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RESEARCH ARTICLE

Thirty-day risk of digoxin toxicity among older adults co-prescribed trimethoprim-sulfamethoxazole versus amoxicillin: A population-based cohort study

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Abstract

Importance: Trimethoprim-sulfamethoxazole (TMP-SMX) may increase digoxin concentration, a medication with a narrow therapeutic index. Small changes in digoxin concentration could predispose individuals to the risk of toxicity.

Objective: To characterize the risk of digoxin toxicity in older adults taking digoxin following co-prescription of TMP-SMX compared with co-prescription of amoxicillin.

Design, Settings, and Participants: Retrospective population-based cohort study in Ontario, Canada (2002–2020) using linked health care data. Participants comprised 47,961 older adults taking digoxin (58% women; median age 80 years [interquartile range 74–86]) who were newly treated with TMP-SMX ($n = 10,273$) compared with those newly treated with amoxicillin ($n = 37,688$).

Exposure: Co-prescription of TMP-SMX versus amoxicillin in older adults concurrently taking digoxin.

Main Outcome and Measure: The primary outcome was a hospital encounter (i.e., hospital admission or emergency department visit) with digoxin toxicity within 30 days of the antibiotic prescription. Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. Weighted risk ratios (RR) were obtained using modified Poisson regression and weighted risk differences (RD) using binomial regression. The number needed to harm (NNH) was calculated as 1/RD.

Results: A hospital encounter with digoxin toxicity occurred in 49/10,273 (0.48%) patients treated with TMP-SMX versus 32/37,688 (0.08%) in those treated with amoxicillin (weighted RR, 5.71 [95% confidence interval (CI), 3.19 to 10.24]; weighted RD, 0.39% [95% CI, 0.25% to 0.53%]; NNH 256 [95% CI, 233 to 400]).

Conclusion and Relevance: In older adults taking digoxin, the 30-day risk of a hospital encounter with digoxin toxicity was nearly 6 times higher in those co-prescribed

TMP-SMX versus amoxicillin, although the absolute risk difference was low (0.4%). Physicians should prescribe an alternative antibiotic when clinically appropriate. If TMP-SMX must be co-prescribed with digoxin (if the benefit is believed to outweigh the risk), digoxin should be dose-reduced on an individual basis.

KEYWORDS
amoxicillin, digoxin, drug drug interaction, TMP-SMX, toxicity

1 | INTRODUCTION

Digoxin is used for acute rate control in patients with atrial fibrillation and rapid ventricular response when beta blockers and nondihydropyridine calcium channel blockers are ineffective or contraindicated.[1] Digoxin can be used alone or in combination with beta-blockers and nondihydropyridine calcium channel blockers.[1] In patients with symptomatic heart failure with reduced ejection fraction (HFrEF) despite guideline-directed medical therapy (or who are unable to tolerate guideline-directed medical therapy), digoxin might be considered to decrease hospitalizations for heart failure.[2]

Patients taking digoxin require monitoring of their serum digoxin concentration due to the narrow therapeutic window and potential for toxicity. The optimal concentration of digoxin varies depending on the clinical context. In a small series of patients, digoxin toxicity was observed when concentrations exceeded 2.0 ng/mL and likely at concentrations ≥3.0 ng/mL.[3] Conversely, post hoc analyses of the Digitalis Investigation Group (DIG) trial demonstrated that concentrations between 0.5 and 0.9 ng/mL were associated with significantly lower all-cause mortality rates and hospitalizations compared to concentrations ≥1.0 ng/mL.[4,5] The post hoc digoxin subgroup analysis of the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial showed that serum concentrations greater ≥1.2 ng/mL were associated with an increased risk of death.[5] For patients with heart failure and reduced ejection fraction, serum digoxin concentrations between 0.5 and 0.8 ng/mL were considered the safest in terms of benefit without adverse effects.[6]

Trimethoprim-sulfamethoxazole (TMP-SMX) is a combination of two popular antibiotics used to treat bacterial infections of the urinary tract, skin, and soft tissues.[7] The digoxin product monograph and current guidelines suggest TMP-SMX may inhibit the renal secretion of digoxin and raise the serum concentration of digoxin.[8,9] This evidence comes from a pharmacokinetic study that examined the potential interaction between digoxin and trimethoprim (one component of the TMP-SMX combination) in 10 older adults (median age 78 years) and six younger adults (median age 29 years).[8] This study showed that co-administration of digoxin (0.125–0.25 mg daily) and TMP-SMX (200 mg twice daily) raised the serum digoxin concentration by 22% in the older adults,[8] but no such rise occurred in the younger adults, who may compensate better with alternative routes of digoxin elimination when renal clearance decreases.[8] As a result, the digoxin monograph recommends reducing the dose of digoxin (~15 to 30%) and monitoring serum digoxin concentration in patients on digoxin starting TMP-SMX.[9]

In recent years, the use of digoxin has decreased for several reasons.[10] Several studies have found that digoxin has inferior benefits compared to other drugs for heart failure and atrial fibrillation and may even pose potential risks.[1,2,11–13] For instance, the pivotal DIG trial demonstrated that patients with heart failure treated with digoxin did not experience any survival improvement.[14] Additionally, stronger evidence and guideline recommendations have led to the widespread adoption of alternative heart failure therapies, such as diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers, contributing to reduced use of digoxin.[1,2] A recent study showed a decline in digoxin use in patients with chronic kidney disease in Ontario, Canada, from 2008 to 2019, indicating the current pattern of digoxin prescribing practices in our region.[15] On the other hand, the relative decrease in use of TMP-SMX during the study period may be explained by local uropathogen resistance. For example, urine culture susceptibility to TMP-SMX in Ontario from 2016 to 2017 was 78% and 80% in older adults and outpatient settings, respectively, whereas ciprofloxacin had susceptibility rates of 82% and 87%, respectively.[16]

Therefore, the prevalence of co-prescription of digoxin and TMP-SMX in our region is likely to be low. However, it remains unclear whether this drug–drug interaction increases the risk of digoxin toxicity in older adults in routine care. Our literature search found no studies quantifying the risk for digoxin toxicity when co-prescribed with TMP-SMX.

