



Use of Macrolide Antibiotics to Assess Population-Based Drug Interactions: A Retrospective Cohort Study

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-002857
Article Type:	Research
Date Submitted by the Author:	08-Mar-2013
Complete List of Authors:	Fleet, Jamie; London Health Sciences Centre, Medicine/Nephrology Shariff, Salimah; Institute for Clinical Evaluative Sciences, Bailey, David; Lawson Health Research Institute, Gandhi, Sonja; London Health Sciences Centre, Medicine/Nephrology Juurlink, David; Sunnybrook Health Sciences Centre, Clinical Pharmacology and Toxicology Nash, Danielle; London Health Sciences Centre, Medicine/Nephrology Mamdani, Muhammad; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute Gomes, Tara; Institute for Clinical Evaluative Sciences, Patel, Amit; London Health Sciences Centre, Medicine/Nephrology Garg, Amit; University of Western Ontario
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Public health
Keywords:	PREVENTIVE MEDICINE, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

Use of Macrolide Antibiotics to Assess Population-Based Drug Interactions

Jamie L. Fleet BSc¹, Salimah Z. Shariff PhD^{1,2}, David G. Bailey BScPhm PhD³, Sonja Gandhi BSc^{1,4}, David N. Juurlink MD, PhD^{2,5,6}, Danielle M. Nash MSc^{1,2}, Muhammad Mamdani PharmD, MPH^{2,6,7}, Tara Gomes, MHSc², Amit M. Patel MD¹, Amit. X. Garg MD, PhD^{1,2,4}.

1. Division of Nephrology, Department of Medicine, Western University, London, Canada
2. Institute for Clinical Evaluative Sciences, Ontario, Canada
3. Lawson Health Research Institute, London Health Sciences Centre, London, Canada
4. Department of Epidemiology & Biostatistics, Western University, London, Canada
5. Division of Clinical Pharmacology, Department of Medicine, University of Toronto, Toronto, Canada
6. Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada
7. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Correspondence: Dr. Amit Garg, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5, Tel: 519-685-8502, Fax: 519-685-8072, email: amit.garg@lhsc.on.ca

Publication Type: Research Article

Short Title: Using macrolide antibiotics to assess drug interactions

Financial Disclosures: none

Funding/Support: This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) @ Western Site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-term Care. ICES@Western is funded by operating grants from the Academic Medical Organization of Southwestern Ontario, the Schulich School of Medicine and Dentistry and the Lawson Health Research Institute.

Role of the Sponsor: The opinions, results and conclusions reported in this paper are those of the authors and are independent of the funding sources.

Acknowledgements: We thank Brogan Inc., Ottawa for use of its Drug Product and Therapeutic Class Database. We thank the late Dr. Milton Haines, Ms. Barbara Jones, Mr. Jeff Lamond and others from Gamma Dynacare for their use of the outpatient laboratory database. We thank Mr. Glen Kearns from the London Health Sciences Centre who facilitated the use of linked hospital laboratory databases.

Word count: Abstract 296 (max 300), main text 2399 (max 4000)

Date: March 6th 2013

ABSTRACT

Objective: Clarithromycin but not azithromycin inhibits enzyme cytochrome P450 3A4, preventing the metabolism of some other drugs. Accordingly, blood concentrations of the other drugs increase, leading to adverse events. The two macrolide antibiotics also differ on other properties that may impact outcomes. In this study we compared outcomes in two groups of macrolide antibiotic users in the absence of potentially interacting drugs.

Design: Population-based retrospective cohort study using linked healthcare databases.

Setting: Ontario, Canada, from 2003 to 2010.

Patients: Elderly patients (mean 74 years) prescribed either clarithromycin (n=52,251) or azithromycin (referent group, n=46,618).

Main outcomes: The primary outcomes were hospital admission within 30 days of a new antibiotic prescription with any of 11 medical conditions examined separately (acute kidney injury, acute myocardial infarction, neuroimaging (proxy for delirium), hypotension, syncope, hyperkalemia, hyponatremia, hyperglycemia, arrhythmia, ischemic stroke, and gastrointestinal bleeding). The secondary outcome was mortality.

Results: The baseline characteristics of the two groups, including patient demographics, comorbid conditions, infection type, and specialty of the prescribing physician, were nearly identical. The median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin, and the median duration of antibiotic dispensed was 10 and 5 days, respectively. There was no difference between the two groups in the risk of hospitalization for any condition studied (relative risk ranged from 0.67 to 1.23). Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Conclusions: Clarithromycin can be used to assess drug interactions in population-based studies with azithromycin serving as a control group. However, any differences in mortality observed between the two antibiotic groups in the setting of other drug use may be partially attributable to factors beyond the inhibition of drug metabolizing enzymes and transporters.

ARTICLE SUMMARY

Article Focus

- This study describes the differences in adverse outcomes when either clarithromycin or azithromycin is prescribed in the absence of interacting drugs
- Knowledge of the underlying differences between these two drugs is important for drug-drug interaction studies

Key Messages

- There were no significant differences between clarithromycin and azithromycin on 11 medical conditions, however clarithromycin was associated with a slightly higher risk of all-cause mortality
- Use of azithromycin as a referent group is appropriate in drug-drug interaction studies
- Most outcomes from drug-drug interaction studies can be attributed to the interaction rather than underlying differences in these macrolide antibiotics

Strengths and Limitations

- This is the first population-based study to compare outcomes between clarithromycin and azithromycin while excluding interacting drugs
- Our large sample size allowed greater precision around the estimates reported and is representative of the province of Ontario as a whole
- Further studies describing differences in all-cause mortality between the two antibiotics are warranted

INTRODUCTION

Certain medication combinations can lead to altered pharmacokinetics that result in higher systemic concentration of the drugs and accompanying greater risk of toxicity.[1] The commonly used macrolide antibiotic clarithromycin can inhibit the drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4), as well as the Organic Anion Transporting Polypeptide transporters 1B1 (OATP1B1), and OATP1B3.[2] These transporters and enzyme are present in the liver and small intestine, and about half of all the medications used today are affected by their processes.[3] These include many types of statins, anti-epileptics and anti-psychotics.[4-6] Interestingly, another macrolide antibiotic, azithromycin, is prescribed for similar indications and in comparable patients as clarithromycin, but unlike clarithromycin does not inhibit this enzyme and transporters.[7,8] Thus, there is a growing interest in conducting population based studies examining two groups of individuals newly prescribed either clarithromycin or azithromycin, where all patients are also chronically using another drug such as a statin which may interact with clarithromycin.[9] The outcomes of the two groups can then be compared (with the azithromycin users acting as a control group) to assess the outcomes attributable to the clarithromycin-statin interaction.[9]

However, as per prescribing references, the two macrolide antibiotics do differ on the total daily dose and the recommended duration of therapy to treat infection which may influence compliance, as a dose would be more likely to be missed if taken over a longer period of time.[10,11] It is possible that these, and other properties of macrolide antibiotics, also impact patient outcomes. We wanted to be assured that outcomes observed in population-based drug interaction studies of clarithromycin compared to azithromycin are most likely attributable to the drug interaction being studied rather than other inherent differences between the two macrolide antibiotics.[9,12-14] The purpose of this investigation was to compare the incidence of serious adverse events for these two macrolide antibiotics administered alone in a population based study of elderly patients.

METHODS

Setting and Design

1
2
3 All residents of the province of Ontario, Canada have universal access to hospital care and
4 physician services. Individuals 65 years of age or older (approximately 2 million individuals in
5 Ontario in 2012) also have universal prescription drug coverage.[15] All health care encounters
6 are prospectively recorded in health administrative databases, which are available for evaluation
7 at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. We conducted a
8 population-based retrospective cohort study using these large linked health care databases. We
9 focused on adults over the age of 65 given their risk of drug toxicity and the availability of
10 prescription data. We conducted this study according to a pre-specified protocol that was
11 approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada).
12 The reporting of this study followed guidelines for observational studies (detailed in
13 Appendix A).[16]

24 Data Sources

25
26 We ascertained drug use, covariate information, and outcome data using records from five
27 administrative databases. Outpatient prescription drug information including the dispensing date,
28 quantity of pills, and number of days supplied is accurately recorded in the Ontario Drug Benefit
29 Plan database, with an error rate less than 1%.[17] Detailed diagnosis and procedural
30 information on all inpatient hospitalizations in Ontario are recorded in the Canadian Institute for
31 Health Information Discharge Abstract Database (CIHI-DAD). Up to 25 unique diagnosis codes
32 (i.e. codes for acute kidney injury or hyperkalemia) can be assigned at discharge to each hospital
33 stay. The Ontario Health Insurance Plan database (OHIP) contains all health claims for inpatient
34 and outpatient fee-for-service physician services. The Ontario Registered Persons Database
35 (RPDB) contains demographic and vital statistics information on all Ontario residents who have
36 ever been issued a health card. We have previously used these four databases to research adverse
37 drug events, health outcomes and health services.[18-20] The databases were complete for all
38 variables used in this study. We also used the Ontario Registrar General Database (ORGD) to
39 assess cause of death for patients who died during follow-up.

40
41 Codes used to assess co-morbidities in the five years prior to receipt of the relevant
42 prescription are detailed in Appendix B. This Appendix contains both the International
43 Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10) codes, as both were in
44 use during the study period. Codes used to ascertain outcomes are detailed in Appendix C with
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 information on code validity when available. This Appendix only contains ICD-10 codes as ICD-
4
5 9 codes were no longer used in Canada after March 31 2002.
6
7

8 9 **Patients**

10 We established a cohort of patients with new prescriptions for clarithromycin. Our comparison
11 (referent) group consisted of patients with new azithromycin prescriptions. Erythromycin,
12 another macrolide antibiotic that inhibits several metabolizing enzymes, was not included in our
13 study since the number of prescriptions dispensed during our study period was low.
14
15

16 The date of antibiotic prescription served as the index date, which is the start time for follow-
17 up. We accrued patients from June 2003 to December 2010. We excluded the following
18 antibiotic users from analysis: i) those in their first year of eligibility for prescription drug
19 coverage (age 65) to avoid incomplete past medication records, ii) those who were discharged
20 from hospital in the two days prior to and including the index date to ensure we were studying
21 new outpatient antibiotic prescriptions, iii) those who received a prescription for more than one
22 type of antibiotic on the index date in order to compare mutually exclusive groups, iv) those with
23 end stage renal disease prior to the index date, and v) those who were taking other potential
24 CYP3A4, OATP1B1, or OATP1B3 inhibitors or substrates 180 days prior to the index date
25 (medications such as protease inhibitors, statins, anti-fungals, and calcium channel blockers –
26 See Appendix D for full list).[21,22] When there were multiple episodes of macrolide antibiotic
27 use for a given patient over the study period we only selected the first one. For exclusions and
28 baseline characteristics, we identified comorbidities in the five years prior to the index date and
29 concurrent drug therapy in the 180 days prior to the index date (see Appendix B).
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44

45 **Outcomes**

46 All patients were followed for 30 days after the index date for the assessment of outcomes. We
47 assessed hospital admissions involving any of 11 medical conditions; each condition was
48 examined separately: acute kidney injury, acute myocardial infarction, neuroimaging (computed
49 tomography head scan as a proxy for delirium), hypotension, syncope, hyperkalemia,
50 hyponatremia, hyperglycemia, arrhythmia, ischemic stroke and gastrointestinal bleeding. These
51 conditions are potential adverse events when clarithromycin interferes with the pharmacokinetics
52 of other drugs. For example, use of clarithromycin with a calcium channel blocker may cause
53
54
55
56
57
58
59
60

hypotension and acute kidney injury.[14,23-27] A small number of events in our population precluded analyses of three other conditions of interest: rhabdomyolysis, hypoglycemia, and neuroleptic malignant syndrome. We also assessed all-cause mortality.

There are up to 25 diagnostic codes that can be assigned per hospital admission; patients with multiple codes were accounted for under each outcome of interest. Wherever possible we selected validated codes that performed well for identifying the conditions of interest (code lists and validations fully detailed in Appendix C).

Statistical Analysis

We compared baseline characteristics between new users of clarithromycin and azithromycin using standardized differences.[28,29] This metric describes differences between group means relative to the pooled standard deviation and is considered to indicate a meaningful difference if it is greater than 10%. The risk of developing an outcome was expressed in relative terms. We used multivariable logistic regression analyses to estimate odds ratios and 95% confidence intervals, adjusting for age (per year), sex, and Charlson co-morbidity score (a popular measure of co-morbidity).[30] We interpreted odds ratios as relative risks (appropriate given the incidences observed). We conducted all analyses with SAS 9.2 (SAS Institute Incorporated, Cary, North Carolina, USA, 2008).

RESULTS

There were a total of 1,958,432 macrolide antibiotic prescriptions during our study period. Cohort selection is presented in Appendix E. After applying our exclusion criteria, including evidence of any interacting drug and restricting to the first antibiotic prescription per patient, 98,869 patients remained: 52,251 clarithromycin users and 46,618 azithromycin users.

Baseline characteristics of the two groups with respect to co-morbidities and use of other medications were nearly identical (Table 1; all standardized differences between the groups were less than 3%). For both groups, the median age was 71 years and 54% of patients were women. The cause of infection was recorded in some patients and appeared comparable between the two groups, as were cultures and concurrent bronchodilators and steroid prescriptions around the

1
2
3 time of the index date (Table 1). The specialty of the prescribing physician, when available, was
4 also comparable between the two groups (Table 1).
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Table 1. Baseline Characteristics

BMJ Open

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Clarithromycin n = 52,251	Azithromycin n = 46,618	Standardized Differences*
Demographics			
Age, years, <i>median (IQR)</i>	71 (68-77)	71 (68-77)	
Women, <i>n (%)</i>	27,932 (53.5)	25,682 (55.1)	0.03
Income Quintile			
first (lowest)	8,951 (17.1)	7,706 (16.5)	0.02
second	10,447 (20.0)	8,899 (19.1)	0.02
third (middle)	10,153 (19.4)	8,937 (19.2)	0.01
fourth	10,822 (20.7)	9,633 (20.7)	0
fifth (highest)	11,703 (22.4)	11,285 (24.2)	0.04
Year of Cohort Entry^e, <i>n (%)</i>			
2003 - 2005	21,369 (40.9)	18,979 (40.7)	0.01
2006 - 2008	19,236 (36.8)	17,198 (36.9)	0.01
2009 - 2010	11,646 (22.3)	10,441 (22.4)	0.01
Co-morbidities, <i>n (%)</i>			
Cancer	12,733 (24.4)	11,473 (24.6)	0.01
Chronic kidney disease ‡	644 (1.2)	566 (1.2)	0
Coronary artery disease ¶	7,531 (14.4)	6,956 (14.9)	0.01
Diabetes mellitus #	855 (1.6)	816 (1.8)	0.01
Heart failure	1,656 (3.2)	1,536 (3.3)	0.01
Peripheral vascular disease	175 (0.3)	176 (0.4)	0.01
Stroke/Transient ischemic attack	246 (0.5)	249 (0.5)	0.01
Medication use in prior 6 months, <i>n (%)</i>			
ACE inhibitors or ARBs	2,769 (5.3)	2,543 (5.5)	0.01
Beta blockers	1,787 (3.4)	1,720 (3.7)	0.01
Potassium sparing diuretics	461 (0.9)	389 (0.8)	0.01
Loop diuretics	103 (0.2)	120 (0.3)	0.01
NSAIDs (excluding ASA)	2,483 (4.8)	2,389 (5.1)	0.02
Thiazide diuretics	3,479 (6.7)	3,171 (6.8)	0.01
Cause of infection, <i>n (%)</i>			
Genitourinary infection	261 (0.5)	265 (0.6)	0.01
Oropharyngeal infection	839 (1.6)	1,000 (2.1)	0.04
Respiratory infection	22,084 (42.3)	17,503 (37.5)	0.10
Sinus infection	4,000 (7.7)	3,178 (6.8)	0.03
Skin infection	659 (1.3)	320 (0.7)	0.06
Missing	27,843 (53.3)	22,266 (47.8)	0.11
Cultures⁺, <i>n (%)</i>			
Blood	28 (0.1)	21 (0.0)	0
Genitourinary	26 (0.0)	69 (0.01)	0.03
Gynecology	120 (0.2)	134 (0.3)	0.01
Sputum	127 (0.2)	75 (0.2)	0.02
Urine	1,090 (2.1)	931 (2.0)	0.01
Concurrent medication prescription, <i>n (%)</i>			
Inhaled steroids	28 (0.1)	31 (0.1)	0.01
Bronchodilators	1,202 (2.3)	929 (2.0)	0.02

BMJ Open: first published as 10.1136/bmjopen-2013-002857 on 11 July 2013. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Main specialty of prescribing physician, *n* (%)

GP/FP	39,743 (76.1)	34,308 (73.6)	0.06
Internal medicine	280 (0.5)	260 (0.6)	0.01
General surgery	100 (0.2)	151 (0.3)	0.02
Other	1,148 (2.2)	1,042 (2.2)	0
Missing	10,980 (21.0)	10,857 (23.3)	0.06

Data presented as number (percent) except for age which is presented as mean (standard deviation).

