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Comparative Effectiveness and Harms of Antibiotics for Outpatient Diverticulitis Two Nationwide Cohort Studies

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Abstract

Background—Outpatient diverticulitis is commonly treated with either metronidazole-with-fluoroquinolone or amoxicillin-clavulanate. The U.S. Food and Drug Administration advised that fluoroquinolones be reserved for conditions with no alternative treatment option. The comparative effectiveness of metronidazole-with-fluoroquinolone versus amoxicillin-clavulanate for diverticulitis is uncertain.

Objective—To determine the effectiveness and harms of metronidazole-with-fluoroquinolone versus amoxicillin-clavulanate for outpatient diverticulitis.

Design—Active-comparator new-user retrospective cohort studies.

Setting—Nationwide population-based claims data on US residents age 18-64 with private employer-sponsored insurance (2000-2018) or age 65+ with Medicare (2006-2015).

Participants—Immunocompetent adults with diverticulitis in the outpatient setting.

Intervention—Metronidazole-with-fluoroquinolone or amoxicillin-clavulanate.

Measurements—One-year risks of inpatient admission, urgent surgery, and *Clostridioides difficile* infection, and three-year risk of elective surgery.

Results—In MarketScan, we identified new users of metronidazole-with-fluoroquinolone (n=106,361) and amoxicillin-clavulanate (n=13,160). Comparing groups, there was no difference in 1-year admission risk (risk difference, 0.1%; 95% CI, −0.3% to 0.6%), 1-year urgent surgery risk (risk difference, 0.0%; 95% CI, −0.1% to 0.1%), 3-year elective surgery risk (risk difference, 0.2%; 95% CI, −0.3% to 0.7%), or 1-year *Clostridioides difficile* infection risk (risk difference, 0.0%; 95% CI, −0.1% to 0.1%). In Medicare, we identified new users of metronidazole-with-fluoroquinolone (n=17,639) and amoxicillin-clavulanate (n=2,709). Comparing groups, there was no difference in 1-year admission risk (risk difference, 0.1%; 95% CI, −0.7% to 0.9%), 1-year urgent surgery risk (risk difference, −0.2%, 95% CI −0.6% to 0.1%), or 3-year elective surgery risk (risk difference, −0.3%; 95% CI, −1.1% to 0.4%). The 1-year *Clostridioides difficile* risk was higher for metronidazole-with-fluoroquinolone compared to amoxicillin-clavulanate (risk difference, 0.6%; 95% CI, 0.2% to 1.0%).

Limitations—Residual confounding is possible, and we were unable to assess all harms associated with these antibiotics, most notably drug-induced liver injury.

Conclusion—Treating diverticulitis in the outpatient setting with amoxicillin-clavulanate may reduce the risk of fluoroquinolone-related harms without adversely impacting diverticulitis-specific outcomes.

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INTRODUCTION

Acute diverticulitis is a common inflammatory condition of the colon (209 cases per 100,000 person-years) that is responsible for $5.5 billion in health care expenditures annually in the US.(1, 2) This is a painful and unpredictable disease that often reoccurs and is a detriment to quality of life. The most common manifestation of diverticulitis

is characterized by diverticular inflammation without abscess or perforation (acute uncomplicated diverticulitis) and is managed in the outpatient setting.(1, 2)

Treatment with antibiotics in the outpatient setting is presumed to expedite recovery from the acute episode and reduce the risk of progression to obstruction, abscess, or perforation. The two most commonly prescribed antibiotic regimens for diverticulitis in the outpatient setting are a combination of metronidazole and a fluoroquinolone or amoxicillin-clavulanate only.(3, 4) Despite being commonly prescribed for diverticulitis, the effectiveness and harms of these antibiotics remains unknown. This is a critical gap because the Food and Drug Administration has recommended that fluoroquinolones be reserved for use in conditions with no alternative treatment option due to the risk of potentially permanent and disabling fluoroquinolone-related side effects.(5)

The aim of this study was to compare the effectiveness of treating patients at their first occurrence of outpatient diverticulitis with metronidazole-with-fluoroquinolone combination therapy versus amoxicillin-clavulanate alone, for prevention of diverticulitis-related inpatient admissions, urgent surgery, elective surgery, and emergency department visits. We additionally sought to assess the comparative harm of these treatments for risk of *Clostridioides difficile* infection (CDI). To answer these questions, we used administrative healthcare claims data from two US populations and implemented an active-comparator, new-user cohort study design.

METHODS

Data sources

We conducted separate cohort studies in two data sources from the US population. First, the IBM MarketScan Commercial Claims and Encounters Database contains longitudinal data on patients enrolled in employer-sponsored private health insurance during 2000-2018.(6, 7) Second, a 20% random sample of Medicare claims contains longitudinal data on fee-for-service beneficiaries (i.e., age 65+ years, with disability, or with end-stage renal disease) with Parts A (hospital), B (medical), and D (prescription drug) coverage during 2007-2015. The institutional review board at the University of North Carolina at Chapel Hill reviewed these studies (approved #18-1268, exempted #19-2483).

Study Cohort and Design

We identified a cohort of adults (18-64 years in MarketScan, 65+ years in Medicare) at their first outpatient diagnosis code for diverticulitis. We excluded patients lacking continuous insurance enrollment for 365 days before and 14 days after their first outpatient diverticulitis diagnosis code, as well as patients with any prior diverticulitis-related diagnosis code, percutaneous drain, or colectomy (for any indication).(8) We also excluded patients with any diagnosis code or prescription claim associated with being immunocompromised or immunosuppressed, given increased risk of recurrence and complications. Diagnosis and procedure codes used for these inclusion/exclusion criteria are in eTable 1 in the Supplement.

To classify exposure for our active-comparator new-user cohort study we identified two mutually exclusive groups of antibiotic users who filled an outpatient prescription within three days after their first observed outpatient diverticulitis diagnosis.(9, 10) The first group had a fill for metronidazole with oral ciprofloxacin or levofloxacin (henceforth, “metronidazole-with-fluoroquinolone”), and the second group had a fill for oral amoxicillin-clavulanate. To implement the “new-user” design, we excluded patients with a fill for one of the study antibiotics within 6 months before diverticulitis diagnosis. The flowchart (eTable 2 in the Supplement) provides further detail on cohort identification and antibiotic treatment patterns.

We began outcome follow-up 14 days after the diverticulitis diagnosis date, based on our theory that oral antibiotics may not plausibly affect diverticulitis outcomes immediately at treatment. Follow-up ended at outcome occurrence, death, disenrollment from the database, or the end of the study period, whichever occurred first (eTable 3 in the Supplement).(10)

Covariates and Confounding Control

Baseline covariates, measured during the year before diverticulitis diagnosis, included demographics, concomitant medications, comorbid conditions, and healthcare utilization. CT imaging codes (ascertained in the three days before and after diverticulitis diagnosis) were used as a proxy for diverticulitis severity.

Logistic regression was used to model the propensity score for receiving metronidazole-with-fluoroquinolone versus amoxicillin-clavulanate, predicted by covariates (11) including calendar year, age at diagnosis, sex, race (Medicare data only), geography, concomitant medications, comorbid conditions, CT imaging, outpatient visits in prior year, days spent as an inpatient in prior year, recent prior inpatient admission, and product terms for age-by-sex, age-by-region, age-by-CT imaging, and year-by-CT imaging. To control confounding, we implemented inverse-probability of treatment weights (IPTW) to balance covariates across antibiotic treatment groups. This approach standardized covariates to the overall study population, targets the population average treatment effect, and addresses the question, “how would occurrence of the outcome differ if all antibiotic-treated adults with incident outpatient diverticulitis received metronidazole-with-fluoroquinolone, compared to amoxicillin-clavulanate?”(12, 13) Standardized mean differences were calculated in the crude and weighted data to assess balance of continuous, binary, and polytomous covariates and their potential for measured confounding.(14, 15)

Risks Analysis

Outcomes included inpatient admission for diverticulitis, urgent surgery, and *Clostridioides difficile* infection (CDI) in the year after diagnosis. Inpatient admission for diverticulitis was a binary outcome defined by the presence of any inpatient claim for diverticulitis in any diagnosis position. Urgent surgery was classified using inpatient claims for open or laparoscopic colectomy with diverticulitis in a top 5 diagnosis code position, with an emergency department visit within 7 days prior to surgery. CDI was defined using a claims-based algorithm that required either an inpatient diagnosis code or an outpatient

diagnosis code with anti-CDI medication fill (metronidazole, fidaxomicin, vancomycin, bezlotuximab).(16, 17)

We also assessed risk of elective surgery within three years after diverticulitis diagnosis, since it follows a longer time scale (e.g., patients with an abscess managed successfully non-operatively, patients with recurrent uncomplicated diverticulitis who want to reduce the risk of recurrence, or rarely, patients with diverticular stricture or fistula). Elective surgery was defined similarly to urgent surgery, but with the requirement that the patient *did not have* an emergency department visit within 7 days prior to surgery.

