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



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| Journal: | *BMJ Open* |
| Manuscript ID: | bmjopen-2013-002857 |
| Article Type: | Research |
| Date Submitted by the Author: | 08-Mar-2013 |
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| Primary Subject Heading: | Pharmacology and therapeutics |
| Secondary Subject Heading: | Public health |
| Keywords: | PREVENTIVE MEDICINE, Adverse events < THERAPEUTICS, CLINICAL PHARMACOLOGY, PUBLIC HEALTH |
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# Use of Macrolide Antibiotics to Assess Population-Based Drug Interactions

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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, co-morbid 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

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.[15] 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).[16]

**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%.[17] 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 ever been issued a health card. We have previously used these four databases to research adverse drug events, health outcomes and health services.[18-20] 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).[21,22] 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 11 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. 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.[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 bronchodialators and steroid prescriptions around the

time of the index date (Table 1). The specialty of the prescribing physician, when available, was also comparable between the two groups (Table 1).

**Table 1**. Baseline Characteristics

| | 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[€], *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.[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

| | *Number of Events (%)** | | *Unadjusted Relative Risk (95% CI)* | *Adjusted Relative Risk (95% CI)* ¥ |
|---|---|---|---|---|
| | **Clarithromycin** n = 52,251 | **Azithromycin** n = 46,618 | | |
| 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.

**Table 3.** Deaths due to the following causes

| | *Number of events (%)** | |
|---|---|---|
| | **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 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.

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.[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.[31] On the other hand, clarithromycin is transformed into an active metabolite, where most other macrolide antibiotics are not.[32] 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).[33] Our study has a number of strengths. This study was done in the province of Ontario where residents have the benefit of universal healthcare for all citizens and a province wide drug plan for older adults, with this information accessible for study purposes. Accordingly, there were a large number of patients accrued into our study, which provided reasonable precision for the outcomes that are reported. The large sample size also provided adequate data to reasonably compare clarithromycin and azithromycin on baseline characteristics and patterns of clinical use.

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.

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

Appendix C. Outcome definitions

| *Outcome* | *Code* | *Database* | *Validity where available* |
|---|---|---|---|
| Acute kidney injury[1] | ICD 10 - N17 | CIHI-diagnostic | Sensitivity: 61.6%<br>Positive predictive value: 17.3% |
| Acute myocardial infarction[2] | ICD 10 - I21, I22 | CIHI – diagnostic | Sensitivity: 89%<br>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%<br>Positive predictive value: 62.0% |
| Hyponatremia[4] | ICD 10 - E871 | CIHI – diagnostic | Sensitivity: 10.6%<br>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%<br>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%<br>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, 10th 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. BMJ Open. 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. Institute for Clinical Evaluative Sciences 2006.

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. BMJ Open. 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 10th revision code for hospitalisation with hyponatraemia in elderly patients. BMJ Open. 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).

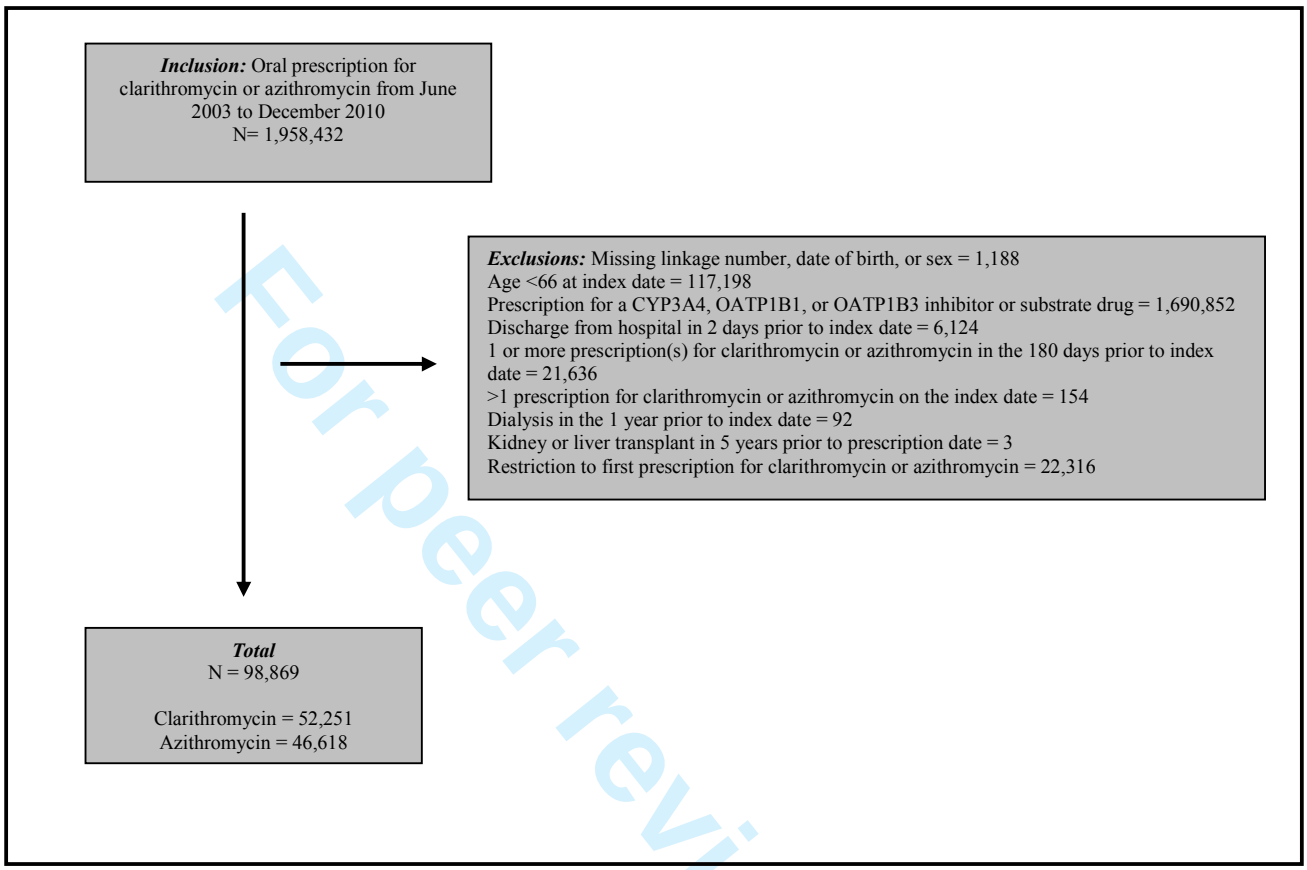
5 Quan H, Li B, Saunders LD, et al. Assessing validity of ICD9-CM and ICD-10 administrative data in recording clinical conditions in a unique dually coded database. Health Serv Res. 2008:1424-1441.

