonprlf diab rtnop w/o mclr edema	E08.329	10
	Diabetes due to undrl cond w moderate nonprlf diabetic rtnop	E08.33	10
	Diab due to undrl cond w mod nonprlf diab rtnop w mclr edema	E08.331	10
	Diab d/t undrl cond w mod nonprlf diab rtnop w/o mclr edema	E08.339	10
	Diabetes due to undrl cond w severe nonprlf diabetic rtnop	E08.34	10
	Diab d/t undrl cond w severe nonprlf diab rtnop w mclr edema	E08.341	10
	Diab d/t undrl cond w sev nonprlf diab rtnop w/o mclr edema	E08.349	10
	Diabetes due to underlying condition w prolif diabetic rtnop	E08.35	10
	Diab due to undrl cond w prolif diab rtnop w macular edema	E08.351	10
	Diab due to undrl cond w prolif diab rtnop w/o macular edema	E08.359	10
	Diabetes due to underlying condition w diabetic cataract	E08.36	10
	Diabetes due to undrl condition w oth diabetic opth comp	E08.39	10
	Diabetes due to underlying condition w neurological comp	E08.4	10
	Diabetes due to underlying condition w diabetic neurop, unsp	E08.40	10
	Diabetes due to undrl condition w diabetic mononeuropathy	E08.41	10
	Diabetes due to underlying condition w diabetic polyneurop	E08.42	10
	Diab due to undrl cond w diabetic autonm (poly)neuropathy	E08.43	10
	Diabetes due to underlying condition w diabetic amyotrophy	E08.44	10
	Diabetes due to undrl condition w oth diabetic neuro comp	E08.49	10
	Diabetes due to underlying condition w circulatory comp	E08.5	10
	Diab due to undrl cond w diab prph angiopath w/o gangrene	E08.51	10
	Diab due to undrl cond w diabetic prph angiopath w gangrene	E08.52	10
	Diabetes due to underlying condition w oth circulatory comp	E08.59	10
	Diabetes due to underlying condition w oth complications	E08.6	10
	Diabetes due to underlying condition w diabetic arthropathy	E08.61	10
	Diabetes due to undrl cond w diabetic neuropathic arthrop	E08.610	10
	Diabetes due to underlying condition w oth diabetic arthrop	E08.618	10
	Diabetes due to underlying condition w skin complications	E08.62	10
	Diabetes due to underlying condition w diabetic dermatitis	E08.620	10
	Diabetes mellitus due to underlying condition w foot ulcer	E08.621	10
	Diabetes due to underlying condition w oth skin ulcer	E08.622	10
	Diabetes due to underlying condition w oth skin comp	E08.628	10
	Diabetes due to underlying condition w oral complications	E08.63	10
	Diabetes due to underlying condition w periodontal disease	E08.630	10
	Diabetes due to underlying condition w oth oral comp	E08.638	10
	Diabetes mellitus due to underlying condition w hypoglycemia	E08.64	10
	Diabetes due to underlying condition w hypoglycemia w coma	E08.641	10
	Diabetes due to underlying condition w hypoglycemia w/o coma	E08.649	10
	Diabetes due to underlying condition w hyperglycemia	E08.65	10
	Diabetes due to underlying condition w oth complication	E08.69	10
	Diabetes due to underlying condition w unsp complications	E08.8	10
	Diabetes due to underlying condition w/o complications	E08.9	10
	Type 1 diabetes mellitus	E10.	10
	Type 1 diabetes mellitus with ketoacidosis	E10.1	10
	Type 1 diabetes mellitus with ketoacidosis without coma	E10.10	10
	Type 1 diabetes mellitus with ketoacidosis with coma	E10.11	10
	Type 1 diabetes mellitus with kidney complications	E10.2	10
	Type 1 diabetes mellitus with diabetic nephropathy	E10.21	10
	Type 1 diabetes mellitus w diabetic chronic kidney disease	E10.22	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Type 1 diabetes mellitus w oth diabetic kidney complication	E10.29	10
	Type 1 diabetes mellitus with ophthalmic complications	E10.3	10
	Type 1 diabetes mellitus with unsp diabetic retinopathy	E10.31	10
	Type 1 diabetes w unsp diabetic retinopathy w macular edema	E10.311	10
	Type 1 diabetes w unsp diabetic rtnop w/o macular edema	E10.319	10
	Type 1 diabetes w mild nonproliferative diabetic retinopathy	E10.32	10
	Type 1 diab w mild nonprlf diabetic rtnop w macular edema	E10.321	10
	Type 1 diab w mild nonprlf diabetic rtnop w/o macular edema	E10.329	10
	Type 1 diabetes w moderate nonprlf diabetic retinopathy	E10.33	10
	Type 1 diab w moderate nonprlf diab rtnop w macular edema	E10.331	10
	Type 1 diab w moderate nonprlf diab rtnop w/o macular edema	E10.339	10
	Type 1 diabetes w severe nonprlf diabetic retinopathy	E10.34	10
	Type 1 diab w severe nonprlf diabetic rtnop w macular edema	E10.341	10
	Type 1 diab w severe nonprlf diab rtnop w/o macular edema	E10.349	10
	Type 1 diabetes w proliferative diabetic retinopathy	E10.35	10
	Type 1 diabetes w prolif diabetic rtnop w macular edema	E10.351	10
	Type 1 diabetes w prolif diabetic rtnop w/o macular edema	E10.359	10
	Type 1 diabetes mellitus with diabetic cataract	E10.36	10
	Type 1 diabetes w oth diabetic ophthalmic complication	E10.39	10
	Type 1 diabetes mellitus with neurological complications	E10.4	10
	Type 1 diabetes mellitus with diabetic neuropathy, unsp	E10.40	10
	Type 1 diabetes mellitus with diabetic mononeuropathy	E10.41	10
	Type 1 diabetes mellitus with diabetic polyneuropathy	E10.42	10
	Type 1 diabetes w diabetic autonomic (poly)neuropathy	E10.43	10
	Type 1 diabetes mellitus with diabetic amyotrophy	E10.44	10
	Type 1 diabetes w oth diabetic neurological complication	E10.49	10
