Annals of Internal Medicine | ORIGINAL RESEARCH

Statin Toxicity From Macrolide Antibiotic Coprescription

A Population-Based Cohort Study

Amit M. Patel, MD; Salimah Shariff, PhD; David G. Bailey, BScPhm, PhD; David N. Juurlink, MD, PhD; Sonja Gandhi, BSc; Muhammad Mamdani, PharmD, MPH; Tara Gomes, MHSc; Jamie Fleet, BSc; Y. Joseph Hwang, BMSc; and Amit X. Garg, MD, PhD

Background: Clarithromycin and erythromycin, but not azithromycin, inhibit cytochrome P450 isoenzyme 3A4 (CYP3A4), and inhibition increases blood concentrations of statins that are metabolized by CYP3A4.

Objective: To measure the frequency of statin toxicity after coprescription of a statin with clarithromycin or erythromycin.

Design: Population-based cohort study.

Setting: Ontario, Canada, from 2003 to 2010.

Patients: Continuous statin users older than 65 years who were prescribed clarithromycin (n = 72 591) or erythromycin (n = 3267) compared with those prescribed azithromycin (n = 68 478).

Measurements: The primary outcome was hospitalization with rhabdomyolysis within 30 days of the antibiotic prescription.

Results: Atorvastatin was the most commonly prescribed statin (73%) followed by simvastatin and lovastatin. Compared with azithromycin, coprescription of a statin with clarithromycin or erythromycin was associated with a higher risk for hospitalization with rhabdomyolysis (absolute risk increase, 0.02% [95% CI, 0.01% to 0.03%]; relative risk [RR], 2.17 [CI, 1.04 to 4.53]) or with acute kidney injury (absolute risk increase, 1.26% [CI, 0.58% to 1.95%]; RR, 1.78 [CI, 1.49 to 2.14]) and for all-cause mortality (absolute risk increase, 0.25% [CI, 0.17% to 0.33%]; RR, 1.56 [CI, 1.36 to 1.80]).

Limitations: Only older adults were included in the study. The absolute risk increase for rhabdomyolysis may be underestimated because the codes used to identify it were insensitive.

Conclusion: In older adults, coprescription of clarithromycin or erythromycin with a statin that is metabolized by CYP3A4 increases the risk for statin toxicity.

Primary Funding Source: Academic Medical Organization of Southwestern Ontario.

Ann Intern Med. 2013;158:869-876. www.annals.org

For author affiliations, see end of text.

Each year, millions of patients worldwide receive 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") to treat dyslipidemia and prevent cardiovascular disease. In the United Kingdom, statins can be obtained without a prescription or medical supervision (1). Atorvastatin, simvastatin, and lovastatin are 3 statins metabolized by cytochrome P450 isoenzyme 3A4 (CYP3A4) (2–6). On 1 March 2012, the U.S. Food and Drug Administration cautioned about a potential drug–drug interaction between CYP3A4-metabolized statins and medications used to treat HIV and hepatitis. It also warned that coadministration of other CYP3A4 inhibitors, including clarithromycin and erythromycin, may increase statin blood concentrations (7). CYP3A4 inhibitors are a potentially frequent cause of drug interactions with statins (8). In one study, one third of patients receiving a statin were coprescribed a CYP3A4 inhibitor over 24 weeks, often clarithromycin or erythromycin (9). In healthy volunteers, coadministration of clarithromycin or erythromycin with atorvastatin, simvastatin, or lovastatin increased blood concentrations of the statin (10–13). Simvastatin and lovastatin display up to a 10-fold increase, whereas the increase is up to 4-fold with atorvastatin (2, 10–13). Several case reports describe rhabdomyolysis, acute kidney injury (AKI), hyperkalemia, and death from statin toxicity after the use of clarithromycin or erythromycin (14–17). The risk is greatest in older adults (18). However, no clinical or epidemiologic studies have quantified the risk for serious statin toxicity from this drug–drug interaction. Thus, we conducted a study to characterize the risk for statin toxicity in a large population of older adults coprescribed clarithromycin or erythromycin.

METHODS

Design and Setting

We conducted a population-based, retrospective cohort study of adults older than 65 years by using linked health care databases in Ontario, Canada. Ontario has approximately 13.5 million residents who have universal access to hospital care and physician services; 14% of residents (1.9 million persons) are aged 65 years or older, and they have universal prescription drug coverage (19). We conducted this study according to a prespecified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Ontario, Canada). The reporting of this study followed guidelines for observational studies (20).

Data Sources

We ascertained drug use, covariate information, and outcome data by using records from 4 databases. The Ontario Drug Benefit database contains accurate records of all outpatient prescriptions dispensed to patients aged 65 years or older, with an error rate of less than 1% (21). The Canadian Institute for Health Information Discharge Abstract Database records detailed diagnosis and procedural information on all hospitalizations in Ontario. Up to 25 unique diagnosis codes (that is, codes for rhabdomyolysis, AKI, or hyperkalemia) can be assigned to each hospitalization. The Ontario Health Insurance Plan database contains

Context

Some antibiotics increase blood values of commonly prescribed statins by inhibiting the liver enzyme that metabolizes them.

Contribution

This study showed that older people taking statins who were prescribed clarithromycin or erythromycin were hospitalized more frequently for rhabdomyolysis and acute kidney injury and had higher all-cause mortality than people who were prescribed azithromycin.

Caution

The outcomes occurred rarely, so there were few additional cases. However, the study used administrative codes to identify rhabdomyolysis and kidney injury, and these codes are insensitive.

Implication

Consider prescribing an antibiotic other than clarithromycin or erythromycin when the patient is taking a statin.

—The Editors

health claims for inpatient and outpatient physician services. The Registered Persons Database of Ontario has demographic and vital status information on all residents who have ever been issued a health card. All 4 databases have been used extensively to research adverse drug events, health outcomes, and health services (22–24). The databases were complete for all variables used in this study, with the exception of antibiotic indication and prescriber. Codes used to assess the baseline comorbid conditions in the 5 years before receiving the relevant coprescription are detailed in **Table 1**. It contains the International Classification of Diseases, Ninth Revision (ICD-9) and Tenth Revision (ICD-10), codes; for some patients, both were in use during the 5-year look-back period. Codes used to ascertain outcomes are detailed in **Table 2**, which lists ICD-10 codes because these were the only ones used in the follow-up for all study patients. A subpopulation in southwestern Ontario had outpatient serum creatinine levels available before a new antibiotic coprescription and was in the catchment area of 12 hospitals in which linked inpatient laboratory values were available (25).