We conducted a new-user, active-comparator, population-based cohort study to quantify the risk of digoxin toxicity in older adults who were newly co-prescribed TMP-SMX. The primary outcome was 30-day hospital encounter with digoxin toxicity, in patients taking digoxin who were newly co-prescribed TMP-SMX versus amoxicillin. We hypothesized that the risk of digoxin toxicity would be higher in patients co-prescribed digoxin and TMP-SMX than in patients co-prescribed digoxin and amoxicillin.

2 | MATERIALS AND METHODS

2.1 | Study design and setting

We conducted a new-user, active-comparator, population-based cohort study using linked administrative health care databases in Ontario, Canada (2002–2020). All Ontario residents (~14 million) have universal access to hospital care and physician services

through a government-funded single-payer system.[17] Those aged 65 years and older (~2.2 million) also receive universal outpatient prescription-drug coverage. The use of data in this study was authorized under section 45 of Ontario's Personal Health Information Protection Act, and did not require review by a Research Ethics Board. Study reporting follows recommended guidelines for observational studies that use routinely collected health data (Table S1).[18,19]

2.2 | Data sources

We obtained information on patient characteristics, prescription drug use, covariates, and the study outcomes from eight databases.[20] The datasets were linked using unique encoded identifiers and analyzed at ICES. We used the following databases: the Canadian Institute for Health Information Discharge Abstract Database, the ICES-derived Physician Database, the National Ambulatory Care Reporting System, the Ontario Drug Benefit Database, the Ontario Health Insurance Plan database, the Ontario Laboratories Information System, the Ontario Mental Health Reporting System, and the Registered Persons Database. Hospital admissions and diagnoses are coded by trained personnel using the *International Classification of Diseases 9th* (ICD-9) *and 10th revision* (ICD-10) systems; personnel only consider physician-recorded diagnoses in a patient's medical chart when assigning codes and do not review or interpret symptoms or test results. We have previously used these databases to study adverse drug events.[21–25] Except for prescriber data (31% missing, recoded as a separate category) and neighborhood income quintile (0.3% missing, recoded as the middle quintile), the databases were complete for all variables used in this study. The codes used to ascertain comorbidities are detailed in Table S2. The date of the first co-prescription for a study antibiotic (TMP-SMX or amoxicillin) dispensed from an outpatient pharmacy served as each patient's cohort entry date. We assessed baseline comorbidities in the 5-year period before cohort entry and health care use in the 1-year period before cohort entry. We used a 120-day look-back period to ascertain prescription drug exposure because the Ontario Drug Benefits program allows a maximum prescription duration of 100 days, and we did not want to miss prescriptions for patients who did not refill their prescriptions promptly.

2.3 | Patients

We assembled a cohort of older adults aged 66 years and older with continuous digoxin use (defined by the presence of at least two prescriptions for digoxin within 210 days) who received a new prescription for oral TMP-SMX or oral amoxicillin (day supply between 3 and 14 days) dispensed from an outpatient pharmacy between April 1, 2002, to March 1, 2020. The age threshold of 66 years and older was used to ensure all patients had at least 1 year of prescription drug coverage before the cohort entry date. The TMP-SMX or amoxicillin prescription date served as the cohort entry date (i.e., the index date). To ensure that digoxin and the study antibiotic were co-prescribed, the dates of the antibiotic prescription had to overlap with the day supply covered by the most recent digoxin prescription.

To ensure patients were new antibiotic users, we excluded those with evidence of TMP-SMX or amoxicillin use in the 180-day period before the cohort entry date. To ensure any observed associations were related to the study drugs, we excluded patients with evidence of concurrent use of other permeability glycoprotein (P-gp) inhibitors (e.g., verapamil, amiodarone, dronedarone, quinidine, ketoconazole, itraconazole) and inducers (e.g, rifampin, cholestyramine, phenytoin, bupropion) in the 120 days before the cohort entry date.[9,26] These drugs are known to substantially increase digoxin concentrations and were frequently used in Ontario. We also excluded those with one or more prescriptions for non-study antibiotics in the 30 days before the cohort entry date. To ensure study antibiotics were initiated in the outpatient setting, we excluded patients discharged from the hospital or emergency department within 2 days before the cohort entry date. To ensure generalizability to usual prescribing, we excluded patients prescribed nonstandard doses of study antibiotics and digoxin (i.e., TMP-SMX single strength 400/80 mg <2 tablets/day or >4 tablets/day; TMP-SMX double strength 800/160 mg <2 tablets/day; amoxicillin <750 mg/day or>2000 mg/day; amoxicillin and clavulanic acid tablets [875 mg amoxicillin and 125 mg clavulanic acid] <2 tablets/day; amoxicillin and clavulanic acid tablets [500 mg amoxicillin and 125 mg clavulanic acid] <2 tablets/day or >3 tablets/day; amoxicillin and clavulanic acid tablets [250 mg amoxicillin and 125 mg clavulanic acid] <2 tablets/days or >3 tablets/day; digoxin <0.0625 mg/day or >0.25 mg/day). Each patient could only enter the cohort once. If a patient met the eligibility criteria multiple times, the first eligibility date served as the cohort entry date.