	Type 1 diabetes mellitus with circulatory complications	E10.5	10
	Type 1 diabetes w diabetic peripheral angiopath w/o gangrene	E10.51	10
	Type 1 diabetes w diabetic peripheral angiopathy w gangrene	E10.52	10
	Type 1 diabetes mellitus with oth circulatory complications	E10.59	10
	Type 1 diabetes mellitus with other specified complications	E10.6	10
	Type 1 diabetes mellitus with diabetic arthropathy	E10.61	10
	Type 1 diabetes mellitus w diabetic neuropathic arthropathy	E10.610	10
	Type 1 diabetes mellitus with other diabetic arthropathy	E10.618	10
	Type 1 diabetes mellitus with skin complications	E10.62	10
	Type 1 diabetes mellitus with diabetic dermatitis	E10.620	10
	Type 1 diabetes mellitus with foot ulcer	E10.621	10
	Type 1 diabetes mellitus with other skin ulcer	E10.622	10
	Type 1 diabetes mellitus with other skin complications	E10.628	10
	Type 1 diabetes mellitus with oral complications	E10.63	10
	Type 1 diabetes mellitus with periodontal disease	E10.630	10
	Type 1 diabetes mellitus with other oral complications	E10.638	10
	Type 1 diabetes mellitus with hypoglycemia	E10.64	10
	Type 1 diabetes mellitus with hypoglycemia with coma	E10.641	10
	Type 1 diabetes mellitus with hypoglycemia without coma	E10.649	10
	Type 1 diabetes mellitus with hyperglycemia	E10.65	10
	Type 1 diabetes mellitus with other specified complication	E10.69	10
	Type 1 diabetes mellitus with unspecified complications	E10.8	10
	Type 1 diabetes mellitus without complications	E10.9	10
	Type 2 diabetes mellitus	E11.	10
	Type 2 diabetes mellitus with hyperosmolarity	E11.0	10
	Type 2 diab w hyprosm w/o nonket hyprgly-hypros coma (NKHHC)	E11.00	10
	Type 2 diabetes mellitus with hyperosmolarity with coma	E11.01	10
	Type 2 diabetes mellitus with kidney complications	E11.2	10
	Type 2 diabetes mellitus with diabetic nephropathy	E11.21	10
	Type 2 diabetes mellitus w diabetic chronic kidney disease	E11.22	10
	Type 2 diabetes mellitus w oth diabetic kidney complication	E11.29	10
	Type 2 diabetes mellitus with ophthalmic complications	E11.3	10
	Type 2 diabetes mellitus with unsp diabetic retinopathy	E11.31	10
	Type 2 diabetes w unsp diabetic retinopathy w macular edema	E11.311	10
	Type 2 diabetes w unsp diabetic rtnop w/o macular edema	E11.319	10
	Type 2 diabetes w mild nonproliferative diabetic retinopathy	E11.32	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Type 2 diab w mild nonprlf diabetic rtnop w macular edema	E11.321	10
	Type 2 diab w mild nonprlf diabetic rtnop w/o macular edema	E11.329	10
	Type 2 diabetes w moderate nonprlf diabetic retinopathy	E11.33	10
	Type 2 diab w moderate nonprlf diab rtnop w macular edema	E11.331	10
	Type 2 diab w moderate nonprlf diab rtnop w/o macular edema	E11.339	10
	Type 2 diabetes w severe nonprlf diabetic retinopathy	E11.34	10
	Type 2 diab w severe nonprlf diabetic rtnop w macular edema	E11.341	10
	Type 2 diab w severe nonprlf diab rtnop w/o macular edema	E11.349	10
	Type 2 diabetes w proliferative diabetic retinopathy	E11.35	10
	Type 2 diabetes w prolif diabetic rtnop w macular edema	E11.351	10
	Type 2 diabetes w prolif diabetic rtnop w/o macular edema	E11.359	10
	Type 2 diabetes mellitus with diabetic cataract	E11.36	10
	Type 2 diabetes w oth diabetic ophthalmic complication	E11.39	10
	Type 2 diabetes mellitus with neurological complications	E11.4	10
	Type 2 diabetes mellitus with diabetic neuropathy, unsp	E11.40	10
	Type 2 diabetes mellitus with diabetic mononeuropathy	E11.41	10
	Type 2 diabetes mellitus with diabetic polyneuropathy	E11.42	10
	Type 2 diabetes w diabetic autonomic (poly)neuropathy	E11.43	10
	Type 2 diabetes mellitus with diabetic amyotrophy	E11.44	10
	Type 2 diabetes w oth diabetic neurological complication	E11.49	10
	Type 2 diabetes mellitus with circulatory complications	E11.5	10
	Type 2 diabetes w diabetic peripheral angiopath w/o gangrene	E11.51	10
	Type 2 diabetes w diabetic peripheral angiopathy w gangrene	E11.52	10
	Type 2 diabetes mellitus with oth circulatory complications	E11.59	10
	Type 2 diabetes mellitus with other specified complications	E11.6	10
	Type 2 diabetes mellitus with diabetic arthropathy	E11.61	10
	Type 2 diabetes mellitus w diabetic neuropathic arthropathy	E11.610	10
	Type 2 diabetes mellitus with other diabetic arthropathy	E11.618	10
	Type 2 diabetes mellitus with skin complications	E11.62	10
	Type 2 diabetes mellitus with diabetic dermatitis	E11.620	10
	Type 2 diabetes mellitus with foot ulcer	E11.621	10
	Type 2 diabetes mellitus with other skin ulcer	E11.622	10
	Type 2 diabetes mellitus with other skin complications	E11.628	10
	Type 2 diabetes mellitus with oral complications	E11.63	10
	Type 2 diabetes mellitus with periodontal disease	E11.630	10
	Type 2 diabetes mellitus with other oral complications	E11.638	10
	Type 2 diabetes mellitus with hypoglycemia	E11.64	10
	Type 2 diabetes mellitus with hypoglycemia with coma	E11.641	10
	Type 2 diabetes mellitus with hypoglycemia without coma	E11.649	10
	Type 2 diabetes mellitus with hyperglycemia	E11.65	10
	Type 2 diabetes mellitus with other specified complication	E11.69	10
