Original Investigation

Calcium-Channel Blocker–Clarithromycin Drug Interactions and Acute Kidney Injury

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IMPORTANCE Calcium-channel blockers are metabolized by the cytochrome P450 3A4 (CYP3A4; EC 1.14.13.97) enzyme. Blood concentrations of these drugs may rise to harmful levels when CYP3A4 activity is inhibited. Clarithromycin is an inhibitor of CYP3A4 and azithromycin is not, which makes comparisons between these 2 macrolide antibiotics useful in assessing clinically important drug interactions.

OBJECTIVE To characterize the risk of acute adverse events following coprescription of clarithromycin compared with azithromycin in older adults taking a calcium-channel blocker.

DESIGN, SETTING, AND PARTICIPANTS Population-based retrospective cohort study in Ontario, Canada, from 2003 through 2012 of older adults (mean age, 76 years) who were newly coprescribed clarithromycin (n = 96 226) or azithromycin (n = 94 083) while taking a calcium-channel blocker (amlodipine, felodipine, nifedipine, diltiazem, or verapamil).

MAIN OUTCOMES AND MEASURES Hospitalization with acute kidney injury (primary outcome) and hospitalization with hypotension and all-cause mortality (secondary outcomes examined separately). Outcomes were assessed within 30 days of a new coprescription.

RESULTS There were no differences in measured baseline characteristics between the clarithromycin and azithromycin groups. Amlodipine was the most commonly prescribed calcium-channel blocker (more than 50% of patients). Coprescribing clarithromycin vs azithromycin with a calcium-channel blocker was associated with a higher risk of hospitalization with acute kidney injury (420 patients of 96 226 taking clarithromycin [0.44%] vs 208 patients of 94 083 taking azithromycin [0.22%]; absolute risk increase, 0.22% [95% CI, 0.16%-0.27%]; odds ratio [OR], 1.98 [95% CI, 1.68-2.34]). In a subgroup analysis, the risk was highest with dihydropyridines, particularly nifedipine (OR, 5.33 [95% CI, 3.39-8.38]; absolute risk increase, 0.63% [95% CI, 0.49%-0.78%]). Coprescription with clarithromycin was also associated with a higher risk of hospitalization with hypotension (111 patients of 96 226 taking clarithromycin [0.12%] vs 68 patients of 94 083 taking azithromycin [0.07%]; absolute risk increase, 0.04% [95% CI, 0.02%-0.07%]; OR, 1.60 [95% CI, 1.18-2.16]) and all-cause mortality (984 patients of 96 226 taking clarithromycin [1.02%] vs 555 patients of 94 083 taking azithromycin [0.59%]; absolute risk increase, 0.43% [95% CI, 0.35%-0.51%]; OR, 1.74 [95% CI, 1.57-1.93]).

CONCLUSIONS AND RELEVANCE Among older adults taking a calcium-channel blocker, concurrent use of clarithromycin compared with azithromycin was associated with a small but statistically significant greater 30-day risk of hospitalization with acute kidney injury. These findings support current safety warnings regarding concurrent use of CYP3A4 inhibitors and calcium-channel blockers.

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The commonly used macrolide antibiotics clarithromycin and erythromycin are clinically important inhibitors of the cytochrome P450 3A4 (CYP3A4; EC 1.14.13.97) enzyme, while azithromycin is much less so.[1,2] In older adults, coprescription of clarithromycin or erythromycin with a CYP3A4 metabolized statin (atorvastatin, simvastatin, and lovastatin) has been shown to be associated with a greater risk of hospitalization with rhabdomyolysis, hospitalization with acute kidney injury, and all-cause mortality compared with azithromycin coprescription.[3]

Calcium-channel blockers are a popular class of antihypertensive drugs that are metabolized by the CYP3A4 enzyme. In pharmacokinetic studies, coadministration of various inhibitors of this enzyme (eg, erythromycin, antifungals, protease inhibitors, and grapefruit juice) raised plasma calcium-channel blocker concentrations by up to 500%.[4-6] As a result, there is the possibility of excessive systemic calcium-channel blocker concentration and associated toxicity with concurrent use of a CYP3A4 inhibitor.

Enhanced blood pressure lowering was observed in several studies (up to 12 healthy volunteers) after a CYP3A4 inhibitor was administrated with a calcium-channel blocker.[4,7,8] Several case reports described hospitalization with hypotension soon after a CYP3A4 inhibitor was taken with a calcium-channel blocker.[9-12] Moreover, a population-based case-crossover study of older adults found a greater risk of hospitalization with hypotension when a calcium-channel blocker was coprescribed with erythromycin or clarithromycin compared with azithromycin.[13] Currently, the US Food and Drug Administration warns that "serious adverse reactions have been reported in patients taking clarithromycin concomitantly with CYP3A4 substrates, which includes hypotension with calcium-channel blockers metabolized by CYP3A4 (eg, verapamil, amlodipine, diltiazem)."[14] Yet calcium-channel blockers and clarithromycin continue to be frequently coprescribed in routine care.

