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ORIGINAL RESEARCH

Azithromycin Exposure in a 10-Day Window of Myocardial Infarction and Short- and Long-Term Outcomes

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ABSTRACT

BACKGROUND The U.S. Food and Drug Administration warned in 2012 that azithromycin (AZM) can cause potentially fatal irregular heart rhythm, particularly in patients with known cardiac risk factors.

OBJECTIVES This study aimed to examine cardiac and hospital readmission outcomes associated with AZM exposure near the time of a myocardial infarction (MI).

METHODS This was a retrospective cohort study using Merative MarketScan databases examining adult inpatients admitted with MI from January 1, 2010 to December 31, 2017. Patients with AZM exposure 7 days pre-MI to 3 days post-MI were compared to unexposed controls. Time to subsequent MI and incident heart failure (HF) were examined up to 5 years post-MI using Cox models. All-cause, MI-related, MI and sequelae-related readmissions and incident HF diagnosis were examined 30 days post-MI using logistic regression.

RESULTS There were 18,066 eligible patients in the full cohort (AZM, N = 3,011), and the HF-free at baseline cohort included 9,180 patients (AZM, N = 1,530). Probability of subsequent MI up to 5 years post-MI was 15.3% in the AZM group vs 9.7% in control (HR: 1.41 [95% CI: 1.10-1.81], $P = 0.0076$). Probability of incident HF was 39.8% in the AZM group vs 35.5% in control (HR: 1.12 [95% CI: 0.91-1.39], $P = 0.2795$). Odds of all 4 30-day outcomes were significantly higher in the AZM group vs control.

CONCLUSIONS We found an increased risk of long-term subsequent MI, 30-day hospital readmissions, and 30-day incident HF among MI patients with AZM exposure compared to controls. Our findings are consistent with the 2012 Food and Drug Administration warning. (JACC Adv. 2024;3:101337) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

AZM = azithromycin

CCI = Charlson comorbidity index

COPD = chronic obstructive pulmonary disease

HF = heart failure

MI = myocardial infarction

PCI = percutaneous coronary intervention

Azithromycin (AZM) is an antibiotic used to treat a wide range of indications, including respiratory, uncomplicated skin, and sexually transmitted infections.[2] AZM is also used off-label for the treatment of bronchiectasis, bronchiolitis obliterans syndrome, and pulmonary inflammation associated with cystic fibrosis due to AZM's immunomodulatory properties.[3-5] AZM is prescribed to more than 30 million patients annually in the United States, and there is evidence that AZM prescribing may be frequently inappropriate in certain patients given its safety concerns.[6,7] In 2012, Ray et al reported a 2.9-fold increase in the risk of cardiac death within 5 days of AZM compared with amoxicillin.[8] Later that year, the U.S. Food and Drug Administration warned that AZM can cause potentially fatal irregular heart rhythm, particularly in patients with known cardiac risk factors.[9] Subsequently, two studies were published with contradictory findings, showing no increased likelihood of negative cardiac outcomes associated with AZM.[10,11] Despite the Food and Drug Administration warning, AZM prescribing practices in at-risk patients remained unchanged, which was hypothesized to be due to the inconsistent evidence in the literature.[6,9,12] Thus, the risks associated with AZM remain inconclusive in at-risk populations.

Myocardial infarction (MI) causes more than 2.4 million deaths in the United States annually, with estimated direct costs of $450 billion per year.[13] Due to irreversible damage to the heart muscle from lack of oxygen, subsequent cardiac complications, including recurrent MI, are possible. After an MI, it is estimated that 6.9% of patients experience a recurrent MI at 3 years.[14] MI is the most common cause of heart failure (HF) (a chronic progressive condition in which the heart cannot pump enough blood and oxygen to support other organs).[15-17] Approximately 13% of MI patients are diagnosed with HF at 30 days, and 20% to 30% at 1-year post-MI.[16,17]

The therapeutic potential of AZM as an immunomodulator has been investigated for multiple conditions, and the drug demonstrated a protective effect in an MI mouse model by decreasing scar size and improving survival.[18,19] This model, in combination with conflicting findings in human studies,[8,10,11] demonstrates an ongoing need to examine the temporal association between AZM exposure proximal to an MI using real-world data. No studies examine outcomes associated with AZM exposure near the time of an MI. This study aims to examine the exposure of AZM in a 10-day window around MI and its association with cardiac outcomes compared to matched, unexposed controls.

