Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Checklist of recommendations for reporting of observational studies using the STROBE guidelines

	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 pre-specified hypotheses	Introduction
Methods			
Study design	4	Present key elements of study design early in the paper	Methods
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Methods
		(b) For matched studies, give matching criteria and number of exposed and unexposed	Not Applicable
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Methods
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	Appendix eTable 2,3
Bias	9	Describe any efforts to address potential sources of bias	Discussion
Study size	10	Explain how the study size was arrived at	Methods, based on availability of the data
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Methods
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	Methods
		(b) Describe any methods used to examine subgroups and interactions	Methods
		(c) Explain how missing data were addressed	Not Applicable
		(d) If applicable, explain how loss to follow-up was addressed	Not Applicable
		(e) Describe any sensitivity analyses	Methods
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	Methods, Results, Appendix eFigure 1, 2
		(b) Give reasons for non-participation at each stage	Methods, Appendix eFigure 1, 2

		(c) Consider use of a flow diagram	Appendix eFigure 1, 2
	Item No	**Recommendation**	**Reported**
Results cont'd			
Descriptive data	14	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Table 1, Appendix eTable 4, eTable 8
		(b) Indicate number of participants with missing data for each variable of interest	Essentially Complete
		(c) Summarise follow-up time (e.g. average and total amount)	Results, Table 2,3, Appendix eTable 5
Outcome data	15	Report numbers of outcome events or summary measures over time	Results, Table 2,3, Figure 1,2, Appendix eTable 5, 6, 7
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 2,3, Appendix eTable 5, 6, 7
		(b) Report category boundaries when continuous variables were categorized	Table 1, Appendix eTable 4, 8
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Results, Table 2,3, Appendix eTable 5,6,7
Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Results, Figure 2,3, Appendix eTable 5,6,7
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

eTable 2. Coding definitions for demographic and comorbid conditions

Characteristics/Condition	Database	Codes
Age	RPDB	
Sex	RPDB	
Socioeconomic Status	Statistics Canada	
Chronic Kidney Disease	CIHI-DAD	**ICD-9** 4030, 4031, 4039, 4040, 4041, 4049, 585, 586. 5888, 5889, 25040.
		ICD-10 E102, E112, E132, E142, I12, I13, N08, N18, N19.
	OHIP	403, 585.
Coronary Artery Disease	CIHI-DAD	**ICD-9** 412, 410, 414, 4292, 4295, 4296, 4297.
		ICD-10 I21, I22, I23, I24, I25, Z955, Z958, Z959, R931, T822.
		CCI 1IJ26, 1IJ27, 1IJ54, 1IJ57, 1IJ50, 1IJ76.
		CCP 4801, 4802, 4803, 4804, 4805, 481, 482, 483.
	OHIP	R741, R742, R743, G298, E646, E651, E652, E654, E655, G262, Z434, Z448, 410, 412.
Peripheral Vascular Disease	CIHI-DAD	**ICD-9** 4402, 4408, 4409, 5571, 4439, 444.
		ICD-10 I700, I702, I708, I709, I731, I738, I739, K551.
		CCP 5125, 5129, 5014, 5016, 5018, 5028, 5038.
		CCI 1KA76, 1KA50, 1KE76, 1KG26, 1KG50, 1KG57, 1KG76MI, 1KG87.
	OHIP	R787, R780, R797, R804, R809, R875, R815, R936, R783, R784, R785, E626, R814, R786, R937, R860, R861, R855, R856, R933, R934, R791, E672, R794, R813, R867, E649.
Heart Failure	CIHI-DAD	**ICD-9** 425, 5184, 514, 428.
		ICD-10 I500, I501, I509, I255, J81.
		CCP 4961, 4962, 4963, 4964.
		CCI 1HP53, 1HP55, 1HZ53GRFR, 1HZ53LAFR, 1HZ53SYFR.

Characteristics/Condition	Database	Codes
Heart Failure	OHIP	R701, R702, Z429, 428.
Cerebrovascular Disease	CIHI-DAD	**ICD-9** 434, 436, 431, 4358, 4359.
		ICD-10 H341, I630, I631, I632, I633, I634, I635, I638, I639, I629, I64, G45, I61.
Major Cancers	CIHI-DAD	**ICD-9** 150, 154, 155, 157, 162, 174, 175, 185, 203, 204, 205, 206, 207, 208.
		ICD-10 971, 980, 982, 984, 985, 986, 987, 988, 989, 990, 991, 993, C15, C18, C19, C20, C22, C25, C34, C50, C56, C61, C82, C83, C85, C91, C92, C93, C94, C95, D00, D05.
	OHIP	203, 204, 205, 206, 207, 208, 150, 154, 155, 157, 162, 174, 175, 183, 185.