When hypotension occurs, the kidney is particularly prone to acute ischemic injury from poor perfusion. Acute kidney injury is a clinically important event that impacts morbidity, mortality, and resource use.[15] Despite this knowledge, the risk of acute kidney injury following coprescription of clarithromycin with a calcium-channel blocker is unknown. Therefore, we conducted a population-based cohort study of older adults to investigate the interaction between calcium-channel blockers and the antibiotic clarithromycin with a focus on acute kidney injury.

Methods

Study Design and Setting

We conducted this study at the Institute for Clinical Evaluative Sciences (ICES) according to a prespecified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). Participant informed consent was not required for this study.

We conducted a population-based, retrospective cohort study of older adults from June 2003 through March 2012 using linked health care databases in Ontario, Canada. Ontario has approximately 13 million residents, 14% of whom are aged 65 years or older.[16] Residents have universal access to hospital care and physician services and those aged 65 years or older have universal prescription drug coverage. The reporting of this study followed guidelines for observational studies (eTable 1 in the Supplement).[17]

Data Sources

We ascertained patient characteristics, drug use, covariate information, and outcome data using records from 5 databases. We obtained vital statistics from the Ontario Registered Persons Database, which contains demographic information on all Ontario residents who have ever been issued a health card. We used the Ontario Drug Benefit Program database to identify prescription drug use. This database contains highly accurate records of all outpatient prescriptions dispensed to patients aged 65 years or older, with an error rate of less than 1%.[18] We identified diagnostic and procedural information on all hospitalizations from the Canadian Institute for Health Information's Discharge Abstract Database. We obtained covariate information from the Ontario Health Insurance Plan database, which includes health claims for inpatient and outpatient physician services. We also used the ICES Physician Database to ascertain antibiotic prescriber information. Previously, we have used these databases to research adverse drug events and health outcomes (including outcomes of acute kidney injury and health services).[3,19-22]

With the exception of infection type and prescriber (missing in the cohort by approximately 50% for infection type and 14% for prescriber), the databases were complete for all variables used in this study. *International Classification of Diseases, 9th revision* (*ICD-9*; pre-2002) and *10th revision* (*ICD-10*; post-2002) codes were used to assess baseline comorbidities in the 5 years prior to receipt of the relevant coprescription (eTable 2 in the Supplement). Codes used to ascertain outcomes are detailed in eTable 3 in the Supplement, which lists only *ICD-10* codes because all events would have occurred after the implementation of this coding system. A subpopulation in southwestern Ontario had outpatient serum creatinine measurements available before a new antibiotic coprescription and was in the catchment area of 12 hospitals in which linked inpatient serum creatinine values were also available.[23]

Patients

We established a cohort of older adults in Ontario, Canada, with continuous calcium-channel blocker use who also had evidence of a coprescription for the CYP3A4 inhibitor clarithromycin. For the referent group, we considered older adults coprescribed azithromycin. We previously demonstrated that clarithromycin and azithromycin in Ontario are prescribed for near-identical infections (eg, respiratory tract, sinus, and oropharyngeal infections), prescribed by the same type of physicians (approximately 75% primary care physicians), prescribed to patients with similar comorbidities, and are not statistically different in their risk of hospitalization with acute kidney injury or hospitalization with hypotension in the absence of another interacting drug (clarithromycin vs azithromycin: acute kidney injury odds ratio [OR], 1.06 [95% CI, 0.71-

1.58]; hypotension OR, 1.21 [95% CI, 0.61-2.41]).[24] Thus, comparison of outcomes among older adults prescribed 1 of these 2 antibiotics serves as a useful model in which to study CYP3A4 drug interactions with calcium-channel blockers in routine clinical practice. For reasons of statistical power and result interpretation, we elected a priori not to study the CYP3A4 inhibitor erythromycin, because in Ontario this drug was prescribed less than once for every 20 clarithromycin prescriptions.[3]

The date of the clarithromycin or azithromycin prescription served as the index date (referred to as cohort entry date or start time for follow-up). We considered the following CYP3A4 metabolized calcium-channel blockers: amlodipine, felodipine, nifedipine, verapamil, and diltiazem. Continuous use was defined as a second consecutive prescription claim for the same calcium-channel blocker. To ensure that the calcium-channel blocker and macrolide antibiotic were coprescribed, the dates covered by the calcium-channel blocker prescription had to overlap with the dates covered by the antibiotic prescription; in our cohort, the median (interquartile range [IQR]) overlap in each of the 2 macrolide antibiotic groups was 100% (100%-100%).