Risks of inpatient admission, elective surgery, urgent surgery, and CDI were calculated using the IPTW Aalen-Johansen estimator, which adapts Kaplan-Meier estimation to account for competing events.(18) We considered death a competing event (in Medicare data only), and we considered elective and urgent surgeries as competing events for each other.(19) We chose to handle competing events this way so that our analytic approach would reflect our individual-level, data-supported knowledge that a patient could never experience any study outcome after death, and that they could never experience a first surgery after having had surgery during follow-up. Our approach differs from censoring, which would impute outcome data for patients after loss-to-follow-up based on observed outcomes for other patients who were *not* lost-to-follow-up; our Aalen-Johansen approach avoids this error in our setting (where the competing events preclude other outcomes altogether), and subsequently avoids overestimation of risks that would have occurred under censoring.(18)

Burdens Analysis

Recurrent event outcomes focused on diverticulitis-related (i.e., any diagnosis code position) healthcare utilization, including emergency department (ED) visits, outpatient visits, and inpatient hospitalizations in the year after diagnosis. The mean cumulative count was applied to the IPTW population to estimate the cumulative burden of diverticulitis-related healthcare visits during follow-up.(20) Given the non-parametric form of Aalen-Johansen and mean cumulative count estimators, 95% confidence intervals (CIs) for risk differences, risk ratios, and burden differences were obtained via bootstrapping of 1000 resamples.

Analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC), using PROC LOGISTIC for propensity score estimation, PROC PHREG for components needed to construct the Aalen-Johansen estimator, and PROC SURVEYSELECT for bootstrapping.

Role of the Funding source

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RESULTS

Cohort Characteristics

In the MarketScan cohort, we identified 106,361 (89.0%) metronidazole-with-fluoroquinolone users and 13,160 (11.0%) amoxicillin-clavulanate users (Table 1). There was variation in antibiotic prescribing over time; metronidazole-with-fluoroquinolone treatment prevalence for outpatient diverticulitis ranged from 81.8% during 2001-2003 to 90.6% during 2007-2015 (eTable 4 in the Supplement). Prior to weighting, distributions of age, sex, comorbidities, concomitant medication use, and healthcare utilization were similar between treatment groups (standardized mean differences <0.1). Median age was 52 years, and 47.3% were female. CT scans were performed more commonly among metronidazole-with-fluoroquinolone users (60.8%) compared with amoxicillin-clavulanate (49.4%).

In the Medicare cohort, we identified 17,639 (86.7%) metronidazole-with-fluoroquinolone users and 2,709 (13.3%) amoxicillin-clavulanate users (Table 1, eTable 4 in the Supplement). Prior to weighting, distributions of age, sex, race, year, comorbidities, concomitant medication use, and healthcare utilization were similar between treatment groups (standardized mean differences <0.1). Median age was 73 years, 67.9% were female, and 91.1% were White. CT scans were performed more commonly among metronidazole–with-fluoroquinolone users (53.5%) compared with amoxicillin-clavulanate (39.8%).

In both cohorts, covariates were well balanced across treatment groups, evincing clinical equipoise between treatments, and weighting was effective for standardizing data to the target population of all patients in the cohort (eTables 5-10 in the Supplement).

Risks Analysis

In the MarketScan cohort, comparing metronidazole-with-fluoroquinolone to amoxicillin-clavulanate, there was no difference in the diverticulitis-specific 1-year hospital admission risk (risk difference, 0.1%; 95% CI, −0.3% to 0.6%), 1-year urgent surgery risk (risk difference, 0.0%; 95% CI, −0.1% to 0.1%), or 3-year elective surgery risk (risk difference, 0.2%; 95% CI, −0.3% to 0.7%) (Figure 1). The 1-year risk of CDI was 0.3% and similar between treatment groups (risk difference, 0.0%; 95% CI, −0.1% to 0.1%) (Figure 1). Results were robust in a sensitivity analysis that relied only on the primary diagnosis position for 1-year risk of diverticulitis-related hospital admission (eTable 11 in the Supplement).

In the Medicare cohort, comparing metronidazole-with-fluoroquinolone to amoxicillin-clavulanate, there was no difference in diverticulitis-specific 1-year hospital admission risk (risk difference, 0.1%; 95% CI, −0.7% to 0.9%) or 3-year elective surgery risk (risk difference, −0.3%; 95% CI, −1.1% to 0.4%) (Figure 2). The 1-year risk of urgent surgery was lower in the metronidazole-with-fluoroquinolone group, but this estimate was imprecise (risk difference, −0.2%; 95% CI, −0.6% to 0.1%). However, the 1-year risk of CDI was significantly higher for metronidazole-with-fluoroquinolone (risk, 1.2%) compared to amoxicillin-clavulanate (risk, 0.6%) (risk difference, 0.6%; 95% CI, 0.2% to 1.0%). This 0.6% higher absolute risk corresponds to a number needed to treat-to-harm[20] of 167 (95% CI, 100 to 500) – the number of adults age 65+ years with outpatient-managed

diverticulitis would need to be treated with metronidazole-with-fluoroquinolone instead of amoxicillin-clavulanate for one additional adult, on average, to experience CDI within one year.

Burdens Analysis

In the MarketScan cohort, the 1-year weighted cumulative burden of diverticulitis-related ED visits was higher for metronidazole-with-fluoroquinolone (burden, 79.7 visits per 1,000 patients) compared to amoxicillin-clavulanate (burden, 74.2 visits per 1,000 patients), but the difference was imprecise and not statistically significant at an alpha level of 0.05 (burden difference, 5.5; 95% CI, −4.1 to 14.0) (Figure 3). There was no difference between the two antibiotic groups in the cumulative burden of outpatient visits or inpatients visits.

In the Medicare cohort, the 1-year weighted cumulative burden of diverticulitis-related ED visits was higher for metronidazole-with-fluoroquinolone (burden, 61.8 visits per 1,000 patients) compared to amoxicillin-clavulanate (burden, 47.5 visits per 1,000 patients), but the difference was imprecise and not statistically significant at an alpha level of 0.05 (burden difference, 13.8; 95% CI, −3.2 to 29.6) (Figure 3). Similarly, the cumulative burden was higher for metronidazole-with-fluoroquinolone for diverticulitis-related outpatient visits (burden difference, 125.1; 95% CI, −0.3 to 236.8) and inpatient visits (burden difference, 13.4; 95% CI −27.6 to 48.7), again the differences were imprecise.

DISCUSSION

In two large nationwide cohorts of immunocompetent adults with outpatient diverticulitis, the 1-year risk of hospital admission or urgent surgery for diverticulitis was low and there was no difference between antibiotic groups. There was also no difference in long-term risk of elective surgery for diverticulitis. In the cohort of Medicare beneficiaries, treatment with metronidazole-with-fluoroquinolone was associated with increased risk of *Clostridioides difficile* infection (CDI) compared with amoxicillin-clavulanate. Remarkably, metronidazole-with-fluoroquinolone therapy was 7-8 times as common as amoxicillin-clavulanate for outpatient diverticulitis treatment.

The U.S. Food and Drug Administration has recommended that fluoroquinolones be reserved for use in conditions with no alternative treatment option, specifically acute bacterial sinusitis, chronic bronchitis and uncomplicated urinary tract infection.(5) They warn that the potential risks associated with fluoroquinolone use include hypoglycemia, mental health side effects, peripheral neuropathy, aortic dissection and aneurysm, and adverse effects to tendons, muscles, joints, and nerves.(21-25) A fluoroquinolone-sparing approach to outpatient diverticulitis treatment has the potential to reduce the risk of these fluoroquinolone-related harms. Importantly, amoxicillin-clavulanate and two of the most common fluoroquinolones – ciprofloxacin and levofloxacin – have been associated with drug-induced liver injury; claims data are not a reliable method to identify drug-induced liver injury cases.(26-29)

Fluoroquinolones also markedly increase the risk of CDI and guidelines recommend stewardship to reduce fluoroquinolone use.(30, 31) We found that diverticulitis treatment

with metronidazole-with-fluoroquinolone was associated with an increased risk of CDI compared with amoxicillin-clavulanate in older adults. There was no difference in CDI risk in the MarketScan population, likely because the risk of CDI in this younger population was one-quarter the risk in the Medicare cohort, placing a low ceiling on a potential measured effect. When considering these results, it is important to remember that both the indication (diverticulitis) and a potentially avoidable antibiotic treatment complication (CDI) are more common in older adults. At the expense of sensitivity, we used a highly specific CDI definition to estimate risks and contrast treatment groups. As a result, we have likely under-estimated the risk of CDI in the diverticulitis population but minimized bias for the risk ratio for the association between the two antibiotic treatments.(32)

Until recently, using antibiotics to treat outpatient diverticulitis was performed without good evidence. Recent trials have challenged the concept of treating acute uncomplicated diverticulitis with antibiotics.(33, 34) A systematic review and meta-analysis of 9 studies with 2,505 patients with acute uncomplicated diverticulitis found no difference in clinical outcomes between those treated with or without antibiotics.(35) Guidelines now recommend selective antibiotic use for the treatment of acute uncomplicated diverticulitis.(36-38) In the outpatient setting, antibiotics are recommended for patients with acute uncomplicated diverticulitis who are immunosuppressed or who have comorbidities and for patients with refractory or more severe symptoms.(39) There is little to guide which antibiotic therapy for these populations is appropriate.

Only a few studies have compared antibiotic regimens for diverticulitis. A trial of 51 patients hospitalized with diverticulitis compared treatment with cefoxitin to combination gentamicin-with-clindamycin.(40) A retrospective cohort study of 693 patients with outpatient diverticulitis compared metronidazole-with-fluoroquinolone to all other antibiotics.(41) Notably, both of these studies found no difference in outcomes but did not investigate the comparative harms of therapy. Ours is the first study to compare the two most commonly used antibiotic regimens for outpatient diverticulitis using data from two large insured US populations.