CCI, Canadian Classification of Health Interventions; CCP, Canadian Classification of Diagnostic, Therapeutic and Surgical Procedures; CIHI, Canadian Institute for Health Information hospital discharge abstract database; ICD-9-CM, International Classification of Disease, Ninth Revision, Clinical Modification; ICD-10, International Classification of Disease, Tenth Revision; ICD-10-CA, International Classification of Disease, Tenth Revision, Canadian Enhancement; RPDB, Registered Persons Database of Ontario.

eTable 3. Coding definitions for hospitalization with acute kidney injury, hospitalization with hypotension, and all-cause mortality

Condition	Database	Codes
Acute Kidney Injury	CIHI-DAD	ICD-10 NI7
Hypotension	CIHI-DAD	ICD-10 I95
Mortality	RPDB	Vital status field

Validations of acute kidney injury were performed on approximately 39,000 hospitalizations with linked laboratory values. See Methods section of the main manuscript for validation results.See 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(6):1–11.

Mortality has a sensitivity of 94% and a positive predictive value of 100%. See Jha P, Deboer D, Sykora K, Naylor CD. Characteristics and mortality outcomes of thrombolysis trial participants and nonparticipants: a population based comparison. J Am Coll Cardiol. 1996;27:1335-42.

CIHI, Canadian Institute for Health Information hospital discharge abstract database; ICD-10, International Classification of Disease, Tenth Revision; RPDB, Registered Persons Database of Ontario.

eTable 4. Baseline characteristics for subpopulation of patients with linked serum creatinine values

	Clarithromycin n=3,164	**Azithromycin** n = 2,094	**Standardized Differences[a]**
Demographics			
Age, years	76 (7)	76 (7)	0.04
Women	1,882 (59.5)	1,283 (61.3)	0.04
Income Quintile[b]			
One (lowest)	712 (22.5)	472 (22.5)	0.00
Two	695 (22.0)	450 (21.5)	0.01
Three (middle)	637 (20.1)	408 (19.5)	0.02
Four	527 (16.7)	320 (15.3)	0.04
Five (highest)	548 (17.3)	425 (20.3)	0.08
Year of Cohort Entry[c]			
2003-2004	682 (21.6)	509 (24.3)	0.07
2005-2006	777 (24.6)	517 (24.7)	0.00
2007-2008	770 (24.3)	451 (21.5)	0.07
2009-2010	629 (19.9)	396 (18.9)	0.02
2011-2012	295 (9.3)	232 (11.1)	0.06
Long term care	146 (4.6)	47 (2.2)	0.13
Co-morbidities[d]			
Charlson Comorbidity Index[e]			
0	1,883 (59.5)	1,238 (59.1)	0.01
1	499 (15.8)	360 (17.2)	0.04
2	380 (12.0)	249 (11.9)	0.00
≥3	402 (12.7)	247 (11.8)	0.03
Cerebrovascular Disease	112 (3.5)	74 (3.5)	0.00
Peripheral vascular Disease	73 (2.3)	53 (2.5)	0.01
Coronary artery disease[f]	1,506 (47.6)	1027 (49.0)	0.03
Congestive heart failure	586 (18.5)	419 (20.0)	0.04
Major cancers[g]	1063 (33.6)	720 (34.4)	0.02
Calcium Channel Blocker			
Type			
Amlodipine	1,460 (46.1)	1,026 (49.0)	0.06
Felodipine	122 (3.9)	77 (3.7)	0.01
Nifedipine	531 (16.8)	317 (15.1)	0.04
Verapamil	165 (5.2)	109 (5.2)	0.00
Diltiazem	875 (27.7)	576 (27.5)	0.00
Daily dose, mg			
Amlodipine	5 (5-10)	5 (5-10)	0.11
Felodipine	7.5 (5-10)	10 (5-10)	0.08

	Clarithromycin n=3,164	Azithromycin n = 2,094	Standardized Differences[a]
Daily dose, mg (cont'd)			
Nifedipine	30 (30-60)	30 (30-60)	0.10
Verapamil	240 (180-240)	240 (240-240)	0.09
Diltiazem	240 (180-240)	240 (180-240)	0.04
Baseline medication use[h]			
Oral hypoglycemic or insulin	807 (25.5)	528 (25.2)	0.01
Beta-blockers	1,065 (33.7)	746 (35.6)	0.04
Statins	1521 (48.1)	1052 (50.2)	0.04
Potassium sparing diuretics	215 (6.8)	178 (8.5)	0.06
Non-potassium sparing diuretics	1390 (43.9)	920 (43.9)	0.02
NSAIDs (excluding aspirin)	528 (16.7)	355 (17.0)	0.01
ACE inhibitor or ARB	1,894 (59.9)	1,277 (61.0)	0.02
Beta2-agonists	683 (21.6)	388 (18.5)	0.08
Anticholinergics	375 (11.9)	214 (10.2)	0.05
Corticosteroids	287 (9.1)	165 (7.9)	0.04
Antibiotic prescriber			
Family Physician	2,415 (76.3)	1,661 (79.3)	0.07
Internist	16 (0.5)	11 (0.5)	0.00
Surgeon	21 (0.7)	≤5 (≤0.24)	0.06
Other	121 (3.8)	73 (3.5)	0.02
Missing	580 (18.3)	356 (17.0)	0.03
Infection type[i]			
Respiratory	1,370 (43.3)	866 (42.3)	0.04
Other	321 (10.2)	218 (10.4)	0.01
Unknown	1,495 (47.3)	1,043 (49.8)	0.05
Healthcare use in the prior year			
Hospitalizations			
0	1,952 (61.7)	1,274 (60.8)	0.02
1	730 (23.1)	488 (23.3)	0.01
2	309 (9.8)	225 (10.7)	0.03
≥3	173 (5.5)	107 (5.1)	0.02
Emergency room visits			
0	1,708 (54.0)	1,156 (55.2)	0.02
1	785 (24.8)	492 (23.5)	0.03
2	306 (9.7)	215 (10.3)	0.02
≥3	365 (11.5)	231 (11.0)	0.02