Patients

We established a cohort of all older adults in Ontario with ongoing continuous prescriptions for statins metabolized by CYP3A4 (atorvastatin, simvastatin, or lovastatin). Individuals were eligible for this cohort after the second consecutive prescription claim for a statin and remained in it as long as they were receiving a statin. In this group, we identified the first new eligible coprescription for clarithromycin, erythromycin, or azithromycin. Because clarithromycin and erythromycin inhibit CYP3A4 and the latter is rarely used in Ontario, they were considered together. Azithromycin has indications and clinical use patterns similar to those of clarithromycin and erythromycin, but it does not inhibit CYP3A4 or increase blood concentrations of CYP3A4-metabolized statins (1–3, 10). Thus, our comparison (reference) group comprised patients coprescribed azithromycin with a statin.

The date of the first coprescription for a study antibiotic served as the index date. We enrolled patients from June 2003 to December 2010 and excluded the following antibiotic users from analysis: those who received a prescription for more than 1 type of antibiotic on the index date to compare mutually exclusive groups, those in their first year of eligibility for prescription drug coverage (age 65 years) to avoid incomplete medication records, those with inconsistent statin use before the index date, those who were discharged from the hospital in the 2 days before their index date to ensure that prescriptions were new outpatient antibiotic prescriptions, those who had a potent CYP3A4 inhibitor (such as protease inhibitors and antifungals) dispensed within the 30 days before the index date, and those with end-stage renal disease before the index date (2, 7). In the databases, we identified comorbid conditions in the 5-year look-back period before the index date and concurrent drug therapy in the 180 days before the index date.

Outcomes

We followed patients for 30 days after the index date to assess outcomes. The primary outcome was hospitalization with rhabdomyolysis. The 3 secondary outcomes were hospitalization with AKI, hospitalization with hyperkalemia, and all-cause mortality. The diagnostic codes used are presented in **Table 2**. Because up to 25 diagnostic codes can be assigned per hospitalization, patients with codes for several study outcomes were accounted for under each outcome present. A hospital diagnosis code for rhabdomyolysis in Ontario identifies patients with a median peak creatine kinase level of 31.20 μkat/L (interquartile range [IQR], 11.56 to 67.76 μkat/L), whereas its absence indicates patients hospitalized without a creatine kinase level or a measured median level of 2.21 μkat/L (IQR, 1.02 to 6.26 μkat/L). Similarly, a code for AKI identifies a median absolute acute increase in serum creatinine of 98 μmol/L (1.11 mg/dL) (IQR, 43 to 200 μmol/L [IQR, 0.49 to 2.26 mg/dL]) greater than the most recent value before hospitalization, whereas its absence represents a median increase of 6 μmol/L (0.07 mg/dL) (IQR, −4 to 20 μmol/L [IQR, −0.05 to 0.23 mg/dL]) (26). A code for hyperkalemia identifies a median serum potassium concentration of 6.0 mmol/L (IQR, 5.1 to 6.7 mmol/L) and its absence defines a median serum potassium concentration of 4.1 mmol/L (IQR, 3.8 to 4.5 mmol/L) (27). For all of the aforementioned codes, patients with an abnormal laboratory value may or may not have had a code recorded for the given diagnosis. However, as a value becomes more extreme (for example, higher levels of hyperkalemia), a code is more

Table 1. **Coding Definitions for Demographic and Comorbid Conditions**

Characteristic	Database	Code
Age	RPDB	–
Sex	RPDB	–
Socioeconomic status	Statistics Canada	–
Chronic kidney disease	CIHI DAD	ICD-9 585 ICD-10 N18
Coronary artery disease	CIHI DAD	ICD-9 412, 414, 4292, 4295, 4296, 4297 ICD-10 120–125, Z955, Z958, Z959, R931, T822 CCI 1IJ26, 1IJ27, 1IJ50, 1IJ54, 1IJ57, 1IJ76 CCP 48, 4801–4805, 481–483
	OHIP	R741-R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448, 410–413
Peripheral vascular disease	CIHI DAD	ICD-9 4402, 4408, 4409, 5571, 4439, 444 ICD-10 I700, I702, I708, I709, I731, I738, I739, K551 CCP 5125, 5129, 5014, 5016, 5018, 5028, 5038 CCI 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87
	OHIP	R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786. R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, E672, R813, R867, E649
Heart failure	CIHI DAD	ICD-9 428 ICD-10 150
Cerebrovascular disease	CIHI DAD	ICD-9 4340, 431, 436, 4358, 4359 ICD-10 H341, I629–I635, I638, I639, G45, I61, I64
Systemic malignancy	CIHI DAD	ICD-9 V10, 140–165, 170–176, 179, 180–194, 196–198, 1950–1955, 1958
	OHIP	140–165, 170–175, 179–195, 196–208, 1990, 1991, 2000–2002, 2008, 2010–2012, 2014–2020, 2026, 2028, 2029, 203–208, 230–234
Respiratory infections	OHIP	466, 486, 491
Other infections	OHIP	461, 463, 464, 590, 595, 597, 601, 616, 682, 707

CCI = Canadian Classification of Health Interventions; CCP = Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI DAD = Canadian Institute for Health Information Discharge Abstract Database; ICD-9 = International Classification of Diseases, Ninth Revision; ICD-10 = International Classification of Diseases, Tenth Revision; OHIP = Ontario Health Insurance Plan; RPDB = Registered Persons Database of Ontario.

likely to be present for a particular diagnosis. Even though the specificity is greater than 99% with all 3 outcomes, the sensitivity of hospital diagnosis codes is limited, particularly for milder forms of the condition. The incidence can be underestimated up to 10-fold compared with outcomes assessed with laboratory values found in routine care. Therefore, we examined a subpopulation with laboratory values and defined an elevated creatine kinase level as 17.0 μkat/L or greater, AKI as an absolute increase in serum creatinine of at least 27 μmol/L (0.31 mg/dL) or a relative increase of 50% or more (on the basis of the Acute Kidney Injury Network staging system), and hyperkalemia as a serum potassium of at least 5.5 mmol/L (28, 29).

