Pharmacoepidemiology and Drug Safety

WILEY

ORIGINAL ARTICLE OPEN ACCESS

Clarithromycin Versus Azithromycin for Community-Acquired Pneumonia and the Risk of Major Adverse Cardiovascular Events: A Multicentre Cohort Study Using Data From Canada and Denmark

Theis Skovsgaard Itenov[1,2] | Anthony D. Bai[3] | Tor Biering-Sørensen[4,5,6,7] | Amol Verma[8,9,10,11] | Fahad Razak[8,9,11] | Ajay Bhasin[12,13] | Henning Bundgaard[2,6] | Pradeesh Sivapalan[2,14] | Kasper Iversen[2,15] | Christian Rasmussen[16] | Jens Rasmussen[17] | Lotte Klitfod[18] | Kathrine Dircks[16] | Jens-Ulrik S. Jensen[2,14] | Mike Fralick[11,19]

[1]Department of Anesthesiology, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark | [2]Department of Clinical Medicine, University of Copenhagen, Copenhagen, Denmark | [3]Division of Infectious Diseases, Department of Medicine, Queen's University, Kingston, Ontario, Canada | [4]Cardiovascular Non-Invasive Imaging Research Laboratory, Department of Cardiology, Herlev and Gentofte Hospital, University of Copenhagen, Hellerup, Denmark | [5]Center for Translational Cardiology and Pragmatic Randomized Trials, Faculty of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark | [6]Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark | [7]Steno Diabetes Center Copenhagen, Herlev, Denmark | [8]Li Ka Shing Knowledge Institute, St. Michael's Hospital, Unity Health Toronto, Toronto, Canada | [9]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada | [10]Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto, Canada | [11]Department of Medicine, University of Toronto, Toronto, Canada | [12]Department of Medicine, Division of Hospital Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA | [13]Department of Pediatrics, Division of Hospital-Based Medicine, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA | [14]Section of Respiratory Medicine, Department of Medicine, Copenhagen University Hospital – Herlev and Gentofte Hospital, Hellerup, Denmark | [15]Department of Medicine, Copenhagen University Hospital – Herlev and Gentofte Hospital, Hellerup, Denmark | [16]Department of Emergency Medicine, Copenhagen University Hospital – Amager and Hvidovre Hospital, Copenhagen, Denmark | [17]Department of Emergency Medicine, Copenhagen University Hospital – Bispebjerg and Frederiksberg, Copenhagen, Denmark | [18]Department of Emergency Medicine, Copenhagen University Hospital – Herlev and Gentofte Hospital, Hellerup, Denmark | [19]Sinai Health System, Toronto, Canada

Correspondence: Theis Skovsgaard Itenov (theis.skovsgaard.itenov@regionh.dk)

Received: 18 December 2024 | **Revised:** 4 April 2025 | **Accepted:** 9 May 2025

Funding: The authors received no specific funding for this work. This study was supported by GEMINI, a research program based out of Unity Health Toronto. The development of GEMINI's data platform has been supported by several funding partners, which can be found listed at https://geminimedicine.ca/partners/. All analyses, results, conclusions, and opinions presented in this paper are solely those of the listed authors and are independent from GEMINI's funding sources. No endorsement by GEMINI's funding sources is intended, nor should it be inferred.

Keywords: cardiovascular complications | community-acquired pneumonia | macrolides

ABSTRACT

Background: Studies suggest that clarithromycin is associated with an increased risk of major adverse cardiovascular events (MACE) among adults with coronary artery disease. However, data comparing clarithromycin to other macrolides, such as azithromycin, in a broader population are lacking.

Methods: A multicenter study was conducted in 33 hospitals in Ontario, Canada, and Copenhagen, Denmark, using the Target Trial framework. Adults hospitalized with community-acquired pneumonia (CAP) who received either clarithromycin or azithromycin were included. The primary outcome was MACE, defined as the one-year risk of nonfatal myocardial

Theis Skovsgaard Itenov and Anthony D. Bai contributed equally.

infarction, nonfatal stroke, or all-cause mortality. Propensity score matching and Cox proportional hazards models were used for analysis.

Results: In Ontario, we identified 23 081 patients with CAP, and 11 164 received oral macrolides. After propensity score matching, the primary outcome occurred in 7.8% of clarithromycin patients and 9.1% of azithromycin patients (HR 0.85, 95% CI 0.60–1.21). In Copenhagen, there were 11 280 patients with CAP and 3924 received oral macrolides. After propensity score matching, 19% of clarithromycin patients and 12% of azithromycin patients experienced the primary outcome for oral macrolides (HR 1.7, 95% CI 1.2–2.4, $p = 0.002$). Meta-analysis of the point estimate from each country provided an overall HR of 1.21 (95% CI 0.61–2.39). For intravenous macrolides in Copenhagen, the HR was 1.15 (95% CI 1.0–1.3, $p = 0.007$) for clarithromycin compared to azithromycin.

Conclusion: This study did not consistently observe an increased risk of cardiovascular events with clarithromycin among adults hospitalized with CAP. However, the observational nature of the study may introduce selection bias and unmeasured confounding.

1 | Introduction

Macrolide antibiotics are recommended in many national and international guidelines for managing community-acquired pneumonia (CAP) in hospital admitted patients with a CURB65 score of at least 3 [1, 2]. CURB-65 is a validated prognostic tool used to predict mortality in patients admitted with CAP based on cerebral status, blood urea nitrogen, respiratory rate, blood pressure, and age. The most frequently used macrolides for this indication are clarithromycin and azithromycin.