	Clarithromycin n=3,164	**Azithromycin** n = 2,094	**Standardized Differences**[a]
Family physician visits			
0	47 (1.5)	25 (1.2)	0.03
1-2	152 (4.8)	69 (3.3)	0.08
3-4	238 (7.5)	174 (8.3)	0.03
5-6	460 (14.5)	277 (13.2)	0.04
7-8	446 (14.1)	296 (14.1)	0.00
9-10	415 (13.1)	220 (10.5)	0.08
≥11	1,406 (44.4)	1,033 (49.3)	0.10
Cardiologist visits			
0	1,857 (58.7)	1,072 (51.2)	0.15
1	594 (18.8)	449 (21.4)	0.07
2	287 (9.1)	246 (11.8)	0.09
≥3	426 (13.5)	327 (15.6)	0.06
Unique drug products dispensed			
<5	225 (7.1)	127 (6.1)	0.04
5-8	842 (26.6)	532 (25.4)	0.03
9-12	918 (29.0)	652 (31.1)	0.05
13-16	671 (21.2)	421 (20.1)	0.03
>16	508 (16.1)	362 (17.3)	0.03
Procedures			
Chest X-ray	2,589 (81.8)	1,732 (82.7)	0.02
Pulmonary function test	1,056 (33.4)	666 (31.8)	0.03
Echocardiography	1,259 (39.8)	857 (40.9)	0.02
Cardiac stress test	1,257 (39.7)	897 (42.8)	0.06
Carotid ultrasound	656 (20.7)	430 (20.5)	0.00
Renal Function			
serum creatinine, µmol/L	85 (70-105)	85 (71-104)	0.01
eGFR mL/min/1.73 m^2	64 (51-80)	64 (51-79)	0.01
eGFR category			
≥ 60 mL/min/1.73m^2	1,878 (59.4)	1,220 (58.3)	0.02
45-59 mL/min/1.73m^2	742 (23.5)	508 (24.3)	0.02
30-44 mL/min/1.73m^2	377 (11.9)	262 (12.5)	0.02
< 30 mL/min/1.73m^2	167 (5.3)	104 (5.0)	0.01

Data presented as number (percent) except for age which is presented as mean (standard deviation) and daily dose, serum creatinine and eGFR which are presented as median (interquartile range).

Cell sizes less than six were not reported for reasons of privacy.

Abbreviations: Non-steroidal anti-inflammatory (NSAID), angiotensin converting enzyme (ACE), angiotensin II receptor blocker (ARB), estimated glomerular filtration rate (eGFR).

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

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

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

[d]Comorbidities assessed by administrative database codes in the previous 5 years.

[e]Charlson Comorbidity Index[45,46] was calculated using 5 years of hospitalization data. "No hospitalizations" received a score of 0.

[f]Coronary artery disease includes receipt of coronary artery bypass graft surgery and percutaneous coronary intervention.

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

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

[i]Infection types are not mutually exclusive; patients may have had a code for more than one type of infection.

[j]eGFR was calculated using the CKD-Epi equation. The baseline serum creatinine used in this equation was taken in routine care a median of 87 days (interquartile range 27 to 182) prior to the index date, with no appreciable difference in the time to index date between the two groups.

CKD-Epi equation: $141 \times \min([\text{serum creatinine in umol/L} / 88.4]/\kappa, 1)^{\alpha} \times \max([\text{serum creatinine in umol/L} / 88.4]/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$ [if female] $\times 1.159$ [if African American] *κ=0.7 for females and 0.9 for males, α= -0.329 for females and -0.411 for males, min=the minimum of Scr/κ or 1, max=the maximum of Scr/κ or 1.Racial information was not available in our data sources and all patients were assumed not to be of non African-Canadian race. This was a reasonable assumption; as of 2006, African-Canadians represented less than 7% of the Ontario population.*
Source: http://www12.statcan.ca/census-recensement/2006/dp-pd/hlt/97-562/index.cfm?Lang=E

eTable 5. Acute Kidney Injury assessed using hospital-based serum creatinine data. Coprescriptions of clarithromycin with calcium-channel blockers and the 30-day risk of hospitalization with acute kidney injury