Statistical Analysis

We compared baseline characteristics between new users of clarithromycin or erythromycin and azithromycin by using standardized differences (30, 31). This metric describes differences between group means relative to the pooled SD and indicates a meaningful difference if it is greater than 10%. We expressed the risk for an outcome in relative and absolute terms. Absolute risk was further quantified as the "number needed to harm" (1/absolute risk difference), a measure that indicates how many patients need to receive a coprescription for clarithromycin or erythromycin to cause harm to 1 patient who otherwise would not have been harmed (a lower number indicating greater harm). The number needed to harm was calculated for ease of interpretation and not to imply causality. We used multivariable logistic regression analyses (PROC LOGISTIC; SAS Institute, Cary, North Carolina) to estimate odds ratios and 95% CIs. We adjusted for the following 16 covariates: age (per year); sex; baseline use of angiotensin-converting enzyme inhibitors or angiotensin II–receptor blockers, nonsteroidal anti-inflammatory agents, oral hypoglycemic agents or insulin, non–potassium-sparing diuretics, potassium-sparing diuretics, diltiazem or verapamil, other calcium-channel blockers, and β-blockers; and baseline evidence of chronic kidney disease, coronary artery disease, cerebrovascular disease, peripheral vascular disease, congestive heart failure, and systemic malignancy. Odds ratios were interpreted as relative risks (RRs) (appropriate given the incidences observed). We did a conditional logis-

Table 2. **Coding Definitions for Hospitalization With Rhabdomyolysis, Acute Kidney Injury, or Hyperkalemia and All-Cause Mortality***

Condition	Database	Code
Rhabdomyolysis	CIHI DAD	ICD-10 M628, T796
Acute kidney injury	CIHI DAD	ICD-10 N17, N19, R34
Hyperkalemia	CIHI DAD	ICD-10 E875
All-cause mortality†	RPDB	Vital status field

CIHI DAD = Canadian Institute for Health Information Discharge Abstract Database; ICD-10 = International Classification of Diseases, Tenth Revision; RPDB = Registered Persons Database of Ontario.
* Validations of rhabdomyolysis, acute kidney injury, and hyperkalemia were performed on 39 500 hospitalizations with linked laboratory values. See Methods section for results and references 26 and 27.
† Has a sensitivity of 94% and a positive predictive value of 100% (44).

tic regression analysis stratifying by provider to investigate possible confounding among providers, outcomes, and the use of drugs. We conducted all analysis with SAS, version 9.2.

Role of the Funding Source

The Academic Medical Organization of Southwestern Ontario provided funding for the study. The study design and conduct, opinions, results, and conclusions in this paper are those of the authors and independent of the funding sources.

RESULTS

The study included 721 277 eligible continuous statin users. Cohort selection is presented in the **Appendix Figure** (available at www.annals.org). After we applied our exclusions and restricted the cohort to the first eligible coprescribed study antibiotic, 144 336 patients remained. Of these, 75 858 patients received clarithromycin (n = 72 591 [96%]) or erythromycin (n = 3267 [4%]) and 68 478 received azithromycin. Baseline characteristics of the 2 groups were very similar (**Table 3**), including the dose of statin when potency was categorized by using low-density lipoprotein–lowering capability (**Table 3**) (32). The median daily dose was 1000 mg each for clarithromycin and erythromycin and 300 mg for azithromycin. The median duration of antibiotic therapy dispensed was 10 days for clarithromycin or erythromycin and 5 days for azithromycin (values consistent with drug-prescribing references) (33–35).

Patient outcomes assessed with hospital diagnosis codes are presented in **Table 4**. Results are expressed with patients receiving azithromycin coprescription as the referent group. Coprescription of clarithromycin or erythromycin with a CYP3A4-metabolized statin was associated with a higher risk for hospitalization with rhabdomyolysis (RR, 2.17 [95% CI, 1.04 to 4.53]) and AKI (RR, 1.78 [CI, 1.49 to 2.14]). The risk for hospitalization with hyperkalemia was not statistically different (RR, 1.31 [CI, 0.89 to 1.94]). The risk for all-cause 30-day mortality was higher with clarithromycin or erythromycin (RR, 1.56 [CI, 1.36 to 1.80]). When risk was expressed in absolute terms, a coprescription for clarithromycin or erythromycin was associated with a 0.02% (CI, 0.01% to 0.03%) higher incidence of hospitalization with rhabdomyolysis and a 0.25% (CI, 0.17% to 0.33%) higher incidence of all-cause mortality. Corresponding numbers needed to harm were 5870 (CI, 3068 to 67 758) and 399 (CI, 304 to 577), respectively. Results were consistent in all adjusted analyses (**Table 4**) and in the sensitivity analyses that stratified by provider (data not shown).

The baseline characteristics and outcomes for the subpopulation with linked laboratory values are presented in **Appendix Table 1** (available at www.annals.org) and **Table 5**. Characteristics between CYP3A4-metabolized statin users with a coprescription for clarithromycin or erythromycin (n = 2427) and azithromycin (n = 1488) were nearly identical. Forty percent of patients had a baseline estimated glomerular filtration rate below 60 mL/min per 1.73 m^2. Across groups, 6 patients had evidence of hospitalization with a creatine kinase level greater than 17.0 μkat/L, with the small numbers in each group precluding meaningful comparisons. Coprescription of clarithromycin or erythromycin was associated with a higher risk for hospitalization with AKI (RR, 2.92 [CI, 1.47 to 5.79]) and hyperkalemia (RR, 11.04 [CI, 1.48 to 82.58]). When risk was expressed in absolute terms, a coprescription for clarithromycin or erythromycin was associated with a 1.26% (CI, 0.58% to 1.95%) higher incidence of hospitalization with AKI and a 0.74% (CI, 0.40% to 1.08%) higher incidence of hospitalization with hyperkalemia. Corresponding numbers needed to harm were 79 (CI, 51 to 173) and 135 (CI, 92 to 250), respectively.

DISCUSSION

In this population-based study of older adults, we found that coprescription of clarithromycin or erythromycin with atorvastatin, simvastatin, or lovastatin was associated with an increased risk for hospitalization with rhabdomyolysis, hospitalization with AKI, and all-cause mortality. Given the frequency at which statins are prescribed (atorvastatin is currently the most commonly prescribed drug in Canada), and the high rate of coprescription seen in our study and in other jurisdictions, this preventable drug–drug interaction remains clinically important (36, 37). The results suggest that many deaths and hospitalizations with AKI in Ontario may have been attributable to this interaction.

The 30-day incidence of rhabdomyolysis as assessed by database codes for patients coprescribed azithromycin was 1.5 in 10 000 coprescriptions. For reference, other studies have quantified the absolute risk for rhabdomyolysis from statins to be 0.5 to 1 per 10 000 person-years; however, these studies also used database codes for outcome assessment and considered statin users of all ages and not only older adults (38, 39). Because database codes are insensitive for the diagnosis of rhabdomyolysis, the absolute risk increase we report is an underestimate of the true rate. Assuming these codes underestimate the incidence of rhabdomyolysis by 10-fold, the absolute risk increase from clarithromycin or erythromycin coprescription compared with azithromycin is higher than we report but still remains low (increase in 1 event for every 500 coprescriptions); however, the assessment of AKI from laboratory data and mortality is better in our data sources, and the absolute risk increase we report for these outcomes is more accurate.