Abbreviations: Non-steroidal anti-inflammatory (NSAID), angiotensin converting enzyme (ACE), angiotensin II receptor blocker (ARB), general practitioner (GP), family practitioner (FP)

*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.

€ The year of cohort entry is also referred to as the index date.

‡ Assessed by administrative database codes

¶ Coronary artery disease includes receipt of coronary artery bypass graft surgery, percutaneous coronary intervention and diagnoses of angina.

#Assessed by receipt of insulin or oral antihyperglycemics

+ Cultures recorded within two weeks prior and one week after the index date

Consistent with drug prescribing references, the median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin. The median duration of antibiotic dispensed was 10 days for clarithromycin and 5 days for azithromycin.[10,11]

The outcome of hospitalization with each of the 11 conditions examined separately is presented in Table 2. Results are expressed with patients receiving azithromycin as the referent group. There were no significant difference between the clarithromycin and azithromycin groups on any of the 11 hospitalization outcomes, and the relative risk ranged from 0.67 to 1.23. Results were consistent across all adjusted analyses (Table 2).

The results of all-cause mortality within 30 days of the antibiotic prescription are also presented in Table 2. Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Table 2. Hospitalizations with various conditions and all-cause mortality

	<i>Number of Events (%)</i> *		<i>Unadjusted Relative Risk (95% CI)</i>	<i>Adjusted Relative Risk (95% CI)</i> ‡
	<i>Clarithromycin n = 52,251</i>	<i>Azithromycin n = 46,618</i>		
Acute kidney injury	52 (0.10)	44 (0.09)	1.05 (0.71 – 1.58)	1.06 (0.71 – 1.58)
Myocardial infarction	39 (0.07)	30 (0.06)	1.16 (0.72 – 1.87)	1.15 (0.71 – 1.85)
Neuroimaging ⁺	582 (1.11)	496 (1.06)	1.05 (0.93 – 1.18)	1.04 (0.93 – 1.18)
Hypotension	19 (0.04)	14 (0.03)	1.21 (0.61 – 2.42)	1.21 (0.61 – 2.41)
Syncope	14 (0.03)	12 (0.03)	1.04 (0.48 – 2.25)	1.04 (0.48 – 2.25)
Hyperkalemia	9 (0.02)	12 (0.03)	0.67 (0.28 – 1.59)	0.67 (0.28 – 1.60)
Hyponatremia	29 (0.06)	29 (0.06)	0.89 (0.53 – 1.49)	0.90 (0.54 – 1.51)
Hyperglycemia	22 (0.04)	16 (0.03)	1.23 (0.64 – 2.34)	1.22 (0.64 – 2.33)
Arrhythmia	49 (0.09)	52 (0.11)	0.84 (0.57- 1.24)	0.84 (0.57 – 1.24)
Ischemic stroke	17 (0.03)	16 (0.3)	0.95 (0.48 – 1.88)	0.94 (0.47 – 1.86)
Gastrointestinal bleeding	32 (0.06)	30 (0.06)	0.95 (0.58 – 1.57)	0.95 (0.58 – 1.56)
All-cause mortality	241 (0.46)	172 (0.37)	1.25 (1.03 – 1.52)	1.27 (1.04 – 1.55)

Patients prescribed azithromycin served as the comparator group.

* 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. For some outcomes this underestimates the true event rate because these codes have high specificity but low sensitivity.

‡ Adjusted for 3 covariates: Age, sex, and Charlson co-morbidity score

+ Neuroimaging consisted of codes for computed tomography head scan as a proxy for delirium.

After observing a difference in all-cause mortality between our groups, we considered the five most common causes of death (Table 3). There were no significant differences in these causes of death between the two groups.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33

Table 3. Deaths due to the following causes		
	<i>Number of events (%)*</i>	
	Clarithromycin n = 52,251	Azithromycin n = 46,618
Disease of circulatory system	64 (0.12)	50 (0.11)
Neoplasm	48 (0.09)	32 (0.07)
Disease of respiratory system	35 (0.07)	32 (0.07)
Mental disorder	28 (0.05)	13 (0.03)
Disease of the nervous system	25 (0.05)	13 (0.03)
Other	41 (0.08)	32 (0.07)
*There were 241 total deaths in the clarithromycin group and 172 in the azithromycin group		

DISCUSSION

34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53

Contrasting outcomes of patients prescribed clarithromycin to those prescribed azithromycin presents a potentially attractive method of assessing population-based drug interactions in routine care. However, these two macrolide antibiotics also differ on other properties besides their inhibition of drug metabolizing enzymes and transporters that may impact patient outcomes. In this study we compared the baseline characteristics and outcomes of patients prescribed either clarithromycin or azithromycin in the absence of potentially interacting drugs. The two groups did not differ in patient baseline demographics, co-morbid characteristics, the type of infection, or the specialty of the prescribing physician. In other words, the two drugs appeared to be used for similar indications and demonstrated similar clinical usage patterns. With respect to the study outcomes there were no differences between the two groups on any of the 11 hospitalization conditions that we studied.

54
55
56
57
58
59
60

Overall, these results support the utility of macrolide antibiotics to assess population-based drug interactions for the hospital conditions presented in this report. This is particularly true when conducting studies in settings where the observed results are consistent with medications

1
2
3 known to have potential for drug-drug interactions based on pharmacokinetic data and case
4 reports. For example, a high blood concentration of some statins is realized when taken
5 concurrently with clarithromycin, as the latter inhibits the CYP3A4 enzyme responsible for statin
6 metabolism.[9] This can lead to rhabdomyolysis and acute kidney injury. In the present study, in
7 the absence of statin use, there was no difference in hospitalization with acute kidney injury
8 between the two macrolide antibiotic groups. Thus there is more assurance that the outcomes
9 observed in the aforementioned study of clarithromycin co-prescribed with a statin are
10 attributable to the interaction between the drugs.
11

12
13
14
15
16
17
18 In the present study there was a small absolute difference in all-cause mortality with
19 clarithromycin compared to azithromycin, without any clear difference in the cause of death.
20 While this may be a chance finding, it is also possible that there may be inherent differences in
21 the use or nature of these two antibiotics that impacts mortality. Consistent with drug prescribing
22 references, the median duration of antibiotic treatment was higher with clarithromycin compared
23 to azithromycin. Additionally, differences in daily dose and day supply between the two
24 macrolide antibiotics were found, and there could be differences in frequency of dose. Because
25 clarithromycin is taken twice a day for the duration of therapy, unlike azithromycin, there could
26 be differences in drug adherence. Other differences exist, for example: azithromycin is less
27 bioavailable than clarithromycin, especially when taken with food.[31] On the other hand,
28 clarithromycin is transformed into an active metabolite, where most other macrolide antibiotics
29 are not.[32] For these reasons, some of the association between macrolide antibiotic type and
30 mortality may partially be attributable to factors beyond the inhibition of drug transporters and
31 metabolizing enzymes, although it also may not be reflective of a difference between the drugs at
32 all. It may also be useful to determine if the magnitude of the association observed in the present
33 study differs with associations observed in other drug-drug interaction studies, using statistical
34 tests of interaction (such as the Bland Altman Test on the two sets of results).[33] Our study has
35 a number of strengths. This study was done in the province of Ontario where residents have the
36 benefit of universal healthcare for all citizens and a province wide drug plan for older adults,
37 with this information accessible for study purposes. Accordingly, there were a large number of
38 patients accrued into our study, which provided reasonable precision for the outcomes that are
39 reported. The large sample size also provided adequate data to reasonably compare
40 clarithromycin and azithromycin on baseline characteristics and patterns of clinical use.
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Our study does have some limitations. Despite the large sample size, we had too few events to meaningfully look at some outcomes such as rhabdomyolysis, neuroleptic malignant syndrome, and hypoglycemia. Also drug-drug interactions are complex and understudied. While we took a comprehensive approach to exclude interacting drugs, it is still possible that interactions with other drugs may have occurred. Finally, because our hospital-based outcomes were assessed using hospital diagnosis codes (which have limited sensitivity for some outcomes), rather than prospective data collection, we most likely underestimated the true event rate of the outcomes. However, because the outcomes were assessed no differently between the clarithromycin and azithromycin groups, we do not anticipate that this biased our relative measures of risk.

CONCLUSION

In conclusion, we have established that patterns of use and common clinical outcomes do not differ appreciably between clarithromycin and azithromycin, suggesting that clarithromycin may be useful medication to assess drug-drug interactions in population-based studies with azithromycin serving as the control group. If in future drug-drug interaction studies, differences in mortality between groups of patients prescribed each of the two antibiotics exist, it should be noted that some of the association may be attributable to factors unrelated to the enzyme metabolism of the drugs.

Contributors

JLF participated in the coordination of the study, study design, provided interpretation of the study results, and drafted the manuscript. SZS participated in the study design, performed the analysis and provided interpretation of the study results. DGB, SG, and DNJ participated in study design, provided drug information, and feedback on the manuscript. DMN, MM, TG, and AMP participated in study design and provided feedback on the manuscript. AXG conceived of the study, participated in its design and interpretation, helped draft the manuscript and provided feedback on the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Data sharing

There are no additional data to report.

Reference List

1. Dresser GK, Spence JD, Bailey DG: **Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition.** *Clin Pharmacokinet* 2000, **38**: 41-57.
2. Wilkinson GR: **Drug metabolism and variability among patients in drug response.** *N Engl J Med* 2005, **352**: 2211-2221.
3. Bailey DG, Dresser G, Arnold JM: **Grapefruit-medication interactions: Forbidden fruit or avoidable consequences?** *CMAJ* 2012.
4. Hutson JR, Fischer HD, Wang X, *et al.*: **Use of clarithromycin and adverse cardiovascular events among older patients receiving donepezil: a population-based, nested case-control study.** *Drugs Aging* 2012, **29**: 205-211.
5. Neuvonen PJ, Niemi M, Backman JT: **Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance.** *Clin Pharmacol Ther* 2006, **80**: 565-581.
6. Pauwels O: **Factors contributing to carbamazepine-macrolide interactions.** *Pharmacol Res* 2002, **45**: 291-298.
7. Seithel A, Eberl S, Singer K, *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**: 779-786.
8. Westphal JF: **Macrolide - induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin.** *Br J Clin Pharmacol* 2000, **50**: 285-295.
9. Patel AM, Shariff S, Bailey DG, *et al.*: **Statin toxicity from macrolide antibiotic co-prescription: A population based study of older adults.** *Ann Intern Med* 2013. Under review
10. Clarithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120. Ref Type: Electronic Citation
11. Azithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120. Ref Type: Electronic Citation
12. McKinnell J, Tayek JA: **Short term treatment with clarithromycin resulting in colchicine-induced rhabdomyolysis.** *J Clin Rheumatol* 2009, **15**: 303-305.
13. Pasqualetti G, Bini G, Tognini S, *et al.*: **Clarithromycin-induced rhabdomyolysis: a case report.** *Int J Gen Med* 2012, **5**: 283-285.

14. Wright AJ, Gomes T, Mamdani MM, *et al*: **The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers.** *CMAJ* 2011, **183**: 303-307.
15. Statistics Canada. Population by sex and age group, by province and territory. Ottawa: Statistics Canada . 2011. 8-10-0120.
Ref Type: Electronic Citation
16. von EE, Altman DG, Egger M, *et al*: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Ann Intern Med* 2007, **147**: 573-577.
17. Levy AR, O'Brien BJ, Sellors C, *et al*: **Coding accuracy of administrative drug claims in the Ontario Drug Benefit database.** *Can J Clin Pharmacol* 2003, **10**: 67-71.
18. Jain AK, Cuerden MS, McLeod I, *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**: 1248-1253.
19. Shih AW, Weir MA, Clemens KK, *et al.*: **Oral bisphosphonate use in the elderly is not associated with acute kidney injury.** *Kidney Int* 2012, **82**: 903-908.
20. Zhao YY, Weir MA, Manno M, *et al.*: **New fibrate use and acute renal outcomes in elderly adults: a population-based study.** *Ann Intern Med* 2012, **156**: 560-569.
21. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. India . 2012.
Ref Type: Electronic Citation
22. Niemi M, Pasanen MK, Neuvonen PJ: **Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake.** *Pharmacol Rev* 2011, **63**: 157-181.
23. **Calcium channel blockers + macrolides: elderly patients hospitalised for low blood pressure.** *Prescrire Int* 2012, **21**: 182.
24. Bode C: **The nasty surprise of a complex drug-drug interaction.** *Drug Discov Today* 2010, **15**: 391-395.
25. Lee CY, Marcotte F, Giraldeau G, *et al*: **Digoxin toxicity precipitated by clarithromycin use: case presentation and concise review of the literature.** *Can J Cardiol* 2011, **27**: 870-876.
26. Trieu J, Emmett L, Perera C, *et al*: **Rhabdomyolysis resulting from interaction of simvastatin and clarithromycin demonstrated by Tc-99m MDP scintigraphy.** *Clin Nucl Med* 2004, **29**: 803-804.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
27. Kute VB, Shah PR, Goplani KR, *et al*: **Successful treatment of refractory hypotension, noncardiogenic pulmonary edema and acute kidney injury after an overdose of amlodipine.** *Indian J Crit Care Med* 2011, **15**: 182-184.
 28. 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**: 1228-1234.
 29. Mamdani M, Sykora K, Li P, *et al*: **Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding.** *BMJ* 2005, **330**: 960-962.
 30. Charlson ME, Pompei P, Ales KL, *et al*: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**: 373-383.
 31. Kanatani MS, Guglielmo BJ: **The new macrolides. Azithromycin and clarithromycin.** *West J Med* 1994, **160**: 31-37.
 32. Davey PG: **The pharmacokinetics of clarithromycin and its 14-OH metabolite.** *J Hosp Infect* 1991, **19 Suppl A**: 29-37.
 33. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement.** *Lancet* 1986, **1**: 307-310.

Appendix A: STROBE Statement

	Item No	Recommendation
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported
Objectives	3	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4	Present key elements of study design early in the paper
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9	Describe any efforts to address potential sources of bias
Study size	10	Explain how the study size was arrived at
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses
Results		
Participants	13	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram
Descriptive data	14	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)
Outcome data	15	Report numbers of outcome events or summary measures over time
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a

		meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

Appendix B. Coding definitions for demographic and co-morbid conditions.