	Number of Events (%)		Absolute Risk Difference (%) (95% CI)	Number Needed to Harm (95% CI)[b]	Unadjusted Relative Risk (95% CI)	Adjusted Relative Risk (95% CI)[c]
	Clarithromycin *n=3,164*	***Azithromycin*** *n=2,094*				
Acute kidney injury[a]	63 (1.99%)	26 (1.24%)	0.75 (0.03 to 1.42)	133 (70 to 3,004)	1.62 (1.02 to 2.56)	1.63 (1.03 to 2.59)

Patients prescribed azithromycin served as the comparator group.

Abbreviations: confidence interval (CI).

[a]Defined as evidence of an absolute increase in serum creatinine value ≥27 μmol/L or an increase of 50% or more from baseline serum creatinine value prior to study antibiotic use.
[b]Number Number Needed to Harm (NNH) does not imply causality as all the results are associations. NNH is provided for ease of interpretation.
[c]Adjusted for age, sex, and chronic kidney disease.

eTable 6. Outcomes assessed using hospital-based diagnosis codes, stratified by prescribing physician. Coprescriptions of clarithromycin with cytochrome P450 3A4 metabolized calcium-channel blockers and the 30-day risk of hospitalization with acute kidney injury, hospitalization with hypotension, and all-cause mortality: stratified by provider

	Number of Events (%)[a]		Absolute Risk Difference (%) (95% CI)	Number Needed to Harm (95% CI)[b]	Relative Risk (95% CI)
	Clarithromycin *n=85,795*	***Azithromycin*** *n=83,734*			
Acute kidney injury	393 (0.46)	181 (0.22)	0.24 (0.19 to 0.30)	415 (337 to 537)	2.14 (1.69 to 2.71)
Hypotension	98 (0.11)	58 (0.07)	0.04 (0.02 to 0.07)	2,224 (1,344 to 6,190)	1.62 (1.05 to 2.52)
Mortality	884 (1.03)	499 (0.60)	0.43 (0.35 to 0.52)	230 (192 to 286)	1.76 (1.52 to 2.04)

Patients prescribed azithromycin served as the comparator group.

There were a mean of 7 patients per prescriber (standard deviation 9.7 and 10.6) in clarithromycin and azithromycin groups, respectively.

Abbreviations: confidence interval (CI).

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

[b]Number Needed to Harm does not imply causality as all the results are associations. The number needed to harm is provided for ease of interpretation.

eTable 7. Outcomes assessed using hospital-based diagnosis codes, high-dose and low-dose clarithromycin. Coprescriptions of a higher versus lower dose of clarithromycin with cytochrome P450 3A4 metabolized calcium-channel blockers and the 30-day risk of hospitalization with acute kidney injury.

	Number of Events (%)[a]		Absolute Risk Difference (%) (95% CI)	Number Needed to Harm (95% CI)[b]	Relative Risk (95% CI)
	Clarithromycin 1000 mg/day *n=28,591*	***Clarithromycin 500 mg/day*** *n=65,801*			
Acute kidney injury	307 (0.47)	95 (0.33)	0.13 (0.05 to 0.22)	745 (463 to 2,191)	1.42 (1.13 to 1.79)

Patients prescribed clarithromycin 500 mg/day served as the comparator group.

Abbreviations: confidence interval (CI).

[a]The number of acute kidney injury events (and the proportion of patients who experienced an event) is an underestimate because these codes have high specificity but low sensitivity. Similarly, the absolute risk difference and the number needed to harm is underestimated for these outcomes.

[b]Number Needed to Harm does not imply causality as all the results are associations. The number needed to harm is provided for ease of interpretation.

eTable 8. Baseline characteristics for a restricted group of patients with and without coprescriptions for clarithromycin and azithromycin who could be assessed at 3 different periods