We excluded the following patients from analysis: (1) those in their first year of eligibility for prescription drug coverage (aged 65 years) to avoid incomplete medication records, (2) those who received a prescription for more than 1 type of antibiotic on the index date to compare mutually exclusive groups, (3) those who received any antibiotic in the 30 days prior to the index date to ensure new antibiotic use and to exclude patients with severe infections that failed to respond to initial antibiotic treatment, (4) those with 1 or more prescriptions for a nonstudy calcium-channel blocker to ensure any observed associations were due to the study drugs, (5) those who were discharged from the hospital in the 2 days prior to their index date to ensure these were new outpatient antibiotic prescriptions (because in Ontario, patients continuing an antibiotic treatment initiated in the hospital would have their oral outpatient antibiotic prescription dispensed on the same day or the day after hospital discharge), (6) those who had potent CYP3A4 inhibitors (such as protease inhibitors or antifungals) dispensed within the 30 days prior to the index date,[25] and (7) those with a history of end-stage renal disease receiving chronic dialysis because the assessment of acute kidney injury is no longer relevant in such individuals. A patient could only enter the cohort once.

Outcomes

The primary outcome was hospitalization with acute kidney injury and the 2 secondary outcomes were hospitalization with hypotension and all-cause mortality. We assessed these outcomes within 30 days of the index date (because macrolide antibiotics are prescribed for short durations and adverse events due to drug interactions would occur soon thereafter). The diagnostic codes used to identify the outcomes are presented in eTable 3 in the Supplement. For hospitalization records, up to 25 diagnostic codes can be assigned per hospitalization. As such, patients with codes for multiple study outcomes were accounted for in the assessment of each outcome.

In Ontario, we previously demonstrated that a database code for hospitalization with acute kidney injury identifies a median absolute acute increase in serum creatinine of 1.11 mg/dL (to convert to micromoles per liter, multiply by 88.4) at the time of hospital presentation (IQR, 0.49 to 2.26) above the most recent value prior to hospitalization, and the absence of such a code represents no significant change in serum creatinine (0.07 mg/dL; IQR, −0.04 to 0.23).[26] As the absolute increase in a serum creatinine value becomes more extreme (ie, higher levels of acute kidney injury) a code is more likely to be recorded for a particular diagnosis. Although the specificity is greater than 95%, the sensitivity of the hospital diagnosis code is limited particularly for milder forms of the condition. Specifically, the incidence of acute kidney injury, as defined by the diagnosis code, can be underestimated up to 5-fold compared with definitions using serum creatinine measurements. For this reason we examined a subpopulation with linked hospital laboratory values and defined hospitalization with acute kidney injury by evidence of an absolute increase in serum creatinine of 0.3 mg/dL or more from the baseline (preantibiotic) value or a relative increase of 50% or more.[27]

The code for hospitalization with hypotension has not been validated in our region but is expected to be insensitive. Mortality data are coded accurately in our region with a sensitivity of 97.8% and specificity of 100% for the finding of death.[28]

Statistical Analyses

We compared baseline characteristics between those coprescribed clarithromycin or azithromycin with calcium-channel blockers using standardized differences.[29,30] This metric describes differences between group means relative to the pooled standard deviation and is considered a clinically meaningful difference if greater than 10%. We expressed the risk of developing an outcome in both relative and absolute terms. Absolute risk was also expressed as the number needed to harm (NNH) (1 / absolute risk difference). This measure indicates how many patients need to receive a coprescription with clarithromycin to cause harm to 1 patient who otherwise would not have been harmed if all patients received a coprescription with azithromycin (a lower number indicating greater harm). The NNH was calculated for ease of interpretation, and not to imply causality.

We used PROC LOGISTIC, SAS version 9.2, for multivariable logistic regression analyses to estimate ORs and 95% CIs. We adjusted for 17 potential confounders: age, sex, baseline use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, nonsteroidal anti-inflammatory agents, oral hypoglycemic agents or insulin, nonpotassium-sparing diuretics or potassium-sparing diuretics, statins, β-blockers, β_2-agonists, anticholinergics, and corticosteroids (with all drugs defined by evidence of at least 1 prescription in the preceding 6 months), as well as baseline evidence of chronic kidney disease, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, and major cancers (defined using hospital diagnosis and physician claim codes in the preceding 5 years; in Ontario the validated algorithm for chronic kidney disease identifies older adults with a

median estimated glomerular filtration rate [eGFR] of 38 mL/min per 1.73 m^2 [IQR, 27-52], whereas its absence identifies those with a median eGFR of 69 mL/min per 1.73 m^2 [IQR, 56-82]).[31]

We also evaluated the association between coprescription and hospitalization with acute kidney injury in 3 prespecified subgroups. The first subgroup analysis consisted of the type of calcium-channel blocker. The second subgroup analysis consisted of patients with and without chronic kidney disease. It is recommended that the clarithromycin dose be reduced by 50% in chronic kidney disease due to impaired clearance, but in practice this seldom occurs.[32] Thus, we thought the relative association between coprescription with clarithromycin and hospitalization with acute kidney injury might be greater in those with chronic kidney disease than in those without. The third subgroup analysis examined effect modification by statin use, as we recently showed that coprescriptions with clarithromycin lead to rhabdomyolysis and acute kidney injury from statin toxicity.[3]

Odds ratios can be interpreted as relative risks (appropriate given the incidences observed). We conducted all analyses with SAS version 9.2. This includes additional analyses we undertook after knowledge of the primary results (see Results section). In all outcome analyses we interpreted 2-tailed *P* values lower than .05 as statistically significant.