2.4 | Exposed and comparator groups

The exposed group comprised outpatients newly treated with oral TMP-SMX. The comparator group comprised outpatients newly treated with oral amoxicillin (amoxicillin alone or in combination with clavulanic acid). According to the digoxin product monograph, there is no evidence to suggest that amoxicillin alone or in combination with clavulanic acid can increase serum digoxin concentration.[9] Our literature review also did not yield any studies examining the interaction between amoxicillin and digoxin, except for one study that found no significant modification of serum digoxin concentration with the concomitant use of ticarcillin and clavulanic acid.[27]

2.5 | Outcomes

We prespecified the outcomes. The primary outcome was a hospital admission or emergency department visit with digoxin toxicity

diagnosis within 30 days of starting TMP-SMX or amoxicillin. The two secondary outcomes were all-cause hospitalization and all-cause mortality.

Information on deaths occurring during an emergency department visit, hospitalization, as well as outside of hospitals was captured using the Registered Persons Database, which contains information on demographic characteristics and vital status.[28] In a population-based study of 11,755 older adults with chronic kidney disease, the median time from starting digoxin to a hospital visit with toxicity was 26 days in patients who initiated digoxin at a dose >0.125 mg/day.[15] In practice, the median duration of outpatient treatment with antibiotics for common outpatient infections is 10 days in the United States, regardless of guideline recommendations for specific antibiotics.[29] Therefore, we examined the risk of toxicity in the 30-day period after patients taking digoxin were co-prescribed either TMP-SMX or amoxicillin. An algorithm used in a validation study to identify a hospital admission with digoxin toxicity using ICD-9 codes demonstrated high sensitivity (84%, [interquartile range (IQR), 71%–93%]) and specificity (99% [IQR, 99%–99%]), but a low positive predictive value (57% [IQR, 45%–68%]).[30] In this study, we used the corresponding ICD-10 codes, and we also captured patients with digoxin toxicity who visited the emergency department.

2.6 | Statistical analysis

Analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC). We used inverse probability of treatment weighting on the propensity score to balance the two comparison groups (TMP-SMX vs. amoxicillin) on baseline health indicators.[31–33] We estimated the propensity score using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3) because they were known confounders or risk factors for digoxin toxicity.[33–35] We weighted patients in the reference group (amoxicillin) using average treatment effect on the treated (ATT) weights defined as [propensity score/(1−propensity score)], with patients in the exposed group (TMP-SMX) receiving weights of 1.[31–33] This method produces a weighted pseudo-sample of patients in the reference group with a similar distribution of measured covariates as the exposed group.[31,32] We compared between-group differences in baseline characteristics using standardized differences in both the unweighted and weighted samples (differences >10% are considered meaningful).[36] We obtained weighted risk ratios with 95% confidence intervals (CIs) using modified Poisson regression[37] and weighted risk differences with 95% CIs using a binomial regression model with an identity link function. We calculated the number needed to harm (NNH) as the reciprocal of the risk difference (1/risk difference). We interpreted two-tailed p values <0.05 as statistically significant.

We conducted the following pre-specified sensitivity analysis to further control for confounding by indication. We compared the 30-day risk of hospital encounters with digoxin toxicity in patients co-prescribed digoxin and TMP-SMX versus digoxin and amoxicillin in a cohort of patients who had a urine culture in the 7 days before the antibiotic prescription to increase the probability that patients in the two groups received the study antibiotics for similar reasons.

We conducted seven post hoc sensitivity analyses to assess the robustness of the main results. (i) We quantified the 7-day risk of hospital encounter with digoxin toxicity in patients co-prescribed digoxin and TMP-SMX versus digoxin and amoxicillin in this study, the median duration of antibiotic prescription was 7 days (IQR, 7 to 10) for both TMP-SMX and amoxicillin. (ii) We conducted an E-value analysis to assess the extent of unmeasured confounding that would be required to negate the observed results.[38] (iii) We conducted an analysis using a negative-control outcome,[39] which was a hospital admission with heart failure as the main diagnosis (this outcome should not differ between comparison groups). (iv) We conducted an analysis using propensity score matching to balance comparison groups on baseline health indicators.[33] Similar to the inverse probability of treatment weighting method, the propensity score matching technique estimates the ATT but is not sensitive to the influence of extreme weights.

(v) We conducted an additional analysis by excluding drugs on the index date that are known to moderately increase digoxin concentration, such as atorvastatin, carvedilol, rabeprazole, and ticagrelor.[9,26] (vi) We conducted a survival analysis (with 30-day follow-up censoring on death) that met the proportional hazards assumption (nonsignificant TMP-SMX *follow-up time interaction term, $p=0.94$). No differential censoring was observed between the two groups. (vii) We also examined effect modification by age categories (≥ 75 vs. <75 years), different accrual periods (2002–2006 vs. 2007–2020), and history of kidney disease (i.e., acute kidney disease or renal disease) (interaction terms were included in the models).