	Co-prescription Date			90 Days Prior to Co-prescription Date			90 Days Following Co-prescription Date		
	Clarithromycin *n=53,070*	**Azithromycin** *n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**
Demographics									
Age, years	76 (7.2)	76 (7.2)	0.02	76 (7.1)	76 (7.2)	0.02	76 (7.2)	76 (7.2)	0.02
Women	32,848 (61.9)	32,299 (61.8)	0.00	32,848 (61.9)	32,299 (61.8)	0.00			
Income Quintile[b]									
One (lowest)	11,459 (21.6)	10,975 (21.0)	0.01	11,459 (21.6)	10,975 (21.0)	0.01	11,459 (21.6)	10,975 (21.0)	0.01
Two	11,808 (22.3)	11,250 (21.5)	0.02	11,808 (22.3)	11,250 (21.5)	0.02	11,808 (22.3)	11,250 (21.5)	0.02
Three (middle)	10,453 (19.7)	10,469 (20.0)	0.01	10,453 (19.7)	10,469 (20.0)	0.01	10,453 (19.7)	10,469 (20.0)	0.01
Four	10,072 (19.0)	9,912 (19.0)	0.00	10,072 (19.0)	9,912 (19.0)	0.00	10,072 (19.0)	9,912 (19.0)	0.00
Five (highest)	9,126 (17.2)	9,442 (18.1)	0.02	9,126 (17.2)	9,442 (18.1)	0.02	9,126 (17.2)	9,442 (18.1)	0.02
Year of Cohort Entry[c]									
2003-2004	12,084 (22.8)	11,753 (22.5)	0.01	14,983 (28.2)	14,514 (27.8)	0.01	10,311 (19.4)	10,024 (19.2)	0.01
2005-2006	13,239 (24.9)	12,283 (23.5)	0.03	12,462 (23.5)	11,436 (21.9)	0.04	13,310 (25.1)	12,377 (23.7)	0.03
2007-2008	11,817 (22.3)	11,388 (21.8)	0.01	11,527 (21.7)	11,452 (21.9)	0.00	12,082 (22.8)	11,516 (22.0)	0.02
2009-2010	11,312 (21.3)	11,186 (21.4)	0.00	11,365 (21.4)	11,140 (21.3)	0.00	11,152 (21.0)	11,115 (21.3)	0.01
2011-2012	4,618 (8.7)	5,635 (10.8)	0.07	2,733 (5.1)	3,702 (7.1)	0.08	6,215 (11.7)	7,212 (13.8)	0.06
Co-morbidities[d]									
Charlson Comorbidity Index[e]									
0	36,242 (68.3)	35,278 (67.5)	0.03	37,329 (70.3)	36,200 (69.3)	0.02	35,727 (67.3)	34,920 (66.8)	0.01
1	7,133 (13.4)	7,220 (13.8)	0.01	6,778 (12.8)	6,895 (13.2)	0.01	7,234 (13.6)	7,324 (14.0)	0.01
2	5,166 (9.7)	5,039 (9.7)	0.00	4,814 (9.1)	4,788 (9.2)	0.00	5,256 (9.9)	5,113 (9.8)	0.00
≥3	4,529 (8.5)	4,707 (9.0)	0.02	4,149 (7.8)	4,361 (8.4)	0.02	4,853 (9.1)	4,887 (9.4)	0.01
Chronic kidney disease	4,171 (7.9)	4,093 (7.8)	0.00	4,046 (7.6)	3,975 (7.6)	0.00	4,354 (8.2)	4,250 (8.1)	0.00
Cerebrovascular disease	1,552 (2.9)	1,590 (3.0)	0.01	1,559 (2.9)	1,602 (3.1)	0.01	1,571(3.0)	1,602 (3.1)	0.01
Peripheral vascular disease	965 (1.8)	1,115 (2.1)	0.02	988 (1.9)	1,123 (2.1)	0.02	966 (1.8)	1,115 (2.1)	0.02