Results

Baseline Characteristics

We identified 190 309 patients taking a calcium-channel blocker who received a coprescription for clarithromycin (n = 96 226) or azithromycin (n = 94 083) (eFigure 1 in the Supplement). Baseline characteristics of the 2 groups were nearly identical, including type and dose of calcium-channel blocker used (**Table 1**; all standardized differences for 38 characteristics were less than 10%). More than half the patients in each group received amlodipine. The median dosage for coprescribed clarithromycin was 1000 mg daily for 10 days and 300 mg daily for 5 days for azithromycin, which was consistent with drug prescribing references.[32] Coprescriptions of calcium-channel blockers and clarithromycin continued to occur in each year of the study period including the years of most recent accrual (Table 1).

Primary Outcome

Results for the outcome of hospitalization with acute kidney injury are presented in **Table 2** (using hospital-based diagnosis codes). Coprescribing clarithromycin with a calcium-channel blocker was associated with a higher risk compared with coprescribing azithromycin (420 patients of 96 226 taking clarithromycin [0.44%] vs 208 patients of 94 083 taking azithromycin [0.22%]; OR, 1.98 [95% CI, 1.68-2.34]). In absolute terms, coprescription with clarithromycin resulted in a 0.22% (95% CI, 0.16%-0.27%) higher incidence of hospitalization with acute kidney injury. The NNH was 464 (95% CI, 374-609).

Results from subgroup analyses are presented in **Figure 1** and **Figure 2**. When examined by type of calcium-channel blocker, the risk of hospitalization with acute kidney injury was highest among patients coprescribed clarithromycin with nifedipine (OR, 5.33 [95% CI, 3.39-8.38]; absolute risk increase, 0.63% [95% CI, 0.49%-0.78%]; *P* value for interaction, <.001 with amlodipine as the reference group). The corresponding NNH was lowest at 160 (95% CI, 128-205). Median doses of clarithromycin were similar among patients with and without chronic kidney disease (1000 mg/d in each group; standardized difference, <1%). The risk of hospitalization with acute kidney injury following clarithromycin coprescription was not modified by the presence of chronic kidney disease (*P* value for interaction = .47) or statin use (*P* value for interaction= .48). However, the NNH was lower in patients with chronic kidney disease compared with those without it (95 [95% CI, 70-145] for patients with chronic kidney disease vs 723 [95% CI, 545-1059] for patients without.

The baseline characteristics for the subpopulation with linked hospital serum creatinine measurements were similar between treatment groups (clarithromycin, n = 3164; azithromycin, n = 2094) (eTable 4 in the Supplement). Approximately 40% of patients had a baseline eGFR lower than 60 mL/min per 1.73 m^2. With the outcome of hospitalization with acute kidney injury defined using changes in serum creatinine, coprescribing clarithromycin with a calcium-channel blocker remained associated with a higher risk compared with coprescribing azithromycin (63 patients of 3164 taking clarithromycin [1.99%] vs 26 patients of 2094 taking azithromycin [1.24%]; OR, 1.62 [95% CI, 1.02-2.56]) (eTable 5 in the Supplement). The absolute risk increase was 0.75% (95% CI, 0.03%-1.42%) and the NNH was 133 (95% CI, 70-3004).

Secondary Outcomes

Coprescribing clarithromycin with a calcium-channel blocker was associated with a higher risk of hospitalization with hypotension (111 patients of 96 226 taking clarithromycin [0.12%] vs 68 patients of 94 083 taking azithromycin [0.07%]; absolute risk increase, 0.04% [95% CI, 0.02%-0.07%]; OR, 1.60 [95% CI, 1.18-2.16]) and all-cause mortality (984 patients of 96 226 taking clarithromycin [1.02%] vs 555 patients of 94 083 taking azithromycin [0.59%]; absolute risk increase, 0.43% [95% CI, 0.35%-0.51%]; OR, 1.74 [95% CI, 1.57-1.93]), compared with coprescribing azithromycin (Table 2).