Condition/Characteristic	Database	Codes
Age	RPDB	
Sex	RPDB	
Socioeconomic Status	Statistics Canada	
Chronic Kidney Disease	CIHI-DAD	ICD9: 4030, 4031, 4039, 4040, 4041, 4049, 585, 586, 5888, 25040 ICD10: E102, E112, E132, E142, I12, I13, N08, N18, N19
Coronary Artery Disease	OHIP	OHIP Diagnostic: 403, 585
	CIHI-DAD	ICD9: 412, 414, 4292, 4295, 4296, 4297 ICD10: I20-I25, Z955, Z958, Z959, R931, T822 CCI: 1IJ26, 1IJ27, 1IJ50 1IJ54, 1IJ57, 1IJ76 CCP: 4801-4805, 481-483
Heart Failure	OHIP	OHIP Fee: R741-R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 OHIP Diagnostic: 410, 412, 413
	CIHI-DAD	ICD9: 425, 5184, 514, 428 ICD10: I500, I501, I509, I255, J81 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR CCP: 4961-4964
Peripheral Vascular Disease	OHIP	OHIP Fee: R701, R702, Z429 OHIP Diagnostic: 428
	CIHI-DAD	ICD9: 4402, 4403, 4408, 4409, 5571, 4439, 444 ICD10: I700, I702, I708, I709, I731, I738, I739, K551 CCI: 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038
Stroke/Transient Ischemic Attack	OHIP	OHIP Fee: 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
	CIHI-DAD	ICD9: 434, 436, 431, 4358, 4359 ICD10: H341, I630-I635, I638, I639, I629, I64, G45, I61

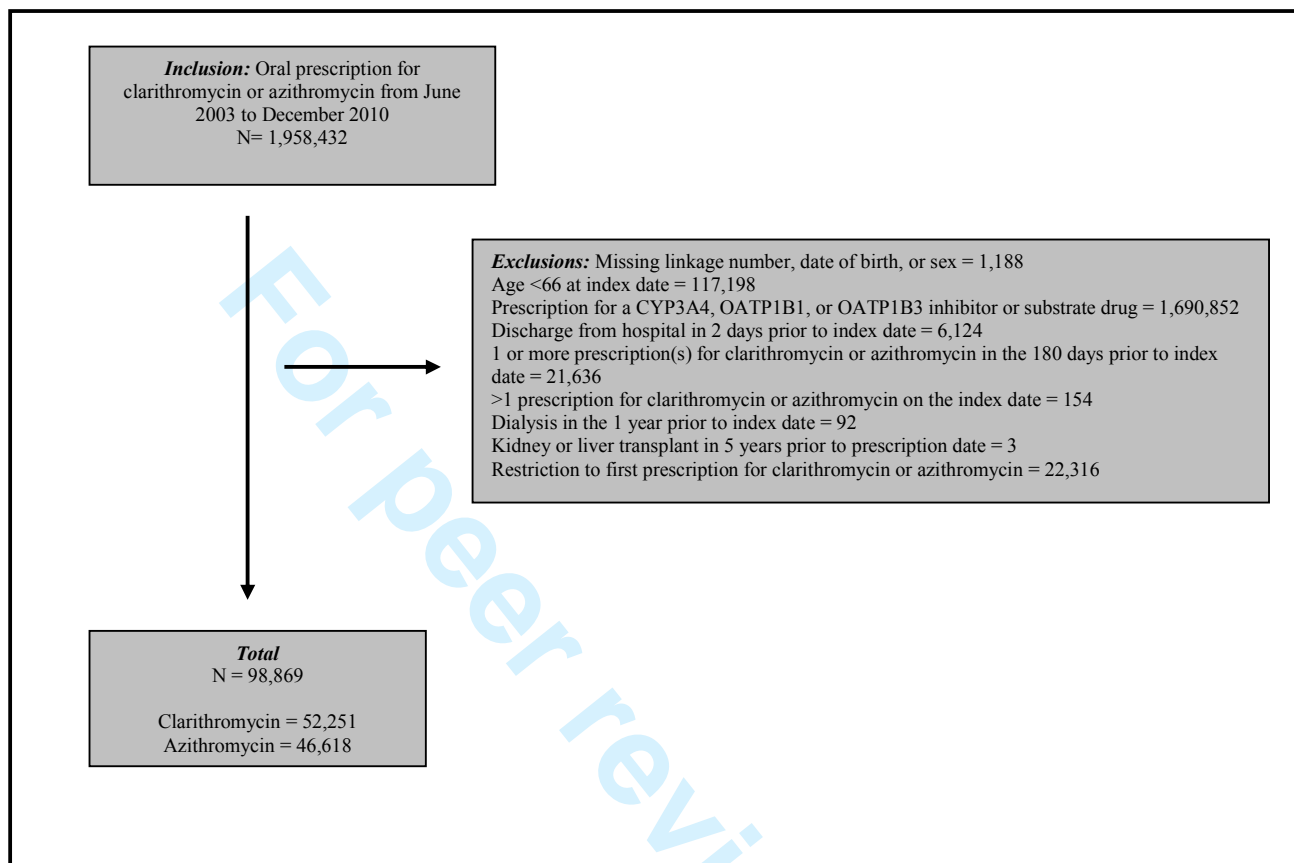
Appendix C. Outcome definitions

<i>Outcome</i>	<i>Code</i>	<i>Database</i>	<i>Validity where available</i>
Acute kidney injury ¹	ICD 10 - N17	CIHI-diagnostic	Sensitivity: 61.6% Positive predictive value: 17.3%
Acute myocardial infarction ²	ICD 10 - I21, I22	CIHI – diagnostic	Sensitivity: 89% Positive predictive value: 87%
Neuroimaging (Computed topography head scan)	CCI - 3AN20, 3EA20, 3ER20	CIHI - procedure	
	OHIP fee - X188, X400, X401, X402, X405, X408	OHIP - procedure	
Hypotension	ICD 10 - I95	CIHI – diagnostic	
Syncope	ICD 10 - R55	CIHI – diagnostic	
Hyperkalemia ³	ICD 10 - E875	CIHI – diagnostic	Sensitivity: 14.6% Positive predictive value: 62.0%
Hyponatremia ⁴	ICD 10 - E871	CIHI – diagnostic	Sensitivity: 10.6% Positive predictive value: 82.3%
Hyperglycemia	ICD 10 - R73	CIHI – diagnostic	
Arrhythmia ⁵	ICD 10 - I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001	CIHI – diagnostic	Sensitivity: 39.0% Positive predictive value: 93.4%
	OHIP fee - G178, G179, G249, G261, G259, Z443, Z431, Z437	OHIP - procedure	
Ischemic stroke ⁶	ICD 10 - H341, I630, I631, I632, I633, I634, I635, I638, I639	CIHI – diagnostic	Sensitivity: 58% Specificity: 97%
Gastrointestinal bleeding	ICD 10 - K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K920, K921, K922, K5520, K226, I850	CIHI – diagnostic	
Abbreviations: ICD10, International Classification of Diseases, 10 th revision; CCI, Canadian Classification of (health) Interventions; OHIP, Ontario Health Insurance Plan			
1 Hwang YJ, Shariff SZ, Gandhi S, 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. <i>BMJ Open</i> . 2012:2 Note: The presence of a hospital diagnosis code for acute kidney injury in Ontario identifies a median absolute acute increase in serum creatinine of 98 µmol/L (interquartile range (IQR) 43 to 200) above the most recent value prior to hospitalization, while the absence of such a code represents a median increase of 6 µmol/L (IQR -4 to 20 µmol/L).			
2 Juurlink DN, Preyra C, Croxford R, et al. Canadian Information Discharge Abstract Database: a validation study. <i>Institute for Clinical Evaluative Sciences</i> 2006.			
3 Fleet JL, Shariff SZ, Gandhi S, et al. Validity of the International Classification of Diseases, 10 th revision code for hyperkalaemia in elderly patients at presentation to an emergency department and at hospital admission. <i>BMJ Open</i> . 2012:2. Note: A code for hyperkalemia identifies a median potassium value of 6.0 mmol/L (IQR 5.1 to 6.7 mmol/L), and the absence of a code a median value of 4.1 mmol/L (IQR 3.8 to 4.5 mmol/L).			
4 Gandhi S, Shariff SZ, Fleet JL, et al. Validity of the International Classification of Diseases 10 th revision code for hospitalisation with hyponatraemia in elderly patients. <i>BMJ Open</i> . 2012:2. Note: A code for hyponatremia identifies a median sodium value of 125 mmol/L (IQR 120 to 130 mmol/L) and the absence of a code a median value of 137 (IQR 135 to 139 mmol/L).			
5 Quan H, Li B, Saunders LD, et al. Assessing validity of ICD9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. <i>Health Serv Res</i> . 2008:1424-1441.			
6 Kokotailo RA & Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, Revisions 9 and 10. <i>Stroke</i> . 2005:177601781.			

Appendix D. Exclusion medications

Codeine	Budesonide	Cyclosporine	Everolimus	Mephobarbital
Aliskiren	Buspiron	Dapsone	Felodipine	Mestranol
Alprazolam	Butabarbital	Dasatinib	Fentanyl	Methadone
Amiodarone	Carbamazepine	Delavirdine	Fexofenadine	Methylprenisolone
Amlodipine	Carvedilol	Dexamethasone	Finasteride	Methyltestosterone
Amobarbital	Cerivastatin	Dextromethorphan	Fluconazole	Midazolam
Anagrelide	Chloramphenicol	Diazepam	Flunarizone	Modafinil
Aprepitant	Chlorpheniramine	Dienogest	Fluvastatin	Nateglinide
Astemizole	Cimetidine	Diltiazem	Fluvoxamine	Nefazodone
Atenolol	Ciprofloxacin	Disulfiram	Haloperidol	Nelfinavir
Atorvastatin	Cisapride	Domperidone	Imatinib	Nevirapine
Beclomethasone	Clomipramine	Efavirenz	Indinavir	Nicardipine
Phenobarbital	Clopidogrel	Eplerenone	Irinotecan	Nifedipine
Hydrocortisone	Colchicines	Ergotamine	Itraconazole	Nilotinib
Betamethasone	Estrogen/estradiol	Erlotinib	Ketamine	Nimodipine
Oxycodone	Cortisone	Erythryl	Ketoconazole	Norfloxacin
Pentobarbital	Cyclophosphamide	tetranitrate	Lidocaine	Ondansetron
Phenytoin	Risperidone	Etoposide	Lopinavir	Oxcarbazepine
Pimozide	Ritonavir	Etravirine	Losartan	Triamcinolone
Pioglitazone	Rivaroxaban	Sirolimus	Lovastatin	Triazolam
Pravastatin	Rosuvastatin	Sunitinib	Maraviroc	Verapamil
Praziquantel	Salmeterol	Tacrolimus	Medroxyprogesterone	Vincristine
Prednisolone	Saquinavir	Tadalafil	Triamcinolone	Voriconazole
Prednisone	Secobarbital	Tamoxifen	Triazolam	Ziprasidone
Primaquine	Sertraline	Tamulosin	Verapamil	Omeprazole
Primidone	Sildenafil	Telithromycin	Vincristine	Fluticasone
Progesterone	Simvastatin	Terfenadine	Voriconazole	Rabeprazole
Propafenone	Bosentan	Testosterone	Ziprasidone	Lansoprazole
Quetiapine	Bromocriptine	Tobramycin	Omeprazole	Trimethoprim
Quinidine	Caspofungin	Trazodone	Fluticasone	Calcium carbonate
Quinine	Cefazolin	Enalapril	Rabeprazole	Amprenavir
Repaglinide	Cefoperazone	Estropipate	Lansoprazole	Atazanavir
Rifabutin	Clotrimazole	Ezetimibe	Trimethoprim	Bezafibrate
Rifampin	Darunavir	Fenofibrate	Calcium carbonate	Telmisartan
Metyrapone	Digoxin	Gemfibrozil	Amprenavir	Levothyroxine
Miconazole	Pantoprazole	Glyburide	Atazanavir	Dextrothyroxine
Mycophenolic	Ramipril	Methotrexate	Bezafibrate	Valsartan
Olmesartan	Rosiglitazone			

Appendix E. Cohort Creation





Comparing Two Types of Macrolide Antibiotics for the Purpose of Assessing Population-Based Drug Interactions

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2013-002857.R1
Article Type:	Research
Date Submitted by the Author:	24-May-2013
Complete List of Authors:	Fleet, Jamie; London Health Sciences Centre, Medicine/Nephrology Shariff, Salimah; Institute for Clinical Evaluative Sciences, Bailey, David; Lawson Health Research Institute, Gandhi, Sonja; London Health Sciences Centre, Medicine/Nephrology Juurlink, David; Sunnybrook Health Sciences Centre, Clinical Pharmacology and Toxicology Nash, Danielle; London Health Sciences Centre, Medicine/Nephrology Mamdani, Muhammad; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute Gomes, Tara; Institute for Clinical Evaluative Sciences, Patel, Amit; London Health Sciences Centre, Medicine/Nephrology Garg, Amit; University of Western Ontario
Primary Subject Heading:	Pharmacology and therapeutics
Secondary Subject Heading:	Public health
Keywords:	PREVENTIVE MEDICINE, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, PUBLIC HEALTH

SCHOLARONE™
Manuscripts

Comparing Two Types of Macrolide Antibiotics for the Purpose of Assessing Population-Based Drug Interactions

Jamie L. Fleet BSc¹, Salimah Z. Shariff PhD^{1,2}, David G. Bailey BScPhm PhD³, Sonja Gandhi BSc^{1,4}, David N. Juurlink MD, PhD^{2,5,6}, Danielle M. Nash MSc^{1,2}, Muhammad Mamdani PharmD, MPH^{2,6,7}, Tara Gomes, MSc², Amit M. Patel MD¹, Amit. X. Garg MD, PhD^{1,2,4}.

1. Division of Nephrology, Department of Medicine, Western University, London, Canada
2. Institute for Clinical Evaluative Sciences, Ontario, Canada
3. Lawson Health Research Institute, London Health Sciences Centre, London, Canada
4. Department of Epidemiology & Biostatistics, Western University, London, Canada
5. Division of Clinical Pharmacology, Department of Medicine, University of Toronto, Toronto, Canada
6. Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada
7. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Correspondence: Dr. Amit Garg, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5, Tel: 519-685-8502, Fax: 519-685-8072, email: amit.garg@lhsc.on.ca

Publication Type: Research Article

Short Title: Using macrolide antibiotics to assess drug interactions

Financial Disclosures: none

Funding/Support: This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) @ Western Site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-term Care. ICES@Western is funded by operating grants from the Academic Medical Organization of Southwestern Ontario, the Schulich School of Medicine and Dentistry and the Lawson Health Research Institute.

Role of the Sponsor: The opinions, results and conclusions reported in this paper are those of the authors and are independent of the funding sources.

Acknowledgements: We thank Brogan Inc., Ottawa for use of its Drug Product and Therapeutic Class Database. We thank the late Dr. Milton Haines, Ms. Barbara Jones, Mr. Jeff Lamond and others from Gamma Dynacare for their use of the outpatient laboratory database. We thank Mr. Glen Kearns from the London Health Sciences Centre who facilitated the use of linked hospital laboratory databases.

Word count: Abstract 300 (max 300), main text 2580 (max 4000)

Date: May 24th 2013

ABSTRACT

Objective: Clarithromycin strongly inhibits enzyme cytochrome P450 3A4, preventing the metabolism of some other drugs, while azithromycin is a weak inhibitor. Accordingly, blood concentrations of other drugs increase with clarithromycin co-prescription leading to adverse events. These macrolide antibiotics also differ on other properties that may impact outcomes. In this study we compared outcomes in two groups of macrolide antibiotic users in the absence of potentially interacting drugs.