	Type 2 diabetes mellitus with unspecified complications	E11.8	10
	Type 2 diabetes mellitus without complications	E11.9	10
	Other specified diabetes mellitus	E13.	10
	Other specified diabetes mellitus with hyperosmolarity	E13.0	10
	Oth diab w hyprosm w/o nonket hyprgly-hypros coma (NKHHC)	E13.00	10
	Oth diabetes mellitus with hyperosmolarity with coma	E13.01	10
	Other specified diabetes mellitus with ketoacidosis	E13.1	10
	Oth diabetes mellitus with ketoacidosis without coma	E13.10	10
	Oth diabetes mellitus with ketoacidosis with coma	E13.11	10
	Other specified diabetes mellitus with kidney complications	E13.2	10
	Other specified diabetes mellitus with diabetic nephropathy	E13.21	10
	Oth diabetes mellitus with diabetic chronic kidney disease	E13.22	10
	Oth diabetes mellitus with oth diabetic kidney complication	E13.29	10
	Oth diabetes mellitus with ophthalmic complications	E13.3	10
	Oth diabetes mellitus with unspecified diabetic retinopathy	E13.31	10
	Oth diabetes w unsp diabetic retinopathy w macular edema	E13.311	10
	Oth diabetes w unsp diabetic retinopathy w/o macular edema	E13.319	10
	Oth diabetes w mild nonproliferative diabetic retinopathy	E13.32	10
	Oth diabetes w mild nonprlf diabetic rtnop w macular edema	E13.321	10
	Oth diabetes w mild nonprlf diabetic rtnop w/o macular edema	E13.329	10
	Oth diabetes w moderate nonprlf diabetic retinopathy	E13.33	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Oth diab w moderate nonprlf diabetic rtnop w macular edema	E13.331	10
	Oth diab w moderate nonprlf diabetic rtnop w/o macular edema	E13.339	10
	Oth diabetes w severe nonproliferative diabetic retinopathy	E13.34	10
	Oth diabetes w severe nonprlf diabetic rtnop w macular edema	E13.341	10
	Oth diab w severe nonprlf diabetic rtnop w/o macular edema	E13.349	10
	Oth diabetes mellitus w proliferative diabetic retinopathy	E13.35	10
	Oth diabetes w prolif diabetic retinopathy w macular edema	E13.351	10
	Oth diabetes w prolif diabetic retinopathy w/o macular edema	E13.359	10
	Other specified diabetes mellitus with diabetic cataract	E13.36	10
	Oth diabetes mellitus w oth diabetic ophthalmic complication	E13.39	10
	Oth diabetes mellitus with neurological complications	E13.4	10
	Oth diabetes mellitus with diabetic neuropathy, unspecified	E13.40	10
	Oth diabetes mellitus with diabetic mononeuropathy	E13.41	10
	Oth diabetes mellitus with diabetic polyneuropathy	E13.42	10
	Oth diabetes mellitus w diabetic autonomic (poly)neuropathy	E13.43	10
	Other specified diabetes mellitus with diabetic amyotrophy	E13.44	10
	Oth diabetes w oth diabetic neurological complication	E13.49	10
	Oth diabetes mellitus with circulatory complications	E13.5	10
	Oth diabetes w diabetic peripheral angiopathy w/o gangrene	E13.51	10
	Oth diabetes w diabetic peripheral angiopathy w gangrene	E13.52	10
	Oth diabetes mellitus with other circulatory complications	E13.59	10
	Oth diabetes mellitus with other specified complications	E13.6	10
	Other specified diabetes mellitus with diabetic arthropathy	E13.61	10
	Oth diabetes mellitus with diabetic neuropathic arthropathy	E13.610	10
	Oth diabetes mellitus with other diabetic arthropathy	E13.618	10
	Other specified diabetes mellitus with skin complications	E13.62	10
	Other specified diabetes mellitus with diabetic dermatitis	E13.620	10
	Other specified diabetes mellitus with foot ulcer	E13.621	10
	Other specified diabetes mellitus with other skin ulcer	E13.622	10
	Oth diabetes mellitus with other skin complications	E13.628	10
	Other specified diabetes mellitus with oral complications	E13.63	10
	Other specified diabetes mellitus with periodontal disease	E13.630	10
	Oth diabetes mellitus with other oral complications	E13.638	10
	Other specified diabetes mellitus with hypoglycemia	E13.64	10
	Oth diabetes mellitus with hypoglycemia with coma	E13.641	10
	Oth diabetes mellitus with hypoglycemia without coma	E13.649	10
	Other specified diabetes mellitus with hyperglycemia	E13.65	10
	Oth diabetes mellitus with other specified complication	E13.69	10
	Oth diabetes mellitus with unspecified complications	E13.8	10
	Other specified diabetes mellitus without complications	E13.9	10
GERD	Dyspepsia and other specified disorders of function of stomach	536.8	9
	Unspecified functional disorder of the stomach	536.9	9
	GERD	530.81	9
	Gastro-esophageal reflux disease	K21	10
	Gastro-esophageal reflux disease with esophagitis	K21.0	10
	Gastro-esophageal reflux disease without esophagitis	K21.9	10
	Heartburn	R12	10
	Functional dyspepsia	K30	10
Barrett's disease	Barrett's esophagus	530.85	9
	Barrett's esophagus	K22.7	10
	Barrett's esophagus... without dysplasia	K22.70	10
	Barrett's esophagus with dysplasia	K22.71	10
	Barrett's esophagus with low grade dysplasia	K22.710	10
	Barrett's esophagus with high grade dysplasia	K22.711	10
	Barrett's esophagus with dysplasia... unspecified	K22.719	10
Gastroduodenal ulcer	Gastric ulcer	531	9
	Acute gastric ulcer with hemorrhage	531.0	9
	Acute gastric ulcer with hemorrhage, without mention	531.00	9
	Acute gastric ulcer with hemorrhage, with obstruction	531.01	9