	Co-prescription Date			90 Days Prior to Co-prescription Date			90 Days Following Co-prescription Date		
	Clarithromycin *n=53,070*	**Azithromycin** *n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**
Co-morbidities (cont'd)[d]									
Coronary artery disease[f]	19,509 (36.8)	20,430 (39.1)	0.05	19,544 (36.8)	20,471 (39.2)	0.05	19,598 (36.9)	20,508 (39.3)	0.05
Congestive heart failure	7,303 (13.8)	7,658 (14.7)	0.03	7,135 (13.4)	7,528 (14.4)	0.03	7,751 (14.6)	7,978 (15.3)	0.02
Major cancers[g]	6,632 (12.5)	6,547 (12.5)	0.00	6,569 (12.4)	6,476 (12.4)	0.00	6,859 (12.9)	6,738 (12.9)	0.00
Calcium Channel Blocker Characteristics									
Amlodipine	27,505 (51.8)	27,505 (52.6)	0.02	27,505 (51.8)	27,505 (52.6)	0.02	27,505 (51.8)	27,505 (52.6)	0.02
Felodipine	2,211 (4.2)	1,927 (3.7)	0.02	2,211 (4.2)	1,927 (3.7)	0.02	2,211 (4.2)	1,927 (3.7)	0.02
Nifedipine	9,433 (17.8)	8,847 (16.9)	0.02	9,433 (17.8)	8,847 (16.9)	0.02	9,433 (17.8)	8,847 (16.9)	0.02
Verapamil	2,134 (4.0)	2,050 (3.9)	0.00	2,134 (4.0)	2,050 (3.9)	0.00	2,134 (4.0)	2,050 (3.9)	0.00
Diltiazem	11,787 (22.2)	11,915 (22.8)	0.01	11,787 (22.2)	11,915 (22.8)	0.01	11,787 (22.2)	11,915 (22.8)	0.01
Daily Dose, mg									
Amlodipine	5 (5-10)	5 (5-10)	0.01	5 (5-10)	5 (5-10)	0.01	5 (5-10)	5 (5-10)	0.01
Felodipine	5 (5-10)	5 (5-10)	0.01	5 (5-10)	5 (5-10)	0.00	5 (5-10)	5 (5-10)	0.00
Nifedipine	30 (30-60)	30 (30-60)	0.01	30 (30-60)	30 (30-60)	0.00	30 (30-60)	30 (30-60)	0.01
Verapamil	240 (180-240)	240 (180-240)	0.05	240 (180-240)	240 (180-240)	0.05	240 (180-240)	240 (180-240)	0.07
Diltiazem	240 (180-240)	180 (180-240)	0.03	240 (180-240)	180 (180-240)	0.03	240 (180-240)	180 (180-240)	0.03
Baseline medication use[h]									
Oral hypoglycemic or insulin	12,676 (23.9)	12,814 (24.5)	0.01	12,525 (23.6)	12,647 (24.2)	0.01	12,869 (24.2)	13,017 (24.9)	0.02
Beta-blockers	17,670 (33.3)	18,052 (34.6)	0.03	17,665 (33.3)	18,047 (34.5)	0.03	17,869 (33.7)	18,218 (34.9)	0.03
Statins	25,834 (48.7)	27,112 (51.9)	0.06	25,657 (48.3)	27,036 (51.7)	0.07	25,891 (48.8)	27,449 (52.5)	0.08
Potassium sparing diuretics	3,219 (6.1)	3,133 (6.0)	0.00	3,271 (6.2)	3,152 (6.0)	0.01	3,325 (6.3)	3,215 (6.2)	0.00
Non-potassium sparing diuretics	20,195 (38.1)	20,373 (39.0)	0.02	20,143 (38.0)	20,384 (39.0)	0.02	21,047 (39.7)	21,026 (40.2)	0.01
NSAIDs (excluding aspirin)	9,333 (17.6)	9,077 (17.4)	0.01	9,771 (18.4)	9,365 (17.9)	0.01	9,317 (17.6)	9,098 (17.4)	0.00
ACE inhibitor or ARB	32,377 (61.0)	32,407 (62.0)	0.02	32,455 (61.2)	32,494 (62.2)	0.02	32,533 (61.3)	32,395 (62.0)	0.01
Beta2-agonists	8,813 (16.6)	8,109 (15.5)	0.03	8,230 (15.5)	7,607 (14.6)	0.03	14,896 (28.1)	13,755 (26.3)	0.04
Anticholinergics	3,842 (7.2)	3,549 (6.8)	0.02	3,677 (6.9)	3,380 (6.5)	0.02	4,908 (9.3)	4,487 (8.6)	0.02

	Co-prescription Date			90 Days Prior to Co-prescription Date			90 Days Following Co-prescription Date		
	Clarithromycin *n=53,070*	**Azithromycin** *n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**
Baseline medication use (cont'd)[h]									
Corticosteroids	4,369 (8.2)	4,007 (7.7)	0.02	4,099 (7.7)	3,846 (7.4)	0.01	7,757 (14.6)	6,987 (13.4)	0.04
Antibiotic Prescriber									
Family Physician	43,475 (81.9)	42,924 (82.2)	0.01	-	-	-	-	-	-
Internist	262 (0.5)	302 (0.6)	0.01	-	-	-	-	-	-
Surgeon	318 (0.6)	59 (0.1)	0.08	-	-	-	-	-	-
Other	1,773 (3.3)	1,432 (2.7)	0.03	-	-	-	-	-	-
Missing	7,242 (13.6)	7,527 (14.4)	0.02	-	-	-	-	-	-
Infection type[i]									
Respiratory	21,701 (40.9)	20,619 (39.5)	0.03	-	-	-	-	-	-
Other	4,859 (9.2)	4,619 (8.8)	0.01	-	-	-	-	-	-
Unknown	27,091 (51.0)	27,602 (52.8)	0.04	-	-	-	-	-	-
Healthcare use in the prior year									
Hospitalizations									
0	37,596 (70.8)	37,134 (71.1)	0.01	37,426 (70.5)	36,324 (69.5)	0.02	37,253 (70.2)	37,116 (71.0)	0.02
1	10,021 (18.9)	9,715 (18.6)	0.01	10,027 (18.9)	10,100 (19.3)	0.01	10,245 (19.3)	9.779 (18.7)	0.01
2	3,604 (6.8)	3,551 (6.8)	0.00	3,661 (6.9)	3,811 (7.3)	0.02	3,724 (7.0)	3,582 (6.9)	0.01
≥3	1,849 (3.5)	1,844 (3.5)	0.00	1,956 (3.7)	2,009 (3.9)	0.01	1,848 (3.5)	1,767 (3.4)	0.01
Emergency room visits									
0	36,264 (68.3)	35,328 (67.6)	0.02	36,526 (68.8)	35,274 (67.5)	0.03	33,844 (63.8)	33,662 (64.4)	0.01
1	9,952 (18.8)	9,972 (19.1)	0.01	9,763 (18.4)	9,909 (18.8)	0.01	11,034 (20.8)	10,566 (20.2)	0.01
2	3,691 (7.0)	3,650 (7.0)	0.00	3,587 (6.8)	3,763 (7.2)	0.02	4,319 (8.1)	4,215 (8.1)	0.00
≥3	3,163 (6.0)	3,294 (6.3)	0.01	3,194 (6.0)	3,298 (6.3)	0.01	3,873 (7.3)	3,801 (7.3)	0.00