Design: Population-based retrospective cohort study.

Setting: Ontario, Canada, from 2003 to 2010.

Patients: Patients (mean 74 years) prescribed clarithromycin (n=52,251) or azithromycin (referent group, n=46,618).

Main outcomes: The primary outcomes were hospital admission within 30 days of a new antibiotic prescription with any of 12 conditions examined separately (acute kidney injury, acute myocardial infarction, neuroimaging (proxy for delirium), hypotension, syncope, hyperkalemia, hyponatremia, hyperglycemia, arrhythmia, ischemic stroke, gastrointestinal bleeding and sepsis). The secondary outcome was mortality.

Results: The baseline characteristics of the two groups, including patient demographics, comorbid conditions, infection type, and prescribing physician specialty, were nearly identical. The median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin, and the median duration of antibiotic dispensed was 10 and 5 days, respectively. There was no difference between the groups in the risk of hospitalization for any condition studied (relative risk ranged from 0.67 to 1.23). Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Conclusions: Clarithromycin can be used to assess drug interactions in population-based studies with azithromycin serving as a control group. However, any differences in mortality observed between the two antibiotic groups in the setting of other drug use may be partially attributable to factors beyond the inhibition of drug metabolizing enzymes and transporters, as the difference for this outcome was significant.

ARTICLE SUMMARY

Article Focus

- This study describes the differences in adverse outcomes when either clarithromycin or azithromycin is prescribed in the absence of interacting drugs
- Knowledge of the underlying differences between these two drugs is important for the interpretation of population-based drug-drug interaction studies

Key Messages

- There were no significant differences between clarithromycin and azithromycin on 12 hospitalization outcomes, however clarithromycin was associated with a slightly higher risk of all-cause mortality
- Since there is no difference between clarithromycin and azithromycin in hospitalization outcomes in the absence of interacting drugs, the use of azithromycin as a reference group is appropriate in drug-drug interaction studies
- Most outcomes from drug-drug interaction studies can be attributed to the interaction rather than underlying differences in these macrolide antibiotics

Strengths and Limitations

- This is the first population-based study to compare outcomes between clarithromycin and azithromycin while excluding interacting drugs
- Our large sample size allowed greater precision around the estimates reported and is representative of the province of Ontario as a whole
- Further studies examining differences in all-cause mortality between the two antibiotics as well as non-macrolide antibiotics are warranted

INTRODUCTION

Certain medication combinations can lead to altered pharmacokinetics that result in higher systemic concentration of the drugs and accompanying greater risk of toxicity.[1] The commonly used macrolide antibiotic clarithromycin can inhibit the drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4), as well as the Organic Anion Transporting Polypeptide transporters 1B1 (OATP1B1), and OATP1B3.[2] These transporters and enzyme are present in the liver and small intestine, and about half of all the medications used today are affected by their processes.[3] These include many types of statins, anti-epileptics and anti-psychotics.[4-6] Interestingly, another macrolide antibiotic, azithromycin, is prescribed for similar indications and in comparable patients as clarithromycin, but unlike clarithromycin, is only a very weak inhibitor of this enzyme and transporters.[7-9] Thus, there is a growing interest in conducting population based studies examining two groups of individuals newly prescribed either clarithromycin or azithromycin, where all patients are also chronically using another drug such as a statin which may interact with clarithromycin.[10] The outcomes of the two groups can then be compared (with the azithromycin users acting as a control group) to assess the outcomes attributable to the clarithromycin-statin interaction.[10]

However, as per prescribing references, the two macrolide antibiotics do differ on the total daily dose and the recommended duration of therapy to treat infection which may influence compliance, as a dose would be more likely to be missed if taken over a longer period of time.[11,12] It is possible that these, and other properties of macrolide antibiotics, also impact patient outcomes. We wanted to be assured that outcomes observed in population-based drug interaction studies of clarithromycin compared to azithromycin are most likely attributable to the drug interaction being studied rather than other inherent differences between the two macrolide antibiotics.[10,13-15] For example, we recently published a study assessing statin and macrolide drug interactions, and noted older patients co-prescribed clarithromycin were more likely to be hospitalized with acute kidney injury in the subsequent 30 days compared to older patients co-prescribed azithromycin.[10] Observing an increase in the risk of acute kidney injury with clarithromycin vs. azithromycin in the presence of a statin, but not in the absence of statin, would provide additional evidence of statin toxicity from clarithromycin.[10] The purpose of the current population-based study was to compare the incidence of serious adverse events for two

1
2
3 groups of older patients either prescribed clarithromycin or azithromycin in the absence of other
4 drugs with metabolism potentially impacted by clarithromycin.
5
6
7

8 9 **METHODS**

10 11 **Setting and Design**

12 All residents of the province of Ontario, Canada have universal access to hospital care and
13 physician services. Individuals 65 years of age or older (approximately 2 million individuals in
14 Ontario in 2012) also have universal prescription drug coverage.[16] All health care encounters
15 are prospectively recorded in health administrative databases, which are available for evaluation
16 at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. We conducted a
17 population-based retrospective cohort study using these large linked health care databases. We
18 focused on adults over the age of 65 given their risk of drug toxicity and the availability of
19 prescription data. We conducted this study according to a pre-specified protocol that was
20 approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada).
21 The reporting of this study followed guidelines for observational studies (detailed in
22 Appendix A).[17]
23
24
25
26
27
28
29
30
31
32

33 34 **Data Sources**

35 We ascertained drug use, covariate information, and outcome data using records from five
36 administrative databases. Outpatient prescription drug information including the dispensing date,
37 quantity of pills, and number of days supplied is accurately recorded in the Ontario Drug Benefit
38 Plan database, with an error rate less than 1%.[18] Detailed diagnosis and procedural
39 information on all inpatient hospitalizations in Ontario are recorded in the Canadian Institute for
40 Health Information Discharge Abstract Database (CIHI-DAD). Up to 25 unique diagnosis codes
41 (i.e. codes for acute kidney injury or hyperkalemia) can be assigned at discharge to each hospital
42 stay. The Ontario Health Insurance Plan database (OHIP) contains all health claims for inpatient
43 and outpatient fee-for-service physician services. The Ontario Registered Persons Database
44 (RPDB) contains demographic and vital statistics information on all Ontario residents who have
45 ever been issued a health card. We have previously used these four databases to research adverse
46 drug events, health outcomes and health services.[19-21] The databases were complete for all
47
48
49
50
51
52
53
54
55
56
57
58
59
60

1
2
3 variables used in this study. We also used the Ontario Registrar General Database (ORGD) to
4 assess cause of death for patients who died during follow-up.
5
6

7 Codes used to assess co-morbidities in the five years prior to receipt of the relevant
8 prescription are detailed in Appendix B. This Appendix contains both the International
9 Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10) codes, as both were in
10 use during the study period. Codes used to ascertain outcomes are detailed in Appendix C with
11 information on code validity when available. This Appendix only contains ICD-10 codes as ICD-
12 9 codes were no longer used in Canada after March 31 2002.
13
14
15
16
17

18 19 **Patients**

20 We established a cohort of patients with new prescriptions for clarithromycin. Our comparison
21 (referent) group consisted of patients with new azithromycin prescriptions. Erythromycin,
22 another macrolide antibiotic that inhibits several metabolizing enzymes, was not included in our
23 study since the number of prescriptions dispensed during our study period was low.
24
25
26
27

28 The date of antibiotic prescription served as the index date, which is the start time for follow-
29 up. We accrued patients from June 2003 to December 2010. We excluded the following
30 antibiotic users from analysis: i) those in their first year of eligibility for prescription drug
31 coverage (age 65) to avoid incomplete past medication records, ii) those who were discharged
32 from hospital in the two days prior to and including the index date to ensure we were studying
33 new outpatient antibiotic prescriptions, iii) those who received a prescription for more than one
34 type of antibiotic on the index date in order to compare mutually exclusive groups, iv) those with
35 end stage renal disease prior to the index date, and v) those who were taking other potential
36 CYP3A4, OATP1B1, or OATP1B3 inhibitors or substrates 180 days prior to the index date
37 (medications such as protease inhibitors, statins, anti-fungals, and calcium channel blockers –
38 See Appendix D for full list).[22,23] When there were multiple episodes of macrolide antibiotic
39 use for a given patient over the study period we only selected the first one. For exclusions and
40 baseline characteristics, we identified comorbidities in the five years prior to the index date and
41 concurrent drug therapy in the 180 days prior to the index date (see Appendix B).
42
43
44
45
46
47
48
49
50
51
52
53

54 55 **Outcomes**

1
2
3 All patients were followed for 30 days after the index date for the assessment of outcomes. We
4 assessed hospital admissions involving any of 12 medical conditions; each condition was
5 examined separately: acute kidney injury, acute myocardial infarction, neuroimaging (computed
6 tomography head scan as a proxy for delirium), hypotension, syncope, hyperkalemia,
7 hyponatremia, hyperglycemia, arrhythmia, ischemic stroke, gastrointestinal bleeding, and sepsis.
8 These conditions are potential adverse events when clarithromycin interferes with the
9 pharmacokinetics of other drugs. For example, use of clarithromycin with a calcium channel
10 blocker may cause hypotension and acute kidney injury.[15,24-28] A small number of events in
11 our population precluded analyses of three other conditions of interest: rhabdomyolysis,
12 hypoglycemia, and neuroleptic malignant syndrome. We also assessed all-cause mortality.

13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

There are up to 25 diagnostic codes that can be assigned per hospital admission; patients with multiple codes were accounted for under each outcome of interest. Wherever possible we selected validated codes that performed well for identifying the conditions of interest (code lists and validations fully detailed in Appendix C).

Statistical Analysis

We compared baseline characteristics between new users of clarithromycin and azithromycin using standardized differences.[29,30] This metric describes differences between group means relative to the pooled standard deviation and is considered to indicate a meaningful difference if it is greater than 10%. The risk of developing an outcome was expressed in relative terms. We used multivariable logistic regression analyses to estimate odds ratios and 95% confidence intervals, adjusting for age (per year), sex, and Charlson co-morbidity score (a popular measure of co-morbidity).[31] We interpreted odds ratios as relative risks (appropriate given the incidences observed). We conducted all analyses with SAS 9.2 (SAS Institute Incorporated, Cary, North Carolina, USA, 2008).

RESULTS

There were a total of 1,958,432 macrolide antibiotic prescriptions during our study period. Cohort selection is presented in Appendix E. After applying our exclusion criteria, including

1
2
3 evidence of any interacting drug and restricting to the first antibiotic prescription per patient,
4
5 98,869 patients remained: 52,251 clarithromycin users and 46,618 azithromycin users.
6
7

8 Baseline characteristics of the two groups with respect to co-morbidities and use of other
9 medications were nearly identical (Table 1; all standardized differences between the groups were
10 less than 3%). For both groups, the median age was 71 years and 54% of patients were women.
11 The cause of infection was recorded in some patients and appeared comparable between the two
12 groups, as were cultures and concurrent bronchodilators and steroid prescriptions around the
13 time of the index date (Table 1). The specialty of the prescribing physician, when available, was
14 also comparable between the two groups (Table 1).
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Table 1. Baseline Characteristics

BMJ Open

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Clarithromycin n = 52,251	Azithromycin n = 46,618	Standardized Differences*
Demographics			
Age, years, median (IQR)	71 (68-77)	71 (68-77)	
Women, n (%)	27,932 (53.5)	25,682 (55.1)	0.03
Income Quintile			
first (lowest)	8,951 (17.1)	7,706 (16.5)	0.02
second	10,447 (20.0)	8,899 (19.1)	0.02
third (middle)	10,153 (19.4)	8,937 (19.2)	0.01
fourth	10,822 (20.7)	9,633 (20.7)	0
fifth (highest)	11,703 (22.4)	11,285 (24.2)	0.04
Year of Cohort Entry^e, n (%)			
2003 - 2005	21,369 (40.9)	18,979 (40.7)	0.01
2006 - 2008	19,236 (36.8)	17,198 (36.9)	0.01
2009 - 2010	11,646 (22.3)	10,441 (22.4)	0.01
Co-morbidities, n (%)			
Cancer	12,733 (24.4)	11,473 (24.6)	0.01
Chronic kidney disease ‡	644 (1.2)	566 (1.2)	0
Coronary artery disease ¶	7,531 (14.4)	6,956 (14.9)	0.01
Diabetes mellitus #	855 (1.6)	816 (1.8)	0.01
Heart failure	1,656 (3.2)	1,536 (3.3)	0.01
Peripheral vascular disease	175 (0.3)	176 (0.4)	0.01
Stroke/Transient ischemic attack	246 (0.5)	249 (0.5)	0.01
Medication use in prior 6 months, n (%)			
ACE inhibitors or ARBs	2,769 (5.3)	2,543 (5.5)	0.01
Beta blockers	1,787 (3.4)	1,720 (3.7)	0.01
Potassium sparing diuretics	461 (0.9)	389 (0.8)	0.01
Loop diuretics	103 (0.2)	120 (0.3)	0.01
NSAIDs (excluding ASA)	2,483 (4.8)	2,389 (5.1)	0.02
Thiazide diuretics	3,479 (6.7)	3,171 (6.8)	0.01
Cause of infection, n (%)			
Genitourinary infection	261 (0.5)	265 (0.6)	0.01
Oropharyngeal infection	839 (1.6)	1,000 (2.1)	0.04
Respiratory infection	22,084 (42.3)	17,503 (37.5)	0.10
Sinus infection	4,000 (7.7)	3,178 (6.8)	0.03
Skin infection	659 (1.3)	320 (0.7)	0.06
Missing	27,843 (53.3)	22,266 (47.8)	0.11
Cultures⁺, n (%)			
Blood	28 (0.1)	21 (0.0)	0
Genitourinary	26 (0.0)	69 (0.01)	0.03
Gynecology	120 (0.2)	134 (0.3)	0.01
Sputum	127 (0.2)	75 (0.2)	0.02
Urine	1,090 (2.1)	931 (2.0)	0.01
Concurrent medication prescription, n (%)			
Inhaled steroids	28 (0.1)	31 (0.1)	0.01
Bronchodilators	1,202 (2.3)	929 (2.0)	0.02

BMJ Open: first published as 10.1136/bmjopen-2013-002857 on 11 July 2013. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

Main specialty of prescribing physician, *n* (%)

GP/FP	39,743 (76.1)	34,308 (73.6)	0.06
Internal medicine	280 (0.5)	260 (0.6)	0.01
General surgery	100 (0.2)	151 (0.3)	0.02
Other	1,148 (2.2)	1,042 (2.2)	0
Missing	10,980 (21.0)	10,857 (23.3)	0.06

Data presented as number (percent) except for age which is presented as mean (standard deviation).

Abbreviations: Non-steroidal anti-inflammatory (NSAID), angiotensin converting enzyme (ACE), angiotensin II receptor blocker (ARB), general practitioner (GP), family practitioner (FP)

*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.

€ The year of cohort entry is also referred to as the index date.

‡ Assessed by administrative database codes

¶ Coronary artery disease includes receipt of coronary artery bypass graft surgery, percutaneous coronary intervention and diagnoses of angina.

#Assessed by receipt of insulin or oral antihyperglycemics

+ Cultures recorded within two weeks prior and one week after the index date

Consistent with drug prescribing references, the median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin. The median duration of antibiotic dispensed was 10 days for clarithromycin and 5 days for azithromycin.[11,12]

The outcome of hospitalization with each of the 12 conditions examined separately is presented in Table 2. Results are expressed with patients receiving azithromycin as the referent group. There were no significant difference between the clarithromycin and azithromycin groups on any of the 11 hospitalization outcomes, and the relative risk ranged from 0.67 to 1.23. Results were consistent across all adjusted analyses (Table 2).