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Acute gastric ulcer with perforation	531.1	9
	Acute gastric ulcer with perforation, without mention	531.10	9
	Acute gastric ulcer with perforation, with obstruction	531.11	9
	Acute gastric ulcer with hemorrhage and perforation	531.2	9
	Acute gastric ulcer with hemorrhage and perforation,	531.20	9
	Acute gastric ulcer with hemorrhage and perforation,	531.21	9
	Acute gastric ulcer without mention of hemorrhage	531.3	9
	Acute gastric ulcer without mention of hemorrhage	531.30	9
	Acute gastric ulcer without mention of hemorrhage	531.31	9
	Chronic or unspecified gastric ulcer with hemorrhage	531.4	9
	Chronic or unspecified gastric ulcer with hemorrhage,	531.40	9
	Chronic or unspecified gastric ulcer with hemorrhage,	531.41	9
	Chronic or unspecified gastric ulcer with perforation	531.5	9
	Chronic or unspecified gastric ulcer with perforation,	531.50	9
	Chronic or unspecified gastric ulcer with perforation,	531.51	9
	Chronic or unspecified gastric ulcer with hemorrhage	531.6	9
	Chronic or unspecified gastric ulcer with hemorrhage	531.60	9
	Chronic or unspecified gastric ulcer with hemorrhage	531.61	9
	Chronic gastric ulcer without mention of hemorrhage	531.7	9
	Chronic gastric ulcer without mention of hemorrhage	531.70	9
	Chronic gastric ulcer without mention of hemorrhage	531.71	9
	Gastric ulcer unspecified as acute or chronic	531.9	9
	Gastric ulcer, unspecified as acute or chronic,	531.90	9
	Gastric ulcer, unspecified as acute or chronic,	531.91	9
	Duodenal ulcer	532	9
	Acute duodenal ulcer with hemorrhage	532.0	9
	Acute duodenal ulcer with hemorrhage, without mention	532.00	9
	Acute duodenal ulcer with hemorrhage, with obstruction	532.01	9
	Acute duodenal ulcer with perforation	532.1	9
	Acute duodenal ulcer with perforation, without mention	532.10	9
	Acute duodenal ulcer with perforation, with obstruction	532.11	9
	Acute duodenal ulcer with hemorrhage and perforation	532.2	9
	Acute duodenal ulcer with hemorrhage and perforation,	532.20	9
	Acute duodenal ulcer with hemorrhage and perforation,	532.21	9
	Acute duodenal ulcer without mention of hemorrhage	532.3	9
	Acute duodenal ulcer without mention of hemorrhage	532.30	9
	Acute duodenal ulcer without mention of hemorrhage	532.31	9
	Chronic or unspecified duodenal ulcer with hemorrhage	532.4	9
	Chronic or unspecified duodenal ulcer with hemorrhage,	532.40	9
	Chronic or unspecified duodenal ulcer with hemorrhage,	532.41	9
	Chronic or unspecified duodenal ulcer with perforation	532.5	9
	Chronic or unspecified duodenal ulcer with perforation,	532.50	9
	Chronic or unspecified duodenal ulcer with perforation,	532.51	9
	Chronic or unspecified duodenal ulcer with hemorrhage	532.6	9
	Chronic or unspecified duodenal ulcer with hemorrhage	532.60	9
	Chronic or unspecified duodenal ulcer with hemorrhage	532.61	9
	Chronic duodenal ulcer without mention of hemorrhage	532.7	9
	Chronic duodenal ulcer without mention of hemorrhage	532.70	9
	Chronic duodenal ulcer without mention of hemorrhage	532.71	9
	Duodenal ulcer unspecified as acute or chronic	532.9	9
	Duodenal ulcer, unspecified as acute or chronic,	532.90	9
	Duodenal ulcer, unspecified as acute or chronic,	532.91	9
	Peptic ulcer site unspecified	533	9
	Acute peptic ulcer of unspecified site with	533.0	9
	Acute peptic ulcer of unspecified site with	533.00	9
	Acute peptic ulcer of unspecified site with	533.01	9
	Acute peptic ulcer of unspecified site with	533.1	9
	Acute peptic ulcer of unspecified site with	533.10	9
	Acute peptic ulcer of unspecified site with	533.11	9
	Acute peptic ulcer of unspecified site with	533.2	9
	Acute peptic ulcer of unspecified site with	533.20	9
	Acute peptic ulcer of unspecified site with	533.21	9