METHODS

STUDY POPULATION. This was a retrospective cohort study using Merative MarketScan Commerical Claims and Encounters and Medicare Supplemental Databases, a nationally representative U.S. claims database of commercially insured patients.[20] The analytical dataset was obtained from the University of Kentucky Center for Clinical and Translational Science, and the study was approved as institutional review board-exempt by the University of Kentucky Office of Research Integrity. The databases include deidentified inpatient, outpatient, prescription drug, procedure, and enrollment records of beneficiaries, dependents, and retirees covered under a variety of fee-for-service and managed care health plans.[20] Adult (≥18 years old) inpatients admitted with MI as the primary diagnosis and discharged with a length of stay of 1 to 30 days occurring from January 1, 2010, to December 31, 2017, were eligible for inclusion (Supplemental Table 1). Patients were required to have continuous pharmacy and medical enrollment during the 1 year prior to and including their date of admission ("baseline period"). The index MI date was defined as the admission date for MI.

Exposure to AZM was any receipt of AZM during a window of 7 days preindex to 3 days postindex MI event date using evidence from outpatient prescription fills (National Drug Codes) and inpatient administration (Healthcare Common Procedure Coding System [HCPCS] codes) (Supplemental Table 1). Patients with AZM prescriptions overlapping at least 1 day of the exposure window were deemed exposed to AZM, and otherwise patients were deemed controls.

LONG-TERM OUTCOMES. Patients were followed up to 5 years postindex MI event to examine: time to subsequent MI (MI in the primary position on the claim[21]) and time to incident HF (first ever HF diagnosis in the database in any position on the claim) (Supplemental Table 1). Patients were followed up to 5 years postindex MI or disenrollment, whichever came first.

SHORT-TERM OUTCOMES. To examine short-term outcomes, patients were followed up to 30 days postindex MI event. The first outcome was all-cause hospitalization, defined as any inpatient admission during the short-term follow-up period. Because all-cause hospitalization includes hospitalization for any reason, we additionally examined cardiac-related hospitalizations via three outcomes: MI-related

hospitalization, defined as inpatient admission with diagnosis of MI/unstable angina, chest pain, ischemic heart disease (any position on the claim); MI-sequelae-related hospitalization, defined as inpatient admission with diagnosis of HF, arrythmia, myocarditis, stroke, or cardiac arrest (any position on the claim); and MI hospitalization (inpatient admission with MI diagnosis) (International Classification of Diseases [ICD]-9/10 codes listed in Supplemental Table 1). Lastly, we examined incident HF, defined as the first ever HF diagnosis in the database.

STATISTICAL ANALYSIS. To balance baseline characteristics and comorbidities in the exposed and control groups, propensity score matching was used to select control patients using a 1:5 matching ratio. Variables used for propensity score matching were selected by reviewing relevant literature to identify factors that could potentially confound the relationship between AZM exposure and outcomes of interest. The selected matching variables were evaluated on the index MI event date (age, sex, U.S. region, Charlson comorbidity index [CCI] score), during the index MI visit (length of stay, non-ST-segment elevation MI [NSTEMI] vs ST-segment elevation MI [STEMI] [mutually exclusive], index MI event year, renal failure, septic shock, blood transfusion, ventilator, cardiogenic shock, intra-aortic balloon pump), or during the baseline period (chronic obstructive pulmonary disease [COPD], glucocorticoid therapy, hypertension, diabetes, carotid artery disease, HF [omitted for analyses of incident HF]). An exact match was required for sex, region, and MI year. All patient characteristics were identified using ICD-9/10 and Current Procedural Terminology codes and are listed in Supplemental Table 1.

Two 1:5 matched cohorts were identified from two underlying populations: 1) all eligible patients (full cohort); and 2) eligible patients free of HF at baseline (HF-free at baseline cohort). The HF-free at baseline cohort was used to examine long- and short-term incident HF outcomes. Both matches were performed using a 1:5 greedy nearest neighbor algorithm (ie, matching without replacement), with no caliper to ensure a complete match.[22,23] Match quality was scrutinized using standardized mean differences (SMD) and visual inspection of the distribution of baseline characteristics by exposure group.