The results of all-cause mortality within 30 days of the antibiotic prescription are also presented in Table 2. Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Table 2. Hospitalizations with various conditions and all-cause mortality

	<i>Number of Events (%)</i> *		<i>Unadjusted Relative Risk (95% CI)</i>	<i>Adjusted Relative Risk (95% CI)</i> ‡
	<i>Clarithromycin n = 52,251</i>	<i>Azithromycin n = 46,618</i>		
Acute kidney injury	52 (0.10)	44 (0.09)	1.05 (0.71 – 1.58)	1.06 (0.71 – 1.58)
Myocardial infarction	39 (0.07)	30 (0.06)	1.16 (0.72 – 1.87)	1.15 (0.71 – 1.85)
Neuroimaging ⁺	582 (1.11)	496 (1.06)	1.05 (0.93 – 1.18)	1.04 (0.93 – 1.18)
Hypotension	19 (0.04)	14 (0.03)	1.21 (0.61 – 2.42)	1.21 (0.61 – 2.41)
Syncope	14 (0.03)	12 (0.03)	1.04 (0.48 – 2.25)	1.04 (0.48 – 2.25)
Hyperkalemia	9 (0.02)	12 (0.03)	0.67 (0.28 – 1.59)	0.67 (0.28 – 1.60)
Hyponatremia	29 (0.06)	29 (0.06)	0.89 (0.53 – 1.49)	0.90 (0.54 – 1.51)
Hyperglycemia	22 (0.04)	16 (0.03)	1.23 (0.64 – 2.34)	1.22 (0.64 – 2.33)
Arrhythmia	49 (0.09)	52 (0.11)	0.84 (0.57- 1.24)	0.84 (0.57 – 1.24)
Ischemic stroke	17 (0.03)	16 (0.3)	0.95 (0.48 – 1.88)	0.94 (0.47 – 1.86)
Gastrointestinal bleeding	32 (0.06)	30 (0.06)	0.95 (0.58 – 1.57)	0.95 (0.58 – 1.56)
Sepsis	28 (0.05)	18 (0.04)	1.39 (0.77 – 2.51)	1.38 (0.76 – 2.49)
All-cause mortality	241 (0.46)	172 (0.37)	1.25 (1.03 – 1.52)	1.27 (1.04 – 1.55)
Patients prescribed azithromycin served as the comparator group.				
* 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. For some outcomes this underestimates the true event rate because these codes have high specificity but low sensitivity.				
‡ Adjusted for 3 covariates: Age, sex, and Charlson co-morbidity score				
+ Neuroimaging consisted of codes for computed tomography head scan as a proxy for delirium.				

After observing a difference in all-cause mortality between our groups, we considered the five most common causes of death (Table 3). There were no significant differences in these causes of death between the two groups.

Table 3. Deaths due to the following causes

	<i>Number of events (%)*</i>	
	Clarithromycin n = 52,251	Azithromycin n = 46,618
Disease of circulatory system	64 (0.12)	50 (0.11)
Neoplasm	48 (0.09)	32 (0.07)
Disease of respiratory system	35 (0.07)	32 (0.07)
Mental disorder	28 (0.05)	13 (0.03)
Disease of the nervous system	25 (0.05)	13 (0.03)
Other	41 (0.08)	32 (0.07)
*There were 241 total deaths in the clarithromycin group and 172 in the azithromycin group		

DISCUSSION

Contrasting outcomes of patients prescribed clarithromycin to those prescribed azithromycin in the presence of a drug with metabolism potentially impacted by clarithromycin presents a potentially attractive method of assessing population-based clarithromycin drug interactions in routine care. However, these two macrolide antibiotics also differ on other properties besides their inhibition of drug metabolizing enzymes and transporters that may impact patient outcomes. In this study we compared the baseline characteristics and outcomes of patients prescribed either clarithromycin or azithromycin in the absence of potentially interacting drugs. The two groups did not differ in patient baseline demographics, co-morbid characteristics, the type of infection, or the specialty of the prescribing physician. In other words, the two drugs appeared to be used for similar indications and demonstrated similar clinical usage patterns. With respect to the study outcomes there were no differences between the two groups on any of the 12 hospitalization conditions that we studied.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Overall, these results support the utility of macrolide antibiotics to assess population-based drug interactions for the hospital conditions presented in this report. This is particularly true when conducting studies in settings where the observed results are consistent with medications known to have potential for drug-drug interactions based on pharmacokinetic data and case reports. For example, a high blood concentration of some statins is realized when taken concurrently with clarithromycin, as the latter inhibits the CYP3A4 enzyme responsible for statin metabolism.[10] This can lead to rhabdomyolysis and acute kidney injury. In the present study, in the absence of statin use, there was no difference in hospitalization with acute kidney injury between the two macrolide antibiotic groups. Thus there is more assurance that the outcomes observed in the aforementioned study of clarithromycin co-prescribed with a statin are attributable to the interaction between the drugs.

In the present study there was a small absolute difference in all-cause mortality with clarithromycin compared to azithromycin, without any clear difference in the cause of death. While this may be a chance finding, it is also possible that there may be inherent differences in the use or nature of these two antibiotics that impacts mortality. Consistent with drug prescribing references, the median duration of antibiotic treatment was higher with clarithromycin compared to azithromycin. Additionally, differences in daily dose and day supply between the two macrolide antibiotics were found, and there could be differences in frequency of dose. Because clarithromycin is taken twice a day for the duration of therapy, unlike azithromycin, there could be differences in drug adherence. Other differences exist, for example: azithromycin is less bioavailable than clarithromycin, especially when taken with food.[32] On the other hand, clarithromycin is transformed into an active metabolite, where most other macrolide antibiotics are not.[33] For these reasons, some of the association between macrolide antibiotic type and mortality may partially be attributable to factors beyond the inhibition of drug transporters and metabolizing enzymes, although it also may not be reflective of a difference between the drugs at all. It may also be useful to determine if the magnitude of the association observed in the present study differs with associations observed in other drug-drug interaction studies, using statistical tests of interaction (such as the Bland Altman Test on the two sets of results).[34] Additionally, in the future, studies with other non-macrolide antibiotics, compared to clarithromycin, may be warranted, as macrolide antibiotics have a higher rate of mortality as they are potentially arrhythmogenic.[35-37]

1
2
3
4 Our study has a number of strengths. This study was done in the province of Ontario where
5 residents have the benefit of universal healthcare for all citizens and a province wide drug plan
6 for older adults, with this information accessible for study purposes. Accordingly, there were a
7 large number of patients accrued into our study, which provided reasonable precision for the
8 outcomes that are reported. The large sample size also provided adequate data to reasonably
9 compare clarithromycin and azithromycin on baseline characteristics and patterns of clinical use.
10

11
12 Our study does have some limitations. Despite the large sample size, we had too few events to
13 meaningfully look at some outcomes such as rhabdomyolysis, neuroleptic malignant syndrome,
14 and hypoglycemia. For reasons of privacy we are not permitted to report information for small
15 cell sizes which also precluded meaningful analysis of some types of cause of death, such as
16 infectious disease. Drug-drug interactions at the population level in routine care are complex
17 and understudied. While we took a comprehensive approach to exclude interacting drugs, it is
18 still possible that interactions with other drugs may have occurred. The efficacy of pathogen
19 eradication is similar between the two macrolides for some illnesses, but was not formally
20 assessed here.[38,39] Finally, because our hospital-based outcomes were assessed using hospital
21 diagnosis codes (which have limited sensitivity for some outcomes), rather than prospective data
22 collection, we most likely underestimated the true event rate of the outcomes. However, because
23 the outcomes were assessed no differently between the clarithromycin and azithromycin groups,
24 we do not anticipate that this biased our relative measures of risk.
25
26
27
28
29
30
31
32
33
34
35
36
37
38

39 CONCLUSION

40
41 In conclusion, we have established that patterns of use and common clinical outcomes do not
42 differ appreciably between clarithromycin and azithromycin, suggesting that clarithromycin may
43 be useful medication to assess drug-drug interactions in population-based studies with
44 azithromycin serving as the control group. If in future drug-drug interaction studies, differences
45 in mortality between groups of patients prescribed each of the two antibiotics exist, it should be
46 noted that some of the association may be attributable to factors unrelated to the enzyme
47 metabolism of the drugs.
48
49
50
51
52
53
54
55
56
57
58
59
60

Contributors

JLF participated in the coordination of the study, study design, provided interpretation of the study results, and drafted the manuscript. SZS participated in the study design, performed the analysis and provided interpretation of the study results. DGB, SG, and DNJ participated in study design, provided drug information, and feedback on the manuscript. DMN, MM, TG, and AMP participated in study design and provided feedback on the manuscript. AXG conceived of the study, participated in its design and interpretation, helped draft the manuscript and provided feedback on the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Data sharing

No additional data available.

Reference List

1. Dresser GK, Spence JD, Bailey DG: **Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition.** *Clin Pharmacokinet* 2000, **38**: 41-57.
2. Wilkinson GR: **Drug metabolism and variability among patients in drug response.** *N Engl J Med* 2005, **352**: 2211-2221.
3. Bailey DG, Dresser G, Arnold JM: **Grapefruit-medication interactions: Forbidden fruit or avoidable consequences?** *CMAJ* 2012.
4. Hutson JR, Fischer HD, Wang X, *et al.*: **Use of clarithromycin and adverse cardiovascular events among older patients receiving donepezil: a population-based, nested case-control study.** *Drugs Aging* 2012, **29**: 205-211.
5. Neuvonen PJ, Niemi M, Backman JT: **Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance.** *Clin Pharmacol Ther* 2006, **80**: 565-581.
6. Pauwels O: **Factors contributing to carbamazepine-macrolide interactions.** *Pharmacol Res* 2002, **45**: 291-298.
7. Seithel A, Eberl S, Singer K, *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**: 779-786.
8. Westphal JF: **Macrolide - induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin.** *Br J Clin Pharmacol* 2000, **50**: 285-295.
9. Polasek TM, Miners JO: **Quantitative prediction of macrolide drug-drug interaction potential from in vitro studies using testosterone as the human cytochrome P4503A substrate.** *Eur J Clin Pharmacol* 2006, **62**: 203-208.
10. Patel AM, Shariff S, Bailey DG, *et al.*: **Statin toxicity from macrolide antibiotic co-prescription: A population based study of older adults.** *Ann Intern Med* 2013.
11. Clarithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120.
Ref Type: Electronic Citation
12. Azithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120.
Ref Type: Electronic Citation

13. McKinnell J, Tayek JA: **Short term treatment with clarithromycin resulting in colchicine-induced rhabdomyolysis.** *J Clin Rheumatol* 2009, **15**: 303-305.
14. Pasqualetti G, Bini G, Tognini S, et al. **Clarithromycin-induced rhabdomyolysis: a case report.** *Int J Gen Med* 2012, **5**: 283-285.
15. Wright AJ, Gomes T, Mamdani MM, et al. **The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers.** *CMAJ* 2011, **183**: 303-307.
16. Statistics Canada. Population by sex and age group, by province and territory. Ottawa: Statistics Canada . 2011. 8-10-0120.
Ref Type: Electronic Citation
17. von EE, Altman DG, Egger M, et al. **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Ann Intern Med* 2007, **147**: 573-577.
18. Levy AR, O'Brien BJ, Sellors C, et al. **Coding accuracy of administrative drug claims in the Ontario Drug Benefit database.** *Can J Clin Pharmacol* 2003, **10**: 67-71.
19. Jain AK, Cuerden MS, McLeod I, 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**: 1248-1253.
20. Shih AW, Weir MA, Clemens KK, et al. **Oral bisphosphonate use in the elderly is not associated with acute kidney injury.** *Kidney Int* 2012, **82**: 903-908.
21. Zhao YY, Weir MA, Manno M, et al. **New fibrate use and acute renal outcomes in elderly adults: a population-based study.** *Ann Intern Med* 2012, **156**: 560-569.
22. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. India . 2012.
Ref Type: Electronic Citation
23. Niemi M, Pasanen MK, Neuvonen PJ: **Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake.** *Pharmacol Rev* 2011, **63**: 157-181.
24. **Calcium channel blockers + macrolides: elderly patients hospitalised for low blood pressure.** *Prescrire Int* 2012, **21**: 182.
25. Bode C: **The nasty surprise of a complex drug-drug interaction.** *Drug Discov Today* 2010, **15**: 391-395.
26. Lee CY, Marcotte F, Giraldeau G, et al. **Digoxin toxicity precipitated by clarithromycin use: case presentation and concise review of the literature.** *Can J Cardiol* 2011, **27**: 870-876.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
27. Trieu J, Emmett L, Perera C, et al. **Rhabdomyolysis resulting from interaction of simvastatin and clarithromycin demonstrated by Tc-99m MDP scintigraphy.** *Clin Nucl Med* 2004, **29**: 803-804.
 28. Kute VB, Shah PR, Goplani KR, et al. **Successful treatment of refractory hypotension, noncardiogenic pulmonary edema and acute kidney injury after an overdose of amlodipine.** *Indian J Crit Care Med* 2011, **15**: 182-184.
 29. 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**: 1228-1234.
 30. Mamdani M, Sykora K, Li P, et al. **Reader's guide to critical appraisal of cohort studies: 2. Assessing potential for confounding.** *BMJ* 2005, **330**: 960-962.
 31. Charlson ME, Pompei P, Ales KL, et al. **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**: 373-383.
 32. Kanatani MS, Guglielmo BJ: **The new macrolides. Azithromycin and clarithromycin.** *West J Med* 1994, **160**: 31-37.
 33. Davey PG: **The pharmacokinetics of clarithromycin and its 14-OH metabolite.** *J Hosp Infect* 1991, **19 Suppl A**: 29-37.
 34. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement.** *Lancet* 1986, **1**: 307-310.
 35. Ray WA, Murray KT, Meredith S, et al. **Oral erythromycin and the risk of sudden death from cardiac causes.** *N Engl J Med* 2004, **351**: 1089-1096.
 36. Ray WA, Murray KT, Hall K, et al. **Azithromycin and the risk of cardiovascular death.** *N Engl J Med* 2012, **366**: 1881-1890.
 37. Zambon A, Polo FH, Contiero P, et al. **Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs.** *Drug Saf* 2009, **32**: 159-167.
 38. Bradbury F: **Comparison of azithromycin versus clarithromycin in the treatment of patients with lower respiratory tract infection.** *J Antimicrob Chemother* 1993, **31 Suppl E**: 153-162.
 39. Muller O: **Comparison of azithromycin versus clarithromycin in the treatment of patients with upper respiratory tract infections.** *J Antimicrob Chemother* 1993, **31 Suppl E**: 137-146.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For peer review only

Use of Macrolide Antibiotics to Assess Population-Based Drug Interactions Comparing Two Types of Macrolide Antibiotics for the Purpose of Assessing Population-Based Drug Interactions

Jamie L. Fleet BSc¹, Salimah Z. Shariff PhD^{1,2}, David G. Bailey BScPhm PhD³, Sonja Gandhi BSc^{1,4}, David N. Juurlink MD, PhD^{2,5,6}, Danielle M. Nash MSc^{1,2}, Muhammad Mamdani PharmD, MPH^{2,6,7}, Tara Gomes, MHSc², Amit M. Patel MD¹, Amit. X. Garg MD, PhD^{1,2,4}.