3 | RESULTS

The flow diagram for the cohort build is shown in Figure 1. The primary cohort included 47,961 patients taking digoxin (median age 80 years [IQR 74–86]; 58% women) who were newly dispensed TMP-SMX ($n=10,273$) or amoxicillin ($n=37,688$) at an outpatient pharmacy.

Characteristics of patients who started TMP-SMX versus amoxicillin are shown in Table 1 (the full set of 146 characteristics is shown in Table S4). After weighting, the two groups were balanced on all 146 variables, including the prescriber type, recorded indication for antibiotic use (i.e., urinary tract infection, community-acquired pneumonia, skin infection, prosthetic joint infection, and other bacterial infections), comorbidities, and concurrent medications (Table S4).

Patients received TMP-SMX or amoxicillin prescriptions primarily from general practitioners (65%). The median prescription duration was 7 days (IQR, 7 to 10) for TMP-SMX and amoxicillin.

Of 10,273 patients co-prescribed digoxin and TMP-SMX, only 492 (5%) had evidence of a digoxin dose reduction when the prescription for TMP-SMX was started (a dose reduction is recommended in the digoxin product monograph).[9]

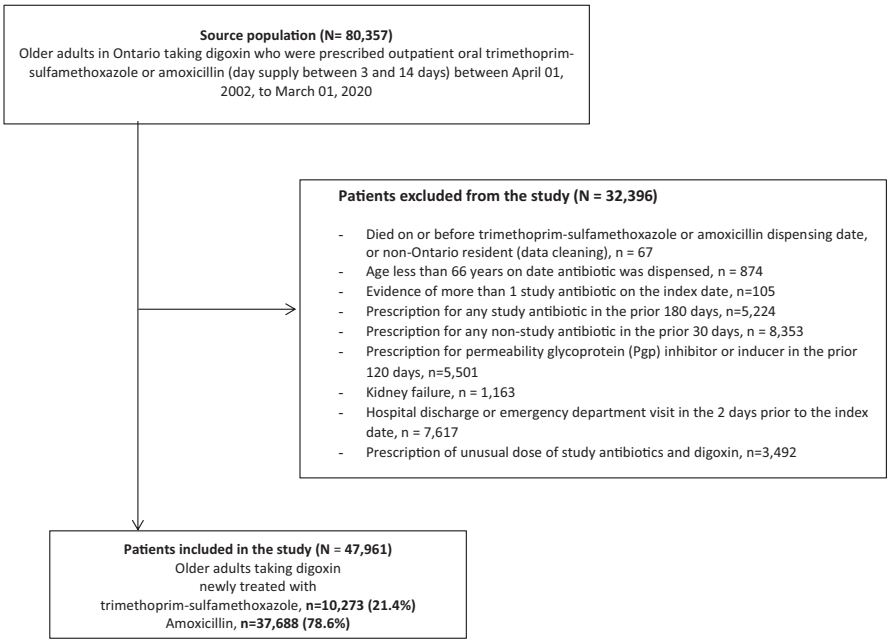

FIGURE 1 Flow diagram of cohort build.

3.1 | Hospital admission or emergency department visit with digoxin toxicity

The primary outcome, a hospital admission or emergency department visit with digoxin toxicity within 30 days, occurred in 49/10,273 (0.48%) patients who started TMP-SMX and in 32/37,688 (0.08%) patients who started amoxicillin.

A co-prescription of digoxin and TMP-SMX versus digoxin and amoxicillin was associated with a higher 30-day risk of a hospital admission or emergency department visit with toxicity: weighted risk ratio, 5.71 (95% CI, 3.19 to 10.24); weighted risk difference, 0.39% (95% CI, 0.25% to 0.53%); NNH 256 (95% CI, 233 to 400). A co-prescription of digoxin and TMP-SMX versus digoxin and amoxicillin was also associated with a higher risk of all-cause hospitalization but not all-cause mortality (Table 2).

3.2 | Prespecified sensitivity analyses

Results were consistent when the primary analysis was restricted to patients who had a recent urine culture before the study antibiotic prescription (Table 3).

3.3 | Post-hoc sensitivity analyses

Results were consistent when the follow-up period was shortened to 7 days after antibiotic initiation (Table 4). The E-values for the risk ratio and lower confidence bound for the primary outcome were 10.9 and 5.83, respectively, indicating that substantial unmeasured confounding would be needed to reduce the observed risk ratio or its 95% CI to the null (Figure S1). Study results were also supported by sensitivity analyses that used a negative control outcome when the data were analyzed using propensity score matching when we excluded drugs that are known to moderately increase digoxin concentration and when we conducted a survival analysis censoring on death (Table 4). None of the factors—age category, different accrual period, and history of kidney disease—significantly altered the association between the risk of digoxin toxicity in older adults taking digoxin and the co-prescription of TMP-SMX compared to amoxicillin (Table 5).

4 | DISCUSSION

In this population-based study of 47,961 older adults taking digoxin, co-prescription of TMP-SMX versus amoxicillin was associated with a higher 30-day risk of a hospital admission or emergency department visit with digoxin toxicity. In absolute terms, 1 in 200 patients prescribed digoxin were admitted to the hospital or visited an emergency department with signs of potentially toxicity within 30 days of starting TMP-SMX compared to approximately 1 in 1000 who started amoxicillin. Results were consistent in multiple sensitivity analyses.