Randomized as well as observational evidence has uncovered that patients with stable coronary artery disease exposed to 2 weeks of treatment with oral clarithromycin have a 17% relative increase in long-term mortality risk (> 2 years) compared to placebo (randomized study) or doxycycline (observational study), and that this excess mortality is mainly driven by increased ischemic cardiovascular events, that is major cardiovascular outcomes (MACE) [3–5]. However, recent observational data showed no difference in these outcomes in patients with COPD exposed to shorter courses of macrolide [6]. There is no current data on the risk profile in a broader population of patients with CAP. Our objective was to assess the risk of MACE among adults hospitalized with CAP who received either clarithromycin or azithromycin.

2 | Methods

2.1 | Study Design

We conducted a retrospective cohort study across 24 hospitals in Ontario, Canada and 9 hospitals in the Capital Region of Denmark. The Unity Health Toronto Research Ethics Board approved this study (Identifier: SMH REB 20–216 CTO ID: 3344) for the Ontario Hospitals, and the Regional Board of Health (j.no R-23056515) approved the study in Denmark, and waived the need for individual patient consent.

2.2 | Data Source

The GEMINI database includes internal medicine inpatients in Ontario, and the database included administrative and clinical data linked at the patient level [7, 8]. GEMINI data included demographics, diagnoses, interventions, medication orders, blood work results, and discharge destination during the initial emergency room visit and hospital stay as well as readmission to a GEMINI hospital site [7, 8]. Diagnoses before, during, and after hospital admission were classified based on the International and Statistical Classification of Diseases and Related Health Problems, Tenth Revision, Canada (ICD-10-CA) [7, 8].

The Capital Region of Denmark (Copenhagen) has a single electronic health record covering and sharing information across hospitals. Data was extracted directly from this system and included the same variables as included within GEMINI in addition to other variables.

2.3 | Study Population

We included consecutive adult patients from two settings: (1) Patients admitted to the medicine inpatient service at 24 acute care hospitals in Ontario, Canada from January 1st, 2015 to June 30th, 2022 (most recent available data), and (2) patients admitted to nine hospitals in Copenhagen from January 1st, 2018 to December 31st, 2022.

In Ontario patients were included if they were diagnosed with CAP and initiated on clarithromycin or azithromycin within 2 days of admission. Community-acquired pneumonia was defined using a previously validated algorithm of ICD-10-CA codes J10–J18 as either the main responsible diagnosis [9], or a pre-admit or secondary diagnosis in context of chronic obstructive pulmonary disease as the main responsible diagnosis [10]. No patients in Ontario were treated with intravenous clarithromycin. For that reason, we compared adults who received oral clarithromycin to oral azithromycin in Ontario. We did not compare oral clarithromycin to IV azithromycin because of confounding by indication as sicker patients were more likely to receive intravenous antibiotics. Therefore, patients who had received only intravenous azithromycin were excluded. In addition, patients who received both clarithromycin and azithromycin during their hospital stay were excluded.

In Copenhagen, patients were included if they were diagnosed with CAP and initiated on clarithromycin or azithromycin (regardless of whether intravenous or oral) within 2 days of admission. CAP diagnosis was based on a previously validated algorithm of ICD-10-CA codes J10–J18 as either the main responsible diagnosis [9].

Summary

- Clarithromycin has been associated with an increased risk of major adverse cardiovascular events (MACE).
- It is unknown whether this also applies to patients with community-acquired pneumonia (CAP) and whether there is a difference compared to azithromycin in CAP patients.
- We conducted a multicenter, observational study with over 10 000 patients from Canada and Denmark.
- We found that the risk of MACE (%) was as follows: Canada—Clarithromycin (7.8) versus Azithromycin (9.1); Denmark—Clarithromycin (19% for oral and 30% for intravenous) versus Azithromycin (12% for oral and 27% for intravenous).
- We found no significant difference in the risk of MACE between oral clarithromycin compared to oral azithromycin (HR 1.21 [95% CI 0.61–2.39]).

2.4 | Exposure

We compared the incidence of the outcomes between adults who received azithromycin and those who received clarithromycin within 2 days of hospital admission for CAP. We did not account for the duration of treatment to avoid introducing immortal time bias [11]. There are national as well as local guidelines for antibiotic treatment for CAP in both Ontario and Copenhagen. Although the primary antibiotic varies and is subject to physician variation in prescription patterns, the general guideline in both Copenhagen and Ontario is that moderate-to-severe CAP should receive a macrolide. During the observation period, there was a guideline change in Copenhagen from clarithromycin to azithromycin on May 27th 2021.

2.5 | Primary and Secondary Outcomes

The primary outcome was major adverse cardiovascular event (MACE), which included all-cause mortality, nonfatal stroke (ICD-10-CA I63.x, I64.x, G45.x, G46.x) or nonfatal myocardial infarction (MI) (ICD-10-CA of I21.x or I22.x) [12] within 1 year from index admission. New MACE was defined as either a post-admission complication during index admission or admission to any GEMINI hospital site with MACE as the main responsible admitting diagnosis within 1 year of follow-up. Likewise, in the Copenhagen cohort, new MACE was defined as the registration of a MACE event following the index admission date at any hospital in the Capital Region of Denmark within 1 year, with MACE as a diagnosis associated with a hospital admission. For patients recruited in December 2022, follow-up was between 364 and 334 days, as data was extracted on November 30th, 2023. The secondary outcome was all-cause mortality within 1 year. The time to MACE was defined as the discharge date for events happening during index admission and the admission day for events occurring during subsequent admissions. In the Copenhagen data, mortality is extracted from national registries. In Ontario, GEMINI captured death during index admission and death after readmission to a GEMINI hospital site within the 1-year follow-up period. The GEMINI database is not linked to national registries, so it would not capture out-of-hospital deaths.