1. Division of Nephrology, Department of Medicine, Western University, London, Canada
2. Institute for Clinical Evaluative Sciences, Ontario, Canada
3. Lawson Health Research Institute, London Health Sciences Centre, London, Canada
4. Department of Epidemiology & Biostatistics, Western University, London, Canada
5. Division of Clinical Pharmacology, Department of Medicine, University of Toronto, Toronto, Canada
6. Department of Health Policy, Management, and Evaluation, University of Toronto, Toronto, Canada
7. Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Canada

Correspondence: Dr. Amit Garg, London Kidney Clinical Research Unit, Room ELL-101, Westminster, London Health Sciences Centre, 800 Commissioners Road East, London, Ontario, Canada N6A 4G5, Tel: 519-685-8502, Fax: 519-685-8072, email: amit.garg@lhsc.on.ca

Publication Type: Research Article

Short Title: Using macrolide antibiotics to assess drug interactions

Financial Disclosures: none

Funding/Support: This project was conducted at the Institute for Clinical Evaluative Sciences (ICES) @ Western Site. ICES is funded by an annual grant from the Ontario Ministry of Health and Long-term Care. ICES@Western is funded by operating grants from the Academic Medical Organization of Southwestern Ontario, the Schulich School of Medicine and Dentistry and the Lawson Health Research Institute.

Role of the Sponsor: The opinions, results and conclusions reported in this paper are those of the authors and are independent of the funding sources.

Acknowledgements: We thank Brogan Inc., Ottawa for use of its Drug Product and Therapeutic Class Database. We thank the late Dr. Milton Haines, Ms. Barbara Jones, Mr. Jeff Lamond and others from Gamma Dynacare for their use of the outpatient laboratory database. We thank Mr. Glen Kearns from the London Health Sciences Centre who facilitated the use of linked hospital laboratory databases.

Word count: Abstract ~~300~~ (max 300), main text ~~2580399~~ (max 4000)

Date: ~~March 6th~~ ~~May 2013~~ ~~24th~~ 2013

ABSTRACT

Objective: Clarithromycin ~~but not azithromycin strongly~~ inhibits enzyme cytochrome P450 3A4, preventing the metabolism of some other drugs, ~~while azithromycin is a weak inhibitor~~. Accordingly, blood concentrations of ~~the~~ other drugs increase ~~with clarithromycin co-prescription~~, leading to adverse events. These ~~two~~ macrolide antibiotics also differ on other properties that may impact outcomes. In this study we compared outcomes in two groups of macrolide antibiotic users in the absence of potentially interacting drugs.

Design: Population-based retrospective cohort study ~~using linked healthcare databases~~.

Setting: Ontario, Canada, from 2003 to 2010.

Patients: ~~Elderly P~~patients (mean 74 years) prescribed ~~either~~ clarithromycin (n=52,251) or azithromycin (referent group, n=46,618).

Main outcomes: The primary outcomes were hospital admission within 30 days of a new antibiotic prescription with any of ~~124 medical~~ conditions examined separately (acute kidney injury, acute myocardial infarction, neuroimaging (proxy for delirium), hypotension, syncope, hyperkalemia, hyponatremia, hyperglycemia, arrhythmia, ischemic stroke, ~~and~~ gastrointestinal bleeding ~~and sepsis~~). The secondary outcome was mortality.

Results: The baseline characteristics of the two groups, including patient demographics, comorbid conditions, infection type, and ~~specialty of the~~ prescribing physician ~~specialty~~, were nearly identical. The median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin, and the median duration of antibiotic dispensed was 10 and 5 days, respectively. There was no difference between the ~~two~~ groups in the risk of hospitalization for any condition studied (relative risk ranged from 0.67 to 1.23). Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Conclusions: Clarithromycin can be used to assess drug interactions in population-based studies with azithromycin serving as a control group. However, any differences in mortality observed between the two antibiotic groups in the setting of other drug use may be partially attributable to factors beyond the inhibition of drug metabolizing enzymes and transporters, ~~as the difference for this outcome was significant~~.

ARTICLE SUMMARY

Article Focus

- This study describes the differences in adverse outcomes when either clarithromycin or azithromycin is prescribed in the absence of interacting drugs
- Knowledge of the underlying differences between these two drugs is important for [the interpretation of population-based](#) drug-drug interaction studies

Key Messages

- There were no significant differences between clarithromycin and azithromycin on [124 medical-hospitalization conditions outcomes](#), however clarithromycin was associated with a slightly higher risk of all-cause mortality
- [Since there is no difference between clarithromycin and azithromycin in patient hospitalization outcomes in the absence of interacting drugs, the Use](#) of azithromycin as a reference group is appropriate in drug-drug interaction studies
- Most outcomes from drug-drug interaction studies can be attributed to the interaction rather than underlying differences in these macrolide antibiotics

Strengths and Limitations

- This is the first population-based study to compare outcomes between clarithromycin and azithromycin while excluding interacting drugs
- Our large sample size allowed greater precision around the estimates reported and is representative of the province of Ontario as a whole
- Further studies examining differences in all-cause mortality between the two antibiotics [as well as non-macrolide antibiotics](#) are warranted

INTRODUCTION

Certain medication combinations can lead to altered pharmacokinetics that result in higher systemic concentration of the drugs and accompanying greater risk of toxicity.[1] The commonly used macrolide antibiotic clarithromycin can inhibit the drug metabolizing enzyme cytochrome P450 3A4 (CYP3A4), as well as the Organic Anion Transporting Polypeptide transporters 1B1 (OATP1B1), and OATP1B3.[2] These transporters and enzyme are present in the liver and small intestine, and about half of all the medications used today are affected by their processes.[3] These include many types of statins, anti-epileptics and anti-psychotics.[4-6] Interestingly, another macrolide antibiotic, azithromycin, is prescribed for similar indications and in comparable patients as clarithromycin, but unlike clarithromycin, is only a very weak inhibitor of does not inhibit this enzyme and transporters.[7-9][7,8] Thus, there is a growing interest in conducting population based studies examining two groups of individuals newly prescribed either clarithromycin or azithromycin, where all patients are also chronically using another drug such as a statin which may interact with clarithromycin.[10][9] The outcomes of the two groups can then be compared (with the azithromycin users acting as a control group) to assess the outcomes attributable to the clarithromycin-statin interaction.[10][9]

However, as per prescribing references, the two macrolide antibiotics do differ on the total daily dose and the recommended duration of therapy to treat infection which may influence compliance, as a dose would be more likely to be missed if taken over a longer period of time.[11,12][10,11] It is possible that these, and other properties of macrolide antibiotics, also impact patient outcomes. We wanted to be assured that outcomes observed in population-based drug interaction studies of clarithromycin compared to azithromycin are most likely attributable to the drug interaction being studied rather than other inherent differences between the two macrolide antibiotics.[10,13-15][9,12-14] For example, we recently published a study assessing statin and macrolide drug interactions, and noted older patients co-prescribed clarithromycin were more likely to be hospitalized with acute kidney injury in the subsequent 30 days compared to older patients co-prescribed azithromycin.[10] Observing an increase in the risk of acute kidney injury with clarithromycin vs. azithromycin in the presence of a statin, but not in the absence of statin, would provide additional evidence of statin toxicity from clarithromycin.[10] The purpose of ~~this investigation~~ the current population-based study was to

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

compare the incidence of serious adverse events for two groups of older patients either prescribed clarithromycin or azithromycin ~~these two macrolide antibiotics administered alone in a population based study of elderly patients~~ in the absence of other drugs with metabolism potentially impacted by clarithromycin.

METHODS

Setting and Design

All residents of the province of Ontario, Canada have universal access to hospital care and physician services. Individuals 65 years of age or older (approximately 2 million individuals in Ontario in 2012) also have universal prescription drug coverage.[16] All health care encounters are prospectively recorded in health administrative databases, which are available for evaluation at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. We conducted a population-based retrospective cohort study using these large linked health care databases. We focused on adults over the age of 65 given their risk of drug toxicity and the availability of prescription data. We conducted this study according to a pre-specified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). The reporting of this study followed guidelines for observational studies (detailed in Appendix A).[17]

Data Sources

We ascertained drug use, covariate information, and outcome data using records from five administrative databases. Outpatient prescription drug information including the dispensing date, quantity of pills, and number of days supplied is accurately recorded in the Ontario Drug Benefit Plan database, with an error rate less than 1%.[18] Detailed diagnosis and procedural information on all inpatient hospitalizations in Ontario are recorded in the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD). Up to 25 unique diagnosis codes (i.e. codes for acute kidney injury or hyperkalemia) can be assigned at discharge to each hospital stay. The Ontario Health Insurance Plan database (OHIP) contains all health claims for inpatient and outpatient fee-for-service physician services. The Ontario Registered Persons Database (RPDB) contains demographic and vital statistics information on all Ontario residents who have

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

ever been issued a health card. We have previously used these four databases to research adverse drug events, health outcomes and health services.[19-21] The databases were complete for all variables used in this study. We also used the Ontario Registrar General Database (ORGD) to assess cause of death for patients who died during follow-up.

Codes used to assess co-morbidities in the five years prior to receipt of the relevant prescription are detailed in Appendix B. This Appendix contains both the International Classification of Diseases, 9th revision (ICD-9) and 10th revision (ICD-10) codes, as both were in use during the study period. Codes used to ascertain outcomes are detailed in Appendix C with information on code validity when available. This Appendix only contains ICD-10 codes as ICD-9 codes were no longer used in Canada after March 31 2002.

Patients

We established a cohort of patients with new prescriptions for clarithromycin. Our comparison (referent) group consisted of patients with new azithromycin prescriptions. Erythromycin, another macrolide antibiotic that inhibits several metabolizing enzymes, was not included in our study since the number of prescriptions dispensed during our study period was low.

The date of antibiotic prescription served as the index date, which is the start time for follow-up. We accrued patients from June 2003 to December 2010. We excluded the following antibiotic users from analysis: i) those in their first year of eligibility for prescription drug coverage (age 65) to avoid incomplete past medication records, ii) those who were discharged from hospital in the two days prior to and including the index date to ensure we were studying new outpatient antibiotic prescriptions, iii) those who received a prescription for more than one type of antibiotic on the index date in order to compare mutually exclusive groups, iv) those with end stage renal disease prior to the index date, and v) those who were taking other potential CYP3A4, OATP1B1, or OATP1B3 inhibitors or substrates 180 days prior to the index date (medications such as protease inhibitors, statins, anti-fungals, and calcium channel blockers – See Appendix D for full list).[22,23] When there were multiple episodes of macrolide antibiotic use for a given patient over the study period we only selected the first one. For exclusions and baseline characteristics, we identified comorbidities in the five years prior to the index date and concurrent drug therapy in the 180 days prior to the index date (see Appendix B).

Outcomes

All patients were followed for 30 days after the index date for the assessment of outcomes. We assessed hospital admissions involving any of 12+ medical conditions; each condition was examined separately: acute kidney injury, acute myocardial infarction, neuroimaging (computed tomography head scan as a proxy for delirium), hypotension, syncope, hyperkalemia, hyponatremia, hyperglycemia, arrhythmia, ischemic stroke, and gastrointestinal bleeding, and sepsis. These conditions are potential adverse events when clarithromycin interferes with the pharmacokinetics of other drugs. For example, use of clarithromycin with a calcium channel blocker may cause hypotension and acute kidney injury.[15,24-28] A small number of events in our population precluded analyses of three other conditions of interest: rhabdomyolysis, hypoglycemia, and neuroleptic malignant syndrome. We also assessed all-cause mortality.

There are up to 25 diagnostic codes that can be assigned per hospital admission; patients with multiple codes were accounted for under each outcome of interest. Wherever possible we selected validated codes that performed well for identifying the conditions of interest (code lists and validations fully detailed in Appendix C).

Statistical Analysis

We compared baseline characteristics between new users of clarithromycin and azithromycin using standardized differences.[29,30] This metric describes differences between group means relative to the pooled standard deviation and is considered to indicate a meaningful difference if it is greater than 10%. The risk of developing an outcome was expressed in relative terms. We used multivariable logistic regression analyses to estimate odds ratios and 95% confidence intervals, adjusting for age (per year), sex, and Charlson co-morbidity score (a popular measure of co-morbidity).[31] We interpreted odds ratios as relative risks (appropriate given the incidences observed). We conducted all analyses with SAS 9.2 (SAS Institute Incorporated, Cary, North Carolina, USA, 2008).

RESULTS

There were a total of 1,958,432 macrolide antibiotic prescriptions during our study period. Cohort selection is presented in Appendix E. After applying our exclusion criteria, including

1
2
3 evidence of any interacting drug and restricting to the first antibiotic prescription per patient,
4
5 98,869 patients remained: 52,251 clarithromycin users and 46,618 azithromycin users.
6

7 Baseline characteristics of the two groups with respect to co-morbidities and use of other
8 medications were nearly identical (Table 1; all standardized differences between the groups were
9 less than 3%). For both groups, the median age was 71 years and 54% of patients were women.
10 The cause of infection was recorded in some patients and appeared comparable between the two
11 groups, as were cultures and concurrent ~~bronchodialators~~bronchodilators and steroid
12 prescriptions around the time of the index date (Table 1). The specialty of the prescribing
13 physician, when available, was also comparable between the two groups (Table 1).
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

	Clarithromycin n = 52,251	Azithromycin n = 46,618	Standardized Differences*
Demographics			
Age, years, median (IQR)	71 (68-77)	71 (68-77)	
Women, n (%)	27,932 (53.5)	25,682 (55.1)	0.03
Income Quintile			
first (lowest)	8,951 (17.1)	7,706 (16.5)	0.02
second	10,447 (20.0)	8,899 (19.1)	0.02
third (middle)	10,153 (19.4)	8,937 (19.2)	0.01
fourth	10,822 (20.7)	9,633 (20.7)	0
fifth (highest)	11,703 (22.4)	11,285 (24.2)	0.04
Year of Cohort Entry^e, n (%)			
2003 - 2005	21,369 (40.9)	18,979 (40.7)	0.01
2006 - 2008	19,236 (36.8)	17,198 (36.9)	0.01
2009 - 2010	11,646 (22.3)	10,441 (22.4)	0.01
Co-morbidities, n (%)			
Cancer	12,733 (24.4)	11,473 (24.6)	0.01
Chronic kidney disease ‡	644 (1.2)	566 (1.2)	0
Coronary artery disease ¶	7,531 (14.4)	6,956 (14.9)	0.01
Diabetes mellitus #	855 (1.6)	816 (1.8)	0.01
Heart failure	1,656 (3.2)	1,536 (3.3)	0.01
Peripheral vascular disease	175 (0.3)	176 (0.4)	0.01
Stroke/Transient ischemic attack	246 (0.5)	249 (0.5)	0.01
Medication use in prior 6 months, n (%)			
ACE inhibitors or ARBs	2,769 (5.3)	2,543 (5.5)	0.01
Beta blockers	1,787 (3.4)	1,720 (3.7)	0.01
Potassium sparing diuretics	461 (0.9)	389 (0.8)	0.01
Loop diuretics	103 (0.2)	120 (0.3)	0.01
NSAIDs (excluding ASA)	2,483 (4.8)	2,389 (5.1)	0.02
Thiazide diuretics	3,479 (6.7)	3,171 (6.8)	0.01
Cause of infection, n (%)			
Genitourinary infection	261 (0.5)	265 (0.6)	0.01
Oropharyngeal infection	839 (1.6)	1,000 (2.1)	0.04
Respiratory infection	22,084 (42.3)	17,503 (37.5)	0.10
Sinus infection	4,000 (7.7)	3,178 (6.8)	0.03
Skin infection	659 (1.3)	320 (0.7)	0.06
Missing	27,843 (53.3)	22,266 (47.8)	0.11
Cultures⁺, n (%)			
Blood	28 (0.1)	21 (0.0)	0
Genitourinary	26 (0.0)	69 (0.01)	0.03
Gynecology	120 (0.2)	134 (0.3)	0.01
Sputum	127 (0.2)	75 (0.2)	0.02
Urine	1,090 (2.1)	931 (2.0)	0.01
Concurrent medication prescription, n (%)			
Inhaled steroids	28 (0.1)	31 (0.1)	0.01
Bronchodilators	1,202 (2.3)	929 (2.0)	0.02

Main specialty of prescribing physician, *n* (%)

GP/FP	39,743 (76.1)	34,308 (73.6)	0.06
Internal medicine	280 (0.5)	260 (0.6)	0.01
General surgery	100 (0.2)	151 (0.3)	0.02
Other	1,148 (2.2)	1,042 (2.2)	0
Missing	10,980 (21.0)	10,857 (23.3)	0.06

Data presented as number (percent) except for age which is presented as mean (standard deviation).