Patient characteristics (demographics [age, sex, region], comorbidities [CCI, cancer, chronic kidney disease, diabetes, end-stage renal disease, HF, hypertension, hyperlipidemia, stroke, peripheral artery disease, glucocorticoid therapy, irritable bowel syndrome, neuromuscular disease, COPD, carotid artery disease], index MI [year, length of stay, NSTEMI vs STEMI {mutually exclusive}, renal failure, septic shock, cardiogenic shock, intra aortic balloon pump, blood transfusion, ventilator, pneumonia at index], and follow-up cardiac medications/procedures [ace inhibitors, angiotensin II receptor blockers, beta blockers, immunosuppressants, P2Y12 inhibitors, and statins; coronary artery bypass graft, and postindex percutaneous coronary intervention {PCI} during index MI hospitalization] information) were summarized overall and stratified by exposure group (AZM vs control). Mortality status was not available in the data. Number of patients with the event per person-year and median time to event were reported by exposure group.

Differences in the long-term outcomes by exposure group were visualized using Kaplan-Meier survival curves. Cox proportional hazards modeling was used to adjust for residual confounding, and to examine the hazards of long-term outcomes in exposure groups. Covariates were included in the Cox model if they met one of three criteria: 1) they were included in propensity score matching and SMD remained above 10%[24]; 2) the variable had potential to change differentially between cases and controls postindex MI event (such variables were included as time-varying covariates); or 3) hypothesized to have a long-term impact on the outcomes. The proportional hazards assumption was assessed using Schoenfeld residuals and log-log survival curves.

To observe short-term outcomes, subgroups of patients with 30-day continuous enrollment post-index MI events from the full and HF-free at baseline cohorts were examined. All-cause hospitalization, MI-related hospitalization, and MI-sequelae-related hospitalization were examined in the full 30-day subgroup, and incident HF was examined in the HF-free at baseline 30-day subgroup. Differences in 30-day outcomes between groups were examined using logistic regression. Variables were included for adjustment if they were included in the propensity score matching and SMD remained above 10%.[24] Analyses were performed using SAS version 9.4.

SENSITIVITY ANALYSIS. It is possible that an active infection, such as pneumonia, at the time of MI could impact outcomes in the long term, particularly time to subsequent MI, due to cardiac remodeling quality and extent of ischemic injury. One study found that patients hospitalized for MI who developed infections during hospitalization for STEMI (median time to diagnosis was 3 days) were associated with significantly higher rates of death or MI at 90 days.[25] However, we opted not to match on pneumonia at