Renal tubular secretion is a major mechanism that accounts for clearance of digoxin.[40] TMP-SMX mediates inhibition of P-gp, located on the luminal membrane of the renal tubular epithelial cells, which will reduce renal tubular secretion of digoxin, increase serum digoxin concentration, and cause toxicity.[8,9] In our region, clinicians may not be aware of this drug–drug interaction. Only 5% of patients co-prescribed digoxin and TMP-SMX had evidence of a digoxin dose reduction when TMP-SMX was prescribed, which is recommended in the digoxin monograph. The prevalence of angiotensin-converting enzyme inhibitors (42%) and beta-blockers (53%) was relatively low in our cohort. Several factors may potentially explain these prevalences. Firstly, our cohort was heterogeneous, including patients

TABLE 1 Baseline characteristics[a] of older adults taking digoxin co-prescribed with TMP-SMX versus amoxicillin in Ontario, Canada (2002–2020).

	Unweighted data ($N = 47,961$)			Weighted data ($N = 20,770$)[b]		
	TMP-SMX ($n = 10,273$)	Amoxicllin ($n = 37,688$)	Standardized difference[c]	TMP-SMX ($n = 10,273$)	Amoxicllin ($n = 10,497$)	Standardized difference[c]
Demographics						
Women, no. (%)	7194 (70.0)	20,728 (55.0)	31%	7194 (70.0)	7413 (70.6)	1%
Age, mean (SD), years	82.2 (7.8)	79.4 (7.9)	36%	82.2 (7.8)	82.4 (4.2)	3%
Residence, no. (%)						
Urban	8362 (81.4)	32,734 (86.9)	15%	8362 (81.4)	8496 (80.9)	1%
Rural	1911 (18.6)	4954 (13.1)	15%	1911 (18.6)	2000 (19.1)	1%
Long-term care	2971 (28.9)	4029 (10.7)	47%	2971 (28.9)	3190 (30.4)	3%
Income quintile, no. (%)[d]						
1 (lowest)	2347 (22.8)	7746 (20.6)	5%	2347 (22.8)	2380 (22.7)	0%
2	2210 (21.5)	8046 (21.3)	0%	2210 (21.5)	2248 (21.4)	0%
3 (middle)	2057 (20.0)	7715 (20.5)	1%	2057 (20.0)	2139 (20.4)	1%
4	1861 (18.1)	7076 (18.8)	2%	1861 (18.1)	1901 (18.1)	0%
5 (highest)	1798 (17.5)	7105 (18.9)	4%	1798 (17.5)	1829 (17.4)	0%
Antibiotic prescriber, no. (%)						
General practitioner[e]	8424 (82.0)	22,627 (60.0)	50%	8424 (82.0)	8664 (82.5)	1%
Internist	73 (0.7)	190 (0.5)	3%	73 (0.7)	71 (0.7%)	0%
Other	398 (3.9)	1003 (2.7)	7%	398 (3.9)	398 (3.8)	1%
Missing	1177 (11.5)	13,728 (36.4)	61%	1177 (11.5)	1137 (10.8)	2%
Comorbidities, no. (%)[f]						
Acute kidney injury	703 (6.8)	2283 (6.1)	3%	703 (6.8)	746 (7.1)	1%
Chronic kidney disease	1378 (13.4)	4636 (12.3)	3%	1378 (13.4)	1444 (13.8)	1%
Atrial fibrillation or flutter	5098 (49.6)	17,975 (47.7)	4%	5098 (49.6)	5223 (49.8)	0%
Heart failure	5918 (57.6)	21,217 (56.3)	3%	5918 (57.6)	6112 (58.2)	1%
Urinary tract infection	2334 (22.7)	4403 (11.7)	29%	2334 (22.7)	2510 (23.9)	3%
Prosthetic joint infection	1483 (14.4)	5357 (14.2)	1%	1483 (14.4)	1525 (14.5)	0%
Skin and soft tissue infection	4412 (42.9)	15,626 (41.5)	3%	4412 (42.9)	4455 (42.4)	1%
Community-acquired pneumonia	1703 (16.6)	4841 (12.8)	11%	1703 (16.6)	1818 (17.3)	2%
Other bacterial infections	4475 (43.6)	17,807 (47.2)	7%	4475 (43.6)	4843 (46.1)	5%
Charlson comorbidity index, mean (SD)[g]	1.4 (1.9)	1.08 (1.7)	18%	1.4 (1.9)	1.4 (1.0)	3%
Tests, no. (%)[h]						

TABLE 1 (Continued)

	Unweighted data (N = 47,961)			Weighted data (N = 20,770)[b]		
	TMP-SMX (n = 10,273)	Amoxicllin (n = 37,688)	Standardized difference[c]	TMP-SMX (n = 10,273)	Amoxicllin (n = 10,497)	Standardized difference[c]
Chest X ray	5517 (53.7)	19,014 (50.5)	6%	5517 (53.7)	5717 (54.5)	2%
Urine culture	6219 (60.5)	18,133 (48.1)	25%	6219 (60.5)	6431 (61.3)	2%
Medication use, no. (%)[i]						
Angiotensin-converting enzyme (ACE) inhibitors	4467 (43.5)	15,825 (42.0)	3%	4467 (43.5)	4522 (43.1)	1%
Angiotensin II receptor blockers	1275 (12.4)	5827 (15.5)	9%	1275 (12.4)	1371 (13.1)	2%
Beta blockers	4912 (47.8)	20,370 (54.0)	12%	4912 (47.8)	4899 (46.7)	2%
Nitrates	2075 (20.2)	5654 (15.0)	14%	2075 (20.2)	2146 (20.4)	0%
Loop diuretics	5129 (49.9)	17,515 (46.5)	7%	5129 (49.9)	5492 (52.3)	5%
Thiazide diuretics	1093 (10.6)	3794 (10.1)	2%	1093 (10.6)	1059 (10.1)	2%
Mineralocorticoid receptor antagonists	1410 (13.7)	5407 (14.3)	2%	1410 (13.7)	1510 (14.4)	2%