The cumulative burden of recurrent health care visits for diverticulitis was remarkably high, likely driven by how commonly patients deal with ongoing symptoms after a diverticulitis episode.(42, 43) We found a numerically higher cumulative burden of diverticulitis-related emergency department and clinic visits among older adults when we compared metronidazole-with-fluoroquinolone users with amoxicillin-clavulanate; although our estimates were imprecise, these differences may be a meaningful reflection of differential effectiveness or differential side effects from each antibiotic.

It is difficult to make an accurate diagnosis of incident diverticulitis and to stage the disease based on history, physical exam, and laboratory data alone. Guidelines recommend imaging to make the diagnosis and we found that computed tomography imaging is, indeed, commonly (40-61%) performed in US insured populations, though it was more common in MarketScan compared with the older Medicare population.(38, 44) This difference may be because more beneficiaries in Medicare had a remote history of diverticulitis (before Medicare coverage began) and recurrent diverticulitis could more confidently be diagnosed

based on history and is less likely to be complicated by abscess compared to a first episode. Imaging was also more common for metronidazole-with-fluoroquinolone compared with amoxicillin-clavulanate, possibly due to differences in disease severity, provider type, or location of diagnosis, although amoxicillin-clavulanate is considered first-line therapy for diverticulitis.(3, 4, 42)

Our study has multiple strengths. First, we used two of the largest available administrative claims data sources in the United States (MarketScan and Medicare) to assess treatments and long-term outcomes in patients across all adult age groups. Second, we implemented a new-user study design to emulate a randomized trial with a washout period, with an active-comparator group (rather than non-users) to compare two common first-line antibiotic regimens head-to-head. By comparing alternative treatments in patients with the same observed indication, our approach mitigated potential confounding-by-indication in the design phase,(45) thus focusing our propensity score analysis on refining control of residual confounding by key factors that influence treatment selection (e.g., CT scan and geography). The lack of strong predictors of treatment choice suggests that our active-comparator choice was appropriate. Further, our approach addressed a tangible clinical question regarding the relative benefits and drawbacks of treating with one medication over another (i.e., active-comparator) at a specific timepoint, rather than a less plausible question (in the United States, at least) of *whether* to treat with medication.(9, 10, 46) In our analysis, we accounted appropriately for competing events, which is critical in the Medicare-based analyses given higher mortality in older patients. Additionally, a novel method for recurrent events analysis was adapted to yield highly interpretable measures of burden for outcomes that can occur more than once.

This study has limitations. First, MarketScan and Medicare claims data do not reflect antibiotic prescribing or use, and so our exposure assessment was based on insurance-reimbursed dispensing of prescription antibiotics. Subsequently, we only know that a prescription was filled but not how much of it was consumed as prescribed; although we do not suspect differential early cessation among patients who filled these acute (approximately 10-day) antibiotic prescriptions, our intention-to-treat analysis would be sensitive to such misclassification bias. As an observational corollary of a trial estimating the intention-to-treat effect, we categorized patients into treatment groups based on the first antibiotic prescription filled, remaining agnostic to treatment switches or augmentation; future research could examine how time-varying antibiotic exposures impact the outcomes we assessed. Second, although we used diagnosis and procedure codes as proxy measures for important clinical characteristics (e.g., comorbidity, severity of diverticulitis), claims data inherently lack clinical details about patient- or provider-level information that might affect antibiotic treatment or outcomes that we studied. This definition of diverticulitis has been used previously,(47, 48) and our claims-based algorithm for identifying CDI events is based on prior studies(16, 17) but has not been validated in the claims data used for this analysis. Third, although some of our outcomes have high validity given that they are billable healthcare encounters (e.g., visits to inpatient, outpatient, or emergency department), the validity of some other outcomes is difficult to estimate; to reduce potential outcome misclassification, we used a consistent approach to identify our cohort (antibiotic fill with a diverticulitis diagnosis code) and to characterize outcomes as being associated with

diverticulitis (e.g., inpatient visit claims with associated diagnosis codes, with sensitivity analyses to vary the diagnosis code position). We lacked the ability to assess confounding by provider or clinic, which may exhibit heterogeneous antibiotic prescribing patterns for outpatient diverticulitis, as well as care for unique patient groups who experienced heterogeneous risks (i.e., beyond those explained by individual-level variables in our study) for the outcomes of interest. Finally, we did not look at all important safety outcomes, including drug-induced liver injury. Instead, we focused on comparative effectiveness and the most suspected harm, *Clostridioides difficile* infection.

We have demonstrated that outpatient diverticulitis treatment with amoxicillin-clavulanate was as effective as treatment with metronidazole-with-fluoroquinolone. There were negligible differences between groups for risk of diverticulitis admissions, visits to the emergency department or outpatient clinics, urgent surgery, and elective surgery. When selectively treating outpatient diverticulitis with antibiotics, physicians might consider treatment with amoxicillin-clavulanate over metronidazole-with-fluoroquinolone to reduce the risk of serious risks associated with fluoroquinolone use, including *Clostridioides difficile* infection.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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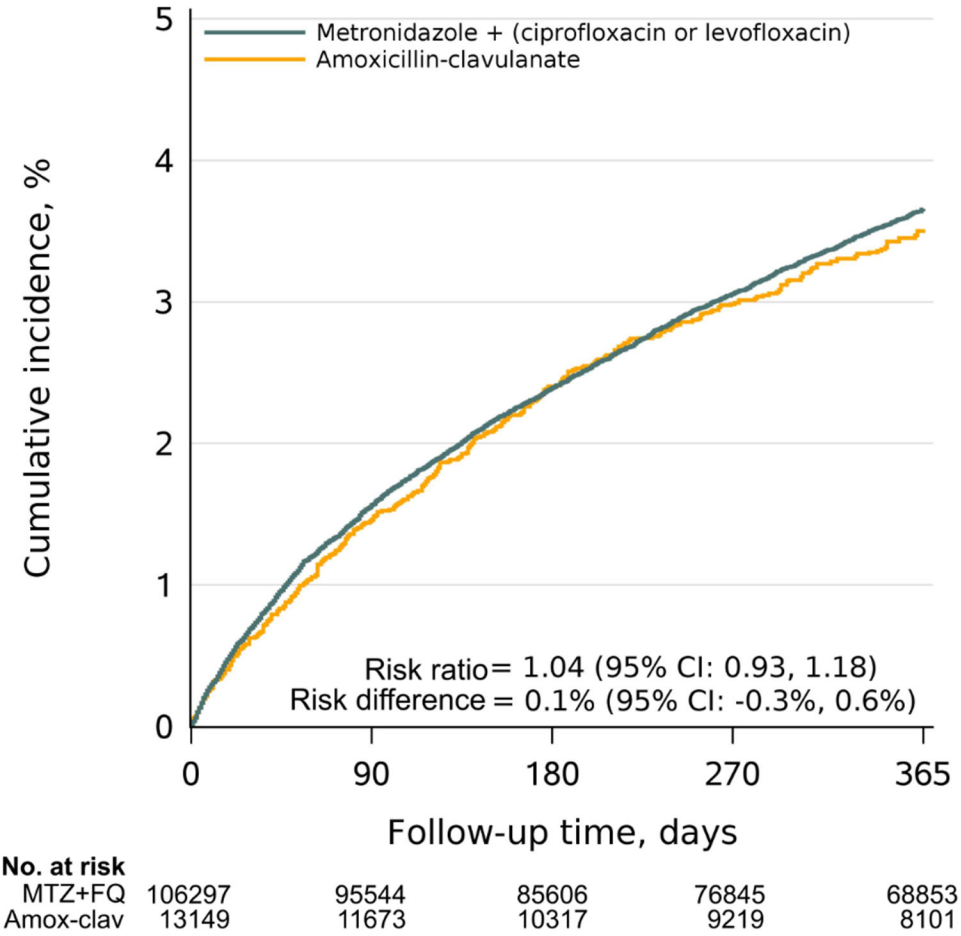
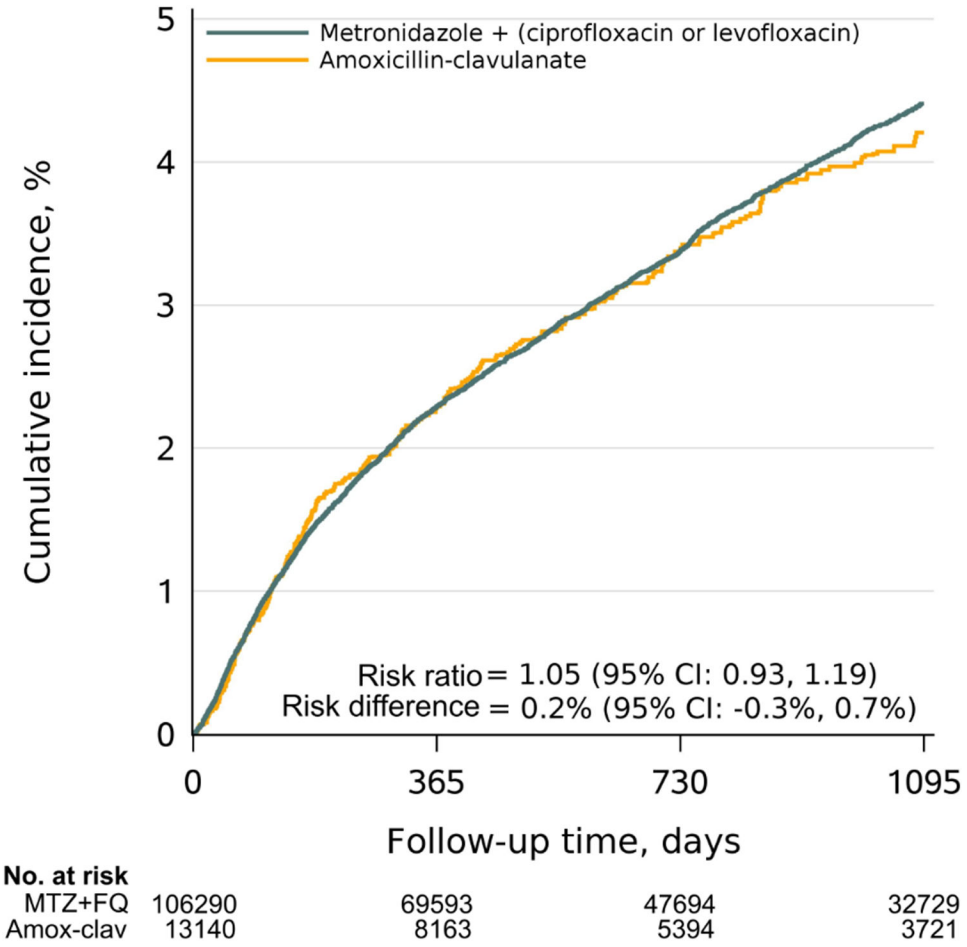
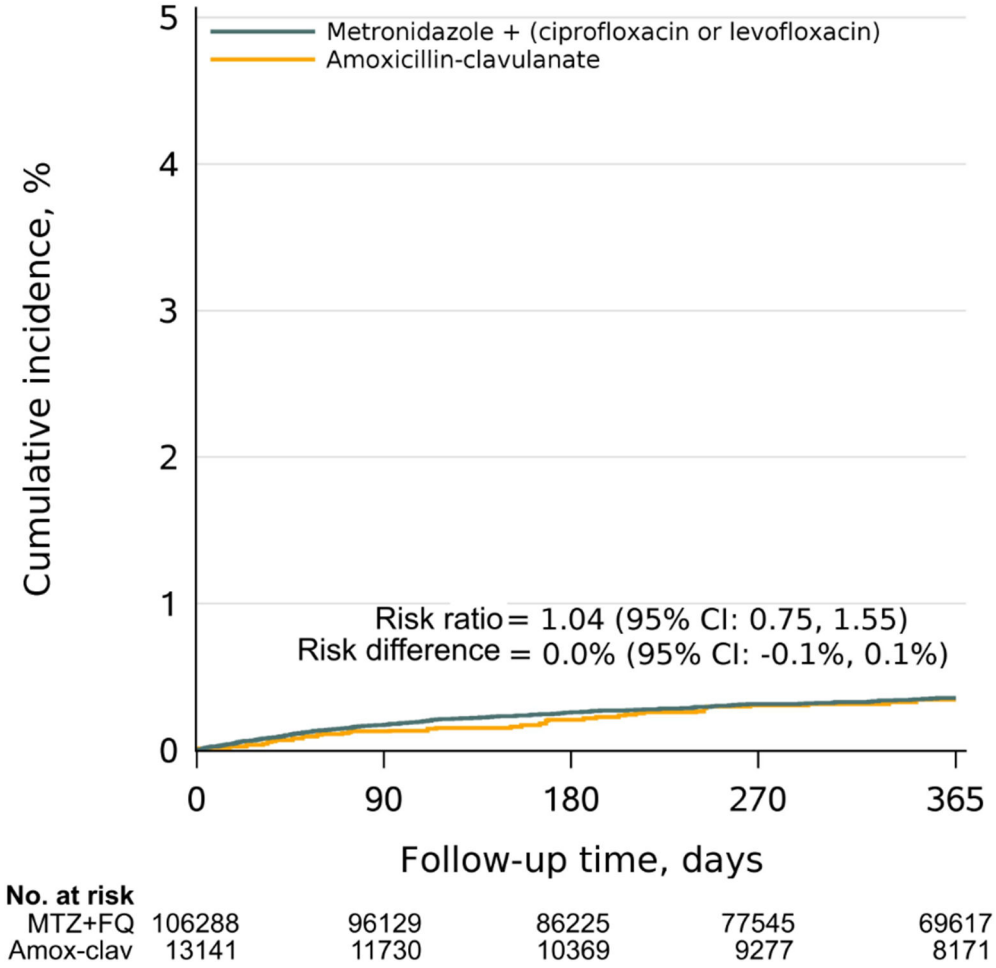