Additional Analyses

The primary associations proved robust in multiple additional analyses. First, we adjusted for 17 relevant confounders and found no meaningful difference with unadjusted results for all 3 outcomes (Table 2). Second, we stratified by physician identification number to account for potential differences in prescribing practices and observed results consistent with the above (eTable 6 in the Supplement). Third, we restricted the cohort only to those coprescribed a calcium-channel blocker with clarithromycin, and compared those coprescribed a higher dose of clarithromycin (1000 mg/d; n = 28 591) with those coprescribed a lower dose of

Table 1. Baseline Characteristics

Characteristics	Clarithromycin (n = 96 226), %	Azithromycin (n = 94 083), %	Standardized Differences[a]
Age, mean (SD), y	76 (7.3)	76 (7.3)	0.01
Women	61.6	61.6	0
Income quintile[b]			
1, lowest	22.0	21.2	0.02
2	22.2	21.6	0.01
3, middle	19.7	19.8	0
4	18.8	19.0	0.01
5, highest	17.1	18.0	0.02
Year of cohort entry[c]			
2003-2004	22.7	22.2	0.01
2005-2006	24.4	22.7	0.04
2007-2008	21.6	21.0	0.02
2009-2010	20.7	20.3	0.01
2011-2012	10.6	13.8	0.1
Long-term care	5.6	4.0	0.08
Charlson comorbidity index[d]			
0	65.6	65.1	0.01
1	14.0	14.3	0.01
2	10.2	10.1	0
≥3	10.3	10.5	0.01
Comorbidities[e]			
Chronic kidney disease	8.5	8.6	0
Cerebrovascular disease	3.2	3.3	0
Peripheral vascular disease	2.1	2.2	0.01
Coronary artery disease[f]	37.6	39.6	0.04
Congestive heart failure	15.4	15.9	0.02
Major cancers[g]	13.0	13.2	0
Calcium-channel blocker type			
Amlodipine	52.7	54.1	0.03
Felodipine	3.8	3.3	0.02
Nifedipine	17.3	16.0	0.04
Verapamil	4.0	3.9	0
Diltiazem	22.2	22.5	0.01
Daily dose, median (IQR), mg			
Amlodipine	5 (5-10)	5 (5-10)	0.01
Felodipine	5 (5-10)	5 (5-10)	0.01
Nifedipine	30 (30-60)	30 (30-60)	0.01
Verapamil	240 (180-240)	240 (180-240)	0.04
Diltiazem	240 (180-240)	180 (180-240)	0.02
Baseline medication use[h]			
Oral hypoglycemic or insulin	24.4	24.9	0.01
β-Blockers	32.5	33.8	0.03
Statins	47.6	50.8	0.06
Potassium-sparing diuretics	6.1	6.0	0
Nonpotassium-sparing diuretics	38.4	39.3	0.02
NSAIDs, excluding aspirin	18.2	18.1	0
ACE inhibitor or ARB	60.4	61.4	0.02
β_2-Agonists	19.5	18.1	0.03
Anticholinergics	8.7	8.0	0.03
Corticosteroids	9.4	8.6	0.03

(continued)

Table 1. Baseline Characteristics (continued)

Characteristics	Clarithromycin (n = 96 226), %	Azithromycin (n = 94 083), %	Standardized Differences[a]
Antibiotic prescriber			
Family physician	81.7	82.0	0.01
Internist	0.5	0.6	0.01
Surgeon	0.5	0.1	0.07
Other	3.6	3.0	0.03
Missing	13.7	14.3	0.02
Infection type[i]			
Respiratory	40.2	38.4	0.04
Other	9.2	8.9	0.01
Unknown	51.8	53.9	0.04
Health care use in the prior year			
Hospitalizations			
0	67.8	67.7	0
1	19.9	19.7	0.01
2	7.8	7.9	0
≥3	4.7	4.7	0
Emergency department visits			
0	64.6	63.8	0.02
1	19.6	19.9	0.01
2	7.9	8.0	0
≥3	7.9	8.3	0.01
Family physician visits			
0	1.9	2.3	0.03
1-2	5.7	5.6	0
3-4	10.9	10.8	0.01
5-6	14.8	14.4	0.01
7-8	14.2	13.8	0.01
9-10	11.8	11.6	0.01
≥11	40.7	41.6	0.02
Cardiologist visits			
0	59.0	56.5	0.05
1	18.3	18.4	0
2	8.5	9.3	0.03
≥3	14.2	15.8	0.05
Unique drug products dispensed			
<5	8.5	8.0	0.02
5-8	28.0	27.7	0.01
9-12	29.2	29.6	0.01
13-16	18.8	18.7	0
>16	15.5	16.0	0.02
Procedures			
Chest x-ray	79.8	79.8	0
Pulmonary function test	29.1	29.5	0.01
Echocardiography	46.6	49.6	0.06
Cardiac stress test	39.4	41.5	0.04
Carotid ultrasound	17.8	19.1	0.03

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IQR, interquartile range; NSAID, nonsteroidal anti-inflammatory drug.

[a] Standardized differences are less sensitive to sample size than traditional hypothesis tests. They provide a measure of the difference between groups divided by the pooled standard deviation; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

[b] Income was categorized into fifths of average neighborhood income on the index date.

[c] The date of cohort entry is also referred to as the index date.

[d] Charlson comorbidity index[33,34] was calculated using 5 years of hospitalization data. No hospitalizations received a score of 0.

[e] Assessed by administrative database codes in the previous 5 years.

[f] Coronary artery disease includes both diagnoses of angina and coronary artery revascularization.