Abbreviations: IQR, interquartile range; SD, standard deviation; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Unless otherwise specified in the footnotes, baseline characteristics were assessed on the date the patient filled the antibiotic (TMP-SMX or amoxicillin) prescription—the cohort entry date.

[b]Weighted using inverse probability of treatment weighting based on propensity scores. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1−propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposure group.

[c]The mean difference between the groups divided by the pooled SD; a value greater than 10% is interpreted as a meaningful difference.

[d]Income was categorized into fifths of average neighborhood income on the cohort entry date; missing data on this variable (0.2%) was recorded as the middle quintile.

[e]A general practitioner, also known as a family physician, is a medical doctor who provides comprehensive health care to patients of all ages. They diagnose and treat acute and chronic illnesses, provide preventive care, and offer health education to help patients maintain good health.

[f]Baseline comorbidities were assessed in the 5-year period before the cohort entry date.

[g]Charlson comorbidity index was calculated based on hospitalization data during the 5 years preceding the index date. For each patient, the index considers hospitalizations with the comorbidities of interest (acute myocardial infarction, heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic lung disease, rheumatic disease, peptic ulcer disease, mild and moderate/severe liver disease, diabetes mellitus with and without complications, hemiplegia/paraplegia, renal disease, cancer and metastatic solid tumor, and AIDS/HIV). It assigns a point score1,2,3, or 6 for each comorbidity and sums them to generate an overall score of disease burden. The final risk scores range between 0 and 13, with higher values associated with higher mortality. Patients without a history of hospitalization received a score of 0.

[h]Tests presented as binary variables in the 365-days before the cohort entry date.

[i]Medication use was examined in the 120-day period before the cohort entry date (the Ontario Drug Benefit program dispenses a maximum 100-day supply). Some of these medications may have been discontinued after the initiation of the study antibiotics.

TABLE 2 Risk of digoxin toxicity in older adults co-prescribed digoxin and TMP-SMX versus amoxicillin[a].

	Unweighted		Weighted[b]				
	No. events (%)		No. events (%)				
	TMP-SMX ($n = 10,273$)	Amoxicillin ($n = 37,688$)	TMP-SMX ($n = 10,273$)	Amoxicillin ($n = 10,497$)	Risk difference, % (95% CI)	Risk ratio (95% CI)	NNH (95% CI)
Primary outcome							
Hospital admission or emergency department visit with digoxin toxicity	49 (0.48)	32 (0.08)	49 (0.48)	9 (0.09)	0.39 (0.25 to 0.53)	5.71 (3.19 to 10.24)	256 (233 to 400)
Secondary outcomes							
All-cause hospitalization	920 (9.0)	2054 (5.5)	920 (9.0)	756 (7.2)	1.76 (1.04 to 2.48)	1.24 (1.14 to 1.36)	57 (40 to 96)
All-cause mortality	294 (2.9)	593 (1.6)	294 (2.9)	287 (2.7)	0.13 (−0.33 to 0.58)	1.05 (0.89 to 1.23)	NA

Abbreviations: CI, confidence interval; NNH, number needed to harm; no., number; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Reference group: Amoxicillin.

[b]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1—propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group. Weighted risk ratios and 95% CIs were obtained using modified Poisson regression, and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.

TABLE 3 Risk of digoxin toxicity in older adults co-prescribed digoxin and TMP-SMX versus amoxicillin: Restricted to adults with a recent urine culture[a].

	Unweighted		Weighted[b]				
	No. events (%)		No. events (%)				
	TMP-SMX ($n = 3412$)	Amoxicillin ($n = 3579$)	TMP-SMX ($n = 3412$)	Amoxicillin ($n = 3408$)	Risk difference, % (95% CI)	Risk ratio (95% CI)	NNH (95% CI)
Primary outcome							
Hospital admission or emergency department visit with digoxin toxicity	17 (0.50)	<6 (<0.17)	17 (0.50)	<6 (<0.18)	0.37 (0.11 to 0.64)	4.01 (1.36 to 11.82)	270 (156 to 909)

Note: Reference group: Amoxicillin.

Abbreviations: CI, confidence interval; NNH, number needed to harm; no., number; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]The recent urine culture was defined as a receipt of a urine culture in the 7-days before the study antibiotic prescription.