	Co-prescription Date			90 Days Prior to Co-prescription Date			90 Days Following Co-prescription Date		
	Clarithromycin *n=53,070*	**Azithromycin** *n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**	*n=53,070*	*n=52,244*	**Standardized Difference[a]**
Family physician visits									
0	1,079 (2.0)	1,271 (2.4)	0.03	1,129 (2.1)	1,276 (2.4)	0.02	810 (1.5)	962 (1.8)	0.02
1-2	3,412 (6.4)	3,147 (6.0)	0.02	3,350 (6.3)	3,124 (6.0)	0.01	2,267 (4.3)	2,166 (4.2)	0.01
3-4	6,413 (12.1)	6,260 (12.0)	0.00	6,282 (11.8)	6,016 (11.5)	0.01	4,704 (8.9)	4,775 (9.1)	0.01
5-6	8,477 (16.0)	8,066 (15.4)	0.01	8,389 (15.8)	7,982 (15.3)	0.01	7,753 (14.6)	7,451 (14.3)	0.01
7-8	7,929 (14.9)	7,693 (14.7)	0.01	7,904 (14.9)	7,557 (14.5)	0.01	8,306 (15.7)	8,031 (15.4)	0.01
9-10	6,386 (12.0)	6,106 (11.7)	0.01	6,297 (11.9)	6,076 (11.6)	0.01	6,982 (13.2)	6,611 (12.7)	0.01
≥11	19,374 (36.5)	19,701 (37.7)	0.02	19,719 (37.2)	20,213 (38.7)	0.03	22,248 (41.9)	22,248 (42.6)	0.01
Cardiologist visits									
0	32,690 (61.6)	30,967 (59.3)	0.05	32,503 (61.3)	30,679 (58.7)	0.05	32,174 (60.6)	30,647 (58.7)	0.04
1	9,610 (18.1)	9,504 (18.2)	0.00	9,478 (17.9)	9,489 (18.2)	0.01	9,859 (18.6)	9,641 (18.5)	0.00
2	4,378 (8.3)	4,665 (8.9)	0.02	4,423 (8.3)	4,635 (8.9)	0.02	4,548 (8.6)	4,806 (9.2)	0.02
≥3	6,392 (12.0)	7,108 (13.6)	0.05	6,666 (12.6)	7,432 (14.2)	0.05	6,489 (12.2)	7,150 (13.7)	0.04
Unique drugs dispensed									
<5	5,285 (10.0)	4,862 (9.3)	0.02	5,286 (10.0)	4,851 (9.3)	0.02	1,929 (3.6)	1,912 (3.7)	0.00
5-8	16,679 (31.4)	16,196 (31.0)	0.01	16,550 (31.2)	16,036 (30.7)	0.01	13,330 (25.1)	12,898 (24.7)	0.01
9-12	15,908 (30.0)	15,932 (30.5)	0.01	15,865 (29.9)	15,835 (30.3)	0.01	17,342 (32.7)	17,218 (33.0)	0.01
13-16	9,183 (17.3)	9,044 (17.3)	0.00	9,201 (17.3)	9,051 (17.3)	0.00	11,726 (22.1)	11,460 (21.9)	0.00
>16	6,015 (11.3)	6,210 (11.9)	0.02	6,168 (11.6)	6,471 (12.4)	0.02	8,743 (16.5)	8,756 (16.8)	0.01
Procedures									
Chest X-ray	41,253 (77.7)	40,705 (77.9)	0.00	40,768 (76.8)	40,382 (77.3)	0.01	43,455 (81.9)	42,530 (81.4)	0.01
Pulmonary function test	14,279 (26.9)	14,266 (27.3)	0.01	14,260 (26.9)	14,221 (27.2)	0.01	14,861 (28.0)	14,757 (28.3)	0.01
Echocardiography	23,759 (44.8)	24,898 (47.7)	0.06	23,590 (44.5)	24,748 (47.4)	0.06	24,202 (45.6)	25,227 (48.3)	0.05
Cardiac stress test	20,421 (38.5)	20,865 (39.9)	0.03	20,503 (38.6)	20,989 (40.2)	0.03	20,458 (38.6)	20,878 (40.0)	0.03
Carotid ultrasound	9,207 (17.4)	9,673 (18.5)	0.03	9,178 (17.3)	9,645 (18.5)	0.03	9,256 (17.4)	9,728 (18.6)	0.03

Data presented as number (percent) except for age which is presented as mean (standard deviation) and daily dose which is presented as median (interquartile range).
Abbreviations: Non-steroidal anti-inflammatory (NSAID), angiotensin converting enzyme (ACE), angiotensin II receptor blocker (ARB), interquartile range (IQR).