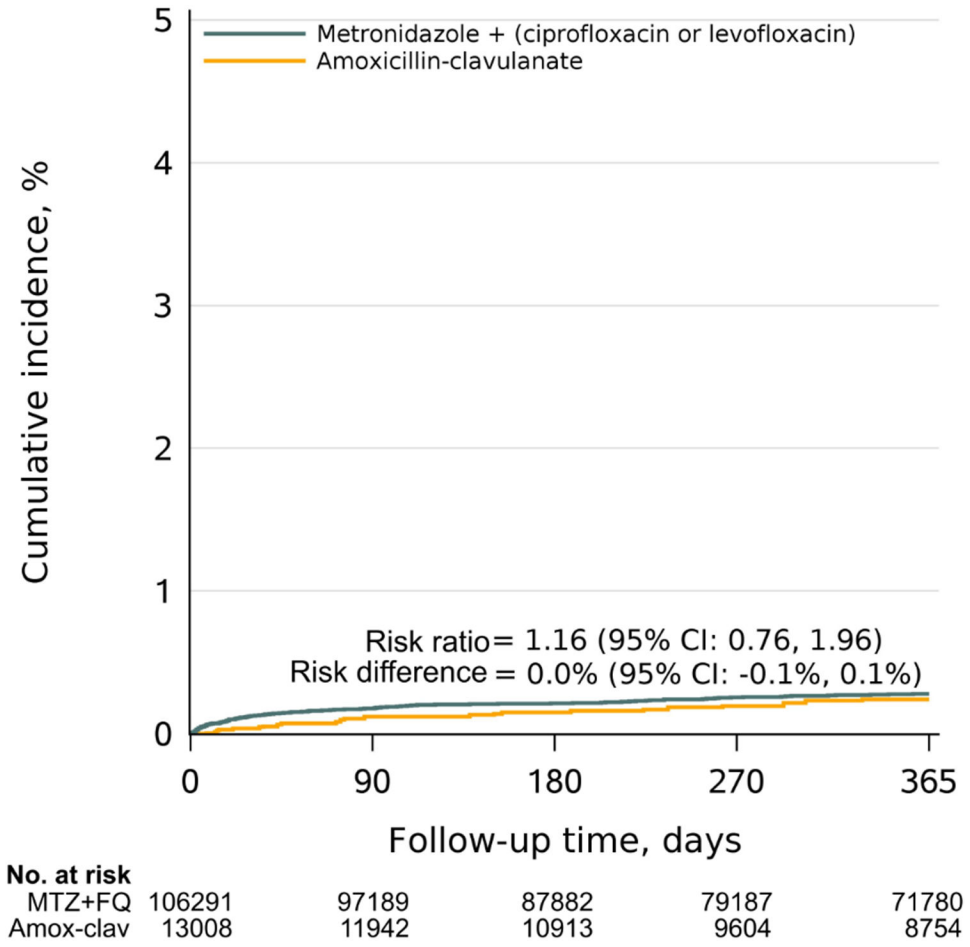
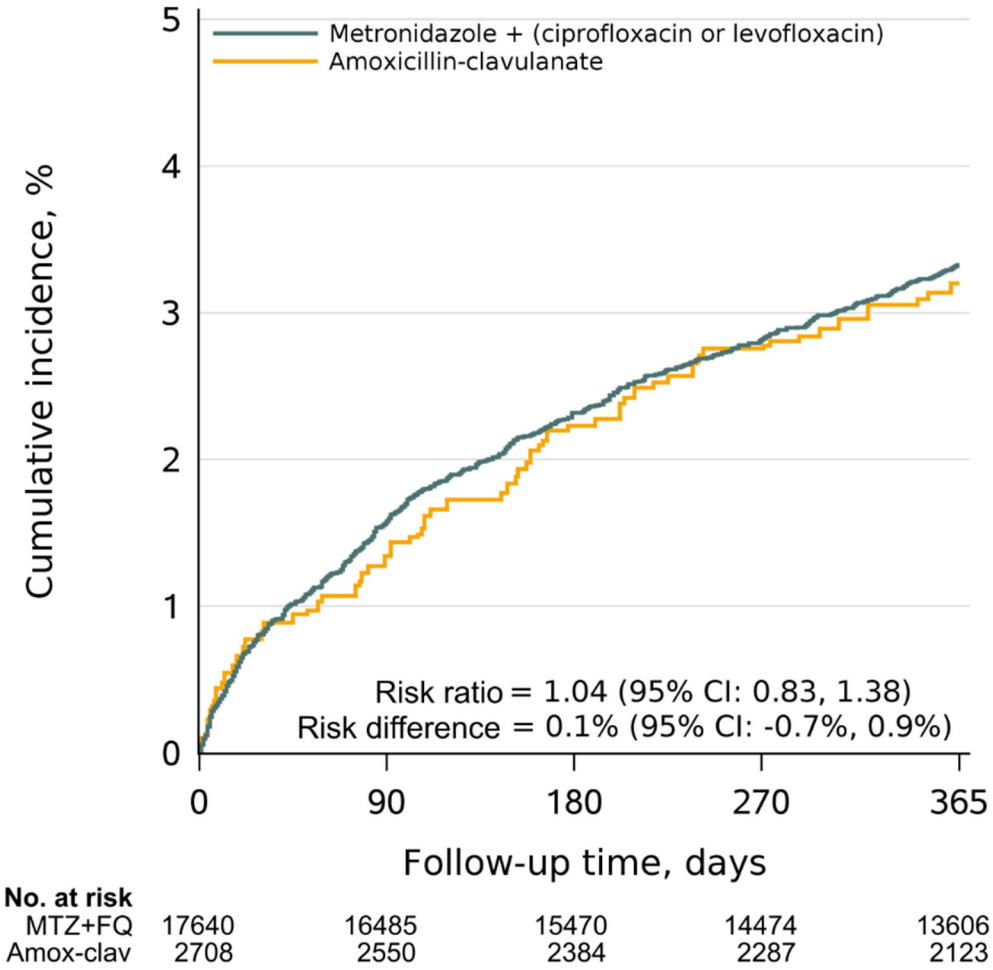