[g] Major cancers include esophagus, lung, bowel, liver, pancreas, breast, male/female reproductive organs, as well as leukemias and lymphomas.

[h] Baseline medication use assessed in the previous 180 days.

[i] Patients may have had a code for more than 1 type of infection.

clarithromycin (500 mg/d; n = 65 801) (eTable 7 in the Supplement). Receiving a higher dose of clarithromycin with a calcium-channel blocker was associated with a higher risk of hospitalization with acute kidney injury compared with a lower dose (307 patients of 28 591 taking a high dose [0.47%] vs 95 patients of 65 801 taking a low dose [0.33%]; absolute risk increase, 0.13% [95% CI, 0.05%-0.22%]; OR, 1.42 [95% CI, 1.131.79]). Finally, we compared 30-day outcomes in a restricted cohort at 3 periods: the time of coprescription, 90 days before the coprescription, and 90 days after the coprescription (clarithromycin, n = 53 070; azithromycin, n = 52 244). Full methods and cohort selection are presented in eFigure 2 in the Supplement. Baseline characteristics are presented in eTable 8 in the Supplement and results are in **Table 3**. As observed in

Table 2. Thirty-Day Outcomes Assessed Using Hospital-Based Diagnosis Codes and All-Cause Mortality

	No. of Events (%)[a]		Absolute Risk Difference (95% CI), %	NNH (95% CI)[c]	OR (95% CI)	
	Clarithromycin (n = 96 226)	Azithromycin (n = 94 083)[b]			Unadjusted	Adjusted[d]
Acute kidney injury	420 (0.44)	208 (0.22)	0.22 (0.16-0.27)	464 (374-609)	1.98 (1.68-2.34)	2.03 (1.72-2.41)
Hypotension	111 (0.12)	68 (0.07)	0.04 (0.02-0.07)	2321 (1406-6416)	1.60 (1.18-2.16)	1.63 (1.21-2.22)
Mortality	984 (1.02)	555 (0.59)	0.43 (0.35-0.51)	231 (195-284)	1.74 (1.57-1.93)	1.74 (1.57-1.94)

Abbreviations: NNH, number needed to harm; OR, odds ratio.

[a] The number of events (and the proportion of patients who experienced an event) for all outcomes except all-cause mortality were assessed by hospital diagnosis codes. This underestimates the true event rate because these codes have high specificity but low sensitivity. Similarly, the NNH is underestimated for these outcomes.

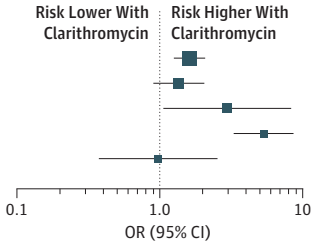
[b] Patients prescribed azithromycin served as the comparator group.

[c] The NNH does not imply causality as all the results are associations. Rather, the NNH is provided for ease of interpretation.

[d] Adjusted for 17 covariates (see Methods section).

Figure 1. Clarithromycin With Each Type of Calcium-Channel Blocker and the Risk of Acute Kidney Injury

	Clarithromycin		Azithromycin				
	Events, No.	No. at Risk (%)	Events, No.	No. at Risk (%)	OR (95% CI)	*P* Value for Interaction	NNH (95% CI)
Amlodipine	202	50706 (0.40)	126	50944 (0.25)	1.61 (1.29-2.02)	[Reference]	663 (451-1223)
Diltiazem	63	21403 (0.29)	46	21207 (0.22)	1.36 (0.93-1.99)	.36	NS[b]
Felodipine[a]	17	3665 (0.46)	≤5	3191 (≤0.16)	2.97 (1.09-8.06)	.19	NR
Nifedipine	129	16644 (0.78)	22	15038 (0.15)	5.33 (3.39-8.38)	<.001	160 (128-205)
Verapamil	9	3808 (0.24)	9	3703 (0.24)	0.97 (0.39-2.45)	.29	NS[b]



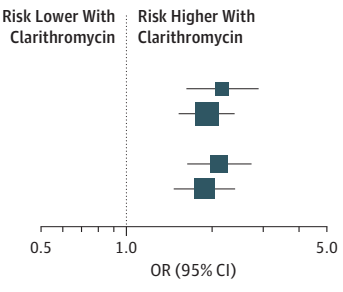
The outcome was 30-day hospitalization with acute kidney injury assessed by diagnostic codes. The referent group was patients with evidence of azithromycin coprescription. NS indicates nonsignificant; NR, not reportable for reasons of small cell size; NNH, number needed to harm; and OR, odds ratio. Data marker size is proportional to the inverse of the source variance.

[a] Cell sizes less than 6 were not reported for reasons of privacy. Accordingly, the NNH is not presented and an OR assuming 5 events in the reference group is presented. This may overestimate the true rate.

[b] Nonsignificant NNH not presented due to the difficulty in interpreting a negative value.