Clinicians should be aware of the most frequently observed drug interactions with statins (8, 9, 36). Our study can help convince health care providers about the importance of these interactions. In addition, a better description of this particular interaction is available in prescribing ref-

Table 3. **Baseline Characteristics***

Characteristic	Clarithromycin and Erythromycin (n = 75 858)†	Azithromycin (n = 68 478)	Standardized Difference‡	*P* Value
Demographic				
Mean age (SD), *y*	74 (6)	74 (6)	0.01	0.73
Women	40 130 (52.9)	36 323 (53.0)	0.01	0.59
Income quintile§				<0.001
1 (low)	15 858 (20.9)	13 686 (20.0)	0.03	
2	16 481 (21.7)	14 408 (21.0)	0.02	
3 (middle)	14 982 (19.8)	13 594 (19.9)	0.01	
4	14 391 (19.0)	13 268 (19.4)	0.01	
5 (high)	13 917 (18.3)	13 272 (19.4)	0.03	
Index date				<0.001
2003–2004	20 972 (27.6)	19 179 (28.0)	0.01	
2005–2006	23 028 (30.4)	20 146 (29.4)	0.02	
2007–2008	18 703 (24.7)	16 841 (24.6)	0.01	
2009–2010	13 155 (17.3)	12 313 (18.0)	0.02	
Comorbid condition				
Chronic kidney disease‖	6210 (8.2)	5530 (8.1)	0.01	0.44
Cerebrovascular disease	3189 (4.2)	2765 (4.0)	0.01	0.113
Peripheral vascular disease	2101 (2.8)	1844 (2.7)	0.01	0.37
Coronary artery disease¶	39 974 (52.6)	36 995 (54.0)	0.03	<0.001
Congestive heart failure	12 652 (16.7)	11 776 (17.2)	0.01	0.009
Systemic malignancy	21 875 (28.8)	19 955 (29.1)	0.01	0.20
Statin characteristic				
Type				0.002
Atorvastatin	55 027 (72.5)	50 111 (73.2)	0.02	
Simvastatin	18 421 (24.3)	16 369 (23.9)	0.01	
Lovastatin	2410 (3.2)	1998 (2.9)	0.02	
Dose				0.26
High-dose statin**	30 296 (40.0)	27 550 (40.2)	0.01	
Low-dose statin††	45 562 (60.0)	40 928 (59.8)	0.01	
Medication use in preceding year				
Oral hypoglycemic or insulin	20 367 (26.8)	17 819 (26.0)	0.02	<0.001
β-Blockers	29 318 (38.6)	27 008 (39.4)	0.02	0.002
Verapamil or diltiazem	7941 (10.5)	7206 (10.5)	0.01	0.73
Use of other calcium-channel blockers	18 521 (24.4)	16 982 (24.8)	0.01	0.091
Potassium-sparing diuretics	3307 (4.4)	2992 (4.4)	0.01	0.93
Non–potassium-sparing diuretics	26 901 (35.5)	24 720 (36.1)	0.01	0.012
NSAIDs (excluding aspirin)	16 516 (21.8)	14 797 (21.6)	0.01	0.45
ACE inhibitor or ARB	49 017 (64.6)	44 323 (64.7)	0.01	0.67
Antibiotic prescriber				<0.001
Family physician	55 607 (73.3)	52 410 (76.5)	0.07	
Internist	2281 (3.0)	1337 (2.0)	0.07	
Surgeon	1428 (1.9)	310 (0.5)	0.13	
Other	2725 (3.6)	2846 (4.2)	0.03	
Missing	13 730 (18.1)	11 541 (16.9)	0.03	
Infection				<0.001
Respiratory	27 076 (35.7)	25 757 (37.6)	0.04	
Other	6716 (8.9)	6049 (8.8)	0.01	
Unknown	42 066 (55.5)	36 672 (53.6)	0.04	

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; NSAID = nonsteroidal anti-inflammatory drug.
* Values are numbers (percentages) unless otherwise indicated.
† Clarithromycin (n = 72 591) and erythromycin (n = 3267).
‡ 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 SD; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.
§ Income was categorized into fifths of average neighborhood income on the index date.
‖ Assessed by administrative database codes.
¶ Includes receipt of coronary artery bypass graft surgery, percutaneous coronary intervention, and diagnoses of angina.
** Atorvastatin ≥20 mg/d, lovastatin ≥80 mg/d, or simvastatin ≥80 mg/d (32).
†† Atorvastatin <20 mg/d, lovastatin <80 mg/d, or simvastatin <80 mg/d (32).

Table 4. **Outcomes Assessed Using Hospital-Based Diagnosis Codes***

Outcome	Events, *n* (%)†		Absolute Risk Difference (95% CI), %	Number Needed to Harm (95% CI)‖	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)¶
	Clarithromycin and Erythromycin (*n* = 75 858)‡	Azithromycin (*n* = 68 478)§				
Rhabdomyolysis	24 (0.03)	10 (0.01)	0.02 (0.01 to 0.03)	5870 (3068 to 67 758)	2.17 (1.04 to 4.53)	2.17 (1.03 to 4.52)
Acute kidney injury	347 (0.46)	176 (0.26)	0.20 (0.14 to 0.26)	499 (382 to 718)	1.78 (1.49 to 2.14)	1.83 (1.52 to 2.19)
Hyperkalemia	61 (0.08)	42 (0.06)	0.02 (−0.01 to 0.05)	–	1.31 (0.89 to 1.94)	1.32 (0.89 to 1.94)
All-cause mortality	529 (0.70)	306 (0.45)	0.25 (0.17 to 0.33)	399 (304 to 577)	1.57 (1.36 to 1.80)	1.57 (1.37 to 1.82)

* Coprescriptions of clarithromycin or erythromycin with CYP3A4-metabolized statins and the 30-day risk for hospitalization with rhabdomyolysis, acute kidney injury, or hyperkalemia and all-cause mortality.
† The number of events (and the proportion of patients who had an event) for all outcomes except all-cause mortality were assessed by using hospital diagnosis codes. This underestimates the true event rate because these codes have high specificity but low sensitivity. Similarly, the number needed to harm is underestimated for these outcomes.
‡ Clarithromycin (*n* = 72 591) and erythromycin (*n* = 3267).
§ Comparator group.
‖ Number needed to harm does not imply causality as all the results are associations. It is provided for ease of interpretation.
¶ Adjusted for 16 covariates (see Methods section). The number of events of rhabdomyolysis was 34. To reduce concerns about model overfitting, we repeated the analysis adjusting only for age, sex, and the presence of baseline chronic kidney disease. The results did not differ.

erences. UpToDate, a popular resource, now warns against this coprescription under statin and antibiotic information sections (**Appendix Table 2**, available at www.annals.org); this warning was not present in all sections several months before our search in March 2012. In terms of prevention, temporary cessation of the CYP3A4-metabolized statin during antibiotic therapy, use of a non–CYP3A4-metabolized statin, or choice of a different antibiotic when clinically appropriate can be considered (2).

Solutions for busy medical practices, including computer software, are being proposed to increase the overall safety of polypharmacy in older adults (40). For clinicians without software, free online drug interaction programs exist (41). Early prevention through multidisciplinary collaboration remains important. In one study, 9 of 10 physicians changed their prescribing habits or monitored closely for potential adverse effects when community pharmacists informed them about the risk associated with coprescription of CYP3A4 inhibitors with simvastatin or atorvastatin (9).