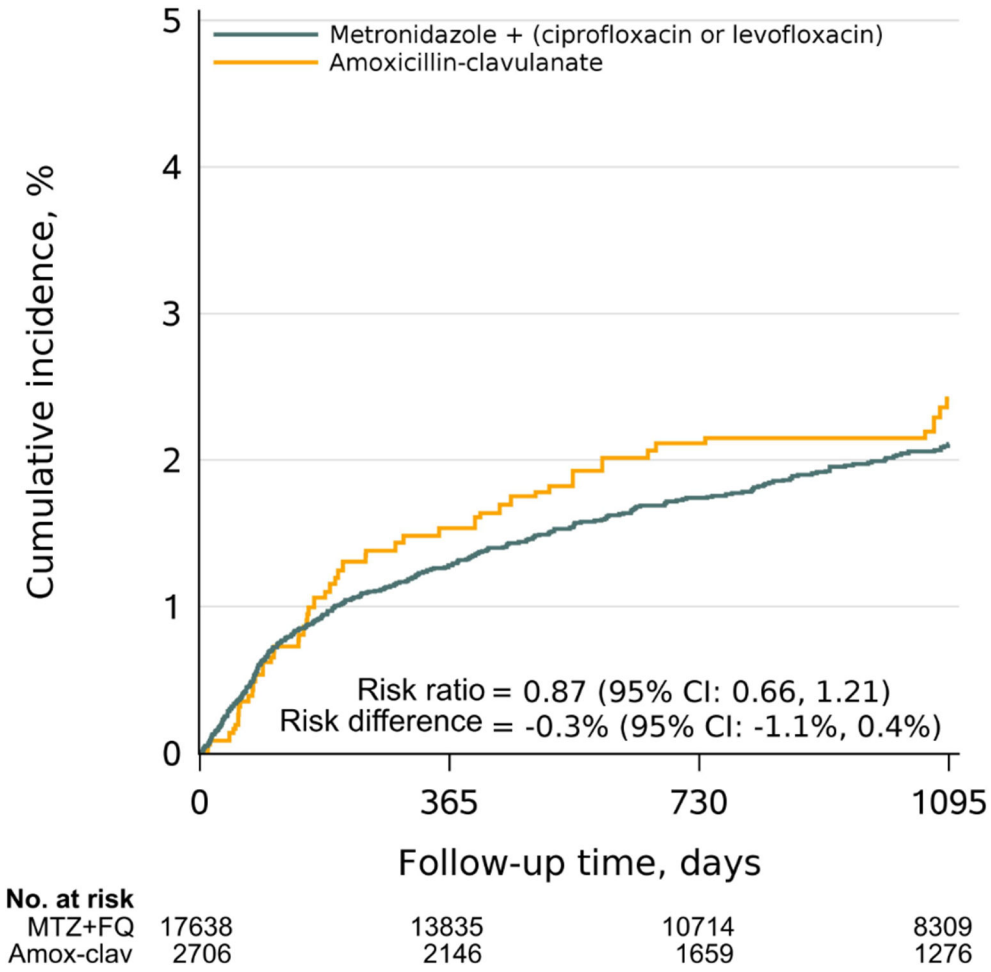
FIGURE 1.

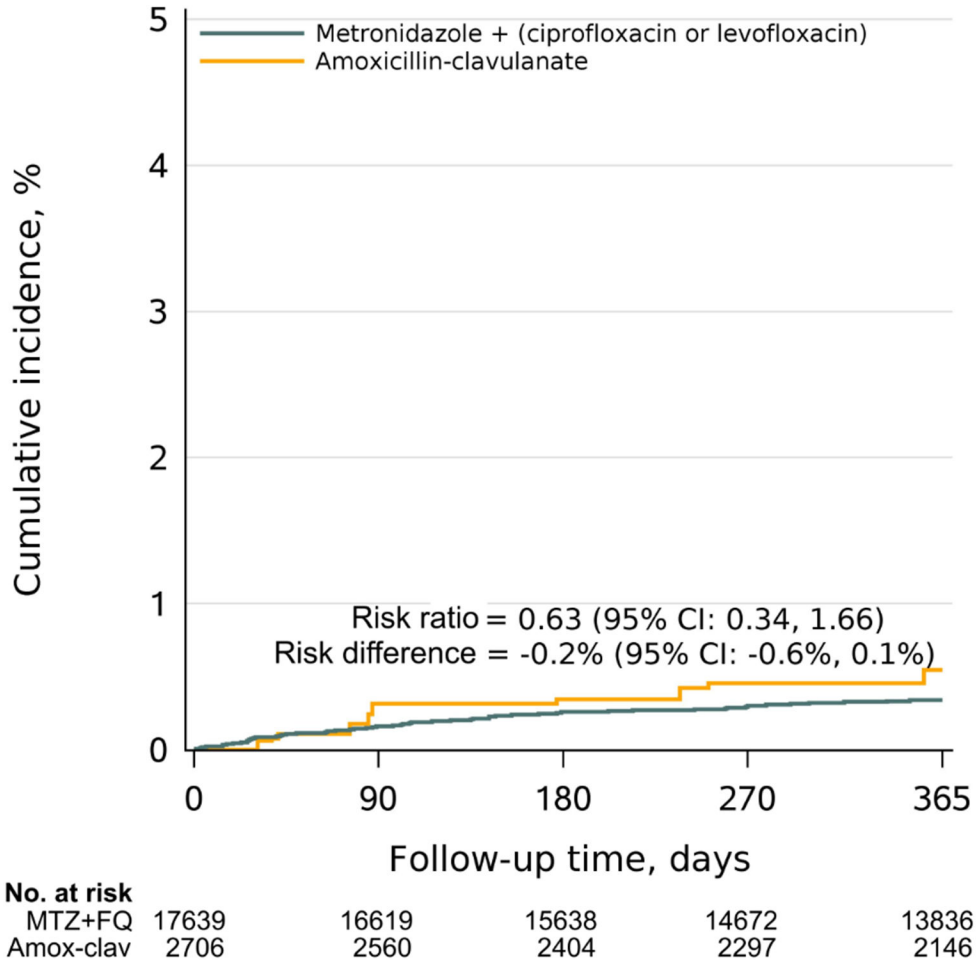
Risk of inpatient admission for diverticulitis, elective colectomy, urgent colectomy, and Clostridium Difficile infection in privately insured adults diagnosed with incident outpatient diverticulitis and treated with metronidazole-with-fluoroquinolone compared to amoxicillin-clavulanate, 2001-2018. A. Inpatient admission for diverticulitis, B. Elective colectomy, C. Urgent colectomy, D. Clostridium difficile infection

Abbreviations: CI, confidence interval; MTZ, metronidazole; FQ, fluoroquinolone; Amox-clav, amoxicillin-clavulanate

Risk ratios and risk differences were calculated at the end of follow-up. 95% CI calculated via nonparametric bootstrap of 1000 resamples.