2.6 | Confounders

We collected data on demographics (age, sex), pre-hospitalization location (e.g., long-term care home), year of hospitalization, prior stroke (ICD-10-CA I63.x, I64.x, G45.x, G46.x), prior MI (ICD-10-CA I21.x, I22.x), diabetes mellitus (ICD-10-CA E10.x, E11.x) and hypertension (ICD-10-CA I10.x, I11.x, I12.x, I13.x, and I15.x), and other comorbidities: Revised updated Charlson comorbidity index [13] that excluded prior stroke, prior MI, and diabetes mellitus to avoid overlap with cardiovascular risk factor variables. We also estimated illness severity using the following: Intensive care unit (ICU) admission within 48 h of admission, modified Laboratory-based Acute Physiology Score (mLAPS) within 24 h of admission based on laboratory parameters (sodium, BUN, creatinine, albumin, hematocrit, WBC count, arterial pH, arterial PaCO2, arterial PaO2, glucose, and bilirubin) [14] and CRP. Higher illness severity had a higher mLAPS score. In a prior study, mLAPS performed as well as CURB-65 score in predicting mortality for CAP [15].

2.7 | Statistical Analysis

Descriptive analysis used mean ± standard deviation (SD) for continuous variables and counts with percentages for categorical variables. Absolute standardized difference of the mean (ASDM) was used to describe the balance of baseline characteristics for which an ASDM of >0.1 represented a meaningful difference [16].

Propensity score matching was used to balance possible confounders between the clarithromycin and azithromycin groups. A logistic regression model of the covariates was used to estimate the probability of receiving clarithromycin versus azithromycin. The model included sex, age, known hypertension at the time of admission, known diabetes at the time of admission, prior myocardial infarction, and prior stroke. Admission year was also included in the model for Ontario data but not in the Copenhagen data due to the temporal change in guidelines. Patients in the azithromycin group were matched to patients in the clarithromycin group with a ratio of up to 4 to 1 in the Ontario data. In the Copenhagen data, patients in the clarithromycin group were matched to patients in the clarithromycin group with a ratio of up to 4 to 1. Matching was done using nearest neighbour matching without replacement. The specified caliper width was 0.2 times the SD of the logit of propensity scores [17].

Survival analysis was used to compare time to MACE between the clarithromycin and azithromycin group before and after propensity score matching. A Cox proportional hazard model of time to MACE was used to estimate the HR for clarithromycin. The proportional hazard assumption was evaluated based on visual inspection of survival curves and

standardized residuals. The interaction effect of delivery method was evaluated by including an interaction term between delivery method and type of macrolide. To provide an overall estimate for the HR across Ontario and Copenhagen, we used a random effects meta-analysis that weighted studies by the inverse of their variance. All analyses were performed using R version 4.1.3 (R Foundation for Statistical Computing, Vienna, Austria). R package MatchIt [18] was used for propensity score matching.

3 | Results

In Ontario, we identified 488 adults who received oral clarithromycin and 10 676 who received oral azithromycin, Figure 1. Adults who received clarithromycin were typically younger, more likely to be female, had fewer comorbid conditions, and had lower illness severity compared to adults who received azithromycin, Table 1. The one-year unadjusted risk of MACE was 7.8% among adults who received clarithromycin and 13.3% among adults who received azithromycin, corresponding to an unadjusted hazard ratio (HR) of 0.56 (95% CI 0.41–0.78). After propensity score matching, all baseline characteristics were balanced, Table S1. Within the propensity score matched population, the 1-year risk of MACE was 7.8% among adults who received clarithromycin and 9.1% among adults who received azithromycin, corresponding to a HR of 0.85 (95% CI 0.60–1.21), Table 2 and Figure 2.

In Copenhagen, we identified 3585 adults who received oral clarithromycin and 339 who received oral azithromycin, Figure 1. Adults who received oral clarithromycin were typically older and had higher disease severity compared to adults who received oral azithromycin. The one-year unadjusted risk of MACE was 21% among adults who received clarithromycin and 12% among adults who received azithromycin, corresponding to an unadjusted HR of 1.9 (95% CI 1.4– 2.7, $p < 0.001$). After propensity score matching, most baseline characteristics were balanced. Within the propensity score matched population, the 1-year risk of MACE was 19% among adults who received