Figure 2. Chronic Kidney Disease, Statin Use, and the Risk of Acute Kidney Injury From Coprescription

	Clarithromycin		Azithromycin				
	Events, No.	No. at Risk (%)	Events, No.	No. at Risk (%)	OR (95% CI)	*P* Value for Interaction	NNH (95% CI)
CKD							
Yes	162	8152 (1.99)	75	8043 (0.93)	2.15 (1.64-2.84)	.47	95 (70-145)
No	258	88074 (0.29)	133	86040 (0.15)	1.90 (1.54-2.34)		723 (545-1059)
Statin							
Yes	197	45766 (0.43)	98	47748 (0.21)	2.10 (1.65-2.68)	.48	445 (334-650)
No	223	50460 (0.44)	110	46335 (0.24)	1.87 (1.48-2.35)		489 (359-758)



The outcome was 30-day hospitalization with acute kidney injury assessed by diagnostic codes. The referent group was patients with evidence of azithromycin coprescription. Data marker size is proportional to the inverse of the source variance. CKD indicates chronic kidney disease; NNH, number needed to harm; and OR, odds ratio.

Table 3. Thirty-Day Outcomes Assessed Using Hospital-Based Diagnosis Codes

Outcome	No. of Events (%)[a]		Absolute Risk Difference, % (95% CI)	NNH (95% CI)[c]	OR (95% CI)
	Clarithromycin (n = 53 070)	Azithromycin[b] (n = 52 244)			
Time of coprescription[d]					
Acute kidney injury	89 (0.17)	30 (0.06)	0.11 (0.07-0.15)	907 (656-1420)	2.92 (1.93-4.42)
Hypotension	29 (0.05)	8 (0.02)	0.04 (0.02-0.06)	2542 (1555-5872)	3.57 (1.63-7.81)
90 Days prior to coprescription[d]					
Acute kidney injury	20 (0.04)	19 (0.04)			1.04 (0.55-1.94)
Hypotension[e]	7 (0.01)	≤5 (≤0.00)			3.46 (0.72-16.64)
90 Days following coprescription[d]					
Acute kidney injury	39 (0.07)	44 (0.08)			0.87 (0.57-1.34)
Hypotension	23 (0.04)	17 (0.03)			1.33 (0.71-2.49)

Abbreviations: NNH, number needed to harm; OR, odds ratio.

[a] Coprescription date refers to the date when either clarithromycin or azithromycin was coprescribed with a CYP3A4 metabolized calcium-channel blocker. In the 90 days prior and 90 days following the initial coprescription date, patients only took a CYP3A4 metabolized calcium-channel blocker (ie, no macrolide antibiotic coprescription).

[b] Patients prescribed azithromycin served as the comparator group.

[c] The NNH does not imply causality as all the results are associations. Rather, the NNH is provided for ease of interpretation.

[d] The number of events (and the proportion of patients who experienced an event) for both outcomes were assessed using hospital diagnosis codes. This underestimates the true event rate because these codes have high specificity but low sensitivity. Similarly, the NNH is underestimated for these outcomes.

[e] Cell sizes less than 6 were not reported for reasons of privacy. Accordingly, the age-adjusted odds ratio is presented.

our primary analyses, coprescribing clarithromycin with a calcium-channel blocker was associated with a higher 30-day risk of hospitalization with acute kidney injury (OR, 2.92 [95% CI, 1.93-4.42]) and hypotension (OR, 3.57 [95% CI, 1.63-7.81]) compared with coprescribing azithromycin. Moreover, no significant difference in the 30-day risk of these outcomes was observed when the start of follow-up was 90 days prior and 90 days following the coprescription.

Discussion

In this population-based study of older adults, we observed that coprescribing clarithromycin with a calcium-channel blocker was common in routine care. This coprescription was associated with a higher risk of hospitalization with acute kidney injury, hypotension, and all-cause mortality compared with coprescription with azithromycin. These findings proved to be robust in multiple additional analyses. Although the absolute increases in the risks were small, these outcomes have important clinical implications. Our results suggest it is possible that hundreds of hospitalizations and deaths in our region may have been associated with this largely preventable drug-drug interaction. This burden on the health care system, given the high costs of managing acute kidney injury, might have been avoided.[35]

Macrolide antibiotics are frequently prescribed medications and different agents within this class (ie, clarithromycin and azithromycin) are used for similar clinical indications. Since clarithromycin is an inhibitor of CYP3A4 metabolism, concurrent use with a CYP3A4-metabolized calcium-channel blocker may intensify the calcium-channel blocker effect. This would not be expected with azithromycin, which is only a weak inhibitor of CYP3A4 metabolism. The kidney is especially prone to injury from poor perfusion and thus hospitalization with acute kidney injury represents a clinically important consequence of the interaction between macrolide antibiotics and calcium-channel blockers. It is reasonable to assume that the mechanism of kidney injury was hemodynamic in nature as we also noted a higher risk of hospitalization with hypotension in this setting. This finding is consistent with the observation made in a prior case-crossover study where a higher risk of hospitalization with hypotension was detected (OR, 3.7 [95% CI, 2.3-6.1]).[13]

We also observed that the risk of hospitalization with acute kidney injury was most pronounced when clarithromycin was coprescribed with nifedipine, followed by felodipine and amlodipine. These 3 drugs are dihydropyridines and are selective arterial vasodilators.[36] The 2 nondihydropyridines (diltiazem and verapamil) are less potent vasodilators but have the additional properties of direct negative effects on cardiac contractility and conduction. However, these subgroup results must be interpreted cautiously as estimates were also less precise from the small sample sizes (particularly for verapamil).