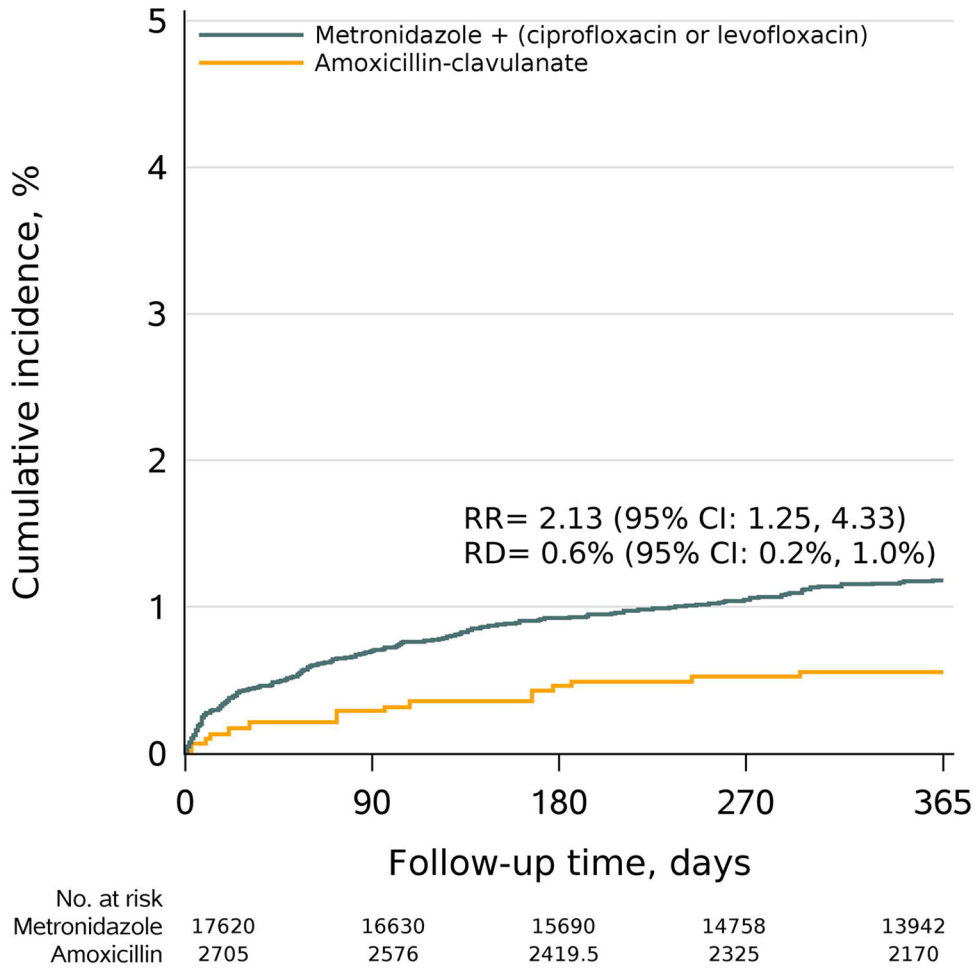
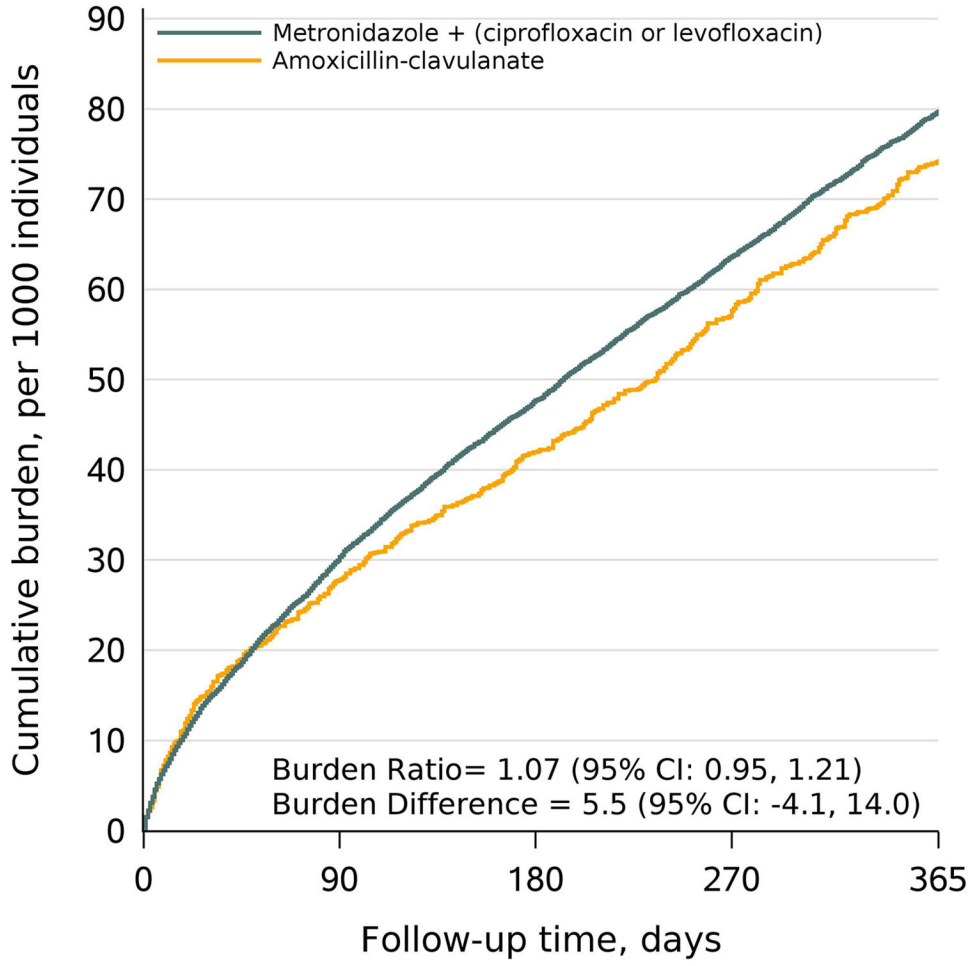


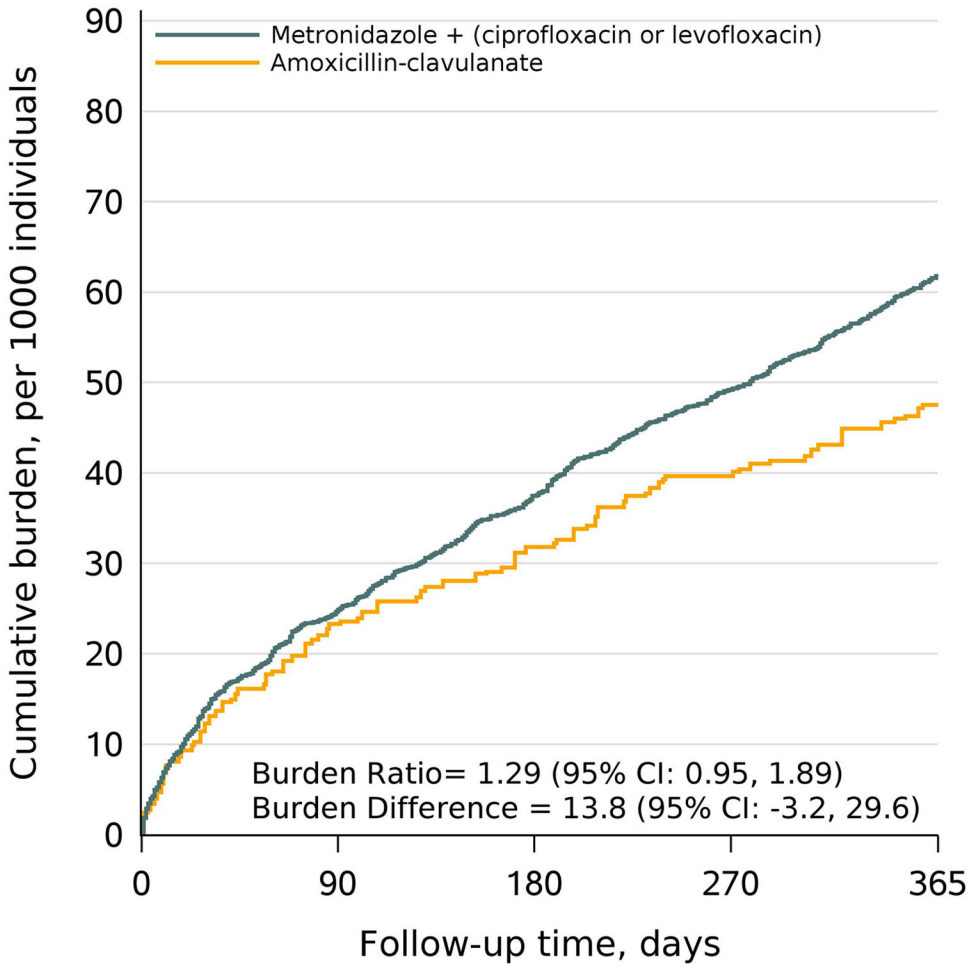
FIGURE 2.

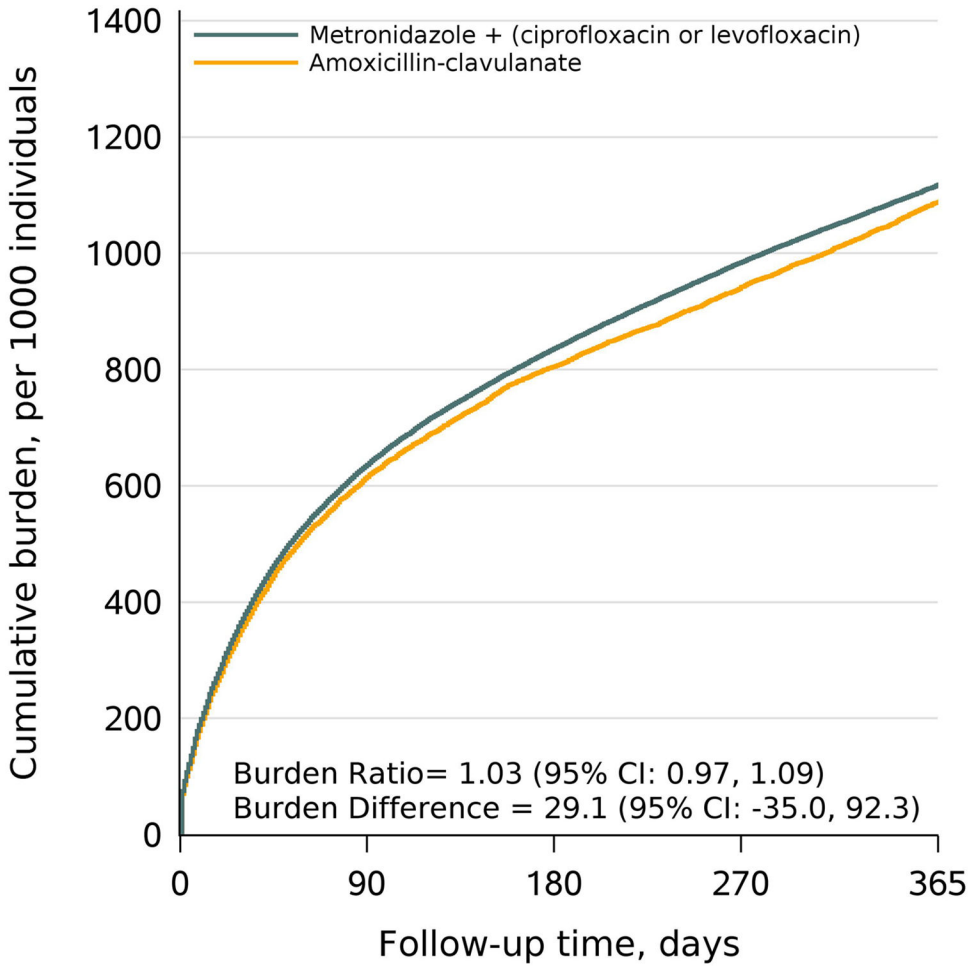
Risk of inpatient admission for diverticulitis, elective colectomy, urgent colectomy, and Clostridium Difficile infection in Medicare-insured adults diagnosed with incident outpatient diverticulitis and treated with metronidazole-with-fluoroquinolone compared to amoxicillin-clavulanate, 2007-2015. A. Inpatient admission for diverticulitis, B. Elective colectomy, C. Urgent colectomy ,D. Clostridium difficile infection