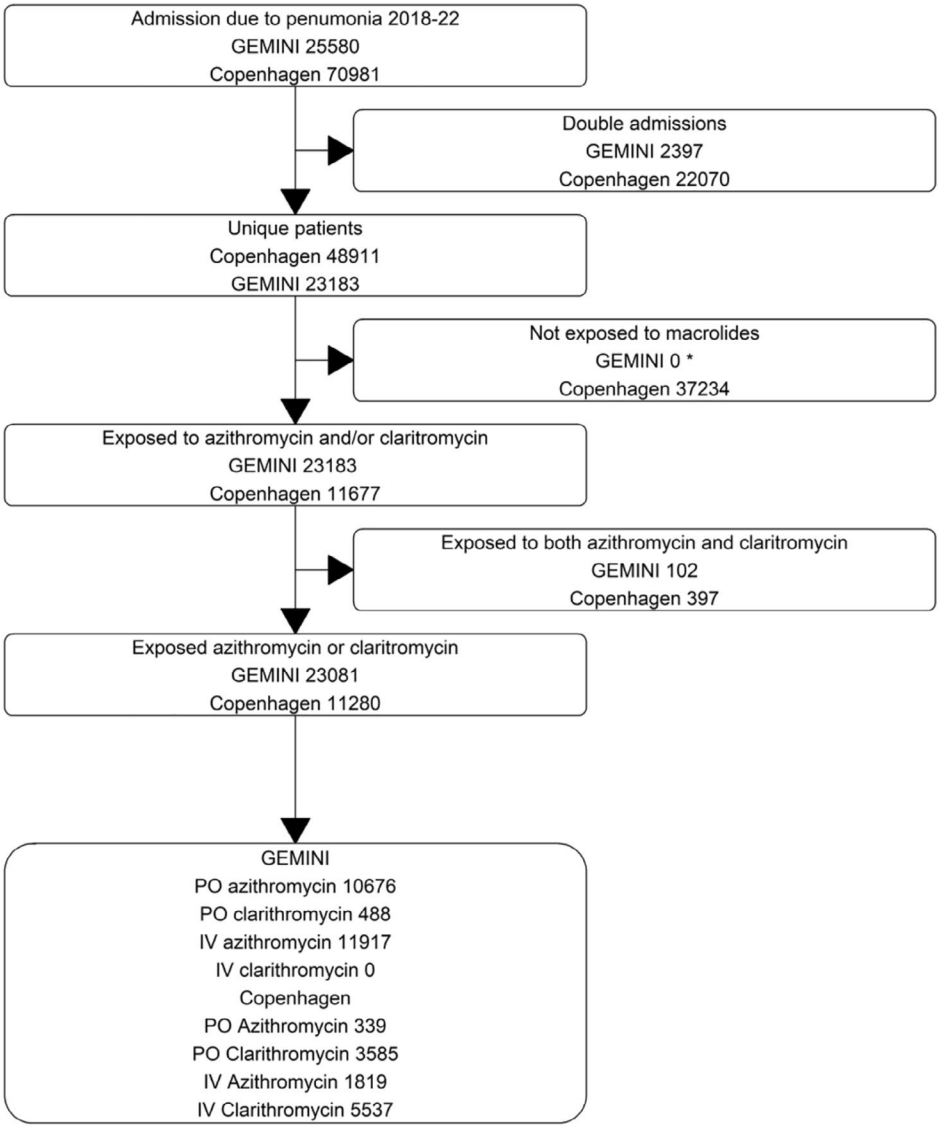

FIGURE 1 | Cohort selection. *Patients not treated with macrolides were removed from the cohort prior to analysis. Abbreviations: PO: oral administration; IV: intravenous administration.

TABLE 1 | Patient characteristics prior to propensity score matching.

	Gemini cohort			Copenhagen cohort					
Characteristic	**Claritho, po *N* = 488**	**Azithro, po *N* = 10 676**	**SMD**	**Clarithro, iv, *N* = 5537**	**Azithro, iv *N* = 1819**	**SMD**	**Clarithro, po, *N* = 3585**	**Azithro, po *N* = 339**	**SMD**
Age (years)	65.1 (18.9)	72.7 (16.3)	0.43	74 (15)	75 (13)	0.07	71 (16)	65 (18)	0.35
Sex			0.20			0.01			0.04
Man	209 (42.8%)	5653 (53.0%)		2860 (52%)	950 (52%)		1748 (49%)	159 (47%)	
Woman	279 (57.2%)	5023 (47.1%)		2677 (48%)	869 (48%)		1837 (51%)	180 (53%)	
From long-term care home	≤5 (≤1.0%)	431 (4.0%)	0.27	—	—		—	—	
Admission year									
2015	119 (24.4%)	997 (9.3%)	0.41	—	—		—	—	
2016	174 (35.7%)	1447 (13.6%)	0.53	—	—		—	—	
2017	111 (22.8%)	1731 (16.2%)	0.17	—	—		—	—	
2018	50 (10.3%)	1982 (18.6%)	0.24	1758 (32%)	3 (0.2%)	0.96	756 (21%)	51 (15%)	0.16
2019	27 (5.5%)	1950 (18.3%)	0.40	1962 (35%)	5 (0.3%)	1.03	1304 (36%)	42 (12%)	0.58
2020	6 (1.2%)	1401 (13.1%)	0.47	1219 (22%)	1 (<0.1%)	0.75	1067 (30%)	29 (8.6%)	0.56
2021	≤5 (≤1.0%)	867 (8.1%)	0.40	516 (9.3%)	451 (25%)	0.42	396 (11%)	74 (22%)	0.29
2022	≤5 (≤1.0%)	301 (2.8%)	0.24	82 (1.5%)	1359 (75%)	2.30	62 (1.7%)	143 (42%)	1.12
CRP (mmol/L)	—	—		144 (110)	160 (119)	0.14	129 (104)	117 (112)	0.11
Creatinine (mmol/L)	—	—		100 (71)	99 (67)	0.02	93 (61)	106 (136)	0.12
Lactate (mmol/L)	—	—		1.72 (1.39)	1.80 (1.58)	0.05	1.41 (1.01)	1.40 (0.98)	0.01
Revised charlson comorbidity index mean (SD)	0.7 (1.2)	1.3 (1.8)	0.36	1.40 (1.56)	1.39 (1.56)	0.003	1.29 (1.52)	1.40 (1.56)	0.04
Hypertension	91 (18.7%)	2713 (25.4%)	0.16	1023 (18%)	409 (22%)	0.10	652 (18%)	57 (17%)	0.04
Diabetes	127 (26.0%)	2886 (27.0%)	0.02	630 (11%)	199 (11%)	0.01	323 (9.0%)	29 (8.6%)	0.02
History of myocardial infarction	≤5 (≤1.0%)	123 (1.2%)	0.01	126 (2.3%)	41 (2.3%)	0.001	80 (2.2%)	5 (1.5%)	0.06
History of stroke	≤5 (≤1.0%)	37 (0.4%)	0.03	386 (7.0%)	173 (9.5%)	0.09	224 (6.2%)	22 (6.5%)	0.01

(Continues)

TABLE 1 | (Continued)

Characteristic	Gemini cohort			Copenhagen cohort				
	Claritho, po $N=488$	Azithro, po $N=10\,676$	SMD	Claritho, iv, $N=5537$	Azithro, iv $N=1819$	SMD	Claritho, po, $N=3585$	Azithro, po $N=339$	SMD
Illness severity									
ICU admission within 48 h of admission	11 (2.3%)	559 (5.2%)	0.16						
CURB +65 (score)				2.45 (0.89)	2.52 (0.88)	0.08	2.21 (0.85)	1.95 (0.83)	0.32
mLAPS score within 24 h mean (SD)	25.0 (16.7)	28.1 (17.7)	0.18						

Note: Mean (SD); *n* (%).
Abbreviations: Azithro, Azithromycin; Claritho, Clarithromycin; ICU, intensive care unit; iv, intravenous administration; mLAPS, modified Laboratory-based Acute Physiology Score; po, oral administration; sd, standard deviation; smd, standardized mean difference.

clarithromycin and 12% among adults who received azithromycin, corresponding to a HR of 1.7 (95% CI 1.2–2.4, $p=0.002$), Table 2. Meta-analyzing the two propensity score matched hazard ratios identified no increased hazard (HR = 1.21, 95% CI 0.61–2.394), Table 2 and Figure 2.