Abbreviations: Non-steroidal anti-inflammatory (NSAID), angiotensin converting enzyme (ACE), angiotensin II receptor blocker (ARB), general practitioner (GP), family practitioner (FP)

*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.

€ The year of cohort entry is also referred to as the index date.

‡ Assessed by administrative database codes

¶ Coronary artery disease includes receipt of coronary artery bypass graft surgery, percutaneous coronary intervention and diagnoses of angina.

#Assessed by receipt of insulin or oral antihyperglycemics

+ Cultures recorded within two weeks prior and one week after the index date

Consistent with drug prescribing references, the median daily dose was 1000 mg for clarithromycin and 300 mg for azithromycin. The median duration of antibiotic dispensed was 10 days for clarithromycin and 5 days for azithromycin.^{[11,12][†0,††]}

The outcome of hospitalization with each of the 12[†] conditions examined separately is presented in Table 2. Results are expressed with patients receiving azithromycin as the referent group. There were no significant difference between the clarithromycin and azithromycin groups on any of the 11 hospitalization outcomes, and the relative risk ranged from 0.67 to 1.23. Results were consistent across all adjusted analyses (Table 2).

The results of all-cause mortality within 30 days of the antibiotic prescription are also presented in Table 2. Compared to azithromycin, clarithromycin was associated with a slightly higher risk of all-cause mortality (0.46% vs. 0.37%, relative risk 1.25, 95% confidence interval 1.03 to 1.52).

Table 2. Hospitalizations with various conditions and all-cause mortality

	<i>Number of Events (%)</i> *		<i>Unadjusted Relative Risk (95% CI)</i>	<i>Adjusted Relative Risk (95% CI)</i> ‡
	<i>Clarithromycin n = 52,251</i>	<i>Azithromycin n = 46,618</i>		
Acute kidney injury	52 (0.10)	44 (0.09)	1.05 (0.71 – 1.58)	1.06 (0.71 – 1.58)
Myocardial infarction	39 (0.07)	30 (0.06)	1.16 (0.72 – 1.87)	1.15 (0.71 – 1.85)
Neuroimaging ⁺	582 (1.11)	496 (1.06)	1.05 (0.93 – 1.18)	1.04 (0.93 – 1.18)
Hypotension	19 (0.04)	14 (0.03)	1.21 (0.61 – 2.42)	1.21 (0.61 – 2.41)
Syncope	14 (0.03)	12 (0.03)	1.04 (0.48 – 2.25)	1.04 (0.48 – 2.25)
Hyperkalemia	9 (0.02)	12 (0.03)	0.67 (0.28 – 1.59)	0.67 (0.28 – 1.60)
Hyponatremia	29 (0.06)	29 (0.06)	0.89 (0.53 – 1.49)	0.90 (0.54 – 1.51)
Hyperglycemia	22 (0.04)	16 (0.03)	1.23 (0.64 – 2.34)	1.22 (0.64 – 2.33)
Arrhythmia	49 (0.09)	52 (0.11)	0.84 (0.57- 1.24)	0.84 (0.57 – 1.24)
Ischemic stroke	17 (0.03)	16 (0.3)	0.95 (0.48 – 1.88)	0.94 (0.47 – 1.86)
Gastrointestinal bleeding	32 (0.06)	30 (0.06)	0.95 (0.58 – 1.57)	0.95 (0.58 – 1.56)
Sepsis	<u>28 (0.05)</u>	<u>18 (0.04)</u>	<u>1.39 (0.77 – 2.51)</u>	<u>1.38 (0.76 – 2.49)</u>
All-cause mortality	241 (0.46)	172 (0.37)	1.25 (1.03 – 1.52)	1.27 (1.04 – 1.55)
Patients prescribed azithromycin served as the comparator group.				
* 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. For some outcomes this underestimates the true event rate because these codes have high specificity but low sensitivity.				
‡ Adjusted for 3 covariates: Age, sex, and Charlson co-morbidity score				
+ Neuroimaging consisted of codes for computed tomography head scan as a proxy for delirium.				

After observing a difference in all-cause mortality between our groups, we considered the five most common causes of death (Table 3). There were no significant differences in these causes of death between the two groups.

Table 3. Deaths due to the following causes

	<i>Number of events (%)*</i>	
	Clarithromycin n = 52,251	Azithromycin n = 46,618
Disease of circulatory system	64 (0.12)	50 (0.11)
Neoplasm	48 (0.09)	32 (0.07)
Disease of respiratory system	35 (0.07)	32 (0.07)
Mental disorder	28 (0.05)	13 (0.03)
Disease of the nervous system	25 (0.05)	13 (0.03)
Other	41 (0.08)	32 (0.07)

*There were 241 total deaths in the clarithromycin group and 172 in the azithromycin group

DISCUSSION

Contrasting outcomes of patients prescribed clarithromycin to those prescribed azithromycin in the presence of a drug with metabolism potentially impacted by clarithromycin presents a potentially attractive method of assessing population-based drug-clarithromycin drug interactions in routine care. However, these two macrolide antibiotics also differ on other properties besides their inhibition of drug metabolizing enzymes and transporters that may impact patient outcomes. In this study we compared the baseline characteristics and outcomes of patients prescribed either clarithromycin or azithromycin in the absence of potentially interacting drugs. The two groups did not differ in patient baseline demographics, co-morbid characteristics, the type of infection, or the specialty of the prescribing physician. In other words, the two drugs appeared to be used for similar indications and demonstrated similar clinical usage patterns. With respect to the study outcomes there were no differences between the two groups on any of the 12+ hospitalization conditions that we studied.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Overall, these results support the utility of macrolide antibiotics to assess population-based drug interactions for the hospital conditions presented in this report. This is particularly true when conducting studies in settings where the observed results are consistent with medications known to have potential for drug-drug interactions based on pharmacokinetic data and case reports. For example, a high blood concentration of some statins is realized when taken concurrently with clarithromycin, as the latter inhibits the CYP3A4 enzyme responsible for statin metabolism.[10][9] This can lead to rhabdomyolysis and acute kidney injury. In the present study, in the absence of statin use, there was no difference in hospitalization with acute kidney injury between the two macrolide antibiotic groups. Thus there is more assurance that the outcomes observed in the aforementioned study of clarithromycin co-prescribed with a statin are attributable to the interaction between the drugs.

In the present study there was a small absolute difference in all-cause mortality with clarithromycin compared to azithromycin, without any clear difference in the cause of death. While this may be a chance finding, it is also possible that there may be inherent differences in the use or nature of these two antibiotics that impacts mortality. Consistent with drug prescribing references, the median duration of antibiotic treatment was higher with clarithromycin compared to azithromycin. Additionally, differences in daily dose and day supply between the two macrolide antibiotics were found, and there could be differences in frequency of dose. Because clarithromycin is taken twice a day for the duration of therapy, unlike azithromycin, there could be differences in drug adherence. Other differences exist, for example: azithromycin is less bioavailable than clarithromycin, especially when taken with food.[32] On the other hand, clarithromycin is transformed into an active metabolite, where most other macrolide antibiotics are not.[33] For these reasons, some of the association between macrolide antibiotic type and mortality may partially be attributable to factors beyond the inhibition of drug transporters and metabolizing enzymes, although it also may not be reflective of a difference between the drugs at all. It may also be useful to determine if the magnitude of the association observed in the present study differs with associations observed in other drug-drug interaction studies, using statistical tests of interaction (such as the Bland Altman Test on the two sets of results).[34] Additionally, in the future, studies with other non-macrolide antibiotics, compared to clarithromycin, may be warranted, as macrolide antibiotics s have a higher rate of mortality as they are potentially arrhythmogenic.[35-37]-(ref)

1
2
3 | Our study has a number of strengths. This study was done in the province of Ontario where
4 residents have the benefit of universal healthcare for all citizens and a province wide drug plan
5 for older adults, with this information accessible for study purposes. Accordingly, there were a
6 large number of patients accrued into our study, which provided reasonable precision for the
7 outcomes that are reported. The large sample size also provided adequate data to reasonably
8 compare clarithromycin and azithromycin on baseline characteristics and patterns of clinical use.

9
10 Our study does have some limitations. Despite the large sample size, we had too few events to
11 meaningfully look at some outcomes such as rhabdomyolysis, neuroleptic malignant syndrome,
12 and hypoglycemia. For reasons of privacy we are not permitted to report information for small
13 cell sizes which also precluded meaningful analysis of some types of cause of death, such as
14 infectious disease. Also ~~D drug~~ Drug-drug interactions at the population level in routine care are
15 complex and understudied. While we took a comprehensive approach to exclude interacting
16 drugs, it is still possible that interactions with other drugs may have occurred. The efficacy of
17 pathogen eradication is similar between the two macrolides for some illnesses, but was not
18 formally assessed here.[38,39] Finally, because our hospital-based outcomes were assessed using
19 hospital diagnosis codes (which have limited sensitivity for some outcomes), rather than
20 prospective data collection, we most likely underestimated the true event rate of the outcomes.
21 However, because the outcomes were assessed no differently between the clarithromycin and
22 azithromycin groups, we do not anticipate that this biased our relative measures of risk.

33 CONCLUSION

34
35 In conclusion, we have established that patterns of use and common clinical outcomes do not
36 differ appreciably between clarithromycin and azithromycin, suggesting that clarithromycin may
37 be useful medication to assess drug-drug interactions in population-based studies with
38 azithromycin serving as the control group. If in future drug-drug interaction studies, differences
39 in mortality between groups of patients prescribed each of the two antibiotics exist, it should be
40 noted that some of the association may be attributable to factors unrelated to the enzyme
41 metabolism of the drugs.

42 Contributors

1
2
3 JLF participated in the coordination of the study, study design, provided interpretation of the
4 study results, and drafted the manuscript. SZS participated in the study design, performed the
5 analysis and provided interpretation of the study results. DGB, SG, and DNJ participated in
6 study design, provided drug information, and feedback on the manuscript. DMN, MM, TG, and
7 AMP participated in study design and provided feedback on the manuscript. AXG conceived of
8 the study, participated in its design and interpretation, helped draft the manuscript and provided
9 feedback on the manuscript. All authors read and approved the final manuscript.
10
11
12
13
14
15
16

17 **Competing interests**

18 The authors declare that they have no competing interests.
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Reference List

1. Dresser GK, Spence JD, Bailey DG: **Pharmacokinetic-pharmacodynamic consequences and clinical relevance of cytochrome P450 3A4 inhibition.** *Clin Pharmacokinet* 2000, **38**: 41-57.
2. Wilkinson GR: **Drug metabolism and variability among patients in drug response.** *N Engl J Med* 2005, **352**: 2211-2221.
3. Bailey DG, Dresser G, Arnold JM: **Grapefruit-medication interactions: Forbidden fruit or avoidable consequences?** *CMAJ* 2012.
4. Hutson JR, Fischer HD, Wang X, Gruneir A, Daneman N, Gill SS *et al.*: **Use of clarithromycin and adverse cardiovascular events among older patients receiving donepezil: a population-based, nested case-control study.** *Drugs Aging* 2012, **29**: 205-211.
5. Neuvonen PJ, Niemi M, Backman JT: **Drug interactions with lipid-lowering drugs: mechanisms and clinical relevance.** *Clin Pharmacol Ther* 2006, **80**: 565-581.
6. Pauwels O: **Factors contributing to carbamazepine-macrolide interactions.** *Pharmacol Res* 2002, **45**: 291-298.
7. 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**: 779-786.
8. Westphal JF: **Macrolide - induced clinically relevant drug interactions with cytochrome P-450A (CYP) 3A4: an update focused on clarithromycin, azithromycin and dirithromycin.** *Br J Clin Pharmacol* 2000, **50**: 285-295.
9. Polasek TM, Miners JO: **Quantitative prediction of macrolide drug-drug interaction potential from in vitro studies using testosterone as the human cytochrome P4503A substrate.** *Eur J Clin Pharmacol* 2006, **62**: 203-208.
10. Patel AM, Shariff S, Bailey DG, Juurlink DN, Gandhi S, Mamdani M *et al.*: **Statin toxicity from macrolide antibiotic co-prescription: A population based study of older adults.** *Ann Intern Med* 2013.
11. Clarithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120.
Ref Type: Electronic Citation
12. Azithromycin Drug Information. UptoDate online V 20.3 . 2012. 5-25-0120.
Ref Type: Electronic Citation
13. McKinnell J, Tayek JA: **Short term treatment with clarithromycin resulting in colchicine-induced rhabdomyolysis.** *J Clin Rheumatol* 2009, **15**: 303-305.

14. Pasqualetti G, Bini G, Tognini S, Polini A, Monzani F: **Clarithromycin-induced rhabdomyolysis: a case report.** *Int J Gen Med* 2012, **5**: 283-285.
15. Wright AJ, Gomes T, Mamdani MM, Horn JR, Juurlink DN: **The risk of hypotension following co-prescription of macrolide antibiotics and calcium-channel blockers.** *CMAJ* 2011, **183**: 303-307.
16. Statistics Canada. Population by sex and age group, by province and territory. Ottawa: Statistics Canada . 2011. 8-10-0120.
Ref Type: Electronic Citation
17. von EE, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP: **The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.** *Ann Intern Med* 2007, **147**: 573-577.
18. 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.
19. 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**: 1248-1253.
20. 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**: 903-908.
21. 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**: 560-569.
22. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. India . 2012.
Ref Type: Electronic Citation
23. Niemi M, Pasanen MK, Neuvonen PJ: **Organic anion transporting polypeptide 1B1: a genetically polymorphic transporter of major importance for hepatic drug uptake.** *Pharmacol Rev* 2011, **63**: 157-181.
24. **Calcium channel blockers + macrolides: elderly patients hospitalised for low blood pressure.** *Prescrire Int* 2012, **21**: 182.
25. Bode C: **The nasty surprise of a complex drug-drug interaction.** *Drug Discov Today* 2010, **15**: 391-395.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
26. Lee CY, Marcotte F, Giraldeau G, Koren G, Juneau M, Tardif JC: **Digoxin toxicity precipitated by clarithromycin use: case presentation and concise review of the literature.** *Can J Cardiol* 2011, **27**: 870-876.
27. Trieu J, Emmett L, Perera C, Thanakrishnan K, Van Der WH: **Rhabdomyolysis resulting from interaction of simvastatin and clarithromycin demonstrated by Tc-99m MDP scintigraphy.** *Clin Nucl Med* 2004, **29**: 803-804.
28. Kute VB, Shah PR, Goplani KR, Gumber MR, Vanikar AV, Trivedi HL: **Successful treatment of refractory hypotension, noncardiogenic pulmonary edema and acute kidney injury after an overdose of amlodipine.** *Indian J Crit Care Med* 2011, **15**: 182-184.
29. 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**: 1228-1234.
30. 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**: 960-962.
31. Charlson ME, Pompei P, Ales KL, MacKenzie CR: **A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.** *J Chronic Dis* 1987, **40**: 373-383.
32. Kanatani MS, Guglielmo BJ: **The new macrolides. Azithromycin and clarithromycin.** *West J Med* 1994, **160**: 31-37.
33. Davey PG: **The pharmacokinetics of clarithromycin and its 14-OH metabolite.** *J Hosp Infect* 1991, **19 Suppl A**: 29-37.
34. Bland JM, Altman DG: **Statistical methods for assessing agreement between two methods of clinical measurement.** *Lancet* 1986, **1**: 307-310.
35. Ray WA, Murray KT, Meredith S, Narasimhulu SS, Hall K, Stein CM: **Oral erythromycin and the risk of sudden death from cardiac causes.** *N Engl J Med* 2004, **351**: 1089-1096.
36. Ray WA, Murray KT, Hall K, Arbogast PG, Stein CM: **Azithromycin and the risk of cardiovascular death.** *N Engl J Med* 2012, **366**: 1881-1890.
37. Zambon A, Polo FH, Contiero P, Corrao G: **Effect of macrolide and fluoroquinolone antibacterials on the risk of ventricular arrhythmia and cardiac arrest: an observational study in Italy using case-control, case-crossover and case-time-control designs.** *Drug Saf* 2009, **32**: 159-167.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
38. Bradbury F: **Comparison of azithromycin versus clarithromycin in the treatment of patients with lower respiratory tract infection.** *J Antimicrob Chemother* 1993, **31 Suppl E**: 153-162.
39. Muller O: **Comparison of azithromycin versus clarithromycin in the treatment of patients with upper respiratory tract infections.** *J Antimicrob Chemother* 1993, **31 Suppl E**: 137-146.