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Acute peptic ulcer of unspecified site without	533.3	9
	Acute peptic ulcer of unspecified site without	533.30	9
	Acute peptic ulcer of unspecified site without	533.31	9
	Chronic or unspecified peptic ulcer of unspecified	533.4	9
	Chronic or unspecified peptic ulcer of unspecified	533.40	9
	Chronic or unspecified peptic ulcer of unspecified	533.41	9
	Chronic or unspecified peptic ulcer of unspecified	533.5	9
	Chronic or unspecified peptic ulcer of unspecified	533.50	9
	Chronic or unspecified peptic ulcer of unspecified	533.51	9
	Chronic or unspecified peptic ulcer of unspecified	533.6	9
	Chronic or unspecified peptic ulcer of unspecified	533.60	9
	Chronic or unspecified peptic ulcer of unspecified	533.61	9
	Chronic peptic ulcer of unspecified site without	533.7	9
	Chronic peptic ulcer of unspecified site without	533.70	9
	Chronic peptic ulcer of unspecified site without	533.71	9
	Peptic ulcer of unspecified site unspecified as	533.9	9
	Peptic ulcer of unspecified site, unspecified as	533.90	9
	Peptic ulcer of unspecified site, unspecified as	533.91	9
	Gastrojejunal ulcer	534	9
	Acute gastrojejunal ulcer with hemorrhage	534.0	9
	Acute gastrojejunal ulcer with hemorrhage, without mention	534.00	9
	Acute gastrojejunal ulcer, with hemorrhage, with obstruction	534.01	9
	Acute gastrojejunal ulcer with perforation	534.1	9
	Acute gastrojejunal ulcer with perforation, without mention	534.10	9
	Acute gastrojejunal ulcer with perforation, with obstruction	534.11	9
	Acute gastrojejunal ulcer with hemorrhage and perforation	534.2	9
	Acute gastrojejunal ulcer with hemorrhage and perforation,	534.20	9
	Acute gastrojejunal ulcer with hemorrhage and perforation,	534.21	9
	Acute gastrojejunal ulcer without mention of hemorrhage	534.3	9
	Acute gastrojejunal ulcer without mention of hemorrhage	534.30	9
	Acute gastrojejunal ulcer without mention of hemorrhage	534.31	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.4	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage,	534.40	9
	Chronic or unspecified gastrojejunal ulcer, with hemorrhage,	534.41	9
	Chronic or unspecified gastrojejunal ulcer with perforation	534.5	9
	Chronic or unspecified gastrojejunal ulcer with perforation,	534.50	9
	Chronic or unspecified gastrojejunal ulcer with perforation,	534.51	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.6	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.60	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage	534.61	9
	Chronic gastrojejunal ulcer without mention of hemorrhage	534.7	9
	Chronic gastrojejunal ulcer without mention of hemorrhage	534.70	9
	Chronic gastrojejunal ulcer without mention of hemorrhage	534.71	9
	Gastrojejunal ulcer unspecified as acute or chronic	534.9	9
	Gastrojejunal ulcer, unspecified as acute or chronic,	534.90	9
	Gastrojejunal ulcer, unspecified as acute or chronic,	534.91	9
	Gastric ulcer	K25	10
	Acute gastric ulcer with hemorrhage	K25.0	10
	Acute gastric ulcer with perforation	K25.1	10
	Acute gastric ulcer with both hemorrhage and perforation	K25.2	10
	Acute gastric ulcer without hemorrhage or perforation	K25.3	10
	Chronic or unspecified gastric ulcer with hemorrhage	K25.4	10
	Chronic or unspecified gastric ulcer with perforation	K25.5	10
	Chronic or unspecified gastric ulcer with both hemorrhage and perforation	K25.6	10
	Chronic gastric ulcer without hemorrhage or perforation	K25.7	10
	Gastric ulcer, unspecified as acute or chronic, without hemorrhage or perforatio	K25.9	10
	Duodenal ulcer	K26	10
	Acute duodenal ulcer with hemorrhage	K26.0	10
	Acute duodenal ulcer with perforation	K26.1	10
	Acute duodenal ulcer with both hemorrhage and perforation	K26.2	10
	Acute duodenal ulcer without hemorrhage or perforation	K26.3	10
	Chronic or unspecified duodenal ulcer with hemorrhage	K26.4	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
Gastritis	Chronic or unspecified duodenal ulcer with perforation	K26.5	10
	Chronic or unspecified duodenal ulcer with both hemorrhage and perforation	K26.6	10
	Chronic duodenal ulcer without hemorrhage or perforation	K26.7	10
	Duodenal ulcer, unspecified as acute or chronic, without hemorrhage or perfora	K26.9	10
	Peptic ulcer, site unspecified	K27	10
	Acute peptic ulcer, site unspecified, with hemorrhage	K27.0	10
	Acute peptic ulcer, site unspecified, with perforation	K27.1	10
	Acute peptic ulcer, site unspecified, with both hemorrhage and perforation	K27.2	10
	Acute peptic ulcer, site unspecified, without hemorrhage or perforation	K27.3	10
	Chronic or unspecified peptic ulcer, site unspecified, with hemorrhage	K27.4	10
	Chronic or unspecified peptic ulcer, site unspecified, with perforation	K27.5	10
	Chronic or unspecified peptic ulcer, site unspecified, with both hemorrhage and	K27.6	10
	Chronic peptic ulcer, site unspecified, without hemorrhage or perforation	K27.7	10
	Peptic ulcer, site unspecified, unspecified as acute or chronic, without hemorrh	K27.9	10
	Acute gastroduodenal ulcer with hemorrhage	K28.0	10
	Acute gastroduodenal ulcer with both hemorrhage and perforation	K28.2	10
	Chronic or unspecified gastroduodenal ulcer with hemorrhage	K28.4	10
	Chronic or unspecified gastroduodenal ulcer with both hemorrhage and perforation	K28.6	10
	Gastritis and duodenitis	535	9
	Acute gastritis	535.0	9
	Acute gastritis, without mention	535.00	9
	Acute gastritis, with hemorrhage	535.01	9
	Atrophic gastritis	535.1	9
	Atrophic gastritis, without mention	535.10	9
	Atrophic gastritis, with hemorrhage	535.11	9
	Gastric mucosal hypertrophy	535.2	9
	Gastric mucosal hypertrophy, without	535.20	9
	Gastric mucosal hypertrophy, with	535.21	9
	Alcoholic gastritis	535.3	9
	Alcoholic gastritis, without mention	535.30	9
	Alcoholic gastritis, with hemorrhage	535.31	9
	Other specified gastritis	535.4	9
	Other specified gastritis, without	535.40	9
	Other specified gastritis, with	535.41	9
	Unspecified gastritis and gastroduodenitis	535.5	9
	Unspecified gastritis and gastroduodenitis,	535.50	9
	Unspecified gastritis and gastroduodenitis,	535.51	9
	Duodenitis	535.6	9
	Duodenitis, without mention of	535.60	9
	Duodenitis, with hemorrhage convert	535.61	9
	Eosinophilic gastritis	535.7	9
	Eosinophilic gastritis, without mention	535.70	9
	Eosinophilic gastritis, with hemorrhage	535.71	9
	Gastritis and duodenitis	K29	10
	Acute gastritis	K29.0	10
	Acute gastritis without bleeding	K29.00	10
	Acute gastritis with bleeding	K29.01	10
	Chronic superficial gastritis	K29.3	10
	Chronic superficial gastritis without bleeding	K29.30	10
	Chronic superficial gastritis with bleeding	K29.31	10
	Chronic atrophic gastritis	K29.4	10
	Chronic atrophic gastritis without bleeding	K29.40	10
	Chronic atrophic gastritis with bleeding	K29.41	10
	Unspecified chronic gastritis	K29.5	10
	Unspecified chronic gastritis without bleeding	K29.50	10
	Unspecified chronic gastritis with bleeding	K29.51	10
	Other gastritis	K29.6	10
	Other gastritis without bleeding	K29.60	10
	Other gastritis with bleeding	K29.61	10
	Gastritis, unspecified	K29.7	10
	Gastritis, unspecified without bleeding	K29.70	10
	Gastritis, unspecified with bleeding	K29.71	10