[b]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1−propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group. Weighted risk ratios and 95% CIs were obtained using modified Poisson regression, and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.

treated with digoxin. Nearly half of the cohort (48%) had a history of atrial fibrillation/flutter, and three-fifths (57%) had a history of heart failure, which may have influenced prescribing patterns. Second, nearly two-thirds (65%) of the study drugs were prescribed by general practitioners who do not always follow clinical guidelines.[41]

To our knowledge, the interaction between digoxin and TMP-SMX in older adults in routine care has not previously been quantified. Our population-based study of 47,961 adults provides robust evidence for the potential harm of prescribing digoxin with TMP-SMX in older adults. These findings support the recommendations in the digoxin product monograph, which indicates that the digoxin dose should be reduced when starting a new prescription for TMP-SMX in older adults, with careful monitoring of serum digoxin concentration and signs of toxicity.

TABLE 4 Risk of digoxin toxicity in older adults co-prescribed TMP-SMX versus amoxicillin with digoxin: Sensitivity analyses.

	Unweighted		Weighted[a]				
	No. events (%)		No. events (%)				
	TMP-SMX	Amoxicillin	TMP-SMX	Amoxicillin	Risk difference, %	Risk ratio	NNH
	(*n* = 10,273)	(*n* = 37,688)	(*n* = 10,273)	(*n* = 10,497)	(95% CI)	(95% CI)	(95% CI)
A. Risk of digoxin toxicity in older adults co-prescribed TMP-SMX versus amoxicillin with digoxin within 7 days of antibiotic initiation.							
Hospital admission or emergency department visit with digoxin toxicity	20 (0.19)	14 (0.04)	20 (0.19)	<6 (<0.06)	0.16 (0.07 to 0.25)	5.90 (2.59 to 13.42)	625 (400 to 1429)
B. The 30-day risk of hospital admission with heart failure (defined as the main diagnosis) in older adults co-prescribed TMP-SMX versus amoxicillin with digoxin							
Hospital admission with heart failure (main diagnosis)	88 (0.86)	265 (0.70)	88 (0.86)	99 (0.95)	−0.09 (−0.34 to 0.16)	0.90 (0.69 to 1.20)	NA
	Unmatched		Matched[b]				
	No. events (%)		No. events (%)				
	TMP-SMX	Amoxicillin	TMP-SMX	Amoxicillin	Risk difference, %	Risk ratio	NNH
	(*n* = 10,273)	(*n* = 37,688)	(*n* = 9982)	(*n* = 9982)	(95% CI)	(95% CI)	(95% CI)
C. Risk of digoxin toxicity in older adults co-prescribed TMP-SMX versus amoxicillin with digoxin after exclusion of drugs that are known to moderately increase digoxin concentration							
Hospital admission or emergency department visit with digoxin toxicity	49 (0.48)	32 (0.08)	49 (0.49)	12 (0.12)	0.37 (0.22 to 0.52)	4.08 (2.17 to 7.68)	270 (192 to 455)
	Unweighted		Weighted[a]				
	No. events (%)		No. events (%)				
	TMP-SMX	Amoxicillin	TMP-SMX	Amoxicillin	Risk difference, %	Risk ratio	NNH
	(*n* = 9781)	(*n* = 37,115)	(*n* = 9781)	(*n* = 10,002)	(95% CI)	(95% CI)	(95% CI)
D. Risk of digoxin toxicity in older adults co-prescribed TMP-SMX versus amoxicillin with digoxin after exclusion of drugs that are known to moderately increase digoxin concentration							
Hospital admission or emergency department visit with digoxin toxicity	47 (0.48)	31 (0.09)	47 (0.48)	9 (0.09)	0.39 (0.25 to 0.54)	5.53 (3.06 to 10.01)	256 (185 to 400)
	Unweighted		Weighted[c]				
	No. events per 1000 person-years		No. events per 1000 person-years				
	TMP-SMX	Amoxicillin	TMP-SMX	Amoxicillin	Hazard ratio (95% CI)		
E. Survival analysis in older adults taking digoxin who started a new prescription for TMP-SMX versus amoxicillin: Risk of a hospital visit with digoxin toxicity							
Hospital admission or emergency department visit with digoxin toxicity	59.08	10.41	59.08	10.59	5.73 (3.18 to 10.32)		

Abbreviations: CI, Confidence Interval; NNH, number needed to harm; no., number; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1−propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group. Weighted risk ratios and 95% CIs were obtained using modified Poisson regression, and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.

[b]Propensity score matching technique was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). TMP-SMX users were matched 1:1 with amoxicillin users using greedy matching without replacement, within 0.2 standard deviations of the logit of the propensity score. Risk ratios and 95% CIs were obtained using modified Poisson regression and risk differences, and 95% CIs were obtained using a binomial regression model with an identity link function.

[c]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1−propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group. Hazard ratios and 95% confidence intervals were obtained using a Cox proportional hazards regression, and 95% confidence intervals were obtained using a bootstrap variance estimator. The proportional hazards assumption was assessed using a time-dependent covariate test and was met for the digoxin toxicity outcome. Death was treated as a censoring event.

TABLE 5 Subgroup analysis for the weighted[c] risk of digoxin toxicity by age category, accrual period, and history of kidney disease.