In Copenhagen, we identified 5537 adults who received intravenous clarithromycin and 1819 who received intravenous azithromycin, Figure 1. Adults who received intravenous clarithromycin were comparable to adults who received intravenous azithromycin. The one-year unadjusted risk of MACE was 30% among adults who received clarithromycin and 27% among adults who received azithromycin, corresponding to an unadjusted HR of 1.15 (95% CI 1.04–1.27, $p=0.007$). After propensity score matching, most baseline characteristics were balanced. Within the propensity score matched population, the 1-year risk of MACE was 30% among adults who received clarithromycin and 27% among adults who received azithromycin, corresponding to a HR of 1.15 (95% CI 1.04–1.27), Table 3 and Figure 2.

In a sensitivity analysis, we investigated short-term outcome (30-day MACE) but found no substantial differences compared to the long-term outcomes.

In the Copenhagen cohort, the effect of clarithromycin versus azithromycin was not modified by the delivery method (oral vs. intravenous) (p for interaction 0.21).

4 | Discussion

In this multicenter study of over 10 000 older adults hospitalized with CAP at 33 hospitals in Ontario and Denmark, we did not observe a consistently increased risk of cardiovascular events or all-cause mortality among adults who received clarithromycin compared to azithromycin. These results provide one of the largest sample sizes available to compare these two commonly used antibiotics for CAP. And while there was an increased risk observed in the Danish cohort, this may represent unmeasured confounding.

The most recent IDSA guidelines indicate that azithromycin or clarithromycin can be used interchangeably for adults hospitalized with CAP. The recommendation is based on a meta-analysis [19] which identified that the addition of a macrolide to beta-lactam therapy was associated with lower mortality compared to a beta-lactam alone. Although the meta-analysis included 17 observational studies and 3 RCTs, none of the included RCTs directly compared azithromycin to clarithromycin. Instead, the trials compared beta-lactam plus macrolide versus beta-lactam alone. Azithromycin was shown to have similar effectiveness as clarithromycin for inpatient treatment of CAP in a prior randomized controlled trial [20] and a prospective observational study [21]. One of the RCTs not included in the meta-analysis was the CLARICOR trial.

The CLARICOR trial randomized adults with cardiovascular disease to receive 14 days of oral clarithromycin 500 mg daily compared to placebo. Importantly, the adults did not have pneumonia. In that study, there was no statistically significant increased risk of the primary outcome of all-cause mortality,

TABLE 2 | MACE events in patients receiving oral macrolide.

	Entire GEMINI cohort (unadjusted)			Gemini propensity score matched		
	Clarithromycin (*N* = 488)	**Azithromycin (*N* = 10 676)**	**HR (95% CI) *p***	**Clarithromycin (*N* = 485)**	**Azithromycin (*N* = 1875)**	**HR (95% CI) *p***
MACE within 1 year*	38 (7.8%)	1422 (13.3%)	0.56 (95% CI 0.41–0.78 $p = 0.0005$	38 (7.8%)	171 (9.1%)	0.85 (95% CI 0.60 to 1.21 $p = 0.3670$).
All-cause mortality	34 (7.0%)	1262 (11.8%)		34 (7.0%)	146 (7.8%)	
Stroke	≤ 5 (≤ 1.0%)	112 (1.1%)		≤ 5 (≤ 1.0%)	13 (0.7%)	
Myocardial infarction	≤ 5 (≤ 1.0%)	124 (1.2%)		≤ 5 (≤ 1.0%)	23 (1.2%)	
	Entire Copenhagen cohort (unadjusted)			**Copenhagen propensity score matched**		
	Clarithromycin oral (*N* = 3585)	**Azithromycin oral (*N* = 339)**	**HR (95% CI) *p***	**Clarithromycin oral (*N* = 1354)**	**Azithromycin oral (*N* = 339)**	**HR (95% CI) *p***
MACE within 1 year	746 (21%)	39 (12%)	1.9 (95% CI 1.4–2.7 $p < 0.001$)	150 (19%)	39 (12%)	1.71 (95% CI 1.22–2.39 $p = 0.002$)
All-cause mortality	681 (19%)	33 (10%)		126 (17%)	33 (10%)	
Stroke	66 (1.5%)	5 (1.5%)		23 (1.7%)	5 (1.5%)	
Myocardial infarction	23 (0.6%)	3 (0.9%)		11 (0.8%)	3 (0.9%)	

Note: MACE included all-cause mortality, stroke, myocardial infarction.
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.
*Patients may encounter more than one MACE qualifying event during follow-up period. Date of first event is used in regression analyzes.

myocardial infarction, or unstable angina, but there was an increased risk of the secondary outcome of all-cause mortality (HR 1.27, 95% CI 1.03–1.54). However, it is well established that secondary outcomes in any study can be positive due to chance alone. Also, patients in that trial did not have pneumonia and thus the risk–benefit profile favors risks because there is no active infection to be treated. Recently, observational data from patients with chronic obstructive pulmonary disease did not find an excess risk of cardiovascular events in patients exposed to macrolides, nor differences between the types of macrolides [6].