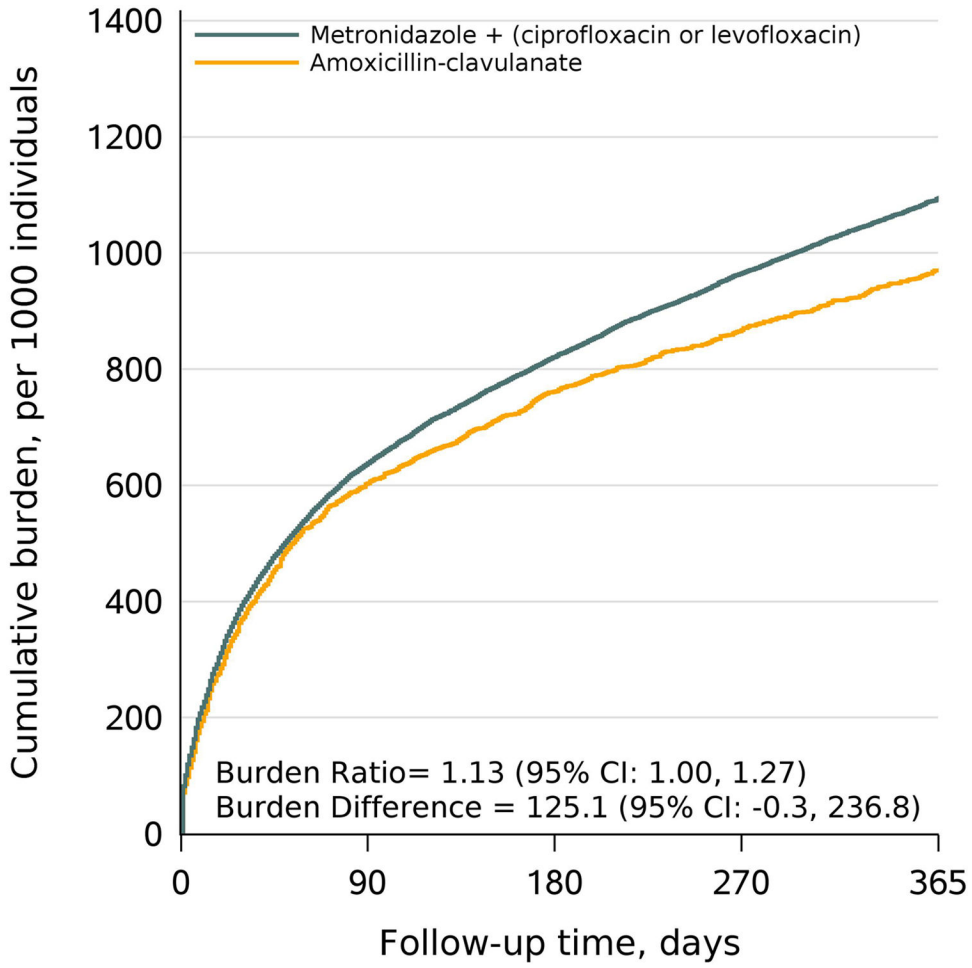
Abbreviations: CI, confidence interval; MTZ, metronidazole; FQ, fluoroquinolone; Amox-clav, amoxicillin-clavulanate

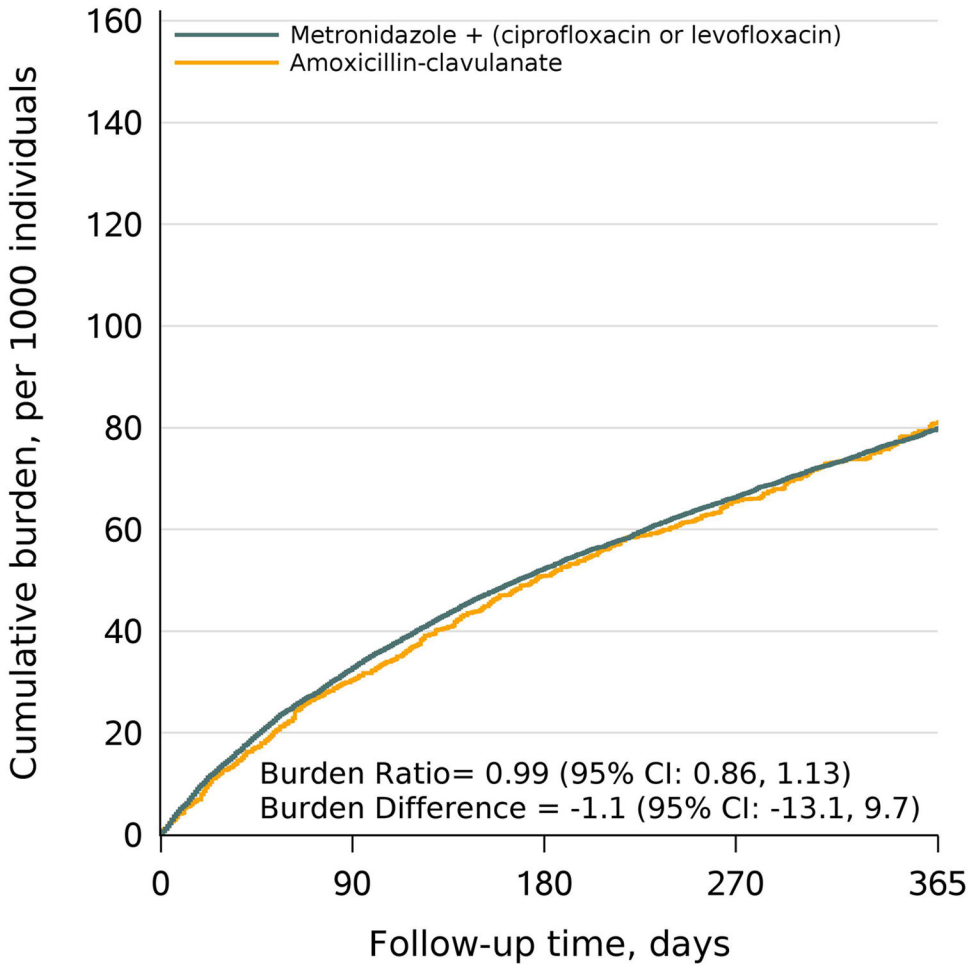
Risk ratios and risk differences were calculated at the end of follow-up. 95% CI calculated via nonparametric bootstrap of 1000 resamples.











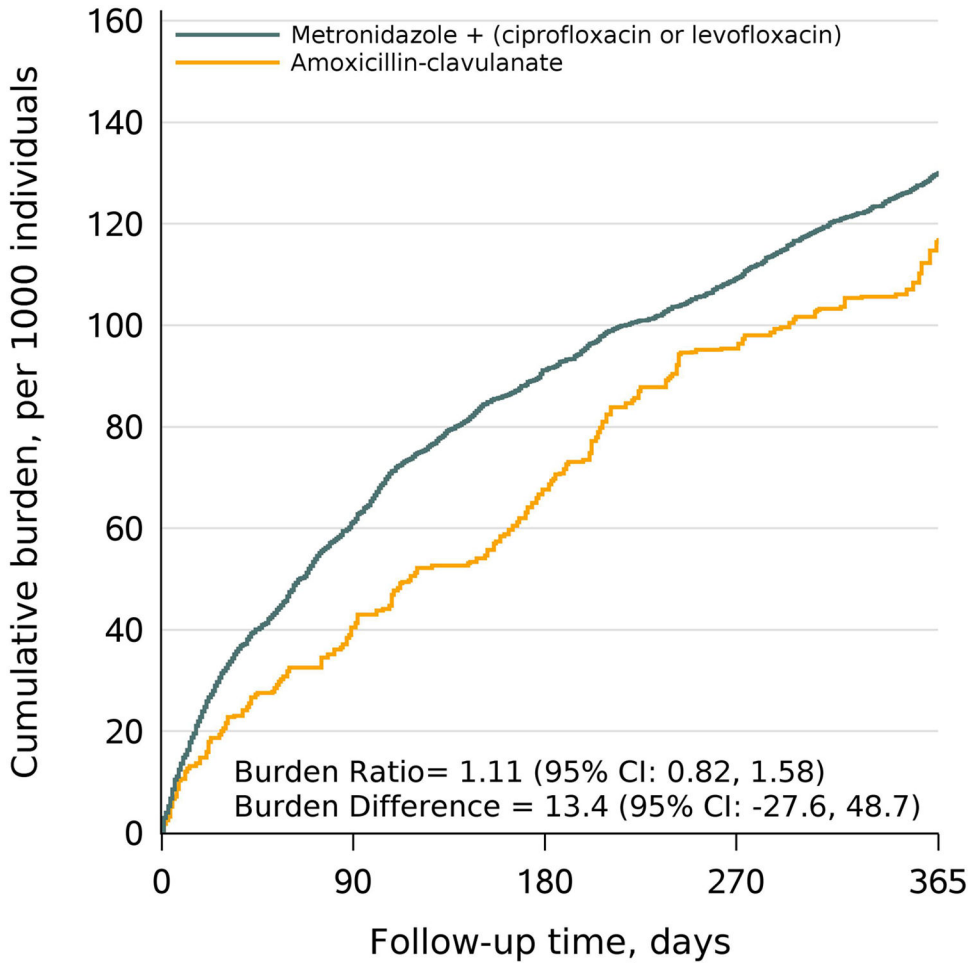


FIGURE 3.