Our study has many strengths. To our knowledge, it is the first population-based study of this drug–drug interaction. It provides data on the frequency and severity of toxicity in routine practice and supports concerns about coprescribing any CYP3A4 inhibitor with a statin (2–17). Many patients received coprescriptions, and this provided good precision for estimates, which are generalizable.

Our study has some limitations. Despite the large sample size, we could not meaningfully examine interactions with each CYP3A4-metabolized statin individually. Atorvastatin represented 73% of our cohort (37). Also, clarithromycin was prescribed more than erythromycin. However, given the known effect on CYP3A4 statin pharmacokinetics, it remains prudent to generalize the coprescription warning to atorvastatin, simvastatin, or lovastatin with clarithromycin or erythromycin.

As with any observational study the associations seen may not be causal. However, the results are consistent with previous warnings about this interaction based on pharmacokinetic data and case reports (2, 8–17). Of importance, we used a related antibiotic (azithromycin) as a comparator group to reduce concerns about confounding by indication. We were further encouraged by the marked similarity of measured baseline characteristics in the 2 groups. Ac-

Table 5. **Outcomes Assessed Using Hospital-Based Laboratory Data***

Outcome	Events, *n* (%)		Absolute Risk Difference (95% CI), %	Number Needed to Harm (95% CI)§	Relative Risk (95% CI)
	Clarithromycin and Erythromycin (*n* = 2427)†	Azithromycin (*n* = 1488)‡			
Acute kidney injury‖	47 (1.94)	10 (0.67)	1.26 (0.58 to 1.95)	79 (51 to 173)	2.92 (1.47 to 5.79)
Hyperkalemia¶	18 (0.74)	0 (0)	0.74 (0.40 to 1.08)	135 (92 to 250)	11.04 (1.48 to 82.58)**

* Coprescriptions of clarithromycin or erythromycin with CYP3A4-metabolized statins and the 30-day risk for hospitalization with acute kidney injury and hyperkalemia.
† Clarithromycin (*n* = 2334) and erythromycin (*n* = 93).
‡ Comparator group.
§ Number needed to harm does not imply causality as all the results are associations. It is provided for ease of interpretation.
‖ Defined as evidence of an absolute increase in serum creatinine ≥27 μmol/L (≥0.31 mg/dL) or an increase of 50% or more from baseline serum creatinine level before study antibiotic use.
¶ Defined as evidence of a serum potassium concentration ≥5.5 mmol/L.
** One event was imputed in the azithromycin group for the purposes of assessing relative risk.

cording to pharmacokinetic data and drug prescribing recommendations, azithromycin does not inhibit CYP3A4 but also differs from clarithromycin and erythromycin in the duration of therapy (10, 33–35). While our study portrays differences in statin toxicity by antibiotic type as used in routine clinical practice, factors beyond CYP3A4 inhibition, such as duration of treatment, may have caused the observed differences. Drug–drug interactions are also complex and understudied. Compared with azithromycin, clarithromycin or erythromycin may have differentially interacted with other drugs commonly used in older adults who are taking statins.

We generalize our findings only to older adults because younger patients are less likely to experience an adverse event from drug–drug interactions (18). In addition, we conducted our primary analysis using hospital diagnosis codes, rather than prospective data collection with independent outcome adjudication. Whereas the latter approach would probably have demonstrated a higher incidence of statin toxicity than we report, such a study might not have been possible to conduct if physicians were required to intervene after learning of the coprescription. We supplemented our findings by observing a subpopulation with laboratory results. These results showed a similar signal of adverse events with clarithromycin or erythromycin coprescription. Finally, coding inaccuracies in hospital diagnoses are unlikely to have occurred differentially between groups because the drug and outcome databases are independent entities.

More research is needed to better understand drug interactions with non–CYP3A4-metabolized statins. In a preliminary analysis of patients receiving these statins (n = 52 684; 70% rosuvastatin), the primary outcome was rare (n = 9), precluding interpretation about the risk for rhabdomyolysis; however, coprescribing clarithromycin or erythromycin was associated with an increased risk for AKI relative to azithromycin (RR, 1.46 [CI, 1.08 to 1.99]). This association may reflect a pharmacokinetic interaction involving the organic anion-transporting polypeptide 1B1 (2). Inhibition of this transporter has been shown to increase rosuvastatin blood levels (42). Clarithromycin and erythromycin inhibit this transporter but azithromycin does not (43). This supports the U.S. Food and Drug Administration's warning about possible drug interactions with rosuvastatin and requires further study (7).

In conclusion, coprescription of clarithromycin or erythromycin with a CYP3A4-metabolized statin increases the risk for serious statin toxicity in older adults. Steps should be taken to minimize preventable adverse events, and the combination should be avoided when possible.

From Western University and Lawson Health Research Institute, London Health Sciences Centre, London, and Institute for Clinical Evaluative Sciences and University of Toronto, Toronto, Ontario, Canada.

Acknowledgment: The authors thank IMS Brogan (Ottawa, Ontario, Canada), for use of their Drug Product and Therapeutic Class Database; the late Dr. Milton Haines, Ms. Barbara Jones, Mr. Jeff Lamond, and others from Gamma Dynacare for use of their outpatient laboratory database; and Mr. Glen Kearns from the London Health Sciences Centre who facilitated the use of linked hospital laboratory databases.

Financial Support: The investigators received grant support from the Academic Medical Organization of Southwestern Ontario to conduct this research. This project was conducted at the Institute for Clinical Evaluative Sciences site at Western University. The Institute for Clinical Evaluative Sciences is funded by an annual grant from the Ontario Ministry of Health and Long-term Care. The Institute for Clinical Evaluative Sciences site at Western University is funded by an operating grant from the Academic Medical Organization of Southwestern Ontario. Dr. Garg was supported by a Canadian Institutes of Health Research Clinician Scientist Award.

Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M12-1300.

Reproducible Research Statement: *Study protocol, statistical code, and data set:* Portions are available to approved individuals through written agreements with Dr. Garg (e-mail, amit.garg@lhsc.on.ca).

Requests for Single Reprints: Amit Garg, MD, PhD, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada; e-mail, amit.garg@lhsc.on.ca.

Current author addresses and author contributions are available at www.annals.org.