Sub-group	Exposure	Unweighted		Weighted risk difference, % (95% CI)	*p* value[a]	NNH (95% CI)	Weighted risk ratio (95% CI)	*p* value[b]
		No. patients	No. events (%)					
Baseline age, year								
<75	TMP-SMX	1928	7 (0.36)	0.28 (0.00 to 0.56)	0.40	NA	4.49 (1.40 to 14.40)	0.68
	Amoxicillin	11,341	9 (0.08)					
≥ 75	TMP-SMX	8345	42 (0.50)	0.42 (0.26 to 0.58)		238 (172 to 385)	5.99 (3.19 to 11.26)	
	Amoxicillin	26,347	23 (0.09)					
Study year, year								
2002 to 2006	TMP-SMX	5050	21 (0.42)	0.33 (0.14 to 0.51)	0.34	303 (196 to 714)	4.70 (2.24 to 9.88)	0.44
	Amoxicillin	14,255	15 (0.11)					
2007 to 2020	TMP-SMX	5223	28 (0.54)	0.46 (0.26 to 0.67)		217 (149 to 384	7.45 (2.83 to 19.65)	
	Amoxicillin	23,433	17 (0.07)					
History of kidney disease								
None	TMP-SMX	1928	7 (0.36)	0.31 (0.17 to 0.46)	0.06	323 (217 to 588)	5.01 (2.48 to 10.14)	0.52
	Amoxicillin	11,341	9 (0.08)					
History of kidney disease	TMP-SMX	1928	7 (0.36)	0.80 (0.32 to 1.27)		125 (79 to 312)	7.26 (3.05 to 17.27)	
	Amoxicillin	11,341	9 (0.08)					

Abbreviations: CI, confidence interval; NA, not applicable; NNH, number needed to harm; no., number; TMP-SMX, trimethoprim-sulfamethoxazole.

[a]*p*-value for additive interaction.

[b]*p*-value for multiplicative interaction.

[c]Inverse probability of treatment weighting on the propensity score was used to balance comparison groups on indicators of baseline health. The propensity score was estimated using multivariable logistic regression with 115 covariates chosen a priori (defined in Table S3). Patients in the reference group were weighted as [propensity score/(1—propensity score)]. This method produces a weighted pseudo-sample of patients in the reference group with the same distribution of measured covariates as the exposed group. Weighted risk ratios and 95% CIs were obtained using modified Poisson regression, and weighted risk differences and 95% CIs were obtained using a binomial regression model with an identity link function.

Our findings have important implications for clinical practice, and we recommend the following actions to protect patients treated with digoxin. First, physicians should prescribe an alternative antibiotic (i.e., a non-P-gp inhibitor), when clinically appropriate. However, if TMP-SMX is prescribed, physicians should reduce the digoxin dose as recommended in the digoxin product monograph. The dose reduction should be done on an individual basis with careful monitoring of digoxin serum concentration and signs of toxicity. Although co-prescribing digoxin and TMP-SMX leads to a small increase in serum digoxin concentration (~22%), the risk of digoxin toxicity is low. Second, pharmacy strategies to reduce polypharmacy-related prescribing errors should be considered such as updating computerized medication-order entry warnings.[42,43] Lastly, regulatory agencies, including Health Canada and the US Food and Drug Administration, should carefully assess the need for warning labels on digoxin to inform prescribers about the potential risks associated with co-prescription with TMP-SMX.

This study has several strengths. To our knowledge, this is the first population-based study to examine the risk of toxicity associated with co-prescription of digoxin and TMP-SMX versus digoxin and amoxicillin in older adults in routine care. This study's findings are likely generalizable to most older adults. The study was conducted in the setting of usual clinical care. It included a representative sample of older adults in Ontario, Canada, where all residents aged 66 and older have universal prescription drug coverage. We were able to produce comparison groups that were balanced on 146 baseline characteristics after using inverse probability of treatment weighting. We conducted several sensitivity analyses, and all supported the main findings. In particular, the E-values' magnitude suggests that the observed association is unlikely to be explained by unmeasured confounding.

This study has some limitations. First, despite using robust statistical techniques to control for confounding by indication and multiple sensitivity analyses, residual confounding remains a possibility in this observational study, although we used an active comparator group that was not a P-gp inhibitor to reduce concern about confounding by indication. Second, drug–drug interactions are complex, and factors beyond P-gp inhibition may have affected the results. Third, despite the use of highly accurate data on TMP-SMX and amoxicillin dispensing, the use of administrative data cannot provide information on the proportion of patients who took their medications as prescribed. Fourth, we only studied patients aged 66 years and older, so our findings may not apply to younger patients co-prescribed digoxin and TMP-SMX. Fifth, this study could not assess the risk–benefit ratio of co-prescribing digoxin with TMP-SMX versus amoxicillin. Sixth, because our algorithm only captured patients with digoxin toxicity who presented

to the hospital (and not cases managed solely as outpatients), the incidence of digoxin toxicity in this study may be underestimated. Seventh, data on serum digoxin concentration was not available in the laboratory database, and therefore, we could not assess serum digoxin concentrations in patients classified as having digoxin toxicity; however, symptoms of toxicity are possible even at therapeutic concentrations of digoxin.[44]

In older adults taking digoxin, the 30-day risk of a hospital encounter with toxicity was nearly six times higher in those co-prescribed TMP-SMX versus amoxicillin, although the absolute risk was low (0.4%). If TMP-SMX must be co-prescribed with digoxin (if the benefit is believed to outweigh the risk), digoxin should be dose reduced on an individual basis.

AUTHOR CONTRIBUTIONS

FTM and AXG developed the initial concept and plan. FA and HS performed initial literature review. FTM, SSA, EM, and AXG provided input and approved the study and analysis plan. FTM completed all statistical analyses. All authors interpreted the results. FTM drafted the initial manuscript, and all other authors critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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