Cumulative burden of recurrent healthcare visits for diverticulitis in privately insured (2001-2018) and Medicare-insured (2007-2015) adults diagnosed with incident outpatient diverticulitis and treated with antibiotics. A. Emergency department visits, MarketScan, B. Emergency department visits, Medicare, C. Outpatient visits, MarketScan, D. Outpatient visits, Medicare, E. Inpatient visits, MarketScan, F. Inpatient visits, Medicare

Abbreviations: CI, confidence interval

Burden ratios and burden differences were calculated at the end of follow-up. 95% CI calculated via nonparametric bootstrap of 1000 resamples.

TABLE 1.

Demographic and clinical characteristics of incident diverticulitis patients initiating metronidazole-with-fluoroquinolone or amoxicillin-clavulanate within 3 days of diagnosis in an outpatient setting, presented by data source.

	MarketScan Cohort (2001-2018) N= 119,521		Medicare Cohort (2007-2015) N= 20,348	
	Metronidazole-with-fluoroquinolone n=106,361	Amoxicillin-clavulanate n= 13,160	Metronidazole-with-fluoroquinolone n= 17,639	Amoxicillin-clavulanate n= 2,709
Age, median (IQR)	52 (45-58)	53 (46-59)	73 (69-79)	74 (69-80)
Female, n (%)	50,178 (47.2)	6,323 (48.1)	11,971 (67.9)	1,843 (68.0)
Race, n (%)				
White	--	--	16,075 (91.1)	2,501 (92.3)
Black	--	--	751 (4.3)	94 (3.5)
Other	--	--	155 (0.9)	26 (1.0)
Asian	--	--	134 (0.8)	31 (1.1)
Hispanic	--	--	364 (2.1)	37 (1.4)
N. American Native or Unknown[a]	--	--	160 (0.9)	20 (0.7)
Year of diverticulitis diagnosis				
2001-2003	2,424 (2.3)	540 (4.1)	--	--
2004-2006	8,918 (8.4)	1,298 (9.9)	--	--
2007-2009	16,066 (15.1)	1,643 (12.5)	4,889 (27.7)	780 (28.8)
2010-2012	27,394 (25.8)	2,780 (21.1)	5,399 (30.6)	811 (29.9)
2013-2015	28,256 (26.6)	3,055 (23.2)	7,351 (41.7)	1,118 (41.3)
2016-2018	23,303 (21.9)	3,844 (29.2)	--	--
Region[b], n (%)[b]				
New England	5,278 (5.0)	923 (7.0)	958 (5.4)	194 (7.2)
Mid-Atlantic	11,660 (11.0)	1552 (11.8)	1,927 (10.9)	304 (11.2)
East North Central	19,185 (18.0)	2,694 (20.5)	2,710 (15.4)	495 (18.3)
West North Central	5,696 (5.4)	840 (6.4)	1,559 (8.8)	270 (10.0)
South Atlantic	20,417 (19.2)	2,287 (17.4)	3,702 (21.0)	503 (18.6)
East South Central	6,352 (6.0)	613 (4.7)	1,194 (6.8)	140 (5.2)
West South Central	12,328 (11.6)	898 (6.8)	1,702 (9.6)	190 (7.0)
Mountain	5,769 (5.4)	866 (6.6)	1,068 (6.1)	182 (6.7)
Pacific	16,690 (15.7)	2,083 (15.8)	2,227 (12.6)	348 (12.8)
PR, USVI, or Unknown[a]	2,986 (2.8)	404 (3.1)	592 (3.4)	83 (3.1)
Comorbidities[c], n (%)				
Arthritis	5,416 (5.1)	616 (4.7)	4,798 (27.2)	755 (27.9)
Cerebrovascular disease	1,591 (1.5)	168 (1.3)	2,490 (14.1)	384 (14.2)
Congestive heart failure	788 (0.7)	114 (0.9)	1,674 (9.4)	328 (12.1)
Chronic kidney disease	666 (0.6)	79 (0.6)	1,461 (8.3)	235 (8.7)
COPD	1,353 (1.3)	162 (1.2)	2,221 (12.6)	317 (11.7)

	MarketScan Cohort (2001-2018) N= 119,521		Medicare Cohort (2007-2015) N= 20,348	
	Metronidazole-with-fluoroquinolone n=106,361	Amoxicillin-clavulanate n= 13,160	Metronidazole-with-fluoroquinolone n= 17,639	Amoxicillin-clavulanate n= 2,709
Dementia	35 (<0.1)	<11 (<0.1)	341 (1.9)	47 (1.7)
Gastritis	591 (0.6)	66 (0.5)	321 (1.8)	53 (2.0)
GERD	7,987 (7.5)	916 (7.0)	4,537 (25.7)	694 (25.6)
Liver disease	38 (<0.1)	<11 (<0.1)	40 (0.2)	<11 (<0.4)
Myocardial infarction	163 (0.2)	28 (0.2)	146 (0.8)	29 (1.1)
Obesity	4,527 (4.3)	431 (3.2)	1,281 (7.3)	188 (6.9)
PVD	1,158 (1.1)	139 (1.1)	2,418 (13.7)	430 (15.9)
Pneumonia	899 (0.9)	123 (0.9)	571 (3.2)	96 (3.5)
Rheumatic disease	894 (0.9)	99 (0.8)	723 (4.1)	130 (4.8)
Ulcer	335 (0.3)	47 (0.4)	305 (1.7)	44 (1.6)
Concomitant medications[c], n (%)				
Anticoagulants	3,593 (3.4)	566 (4.3)	3,178 (18.0)	623 (23.0)
Antidiabetics	8,851 (8.3)	1,099 (8.4)	3,363 (19.1)	493 (18.2)
Antihypertensives	38,412 (36.1)	4,783 (36.3)	13,259 (75.2)	2,094 (77.3)
Bisphosphonates	1,561 (1.5)	193 (1.5)	1,471 (8.3)	216 (8.0)
Clopidogrel	1,507 (1.4)	188 (1.4)	1,447 (8.2)	226 (8.3)
H2RAs	2,703 (2.5)	377 (2.9)	1,527 (8.7)	234 (8.6)
NSAIDs	21,427 (20.2)	2,463 (18.7)	3,596 (20.4)	501 (18.5)
PPIs	16,642 (15.7)	2,027 (15.4)	5,227 (29.9)	809 (29.9)
SSRIs	13,061 (12.3)	1,653 (12.6)	2,720 (15.4)	389 (14.4)
Statins	24,914 (23.4)	3,117 (23.7)	9,219 (52.3)	1,420 (52.4)
CT Scan during diagnosis	64,682 (60.8)	6,507 (49.5)	9,442 (53.5)	1,079 (39.8)
Inpatient admission in prior year, n (%)				
No inpatient admission	102,234 (96.1)	12,572 (95.5)	15,523 (88.0)	2,328 (85.9)
≤30 days prior	381 (0.4)	59 (0.5)	207 (1.2)	29 (1.1)
30-183 days prior	1,557 (1.5)	236 (1.8)	883 (5.0)	162 (6.0)
183-365 days prior	2,189 (2.1)	293 (2.2)	1,026 (5.8)	190 (7.0)
Inpatient days[c], median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)
Outpatient visits[c], median (IQR)	3 (1-5)	3 (1-6)	6 (4-10)	7 (4-11)
Antibiotic days supply, median (IQR)	10 (7-10)	10 (10-10)	10 (7-10)	10 (8-10)

Abbreviations: PR, Puerto Rico; USVI, United States Virgin Islands; COPD, chronic obstructive pulmonary disease; GERD, gastroesophageal reflux disease; PVD, pulmonary vascular disease; H2RAs, histamine-2 receptor antagonists; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton-pump inhibitors; SSRIs, selective serotonin reuptake inhibitors

[a] Combined for confidentiality purposes.

[b] Geographic regions are as follows: New England (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont); Mid-Atlantic (New Jersey, New York, Pennsylvania); East North Central (Illinois, Indiana, Michigan, Ohio, Wisconsin); West North Central (Iowa, Kansas, Minnesota, Missouri, Nebraska, North Dakota, South Dakota); South Atlantic (Washington DC, Delaware, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia); East South Central (Alabama, Kentucky, Mississippi, Tennessee); West South Central (Arkansas, Louisiana, Oklahoma, Texas); Mountain (Arizona, Colorado, Idaho, Montana, Nevada, New Mexico, Utah, Wyoming); Pacific (Alaska, California, Hawaii, Oregon, Washington).

[c] Evaluated in 365 days prior to first outpatient diverticulitis diagnosis (cohort entry date).