References

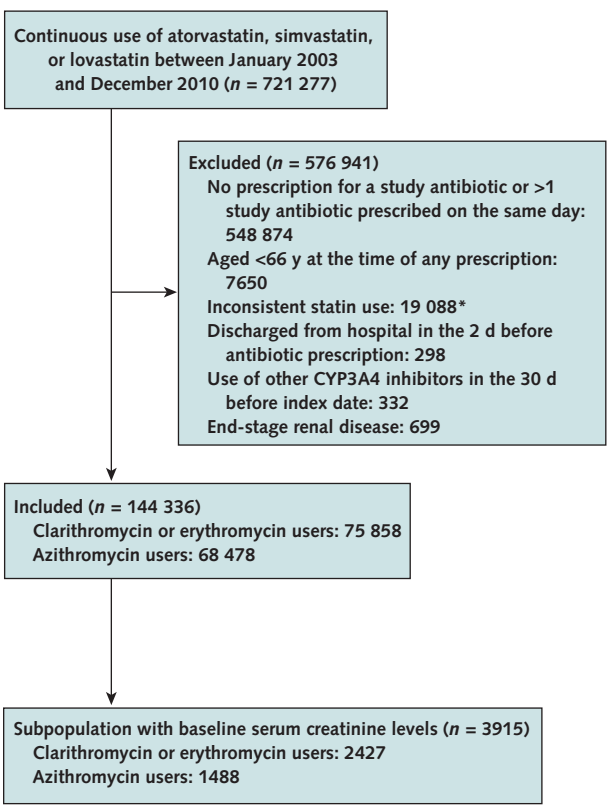
1. **Neuvonen PJ, Backman JT, Niemi M.** Pharmacokinetic comparison of the potential over-the-counter statins simvastatin, lovastatin, fluvastatin and pravastatin. Clin Pharmacokinet. 2008;47:463-74. [PMID: 18563955]
2. **Neuvonen PJ, Niemi M, Backman JT.** Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance. Clin Pharmacol Ther. 2006;80:565-81. [PMID: 17178259]
3. **Wilkinson GR.** Drug metabolism and variability among patients in drug response. N Engl J Med. 2005;352:2211-21. [PMID: 15917386]
4. Lipitor [package insert]. New York: Pfizer; 2012. Accessed at http://labeling.pfizer.com/ShowLabeling.aspx?id=587 on 25 November 2012.
5. Zocor [package insert]. Whitehouse Station, NJ: Merck & Co.; 2012. Accessed at www.accessdata.fda.gov/drugsatfda_docs/label/2012/019766s085lbl.pdf on 25 November 2012.
6. Mevacor [package insert]. Whitehouse Station, NJ: Merck & Co.; 2012. Accessed at www.accessdata.fda.gov/drugsatfda_docs/label/2012/019643s085lbl.pdf on 25 November 2012.
7. **U.S. Food and Drug Administration.** FDA Drug Safety Communication: Interactions between certain HIV or hepatitis C drugs and cholesterol-lowering statin drugs can increase the risk for muscle injury. Washington, DC: U.S. Food and Drug Administration; 1 March 2012. Accessed at www.fda.gov/Drugs/DrugSafety/ucm293877.htm on 25 November 2012.
8. **Rätz Bravo AE, Tchambaz L, Krähenbühl-Melcher A, Hess L, Schlienger RG, Krähenbühl S.** Prevalence of potentially severe drug-drug interactions in ambulatory patients with dyslipidaemia receiving HMG-CoA reductase inhibitor therapy. Drug Saf. 2005;28:263-75. [PMID: 15733030]
9. **Molden E, Skovlund E, Braathen P.** Risk management of simvastatin or atorvastatin interactions with CYP3A4 inhibitors. Drug Saf. 2008;31:587-96. [PMID: 18558792]
10. **Jacobson TA.** Comparative pharmacokinetic interaction profiles of pravastatin, simvastatin, and atorvastatin when coadministered with cytochrome P450 inhibitors. Am J Cardiol. 2004;94:1140-6. [PMID: 15518608]