As the kidney plays an important role in the elimination of clarithromycin, prescribing guidelines state that the dose needs to be reduced in patients with chronic kidney disease.[32] However, we demonstrated that this rarely occurs in routine practice. Furthermore, since chronic kidney disease is the most potent risk factor for acute kidney injury, it is possible that the excess toxicity of calcium-channel blockers from clarithromycin coprescription would be most evident in patients with chronic kidney disease. Although we observed no greater relative risk of hospitalization in this group of patients, the absolute NNH from the coprescription was far lower in patients with chronic kidney disease than in those without.

It is concerning that clarithromycin continues to be coprescribed with calcium-channel blockers despite previous studies, as well as warnings in drug prescribing references.[14,32] The results of this study reinforce our knowledge about the dan-

gers of this type of drug interaction and have the potential to influence prescribing to prevent adverse events. Furthermore, our study highlights the need for quality improvement initiatives that will mitigate the clinical effects of such drug interactions. Potential strategies may include temporary cessation of the calcium-channel blocker for the duration of clarithromycin therapy or selection of a non-CYP3A4-inhibiting antibiotic when clinically appropriate.

Our study has several strengths. To our knowledge it is the first population-based study to assess hospitalization with acute kidney injury from CYP3A4 inhibition of common antihypertensive medications. The use of Ontario's health care databases with data on universal prescription drug coverage in older adults provided us with a large representative sample of patients who received coprescriptions. This allowed us to estimate the risks of uncommon but serious adverse events with good precision and excellent external validity. Although the absolute risk increases may have been underestimated due to the limited sensitivity of the diagnostic codes, we captured the more severe forms of the conditions (ie, requiring hospitalization), making these findings of particular interest to clinicians and policy decision makers. We used the antibiotic azithromycin as a comparator group to clarithromycin to reduce concerns about confounding by indication. Furthermore, there was marked similarity of measured baseline characteristics in the 2 groups. Additionally, we previously confirmed that clarithromycin and azithromycin are not different in the 30-day risk of hospitalization with acute kidney injury in the absence of other interacting medications.[24] We also verified that the calcium-channel blocker prescriptions alone (when assessed 90 days before and after the antibiotic coprescription) did not impact 30-day outcomes. This information reinforces the primary results of our study.

Our study does have some limitations. Prospective data collection with independent outcome adjudication would be the preferred methodology. However, conduct of such a study might not be possible if physicians were required to intervene after learning about a potential coprescription. In this study, we analyzed retrospective data using administrative diagnosis codes, which we did not expect to be assigned in a different manner in the 2 antibiotic groups. Nonetheless, these codes have their shortcomings, and for this reason we supplemented our primary outcome findings by observing a subpopulation with serum creatinine values and showed a similar signal of hospitalization with acute kidney injury following clarithromycin coprescription. Our findings can only be generalized to older adults, as younger patients are often healthier and may not be as susceptible to drug-drug interactions.[37] As with all observational studies, we may have failed to account for important unknown or unmeasured confounding variables. Also, drug-drug interactions are complex and factors beyond CYP3A4 inhibition may have affected the results. For example, we previously observed a small difference in all-cause mortality between clarithromycin and azithromycin alone that we could not explain when causes of death were examined (OR, 1.27 [95% CI, 1.04-1.55]).[24] Thus, it is possible that some of deaths observed in the present study (in which the observed OR was 1.74 [95% CI, 1.57-1.93]) could have been attributed to clarithromycin itself or the unique clinical circumstances that led to clarithromycin being chosen over azithromycin. As such, we cannot be entirely certain that the observed associations are causal or attributable to the mechanism we suggest. However, the results are consistent with the known increase in blood calcium-channel blocker concentrations seen after a CYP3A4 inhibitor is used.

Conclusions

Among older adults taking a calcium-channel blocker, concurrent use of clarithromycin compared with azithromycin was associated with a small but statistically significant greater 30-day risk of hospitalization with acute kidney injury. These findings support current safety warnings regarding concurrent use of CYP3A4 inhibitors and calcium-channel blockers.

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Author Contributions: Dr Garg had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Gandhi, Fleet, Bailey, Rehman, Garg.
Acquisition of data: Gandhi, McArthur, Garg.
Analysis and interpretation of data: Gandhi, Fleet, Bailey, McArthur, Wald, Garg.
Drafting of the manuscript: Gandhi, Bailey, Garg.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: McArthur, Garg.
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