The results of our study help provide observational data for an area lacking randomized trials. Within Ontario, our unadjusted data showed a lower rate of MACE among adults who received clarithromycin. However, after adjustment, that effect was attenuated, which suggests selection bias toward healthier adults receiving clarithromycin compared to azithromycin. The selection bias is supported by the fact that adults who received clarithromycin were approximately 7 years younger than adults who received azithromycin and were less likely to have hypertension or diabetes.

Interestingly, the unadjusted and adjusted results in Copenhagen showed the opposite, with worse outcomes among adults who received oral clarithromycin compared to oral azithromycin. However, adults who received oral clarithromycin were approximately 6 years older and had a higher CRP, and thus this observation may be explained by selection bias or other unmeasured confounding. Because most patients who received clarithromycin did so prior to 2020, the observation we observed may be explained by other time-varying factors not included in our analysis. In a recent RCT in adults with CAP in Greece [22] they did not observe a higher risk of mortality with clarithromycin compared to azithromycin. That provides additional, albeit indirect, evidence that the increased risk we observed might be explained by unmeasured confounders.

There are multiple strengths of our study. First, it was multicenter and included patients from both Canada and Denmark, which helps to improve external generalizability. Second, the average age of patients was over 70 years, which helps provide results in a patient population that is often underrepresented in clinical trials. Third, it is unlikely that a large, randomized trial will be conducted in this patient population comparing azithromycin to clarithromycin, and thus our results provide timely data until such a trial occurs, if it does. Fourth, because our primary outcome included both cardiovascular events and all-cause mortality, it minimizes the risk of our findings being accounted for by competing risks.

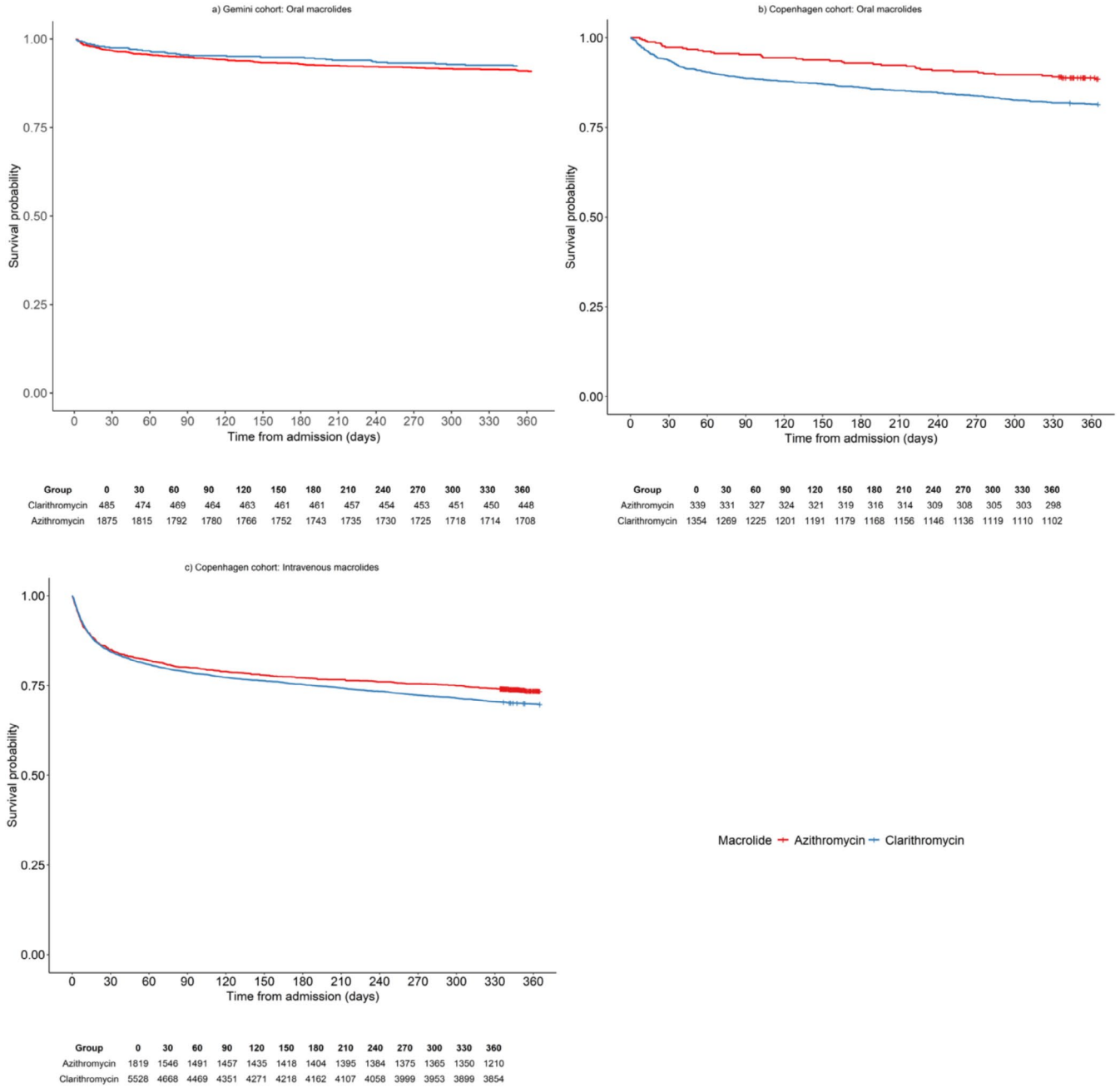

FIGURE 2 | Kaplan–Meier survival curve for MACE within 1 year after propensity score matching.