11. **Amsden GW, Kuye O, Wei GC.** A study of the interaction potential of azithromycin and clarithromycin with atorvastatin in healthy volunteers. J Clin Pharmacol. 2002;42:444-9. [PMID: 11936570]
12. **Kantola T, Kivistö KT, Neuvonen PJ.** Erythromycin and verapamil considerably increase serum simvastatin and simvastatin acid concentrations. Clin Pharmacol Ther. 1998;64:177-82. [PMID: 9728898]
13. **Siedlik PH, Olson SC, Yang BB, Stern RH.** Erythromycin coadministration increases plasma atorvastatin concentrations. J Clin Pharmacol. 1999;39:501-4. [PMID: 10234598]
14. **Trieu J, Emmett L, Perera C, Thanakrishnan K, Van Der Wall H.** Rhabdomyolysis resulting from interaction of simvastatin and clarithromycin demonstrated by Tc-99m MDP scintigraphy. Clin Nucl Med. 2004;29:803-4. [PMID: 15545884]
15. **Campbell G, Jayakumar U, McCracken S, Bene J.** A cautionary tale: delayed onset rhabdomyolysis due to erythromycin/simvastatin interaction. Age Ageing. 2007;36:597. [PMID: 17913761]
16. **Spach DH, Bauwens JE, Clark CD, Burke WG.** Rhabdomyolysis associated with lovastatin and erythromycin use. West J Med. 1991;154:213-5. [PMID: 2006579]
17. **Mah Ming JB, Gill MJ.** Drug-induced rhabdomyolysis after concomitant use of clarithromycin, atorvastatin, and lopinavir/ritonavir in a patient with HIV. AIDS Patient Care STDS. 2003;17:207-10. [PMID: 12816614]
18. **Egger SS, Rätz Bravo AE, Hess L, Schlienger RG, Krähenbühl S.** Age-related differences in the prevalence of potential drug-drug interactions in ambulatory dyslipidaemic patients treated with statins. Drugs Aging. 2007;24:429-40. [PMID: 17503898]
19. **Statistics Canada.** Population by sex and age group, by province and territory. Ottawa: Statistics Canada; 27 September 2012. Accessed at www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo31a-eng.htm on 10 March 2012.
20. **von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP; STROBE Initiative.** The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Ann Intern Med. 2007;147:573-7. [PMID: 17938396]
21. **Levy AR, O'Brien BJ, Sellors C, Grootendorst P, Willison D.** Coding accuracy of administrative drug claims in the Ontario Drug Benefit database. Can J Clin Pharmacol. 2003;10:67-71. [PMID: 12879144]
22. **Shih AW, Weir MA, Clemens KK, Yao Z, Gomes T, Mamdani MM, et al.** Oral bisphosphonate use in the elderly is not associated with acute kidney injury. Kidney Int. 2012;82:903-8. [PMID: 22695327]
23. **Zhao YY, Weir MA, Manno M, Cordy P, Gomes T, Hackam DG, et al.** New fibrate use and acute renal outcomes in elderly adults: a population-based study. Ann Intern Med. 2012;156:560-9. [PMID: 22508733]
24. **Jain AK, Cuerden MS, McLeod I, Hemmelgarn B, Akbari A, Tonelli M, et al.** Reporting of the estimated glomerular filtration rate was associated with increased use of angiotensin-converting enzyme inhibitors and angiotensin-II receptor blockers in CKD. Kidney Int. 2012;81:1248-53. [PMID: 22437415]
25. **Gandhi S, Shariff SZ, Beyea MM, Weir MA, Hands T, Kearns G, et al.** Identifying geographical regions serviced by hospitals to assess laboratory-based outcomes. BMJ Open. 2013;3. [PMID: 23293246]
26. **Hwang YJ, Shariff SZ, Gandhi S, Wald R, Clark E, Fleet JL, et al.** Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. BMJ Open. 2012;2. [PMID: 23204077]
27. **Fleet JL, Shariff SZ, Gandhi S, Weir MA, Jain AK, Garg AX.** Validity of the International Classification of Diseases 10th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. BMJ Open. 2012;2. [PMID: 23274674]
28. **Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, et al; Acute Kidney Injury Network.** Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care. 2007;11:R31. [PMID: 17331245]
29. **Gabow PA, Kaehny WD, Kelleher SP.** The spectrum of rhabdomyolysis. Medicine (Baltimore). 1982;61:141-52. [PMID: 7078398]
30. **Austin PC.** Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. Commun Stat Simulation Comput. 2009;38:1228-34.
31. **Mamdani M, Sykora K, Li P, Normand SL, Streiner DL, Austin PC, et al.** Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding. BMJ. 2005;330:960-2. [PMID: 15845982]
32. **Law MR, Wald NJ, Rudnicka AR.** Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003;326:1423. [PMID: 12829554]
33. UpToDate online V 20.3. Clarithromycin: drug information. Accessed at www.uptodate.com/contents/clarithromycin-drug-information?source=search_result&search=clarithromycin&selectedTitle=1~150 on 20 March 2012.
34. UpToDate online V 20.3. Erythromycin (systemic): drug information. Accessed at www.uptodate.com/contents/erythromycin-systemic-drug-information?source=search_result&search=erythromycin&selectedTitle=1~150 on 20 March 2012.
35. Zithromax [package insert]. Kirkland, Quebec: Pfizer; 2013. Accessed at www.pfizer.ca/en/our_products/products/monograph/136 on 20 April 2013.
36. **Piacentini N, Trifiró G, Tari M, Moretti S, Arcoraci V; UVEC group.** Statin-macrolide interaction risk: a population-based study throughout a general practice database. Eur J Clin Pharmacol. 2005;61:615-20. [PMID: 16044339]
37. **Paquette A.** Top Rx drugs. Pharmacy Practice. 2012;28:45-50.
38. **Floyd JS, Heckbert SR, Weiss NS, Carrell DS, Psaty BM.** Use of administrative data to estimate the incidence of statin-related rhabdomyolysis. JAMA. 2012;307:1580-2. [PMID: 22511681]
39. **Graham DJ, Staffa JA, Shatin D, Andrade SE, Schech SD, La Grenade L, et al.** Incidence of hospitalized rhabdomyolysis in patients treated with lipid-lowering drugs. JAMA. 2004;292:2585-90. [PMID: 15572716]
40. **Tawadrous D, Shariff SZ, Haynes RB, Iansavichus AV, Jain AK, Garg AX.** Use of clinical decision support systems for kidney-related drug prescribing: a systematic review. Am J Kidney Dis. 2011;58:903-14. [PMID: 21944664]
41. Drug Interactions Checker. Drugs.com. Accessed at www.drugs.com/drug_interactions.php on 15 October 2012.
42. **Samineni D, Desai PB, Sallans L, Fichtenbaum CJ.** Steady-state pharmacokinetic interactions of darunavir/ritonavir with lipid-lowering agent rosuvastatin. J Clin Pharmacol. 2012;52:922-31. [PMID: 21712498]
43. **Seithel A, Eberl S, Singer K, Auge D, Heinkele G, Wolf NB, et al.** The influence of macrolide antibiotics on the uptake of organic anions and drugs mediated by OATP1B1 and OATP1B3. Drug Metab Dispos. 2007;35:779-86. [PMID: 17296622]

Current Author Addresses: Drs. Patel, Shariff, and Garg; Ms. Gandhi; Ms. Fleet; and Mr. Hwang: London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario N6A 4G5, Canada.
Dr. Bailey: University Hospital, Room B3-264, London Health Sciences Centre, 339 Windermere Road, London, Ontario N6G 2K3, Canada.
Dr. Juurlink and Ms. Gomes: Sunnybrook Health Sciences Centre, Bayview Avenue, Toronto, Ontario M4N 3M5, Canada.
Dr. Mamdani: Keenan Research Centre, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario M5B 1W8, Canada.

Author Contributions: Conception and design: A.M. Patel, S. Shariff, D.G. Bailey, D.N. Juurlink, S. Gandhi, M. Mamdani, T. Gomes, J. Fleet, Y.J. Hwang, A.X. Garg.
Analysis and interpretation of the data: A.M. Patel, S. Shariff, D.G. Bailey, D.N. Juurlink, S. Gandhi, M. Mamdani, T. Gomes, J. Fleet, Y.J. Hwang, A.X. Garg.
Drafting of the article: A.M. Patel, D.G. Bailey, A.X. Garg.
Critical revision of the article for important intellectual content: A.M. Patel, S. Shariff, D.G. Bailey, D.N. Juurlink, S. Gandhi, M. Mamdani, T. Gomes, J. Fleet, Y.J. Hwang, A.X. Garg.
Final approval of the article: A.M. Patel, S. Shariff, D.G. Bailey, D.N. Juurlink, S. Gandhi, M. Mamdani, T. Gomes, J. Fleet, Y.J. Hwang, A.X. Garg.
Provision of study materials or patients: A.X. Garg.
Statistical expertise: S. Shariff, D.N. Juurlink, M. Mamdani, T. Gomes, A.X. Garg.
Obtaining of funding: A.X. Garg.
Administrative, technical, or logistic support: A.M. Patel, S. Shariff, T. Gomes, J. Fleet, A.X. Garg.
Collection and assembly of data: S. Shariff.

Appendix Figure. **Study flow diagram.**



* Defined as evidence of use of different types of statins (n = 2587), use of a nonstudy statin (n = 118), statin discontinuation (n = 6899), or fluctuating statin dose (n = 9484) before the index date.