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
GI bleed	Duodenitis	K29.8	10
	Duodenitis without bleeding	K29.80	10
	Duodenitis with bleeding	K29.81	10
	Gastroduodenitis, unspecified, with bleeding	K29.91	10
	Ulcer of esophagus with bleeding	530.21	9
	Esophageal varices with bleeding	456.0	9
	Esophageal varices in diseases classified elsewhere with bleeding	456.20	9
	Esophageal hemorrhage	530.82	9
	Acute gastric ulcer with hemorrhage, without mention of obstruction	531.00	9
	Acute gastric ulcer with hemorrhage, with obstruction	531.01	9
	Acute gastric ulcer with hemorrhage and perforation, without mention of obstruction	531.20	9
	Acute gastric ulcer with hemorrhage and perforation, with obstruction	531.21	9
	Chronic or unspecified gastric ulcer with hemorrhage, without mention of obstruction	531.40	9
	Chronic or unspecified gastric ulcer with hemorrhage, with obstruction	531.41	9
	Chronic or unspecified gastric ulcer with hemorrhage and perforation, without	531.60	9
	Chronic or unspecified gastric ulcer with hemorrhage and perforation, with obstruction	531.61	9
	Acute duodenal ulcer with hemorrhage, without mention of obstruction	532.00	9
	Acute duodenal ulcer with hemorrhage, with obstruction	532.01	9
	Acute duodenal ulcer with hemorrhage and perforation, without mention of obstruction	532.20	9
	Acute duodenal ulcer with hemorrhage and perforation, with obstruction	532.21	9
	Chronic or unspecified duodenal ulcer with hemorrhage, without mention of obstruction	532.40	9
	Chronic or unspecified duodenal ulcer with hemorrhage, with obstruction	532.41	9
	Chronic or unspecified duodenal ulcer with hemorrhage and perforation, witho	532.60	9
	Chronic or unspecified duodenal ulcer with hemorrhage and perforation, with	532.61	9
	Chronic duodenal ulcer without mention of hemorrhage or perforation, with ob	532.71	9
	Acute peptic ulcer of unspecified site with hemorrhage, without mention of ob	533.00	9
	Acute peptic ulcer of unspecified site with hemorrhage, with obstruction	533.01	9
	Acute peptic ulcer of unspecified site with hemorrhage and perforation, withou	533.20	9
	Acute peptic ulcer of unspecified site with hemorrhage and perforation, with o	533.21	9
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage, witho	533.40	9
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage, with o	533.41	9
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and p	533.60	9
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and p	533.61	9
	Acute gastrojejunal ulcer with hemorrhage, without mention of obstruction	534.00	9
	Acute gastrojejunal ulcer, with hemorrhage, with obstruction	534.01	9
	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention o	534.20	9
	Acute gastrojejunal ulcer with hemorrhage and perforation, with obstruction	534.21	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage, without mention o	534.40	9
	Chronic or unspecified gastrojejunal ulcer, with hemorrhage, with obstruction	534.41	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation, w	534.60	9
	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation, w	534.61	9
	Gastrojejunal ulcer, unspecified as acute or chronic, without mention of hemo	534.91	9
	Acute gastritis, with hemorrhage	535.01	9
	Atrophic gastritis, with hemorrhage	535.11	9
	Gastric mucosal hypertrophy, with hemorrhage	535.21	9
	Alcoholic gastritis, with hemorrhage	535.31	9
	Other specified gastritis, with hemorrhage	535.41	9
	Unspecified gastritis and gastroduodenitis, with hemorrhage	535.51	9
	Duodenitis, with hemorrhage	535.61	9
	Eosinophilic gastritis with hemorrhage	535.71	9
	Angiodysplasia of stomach and duodenum with hemorrhage	537.83	9
	Dieulafoy lesion (hemorrhagic) of stomach and duodenum	537.84	9
	Hematemesis	578.0	9
	Diverticulosis of small intestine with hemorrhage	562.02	9
	Diverticulitis of small intestine with hemorrhage	562.03	9
	Diverticulosis of colon with hemorrhage	562.12	9
	Diverticulitis of colon with hemorrhage	562.13	9
	Angiodysplasia of intestine with hemorrhage	569.85	9
	Dieulafoy lesion (hemorrhagic) of intestine	569.86	9
	Hemorrhage of rectum and anus	569.3	9
	Blood in stool (melena or hematochezia)	578.1	9
	Hemorrhage of gastrointestinal tract, unspecified	578.9	9