There are also limitations of our study. First, it was observational and thus prone to selection bias, confounding by indication, and unmeasured confounders. Although we used propensity score methods to match on observed confounders, this does not guarantee matching on unmeasured confounders. Second, we planned to complete analyzes of both IV and oral formulations across both countries, but we lacked a sufficient sample size to do so in Ontario because clarithromycin IV is not widely available in Ontario. Third, we focused on adults hospitalized with CAP and thus the results may not apply to outpatients or other patient populations not included in our study (e.g., children) or underrepresented in our study (e.g., middle aged adults). Fourth, we defined CAP using diagnosis codes which are imperfect. However, we do not anticipate the accuracy to be differential among adults who received azithromycin or clarithromycin and thus unlikely to lead to biased results. Fifth, the GEMINI database does not capture cardiovascular events or deaths that occurred outside of a GEMINI hospital site. The omission of out-of-hospital events would occur at a similar rate between the two groups. Nevertheless, the GEMINI database should still capture the vast majority of events, because more than 80% of readmissions in our region occur at the same hospital [23] and GEMINI hospital sites make up approximately half of all acute care hospital beds in Ontario. We did not have access to out-of-hospital medication use, and thus no information on duration of treatment that could stratify patients based on the cumulated dose. Sixth, we have chosen not to include data on second-line antibiotics to simplify analysis and in recognition of the risk of chance finding by including further analyses. Seventh, we did not include a detailed evaluation on more detailed cardiovascular

TABLE 3 | MACE events in patients receiving intravenous macrolide.

	Entire Copenhagen cohort (unadjusted)			Propensity score matched		
	Clarithromycin ($N=5537$)	Azithromycin ($N=1819$)	HR (95% CI) p	Clarithromycin intravenous ($N=5528$)	Azithromycin intravenous ($N=1819$)	HR (95% CI p
MACE within 1 year*	1676 (30%)	484 (27%)	1.15 (95% CI 1.04–1.27 $p=0.008$)	1676 (30%)	484 (27%)	1.15 (95% CI 1.04–1.27 $p=0.007$
All-cause mortality	1582 (29%)	457 (25%)		1582 (29%)	457 (25%)	
Stroke	91 (1.6%)	27 (1.6%)		91 (1.6%)	27 (1.5%)	
Myocardial infarction	30 (0.5%)	7 (0.4%)		30 (0.5%)	7 (0.4%)	

Note: MACE included all-cause mortality, stroke, myocardial infarction.
Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio.
*Patients may encounter more than one MACE qualifying event during follow-up period. Date of first event is used in regression analyzes.

events (i.e., ventricular tachycardia, palpitations, long QT syndrome, syncope, sudden death, or cardiac arrest) as these data points for the most part are not captured in the data.

5 | Conclusion

Data from our multicenter study suggests that clarithromycin is not associated with an increased risk of cardiovascular events among older adults hospitalized with CAP. Until a pragmatic randomized trial is conducted, these results can help inform the management of older adults hospitalized with CAP and are concordant with current clinical practice guidelines.

5.1 | Plain Language Summary

We aimed at determining whether the antibiotic *clarithromycin* increases the risk of heart attack, stroke, or death, compared to a similar antibiotic called *azithromycin*. The study looked at adults hospitalized with pneumonia in hospitals in Canada and Denmark. Over 10000 patients were included. In Canada, people on clarithromycin had slightly fewer cardiovascular events or death (7.8%) than those on azithromycin (9.1%). In Denmark, the opposite was seen—more events with clarithromycin (19% for oral and 30% for intravenous) than azithromycin (12% for oral and 27% for intravenous). When data from both countries were combined, there was no clear difference in cardiovascular risk between the two antibiotics. However, because it was not a clinical trial, other unmeasured factors may have influenced the results.

Author Contributions

Study concept and design: T.S.I., A.D.B., T.B.S., J.S.J., M.F. Acquisition of data: All authors. Analysis/interpretation of data: All authors. Drafting of the manuscript: T.S.I., A.D.B., M.F. Critical revision of the manuscript: All authors. Statistical analysis: A.D.B., T.S.I.

Ethics Statement

The Unity Health Toronto Research Ethics Board approved this study (Identifier: SMH REB 20–216 CTO ID: 3344), and all nine hospitals in the Capital Region of Denmark covering a population of 1.8 million inhabitants. The latter was approved by the Regional Board of Health in the Capital Region of Denmark (j.no R-23056515).

Consent

This study was retrospective in nature, and the need for individual patient consent was waived by regulatory boards.

Conflicts of Interest

M.F. was a consultant for ProofDx, a start-up company creating a point-of-care diagnostic test for COVID-19 and is an advisor for SIGNAL1, a start-up company deploying machine-learned models to improve inpatient care. T.S.I. the department of anesthesiology, Bispebjerg and Frederiksberg Hospital receives reimbursement from Radiometer Medical in relation to testing medical equipment. No personal benefits are received by T.S.I.

Data Availability Statement

Datasets from GEMINI are not permitted to be shared openly given they contain potentially sensitive patient information, based on the data governance policies of the GEMINI research network and its research ethics board-approved study protocols. Data can be accessed in the secure GEMINI research environment. Information about data access can be obtained at www.geminimedicine.ca, by contacting gemini.data@unityhealth.to, or upon request to the corresponding author. The use of data from the Capital Region of Denmark is subject to national and international laws and cannot be shared freely. Please contact the corresponding author for enquiries.

References

1. Dansk Lungemedicinsk Selskab, "Retningslinjer for Håndtering af Voksne Patienter Indlagt Med Pneumoni," 2021, https://lungemedicin.dk/pneumoni/.

2. J. P. Metlay, G. W. Waterer, A. C. Long, et al., "Diagnosis and Treatment of Adults With Community-Acquired Pneumonia. An Official

Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America," *American Journal of Respiratory and Critical Care Medicine* 200 (2019): e45–e67.