44. **Jha P, Deboer D, Sykora K, Naylor CD.** Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population-based comparison. J Am Coll Cardiol. 1996;27:1335-42. [PMID: 8626941]
45. **Statistics Canada.** Ethnocultural portrait of Canada highlight tables, 2006 census. Ottawa: Statistics Canada; 6 October 2010. Accessed at www12.statcan.ca/census-recensement/2006/dp-pd/hlt/97-562/index.cfm?Lang=E on 19 April 2013.
46. UpToDate online V 19.2. Clarithromycin: drug information. Accessed at www.uptodate.com/contents/clarithromycin-drug-information?source=search_result&search=clarithromycin&selectedTitle=1~150 on 20 March 2012.
47. UpToDate online V 19.2. Erythromycin (systemic): drug information. Accessed at www.uptodate.com/contents/erythromycin-systemic-drug-information?source=search_result&search=erythromycin&selectedTitle=1~150 on 20 March 2012.
48. UpToDate online V 19.2. Azithromycin (systemic): drug information. Accessed at www.uptodate.com/contents/azithromycin-systemic-drug-information?source=search_result&search=azithromycin&selectedTitle=1~148 on 20 March 2012.

Appendix Table 1. Baseline Characteristics for Subset of Patients With Linked Laboratory Values*

Characteristic	Clarithromycin and Erythromycin (n = 2427)†	Azithromycin (n = 1488)	Standardized Difference‡	*P* Value
Demographic				
Mean age (SD), *y*	75 (7)	75 (7)	0.02	0.62
Women	1236 (50.9)	777 (52.2)	0.03	0.43
Income quintile				0.24
Low	539 (22.2)	311 (20.9)	0.04	
Middle	475 (19.6)	275 (18.5)	0.03	
High	500 (20.6)	335 (22.5)	0.07	
Index date				0.166
2003–2004	401 (16.5)	276 (18.5)	0.05	
2005–2006	666 (27.4)	390 (26.2)	0.03	
2007–2008	832 (34.3)	476 (32.0)	0.05	
2009–2010	528 (21.8)	346 (23.3)	0.04	
Comorbid condition				
Cerebrovascular disease	105 (4.3)	57 (3.8)	0.02	0.45
Peripheral vascular disease	60 (2.5)	37 (2.5)	0.01	0.98
Coronary artery disease§	1266 (52.2)	826 (55.5)	0.07	0.042
Congestive heart failure	459 (18.9)	322 (21.6)	0.07	0.038
Systemic malignancy	997 (41.1)	620 (41.7)	0.01	0.72
Statin characteristic				
Type				0.124
Atorvastatin	1755 (72.3)	1114 (74.9)	0.06	
Simvastatin	589 (24.3)	336 (22.3)	0.05	
Lovastatin	83 (3.4)	38 (2.6)	0.05	
Dose				0.93
High-dose statin‖	982 (40.5)	600 (40.3)	0.01	
Low-dose statin¶	1445 (59.5)	888 (59.7)	0.01	
Medication use in preceding year				
Oral hypoglycemic or insulin	672 (27.7)	414 (27.8)	0.01	0.93
β-Blockers	1042 (42.9)	632 (42.5)	0.01	0.78
Verapamil or diltiazem	332 (13.7)	198 (13.3)	0.01	0.74
Use of other calcium-channel blockers	573 (23.6)	378 (25.4)	0.04	0.20
Potassium-sparing diuretics	178 (7.3)	104 (7.0)	0.01	0.69
Non–potassium-sparing diuretics	988 (40.7)	603 (40.5)	0.01	0.91
NSAIDs (excluding aspirin)	474 (19.5)	316 (21.2)	0.04	0.197
ACE inhibitor or ARB	1575 (64.9)	953 (64.0)	0.02	0.59
Renal function				
Median serum creatinine level (IQR)				0.80
μmol/L	90 (76–108)	90 (76–108)	0.03	
mg/dL	1.02 (0.86–1.22)	1.02 (0.86–1.22)		
Median eGFR (IQR), *mL/min per 1.73 m²***	66 (51–80)	65 (51–79)	0.02	0.72
eGFR category				0.51
≥90 mL/min per 1.73 m²	170 (7.0)	109 (7.3)	0.01	
60–89 mL/min per 1.73 m²	1294 (53.3)	782 (52.6)	0.02	
45–59 mL/min per 1.73 m²	564 (23.2)	331 (22.2)	0.02	
30–44 mL/min per 1.73 m²	281 (11.6)	199 (13.4)	0.05	
<30 mL/min per 1.73 m²	118 (4.9)	67 (4.5)	0.02	

ACE = angiotensin-converting enzyme; ARB = angiotensin II–receptor blocker; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NSAID = nonsteroidal anti-inflammatory drug.

* Values are numbers (percentages) unless otherwise indicated.

† Clarithromycin (n = 2334) and erythromycin (n = 93).

‡ 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 SD; a value greater than 10% (0.1) is interpreted as a meaningful difference between the groups.

§ Includes receipt of coronary artery bypass graft surgery, percutaneous coronary intervention, and diagnoses of angina.

‖ Atorvastatin ≥20 mg/d, lovastatin ≥80 mg/d, or simvastatin ≥80 mg/d (32).

¶ Atorvastatin <20 mg/d, lovastatin <80 mg/d, or simvastatin <80 mg/d (32).

** eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-Epi) equation. The baseline serum creatinine level used in this equation was taken in routine care at the median of 87 days (IQR, 27 to 182) before the index date, with no appreciable difference in the time to index date between the 2 groups. CKD-Epi equation: $141 \times \min[(\text{serum creatinine level in } \mu\text{mol/L} \div 88.4) \div \kappa, 1]^{\alpha} \times \max[(\text{serum creatinine level in } \mu\text{mol/L} \div 88.4) \div \kappa, 1]^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ (if female) × 1.159 (if African American). $\kappa = 0.7$ for females and 0.9 for males; $\alpha = -0.329$ for females and -0.411 for males; min = the minimum of (serum creatinine level)/κ or 1; max = the maximum of (serum creatinine level)/κ or 1. Race information was not available in our data sources, and all patients were assumed to be of non–African Canadian race. This was a reasonable assumption; as of 2006, African Canadians represented fewer than 7% of the Ontario population (45).

Appendix Table 2. **Current Warnings for Azithromycin, Clarithromycin, and Erythromycin***

Study Drug	Relevant Drug Interactions
Azithromycin	No warning about coprescription with statins.
Clarithromycin	HMG-CoA reductase inhibitors: Macrolide antibiotics may decrease the metabolism of HMG-CoA reductase inhibitors. Management: Avoid lovastatin or simvastatin with erythromycin, clarithromycin, or telithromycin. Limit pitavastatin to a 1-mg/d maximum adult dose with erythromycin. Atovastatin dose adjustments may be required. Increase monitoring for toxicity with any such combination.
Erythromycin	HMG-CoA reductase inhibitors: Macrolide antibiotics may decrease the metabolism of HMG-CoA reductase inhibitors. Management: Avoid lovastatin or simvastatin with erythromycin, clarithromycin, or telithromycin. Limit pitavastatin to a 1-mg/d maximum adult dose with erythromycin. Atorvastatin dose adjustments may be required. Increase monitoring for toxicity with any such combination.

HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A.
* Data from references 46 to 48.