Supplementary Table 1. Continued

Comorbidity	ICD code description	Code	ICD-9 or ICD-10
	Mallory-Weiss Tear	530.7	9
	Ulcer of esophagus with bleeding	K22.11	10
	Esophageal varices with bleeding	I85.01	10
	Esophageal varices in diseases classified elsewhere with bleeding	I85.11	10
	Esophageal hemorrhage	K22.8	10
	Acute gastric ulcer with hemorrhage, without mention of obstruction	K25.0	10
	Acute gastric ulcer with hemorrhage, with obstruction	K25.0	10
	Acute gastric ulcer with hemorrhage and perforation, without mention of obstr	K25.2	10
	Chronic or unspecified gastric ulcer with hemorrhage, without mention of obstr	K25.4	10
	Chronic or unspecified gastric ulcer with hemorrhage and perforation, without	K25.6	10
	Acute duodenal ulcer with hemorrhage, without mention of obstruction	K26.0	10
	Acute duodenal ulcer with hemorrhage and perforation, without mention of ob	K26.2	10
	Chronic or unspecified duodenal ulcer with hemorrhage, without mention of o	K26.4	10
	Chronic or unspecified duodenal ulcer with hemorrhage and perforation, witho	K26.6	10
	Chronic duodenal ulcer without mention of hemorrhage or perforation, with ob	K26.7	10
	Acute peptic ulcer of unspecified site with hemorrhage, without mention of ob	K27.0	10
	Acute peptic ulcer of unspecified site with hemorrhage and perforation, withou	K27.2	10
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage, witho	K27.4	10
	Chronic or unspecified peptic ulcer of unspecified site with hemorrhage and p	K27.6	10
	Acute gastrojejunal ulcer with hemorrhage, without mention of obstruction	K28.0	10
	Acute gastrojejunal ulcer with hemorrhage and perforation, without mention o	K28.2	10
	Chronic or unspecified gastrojejunal ulcer with hemorrhage, without mention o	K28.4	10
	Chronic or unspecified gastrojejunal ulcer with hemorrhage and perforation, w	K28.6	10
	Gastrojejunal ulcer, unspecified as acute or chronic, without mention of hemo	K28.9	10
	Acute gastritis, with hemorrhage	K29.01	10
	Atrophic gastritis, with hemorrhage	K29.41	10
	Atrophic gastritis, with hemorrhage	K29.51	10
	Gastric mucosal hypertrophy, with hemorrhage	K29.61	10
	Alcoholic gastritis, with hemorrhage	K29.21	10
	Other specified gastritis, with hemorrhage	K29.61	10
	Unspecified gastritis and gastroduodenitis, with hemorrhage	K29.71	10
	Unspecified gastritis and gastroduodenitis, with hemorrhage	K29.91	10
	Duodenitis, with hemorrhage	K29.81	10
	Eosinophilic gastritis with hemorrhage	K52.81	10
	Angiodysplasia of stomach and duodenum with hemorrhage	K31.811	10
	Dieulafoy lesion (hemorrhagic) of stomach and duodenum	K31.82	10
	Hematemesis	K92.0	10
	Diverticulosis of small intestine with hemorrhage	K57.11	10
	Diverticulitis of small intestine with hemorrhage	K57.13	10
	Diverticulosis of colon with hemorrhage	K57.31	10
	Diverticulitis of colon with hemorrhage	K57.33	10
	Angiodysplasia of intestine with hemorrhage	K55.21	10
	Dieulafoy lesion (hemorrhagic) of intestine	K63.81	10
	Hemorrhage of rectum and anus	K62.5	10
	Blood in stool (melena or hematochezia)	K92.1	10
	Hemorrhage of gastrointestinal tract, unspecified	K92.2	10
	Mallory-Weiss Tear	K22.6	10
Code type	Code description	Code	
CPT	Revise Stomach-Bowel Fusion	43850	
	L Colectomy/Coloproctostomy	44207	
	Lap Close Enterostomy	44227	
	Partial Removal Of Colon	44144	
	Removal Of Stomach Partial	43633	
	Lap Place Gastr Adj Device	43770	
	Remove Gastric Port Open	43887	
	Revision Gastroplasty	43848	
	Enterectomy Cadaver Donor	44132	
	Partial Removal Of Colon	44143	
	Partial Removal Of Colon	44147	
	Gastric Bypass For Obesity	43846	

Supplementary Table 1. Continued

Code type	Code description	Code
	Lap Colostomy	44188
	Partial Removal Of Colon	44141
	Removal Of Small Intestine	44120
	Laparo Partial Colectomy	44204
	Intestine Transplnt Cadaver	44135
	Gastroplasty W/O V-Band	43843
	Removal Of Stomach	43622
	Partial Removal Of Colon	44140
	Revise Stomach-Bowel Fusion	43860
	Removal Of Stomach Partial	43634
	Enterectomy W/Taper Cong	44127
	Lap Gastr Bypass Incl Smll I	43645
	Lap Replace Gastr Adj Device	43773
	Removal Of Stomach Partial	43631
	Removal Of Stomach Partial	43635
	Removal Of Stomach Partial	43632
	Removal Of Stomach	43620
	Removal Of Stomach	43621
	Revise Stomach-Bowel Fusion	43855
	Fusion Of Stomach And Bowel	43825
	Lap Revise Gastr Adj Device	43771
	Fusion Of Stomach And Bowel	43810
	Fusion Of Stomach And Bowel	43820
	Revise Stomach-Bowel Fusion	43865
	Removal Of Colon	44150
	V-Band Gastroplasty	43842
	L Colectomy/Coloproctostomy	44208
	Removal Of Colon/Ileostomy	44156
	Enterectomy W/O Taper Cong	44126
	Lap Gastric Bypass/Roux-En-Y	43644
	Removal Of Colon	44160
	Bowel To Bowel Fusion	44130
	Gastroplasty Duodenal Switch	43845
	Lap Enterectomy	44202
	Lap Rmvl Gastr Adj Device	43772
	Change Gastric Port Open	43888
	Removal Of Colon/Ileostomy	44151
	Laparo Total Proctocolectomy	44210
	Lap Sleeve Gastrectomy	43775
	Enterectomy Live Donor	44133
	Removal Of Colon/Ileostomy	44155
	Partial Removal Of Colon	44146
	Colectomy W/Neo-Rectum Pouch	44158
	Removal Of Small Intestine	44121
	Lap Colectomy W/Proctectomy	44211
	Lap Jejunostomy	44186
	Revise Gastric Port Open	43886
	Intestine Transplant Live	44136
	Partial Removal Of Colon	44145
	Removal Of Small Intestine	44125
	Enterectomy Cong Add-On	44128
	Lap Resect S/Intestine Addl	44203
	Lap Colectomy Part W/Ileum	44205
	Lap Part Colectomy W/Stoma	44206
	Mobilization Of Colon	44139
	Lap Rmvl Gastr Adj All Parts	43774
	Lap Ileo/Jejuno-Stomy	44187
	Laparo Total Proctocolectomy	44212
	Lap Mobil Splenic Fl Add-On	44213
	Gastric Bypass Incl Small I	43847
	Remove Intestinal Allograft	44137
	Colectomy W/Ileoanal Anast	44157