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. Exclusion 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 | Cyclophsophamide | 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



BMJ open

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



| | |
|---|---|
| Journal: | *BMJ Open* |
| 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<br>Shariff, Salimah; Institute for Clinical Evaluative Sciences,<br>Bailey, David; Lawson Health Research Institute,<br>Gandhi, Sonja; London Health Sciences Centre, Medicine/Nephrology<br>Juurlink, David; Sunnybrook Health Sciences Centre, Clinical Pharmacology and Toxicology<br>Nash, Danielle; London Health Sciences Centre, Medicine/Nephrology<br>Mamdani, Muhammad; St. Michael's Hospital, Applied Health Research Centre, Li Ka Shing Knowledge Institute<br>Gomes, Tara; Institute for Clinical Evaluative Sciences,<br>Patel, Amit; London Health Sciences Centre, Medicine/Nephrology<br>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 |
| | |

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

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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, co-morbid 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

groups of older patients either prescribed clarithromycin or azithromycin 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 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, 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

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 time of the index date (Table 1). The specialty of the prescribing physician, when available, was also comparable between the two groups (Table 1).

**Table 1**. Baseline Characteristics

| | 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[€], *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]

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

| | *Number of Events (%)** | | *Unadjusted Relative Risk (95% CI)* | *Adjusted Relative Risk (95% CI)* ¥ |
|---|---|---|---|---|
| | **Clarithromycin** n = 52,251 | **Azithromycin** n = 46,618 | | |
| 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

| | *Number of events (%)** | |
|---|---|---|
| | **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.

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]

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

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. For reasons of privacy we are not permitted to report information for small cell sizes which also precluded meaningful analysis of some types of cause of death, such as infectious disease. Drug-drug interactions at the population level in routine care 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. The efficacy of pathogen eradication is similar between the two macrolides for some illnesses, but was not formally assessed here.[38,39] 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

No additional data available.

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# ~~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

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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~~399~~ (max 4000)

Date: ~~March 6~~ 24th May ~~2013~~ 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~~ Ppatients (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 12~~1~~ ~~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, co-morbid 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 121 ~~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 ~~U~~use of azithromycin as a referenc~~et~~ 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, w~~W~~e 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

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

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~~1~~ 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

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 ~~bronchodialators~~bronchodilators and steroid prescriptions around the time of the index date (Table 1). The specialty of the prescribing physician, when available, was also comparable between the two groups (Table 1).

**Table 1**. Baseline Characteristics

| | 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$^{\epsilon}$, *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 $^{\ddagger}$ | 644 (1.2) | 566 (1.2) | 0 |
| Coronary artery disease $^{\P}$ | 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]~~[10,11]~~

The outcome of hospitalization with each of the 12~~1~~ 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

| | *Number of Events (%)** | | *Unadjusted Relative Risk (95% CI)* | *Adjusted Relative Risk (95% CI)* ¥ |
|---|---|---|---|---|
| | **Clarithromycin** n = 52,251 | **Azithromycin** n = 46,618 | | |
| 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

| | *Number of events (%)** | |
|---|---|---|
| | **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~~1~~ hospitalization conditions that we studied.

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)~~

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

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. For reasons of privacy we are not permitted to report information for small cell sizes which also precluded meaningful analysis of some types of cause of death, such as infectious disease. ~~Also~~~~D~~ ~~drug~~Drug-drug interactions at the population level in routine care 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. The efficacy of pathogen eradication is similar between the two macrolides for some illnesses, but was not formally assessed here.[38,39] 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.

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

Appendix C. Outcome definitions

| *Outcome* | *Code* | *Database* | *Validity where available* |
|---|---|---|---|
| Acute kidney injury[1] | ICD 10 - N17 | CIHI-diagnostic | Sensitivity: 61.6%<br>Positive predictive value: 17.3% |
| Acute myocardial infarction[2] | ICD 10 - I21, I22 | CIHI – diagnostic | Sensitivity: 89%<br>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%<br>Positive predictive value: 62.0% |
| Hyponatremia[4] | ICD 10 - E871 | CIHI – diagnostic | Sensitivity: 10.6%<br>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%<br>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%<br>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, 10th 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. BMJ Open. 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. Institute for Clinical Evaluative Sciences 2006.
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. BMJ Open. 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 10th revision code for hospitalisation with hyponatraemia in elderly patients. BMJ Open. 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. Health Serv Res. 2008:1424-1441.

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 | Cyclophsophamide | 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