3. C. M. Jespersen, B. Als-Nielsen, M. Damgaard, et al., "Randomised Placebo Controlled Multicentre Trial to Assess Short Term Clarithromycin for Patients With Stable Coronary Heart Disease: CLARICOR Trial," *BMJ* 332 (2006): 22–27.

4. C. Gluud, B. Als-Nielsen, M. Damgaard, et al., "Clarithromycin for 2Weeks for Stable Coronary Heart Disease: 6-Year Follow-Up of the CLARICOR Randomized Trial and Updated Meta-Analysis of Antibiotics for Coronary Heart Disease," *Cardiology* 111 (2008): 280–287.

5. A. D. Mosholder, J. Y. Lee, E. H. Zhou, et al., "Long-Term Risk of Acute Myocardial Infarction, Stroke, and Death With Outpatient Use of Clarithromycin: A Retrospective Cohort Study," *American Journal of Epidemiology* 187 (2018): 786–792.

6. I. A. Alispahic, J. Eklöf, P. Sivapalan, et al., "Risk of Mortality and Cardiovascular Events in Patients With Chronic Obstructive Pulmonary Disease Treated With Azithromycin, Roxithromycin, Clarithromycin, and Amoxicillin," *Journal of Clinical Medical Research* 13 (2024): 1987.

7. A. A. Verma, Y. Guo, J. L. Kwan, et al., "Patient Characteristics, Resource Use and Outcomes Associated With General Internal Medicine Hospital Care: The General Medicine Inpatient Initiative (GEMINI) Retrospective Cohort Study," *CMAJ Open* 5 (2017): E842–E849.

8. A. A. Verma, S. V. Pasricha, H. Y. Jung, et al., "Assessing the Quality of Clinical and Administrative Data Extracted From Hospitals: The General Medicine Inpatient Initiative (GEMINI) Experience," *Journal of the American Medical Informatics Association* 28 (2021): 578–587.

9. S. A. Skull, R. M. Andrews, G. B. Byrnes, et al., "Hospitalized Community-Acquired Pneumonia in the Elderly: An Australian Case-Cohort Study," *Epidemiology and Infection* 137 (2009): 194–202.

10. S. L. Malecki, H. Y. Jung, A. Loffler, et al., "Identifying Clusters of Coexisting Conditions and Outcomes Among Adults Admitted to Hospital With Community-Acquired Pneumonia: A Multicentre Cohort Study," *CMAJ Open* 11 (2023): E799–E808.

11. M. Colacci and M. Fralick, "Methodological Progress Note: Utilizing Inpatient Data Sources to Minimize Common Biases When Emulating Target Trials," *Journal of Hospital Medicine* 18 (2023): 1017–1020.

12. E. Bosco, L. Hsueh, K. W. McConeghy, S. Gravenstein, and E. Saade, "Major Adverse Cardiovascular Event Definitions Used in Observational Analysis of Administrative Databases: A Systematic Review," *BMC Medical Research Methodology* 21 (2021): 241.

13. H. Quan, B. Li, C. M. Couris, et al., "Updating and Validating the Charlson Comorbidity Index and Score for Risk Adjustment in Hospital Discharge Abstracts Using Data From 6 Countries," *American Journal of Epidemiology* 173 (2011): 676–682.

14. S. B. Roberts, M. Colacci, F. Razak, and A. A. Verma, "An Update to the Kaiser Permanente Inpatient Risk Adjustment Methodology Accurately Predicts In-Hospital Mortality: A Retrospective Cohort Study," *Journal of General Internal Medicine* 38 (2023): 3303–3312.

15. A. D. Bai, S. Srivastava, B. K. C. Wong, et al., "Comparative Effectiveness of First-Line and Alternative Antibiotic Regimens in Hospitalized Patients With Nonsevere Community-Acquired Pneumonia: A Multicenter Retrospective Cohort Study," *Chest* 165 (2024): 68–78.

16. P. C. Austin, "Using the Standardized Difference to Compare the Prevalence of a Binary Variable Between Two Groups in Observational Research," *Communications in Statistics - Simulation and Computation* 38 (2009): 1228–1234.

17. P. C. Austin, "An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies," *Multivariate Behavioral Research* 46 (2011): 399–424.

18. D. E. Ho, K. Imai, G. King, and E. A. Stuart, "MatchIt: Nonparametric Preprocessing for Parametric Causal Inference," *Journal of Statistical Software* 42 (2011): i08.

19. J. S. Lee, D. L. Giesler, W. F. Gellad, and M. J. Fine, "Antibiotic Therapy for Adults Hospitalized With Community-Acquired Pneumonia: A Systematic Review," *JAMA* 315 (2016): 593–602.

20. M. Tamm, C. Feldman, J. Garbino, et al., "Clinical and Bacteriological Outcomes in Hospitalised Patients With Community-Acquired Pneumonia Treated With Azithromycin Plus Ceftriaxone, or Ceftriaxone Plus Clarithromycin or Erythromycin: A Prospective, Randomised, Multicentre Study," *Clinical Microbiology and Infection* 13 (2007): 162–171.

21. F. Sánchez, J. Mensa, J. A. Martinez, et al., "Is Azithromycin the First-Choice Macrolide for Treatment of Community-Acquired Pneumonia?," *Clinical Infectious Diseases* 36 (2003): 1239–1245.

22. E. Kyriazopoulou, D. Sinapidis, S. Halvatzis, et al., "Survival Benefit Associated With Clarithromycin in Severe Community-Acquired Pneumonia: A Matched Comparator Study," *International Journal of Antimicrobial Agents* 55 (2020): 105836.

23. J. A. Staples, D. Thiruchelvam, and D. A. Redelmeier, "Site of Hospital Readmission and Mortality: A Population-Based Retrospective Cohort Study," *CMAJ Open* 2 (2014): E77–E85.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.