Supplementary Table 1. Continued

Code type	Code description	Code
ICD9 – Procedure	Gastric Restrictive Procedure, Without Gastric Bypass, For Morbid Obesity; Vertic	44.68
	Gastric Restrictive Procedure, Without Gastric Bypass, For Morbid Obesity; Other	44.69
	Gastric Restrictive Procedure, With Partial Gastrectomy, Pylorus-Preserving Duod	45.91
	Gastric Restrictive Procedure, With Partial Gastrectomy, Pylorus-Preserving Duod	43.89
	Gastric Restrictive Procedure, With Partial Gastrectomy, Pylorus-Preserving Duod	45.51
	Gastric Restrictive Procedure, With Gastric Bypass For Morbid Obesity; With Shor	44.39
	Gastric Restrictive Procedure, With Gastric Bypass For Morbid Obesity; With Smal	44.39
	Revision, Open, Of Gastric Restrictive Procedure For Morbid Obesity, Other Than	44.5
	Gastrectomy, Partial, Distal; With Roux-En-Y Reconstruction	43.7
	Laparoscopy, Surgical, Gastric Restrictive Procedure; With Gastric Bypass And Ro	44.38
	Laparoscopy, Surgical, Gastric Restrictive Procedure; With Gastric Bypass And Sm	44.38
	Unlisted Laparoscopy, Stomach	43.89
	Implantation Of Adjustable Gastric Band And Port, [Laparoscopic]	44.95
	Laparoscopy, Surgical, Gastric Restrictive Procedure; Longitudinal Gastrectomy (I	43.89
	Implantation Of Adjustable Gastric Band And Port, [Laparoscopic]	44.95
	Restrictive Procedure, Non-Vbg, [Open]	44.69
	Removal Of Adjustable Gastric Band And Port	44.97
	Replacement Of Gastric Band And Port	44.96
	Revision Of Gastric Band	44.96
	Removal Of Gastric Band	44.97
	Removal And Replacement Of Gastric Band	44.97
	Implantation Of Gastric Band/Subcutaneous Port (For Individual Component Plac	44.95
	Implantation Of Gastric Band/Subcutaneous Port (For Individual Component Plac	44.98
	Implantation Of Gastric Band/Subcutaneous Port (For Individual Component Plac	44.96
	Implantation Of Gastric Band/Subcutaneous Port (For Individual Component Plac	44.99
	Implantation Of Gastric Band/Subcutaneous Port (For Individual Component Plac	44.97
	Revision Of Subcutaneous Port, Open	44.69
	Revision Of Subcutaneous Port, Open	44.99
	Removal Of Subcutaneous Port, Open	44.99
	Removal And Replacement Of Subcutaneous Port, Open	44.99
	(Laparoscopic) Adjustment Of Size Of Adjustable Gastric Restrictive Device. Infusio	44.98
	Revision Of Band To Rygb, Laparoscopic	44.38
	Revision Of Band To Rygb, Laparoscopic	44.97
	Revision Of Band To Rygb, Laparoscopic	44.99
	Removal Of Band To Rygb, Open	44.5
	Placement Of Band For Revision Of Rygb, Laparoscopic (Increased Procedural Serv	44.95
	Revision Of Sleeve Gastrectomy To Rygb, Laparoscopic (Increased Procedural Serv	43.38
	Revision Of Subcutaneous Port, Open	44.69
	Revision Of Subcutaneous Port, Open	44.99
	Revision Of Gastric Band	44.96
	Laparoscopic Removal Of Band And Revision Laparoscopic Sleeve Gastrectomy	44.97
	Laparoscopic Removal Of Band And Revision Laparoscopic Sleeve Gastrectomy	43.89
	Revision, Open, Of Gastric Restrictive Procedure For Morbid Obesity, Other Than	44.5
	Revision Of Gastroduodenal Anastomosis (Gastrojejunostomy) With Reconstruct	44.00
	Revision Of Gastroduodenal Anastomosis (Gastrojejunostomy) With Reconstruct	44.03
	Revision Of Gastroduodenal Anastomosis (Gastrojejunostomy) With Reconstruct	44.01
	Revision Of Gastroduodenal Anastomosis (Gastrojejunostomy) With Reconstruct	44.5
	Revision Of Gastroduodenal Anastomosis (Gastrojejunostomy) With Reconstruct	44.02
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	43.7
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	44.02
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	44.00
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	44.03
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	44.01
	Revision Of Gastrojejunal Anastomosis (Gastrojejunostomy) With Reconstruction	44.39
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	45.61
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	46.02
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	45.62
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	46.03
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	46.01
	Enterectomy, Resection Of Small Intestine; Single Resection And Anastomosis	46.20
	Laparoscopy, Surgical; Enterectomy, Resection Of Small Intestine, Single Resection	45.62

ICD10 - Procedure^a

Supplementary Table 1. Continued

Code type	Code description	Code
	Bypass	0D1%
	Change	0D2%
	Destruction	0D5%
	Excision	0D8%
	Reattachment	0DM%
	Removal	0DP%
	Resection	0DT%
	Transplantation	0DY%

CPT, Current Procedural Terminology; GERD, gastroesophageal reflux disease; GI, gastrointestinal; ICD-9, International Classification of Diseases–Ninth Revision; ICD-9, International Classification of Diseases–Tenth Revision.

^aThe percent sign signifies any terminating characters.

Supplementary Table 2. Medication Definitions Used in Medication Usage Measurement

Category	Medication
PPI	omeprazole
	pantoprazole
	dexlansoprazole
	lansoprazole
	rabeprazole
H2RAs	esomeprazole
	ranitidine
	famotidine
	cimetidine
	nizatidine
Thiazide diuretics	chlorothiazide
	chlorthalidone
	indapamide
	hydrochlorothiazide
	methyclothiazide
	hydrochlorothiazide
Loop diuretics	metolazone
	furosemide
	bumetanide
	ethacrynic acid
Gout medications	torsemide
	allopurinol
	febuxostat
	probenecid

H2RA, histamine-2 receptor antagonist; PPI, proton pump inhibitor.

Supplementary Table 3. Hazard Ratios for Time-Varying Cox Model for Unadjusted and Adjusted Analysis

Model	Hazard Ratio (95% CI)
Unadjusted analysis	1.74 (1.67–1.82)
Adjusted analysis	
Demographics	1.71 (1.63–1.80)
Medications	1.60 (1.52–1.68)
Comorbidities	1.49 (1.41–1.58)
Renal function	1.49 (1.41–1.58)
Health care utilization	1.46 (1.38–1.55)

Adjusted analysis performed in a stepwise fashion such that each subsequent model incorporates all covariates from the model.

CI, confidence interval.