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

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

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

[d]Comorbidities assessed by administrative database codes in the previous 5 years.

[e]Charlson Comorbidity Index[45,46] was calculated using 5 years of hospitalization data. "No hospitalizations" received a score of 0.

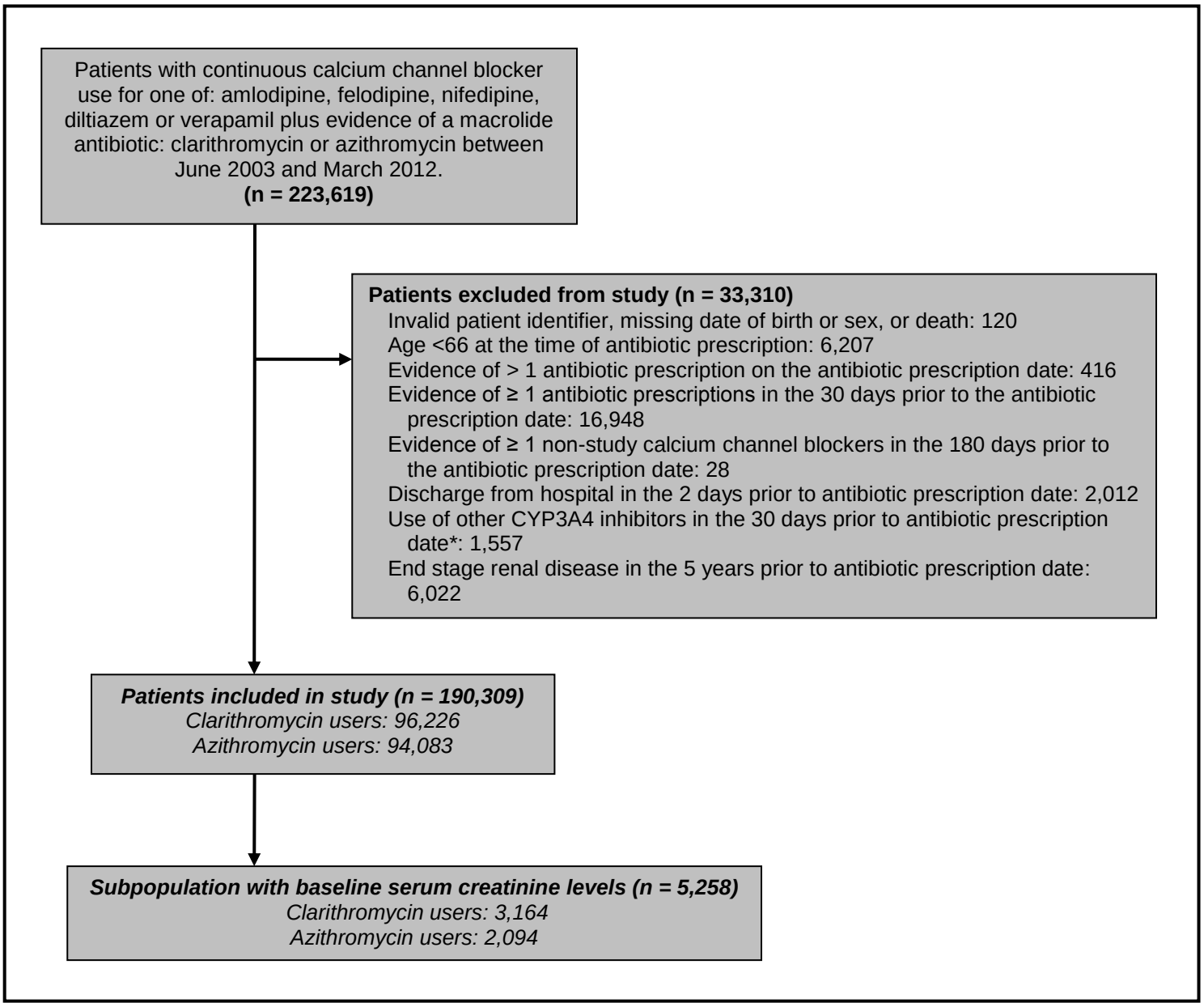
[f]Coronary artery disease includes receipt of coronary artery bypass graft surgery and percutaneous coronary intervention.

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

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

[i]Infection types are not mutually exclusive; patients may have had a code for more than one type of infection.

eFigure 1. Flow Diagram of Cohort Selection



*other CYP3A4 inhibitors included protease inhibitors and anti-fungals.

eFigure 2. Flow Diagram of Restricted Cohort Selection