For peer review only

Appendix A: STROBE Statement

	Item No	Recommendation	Reported
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract	Abstract
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	Abstract
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods – setting and design
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods – setting and design; data sources
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods - participants
		(b) For matched studies, give matching criteria and number of exposed and unexposed	n/a
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods – outcomes
Data sources/measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods – data sources
Bias	9	Describe any efforts to address potential sources of bias	Methods – statistical analysis; Discussion
Study size	10	Explain how the study size was arrived at	n/a
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	n/a
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods – statistical analysis
		(b) Describe any methods used to examine subgroups and interactions	n/a
		(c) Explain how missing data were addressed	n/a
		(d) If applicable, explain how loss to follow-up was addressed	n/a
		(e) Describe any sensitivity analyses	Results –
Results			
Participants	13	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Results; Appendix E
		(b) Give reasons for non-participation at each stage	Appendix E
		(c) Consider use of a flow diagram	Appendix E
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Methods – participants; Results; Table 1
		(b) Indicate number of participants with missing data for each variable of interest	Complete with exception of specialty of prescribing physician and cause of infection described in

			Table 1)
		(c) Summarise follow-up time (e.g. average and total amount)	n/a
Outcome data	15	Report numbers of outcome events or summary measures over time	Results; Table 2; Table 3
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g. 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Results; Table 2
		(b) Report category boundaries when continuous variables were categorized	n/a
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results; Table 3
Discussion			
Key results	18	Summarise key results with reference to study objectives	Discussion
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Discussion
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Discussion
Generalisability	21	Discuss the generalisability (external validity) of the study results	Discussion
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Cover page

Appendix B. Coding definitions for demographic and co-morbid conditions.

Condition/Characteristic	Database	Codes
Age	RPDB	
Sex	RPDB	
Socioeconomic Status	Statistics Canada	
Chronic Kidney Disease	CIHI-DAD	ICD9: 4030, 4031, 4039, 4040, 4041, 4049, 585, 586, 5888, 25040 ICD10: E102, E112, E132, E142, I12, I13, N08, N18, N19
Coronary Artery Disease	OHIP	OHIP Diagnostic: 403, 585
	CIHI-DAD	ICD9: 412, 414, 4292, 4295, 4296, 4297 ICD10: I20-I25, Z955, Z958, Z959, R931, T822 CCI: 1I126, 1I127, 1I150 1I154, 1I157, 1I176 CCP: 4801-4805, 481-483
Heart Failure	OHIP	OHIP Fee: R741-R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448 OHIP Diagnostic: 410, 412, 413
	CIHI-DAD	ICD9: 425, 5184, 514, 428 ICD10: I500, I501, I509, I255, J81 CCI: 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR CCP: 4961-4964
Peripheral Vascular Disease	OHIP	OHIP Fee: R701, R702, Z429 OHIP Diagnostic: 428
	CIHI-DAD	ICD9: 4402, 4403, 4408, 4409, 5571, 4439, 444 ICD10: I700, I702, I708, I709, I731, I738, I739, K551 CCI: 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87 CCP: 5125, 5129, 5014, 5016, 5018, 5028, 5038
Stroke/Transient Ischemic Attack	OHIP	OHIP Fee: 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
	CIHI-DAD	ICD9: 434, 436, 431, 4358, 4359 ICD10: H341, I630-I635, I638, I639, I629, I64, G45, I61

Appendix C. Outcome definitions

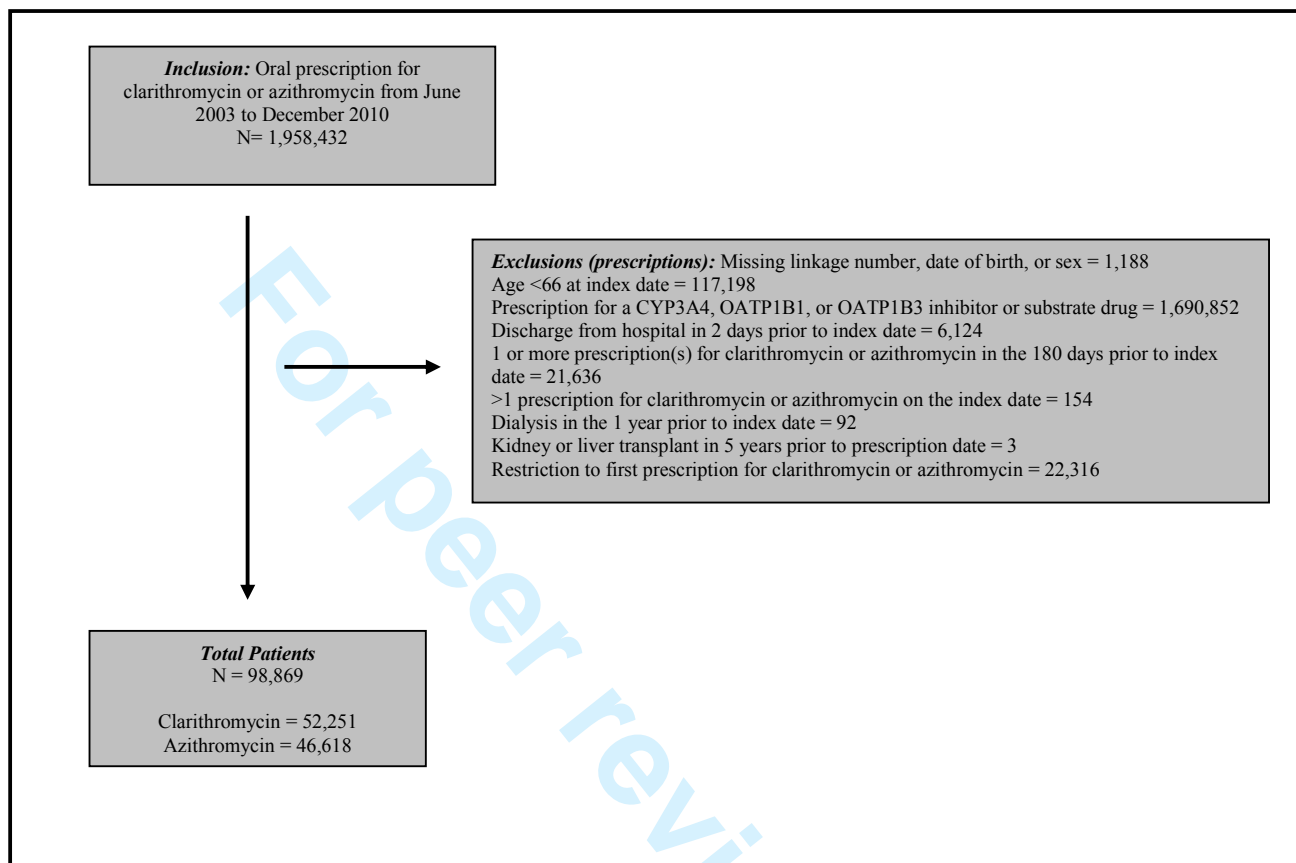
<i>Outcome</i>	<i>Code</i>	<i>Database</i>	<i>Validity where available</i>
Acute kidney injury ¹	ICD 10 - N17	CIHI-diagnostic	Sensitivity: 61.6% Positive predictive value: 17.3%
Acute myocardial infarction ²	ICD 10 - I21, I22	CIHI – diagnostic	Sensitivity: 89% Positive predictive value: 87%
Neuroimaging (Computed topography head scan)	CCI - 3AN20, 3EA20, 3ER20	CIHI - procedure	
	OHIP fee - X188, X400, X401, X402, X405, X408	OHIP - procedure	
Hypotension	ICD 10 - I95	CIHI – diagnostic	
Syncope	ICD 10 - R55	CIHI – diagnostic	
Hyperkalemia ³	ICD 10 - E875	CIHI – diagnostic	Sensitivity: 14.6% Positive predictive value: 62.0%
Hyponatremia ⁴	ICD 10 - E871	CIHI – diagnostic	Sensitivity: 10.6% Positive predictive value: 82.3%
Hyperglycemia	ICD 10 - R73	CIHI – diagnostic	
Arrhythmia ⁵	ICD 10 - I48, I44, I45, I47, I4900, I4901, I491, I492, I493, I494, I498, I499, R000, R001	CIHI – diagnostic	Sensitivity: 39.0% Positive predictive value: 93.4%
	OHIP fee - G178, G179, G249, G261, G259, Z443, Z431, Z437	OHIP - procedure	
Ischemic stroke ⁶	ICD 10 - H341, I630, I631, I632, I633, I634, I635, I638, I639	CIHI – diagnostic	Sensitivity: 58% Specificity: 97%
Gastrointestinal bleeding	ICD 10 - K250, K252, K254, K256, K260, K262, K264, K266, K270, K272, K274, K276, K280, K282, K284, K286, K920, K921, K922, K5520, K226, I850	CIHI – diagnostic	
Sepsis	ICD 10 – A267, A400, A410, A411, A412, A413, A415, A4188, A419	CIHI-diagnostic	
Abbreviations: ICD10, International Classification of Diseases, 10 th revision; CCI, Canadian Classification of (health) Interventions; OHIP, Ontario Health Insurance Plan			
<p>1 Hwang YJ, Shariff SZ, Gandhi S, 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. <i>BMJ Open</i>. 2012:2</p> <p>Note: The presence of a hospital diagnosis code for acute kidney injury in Ontario identifies a median absolute acute increase in serum creatinine of 98 µmol/L (interquartile range (IQR) 43 to 200) above the most recent value prior to hospitalization, while the absence of such a code represents a median increase of 6 µmol/L (IQR -4 to 20 µmol/L).</p> <p>2 Juurlink DN, Preyra C, Croxford R, et al. Canadian Information Discharge Abstract Database: a validation study. <i>Institute for Clinical Evaluative Sciences</i> 2006.</p> <p>3 Fleet JL, Shariff SZ, Gandhi S, et al. 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. <i>BMJ Open</i>. 2012:2.</p> <p>Note: A code for hyperkalemia identifies a median potassium value of 6.0 mmol/L (IQR 5.1 to 6.7 mmol/L), and the absence of a code a median value of 4.1 mmol/L (IQR 3.8 to 4.5 mmol/L).</p> <p>4 Gandhi S, Shariff SZ, Fleet JL, et al. Validity of the International Classification of Diseases 10th revision code for hospitalisation with hyponatraemia in elderly patients. <i>BMJ Open</i>. 2012:2.</p> <p>Note: A code for hyponatremia identifies a median sodium value of 125 mmol/L (IQR 120 to 130 mmol/L) and the absence of a code a median value of 137 (IQR 135 to 139 mmol/L).</p> <p>5 Quan H, Li B, Saunders LD, et al. Assessing validity of ICD9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. <i>Health Serv Res</i>. 2008:1424-1441.</p>			

6 Kokotailo RA & Hill MD. Coding of stroke and stroke risk factors using International Classification of Diseases, Revisions 9 and 10. Stroke. 2005;177601781.

Appendix D. Excluded medications

Codeine	Budesonide	Cyclosporine	Everolimus	Mephobarbital
Aliskiren	Buspirone	Dapsone	Felodipine	Mestranol
Alprazolam	Butabarbital	Dasatinib	Fentanyl	Methadone
Amiodarone	Carbamazepine	Delavirdine	Fexofenadine	Methylprenisolone
Amlodipine	Carvedilol	Dexamethasone	Finasteride	Methyltestosterone
Amobarbital	Cerivastatin	Dextromethorphan	Fluconazole	Midazolam
Anagrelide	Chloramphenicol	Diazepam	Flunarizone	Modafinil
Aprepitant	Chlorpheniramine	Dienogest	Fluvastatin	Nateglinide
Astemizole	Cimetidine	Diltiazem	Fluvoxamine	Nefazodone
Atenolol	Ciprofloxacin	Disulfiram	Haloperidol	Nelfinavir
Atorvastatin	Cisapride	Domperidone	Imatinib	Nevirapine
Beclomethasone	Clomipramine	Efavirenz	Indinavir	Nicardipine
Phenobarbital	Clopidogrel	Eplerenone	Irinotecan	Nifedipine
Hydrocortisone	Colchicines	Ergotamine	Itraconazole	Nilotinib
Betamethasone	Estrogen/estradiol	Erlotinib	Ketamine	Nimodipine
Oxycodone	Cortisone	Erythrityl	Ketoconazole	Norfloxacin
Pentobarbital	Cyclophosphamide	tetranitrate	Lidocaine	Ondansetron
Phenytoin	Risperidone	Etoposide	Lopinavir	Oxcarbazepine
Pimozide	Ritonavir	Etravirine	Losartan	Triamcinolone
Pioglitazone	Rivaroxaban	Sirolimus	Lovastatin	Triazolam
Pravastatin	Rosuvastatin	Sunitinib	Maraviroc	Verapamil
Praziquantel	Salmeterol	Tacrolimus	Medroxyprogesterone	Vincristine
Prednisolone	Saquinavir	Tadalafil	Triamcinolone	Voriconazole
Prednisone	Secobarbital	Tamoxifen	Triazolam	Ziprasidone
Primaquine	Sertraline	Tamulosin	Verapamil	Omeprazole
Primidone	Sildenafil	Telithromycin	Vincristine	Fluticasone
Progesterone	Simvastatin	Terfenadine	Voriconazole	Rabeprazole
Propafenone	Bosentan	Testosterone	Ziprasidone	Lansoprazole
Quetiapine	Bromocriptine	Tobramycin	Omeprazole	Trimethoprim
Quinidine	Casposfungin	Trazodone	Fluticasone	Calcium carbonate
Quinine	Cefazolin	Enalapril	Rabeprazole	Amprenavir
Repaglinide	Cefoperazone	Estropipate	Lansoprazole	Atazanavir
Rifabutin	Clotrimazole	Ezetimibe	Trimethoprim	Bezafibrate
Rifampin	Darunavir	Fenofibrate	Calcium carbonate	Telmisartan
Metyrapone	Digoxin	Gemfibrozil	Amprenavir	Levothyroxine
Miconazole	Pantoprazole	Glyburide	Atazanavir	Dextrothyroxine
Mycophenolic	Ramipril	Methotrexate	Bezafibrate	Valsartan
Olmesartan	Rosiglitazone			

Appendix E. Cohort Creation



BMJ Open: first published as 10.1136/bmjopen-2013-002857 on 11 July 2013. Downloaded from <http://bmjopen.bmj.com/> on April 20, 2024 by guest. Protected by copyright.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60