TABLE 1 Patient Characteristics in Matched Full Cohort

	Overall (N = 18,066)	AZM (n = 3,011)	Control (n = 15,055)
Total observation, y (sum)	35,753.0	6,022.8	29,730.2
Age, y	67.4 ± 14.4	67.5 ± 14.9	67.3 ± 14.3
Male	9,852 (54.5%)	1,642 (54.5%)	8,210 (54.5%)
Region			
Northeast	3,522 (19.5%)	587 (19.5%)	2,935 (19.5%)
North Central	6,084 (33.7%)	1,014 (33.7%)	5,070 (33.7%)
South	6,024 (33.3%)	1,004 (33.3%)	5,020 (33.3%)
West	2,286 (12.7%)	381 (12.7%)	1,905 (12.7%)
Unknown	150 (0.8%)	25 (0.8%)	125 (0.8%)
Baseline comorbidities			
CCI	6.3 ± 3.2	6.3 ± 3.0	6.3 ± 3.2
Cancer	5,246 (29.0%)	904 (30.0%)	4,342 (28.8%)
Chronic kidney disease	3,353 (18.6%)	540 (17.9%)	2,813 (18.7%)
Diabetes	7,293 (40.4%)	1,219 (40.5%)	6,074 (40.3%)
End-stage renal disease	788 (4.4%)	106 (3.5%)	682 (4.5%)
Heart failure	8,867 (49.1%)	1,481 (49.2%)	7,386 (49.1%)
Hypertension	14,198 (78.6%)	2,357 (78.3%)	11,841 (78.7%)
Hyperlipidemia	1,962 (10.9%)	299 (9.9%)	1,663 (11.0%)
Stroke	1,210 (6.7%)	605 (20.1%)	605 (4.0%)
Peripheral artery disease	2,191 (12.1%)	314 (10.4%)	1,877 (12.5%)
Glucocorticoid therapy	7,537 (41.7%)	1,251 (41.5%)	6,286 (41.8%)
IBD	269 (1.5%)	41 (1.4%)	228 (1.5%)
Neuromuscular disease	5 (0.0%)	3 (0.1%)	2 (0.0%)
COPD	6,726 (37.2%)	1,133 (37.6%)	5,593 (37.2%)
Carotid artery disease	1,865 (10.3%)	309 (10.3%)	1,556 (10.3%)
Index MI event variables			
Index MI year			
2010	2,448 (13.6%)	408 (13.6%)	2,040 (13.6%)
2011	3,300 (18.3%)	550 (18.3%)	2,750 (18.3%)
2012	2,904 (16.1%)	484 (16.1%)	2,420 (16.1%)
2013	2,394 (13.3%)	399 (13.3%)	1,995 (13.3%)
2014	2,340 (13.0%)	390 (13.0%)	1,950 (13.0%)
2015	1,776 (9.8%)	296 (9.8%)	1,480 (9.8%)
2016	1,500 (8.3%)	250 (8.3%)	1,250 (8.3%)
2017	1,404 (7.8%)	234 (7.8%)	1,170 (7.8%)
Index MI event length of stay, d	5.7 ± 5.1	5.7 ± 4.9	5.6 ± 5.2
NSTEMI	9,257 (51.2%)	1,531 (50.8%)	7,726 (51.3%)
Renal failure	4,082 (22.6%)	678 (22.5%)	3,404 (22.6%)
Septic shock	738 (4.1%)	135 (4.5%)	603 (4.0%)
Cardiogenic shock	926 (5.1%)	149 (4.9%)	777 (5.2%)
Intra-aortic balloon pump	369 (2.0%)	58 (1.9%)	311 (2.1%)
Blood transfusion	33 (0.2%)	7 (0.2%)	26 (0.2%)
Ventilator	124 (0.7%)	28 (0.9%)	96 (0.6%)
Pneumonia at index	3,469 (19.2%)	1,062 (35.3%)	2,407 (16.0%)
Follow-up cardiac medications and procedures			
Ace inhibitor	862 (4.8%)	149 (4.9%)	713 (4.7%)
Angiotensin II receptor blocker	792 (4.4%)	137 (4.5%)	655 (4.4%)
Beta blocker	1,940 (10.7%)	335 (11.1%)	1,605 (10.7%)
Immunosuppressant	153 (0.8%)	23 (0.8%)	130 (0.9%)
P2Y12 inhibitor	777 (4.3%)	135 (4.5%)	642 (4.3%)
Statin	1,990 (11.0%)	346 (11.5%)	1,644 (10.9%)
PCI	1,371 (7.6%)	155 (5.2%)	1,216 (8.1%)
CABG	994 (5.5%)	141 (4.7%)	853 (5.7%)

Values are mean ± SD or n (%).

AZM = azithromycin; CABG = coronary-artery bypass grafting; CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention.

index MI event in this study to avoid the unintended consequence of selecting control subjects with AZM exposure undocumented by NDCs and HCPCS codes in the claims data set (eg, taking a family member's AZM or an old AZM prescription). To explore the potential impact of pneumonia diagnosis on the association between AZM exposure and time to subsequent MI, we performed a sensitivity analysis excluding patients with pneumonia at index MI event from both AZM and control groups in the Cox model.

RESULTS

BASELINE CHARACTERISTICS. A total of 424,515 patients met inclusion/exclusion criteria, and 267,832 had no HF at baseline. After matching, the full cohort included 18,066 patients, and the HF-free at baseline cohort included 9,180 patients. Supplemental Table 2 contains the SMDs for the full cohort and HF-free at baseline cohort before and after matching.

The full cohort contained 3,011 patients exposed to AZM and 15,055 controls. Baseline variables were well-balanced between the AZM and control groups, with overall characteristics including: age (mean 67.4 ± 14.4 years; sex (54.7% male); region (33.7% North Central); CCI score (mean 6.3 ± 3.2); index MI length of stay (mean 5.7 ± 5.1 days); NSTEMI (51.2%); index MI year (18.3% in 2011); renal failure (22.6%); septic shock (4.1%); blood transfusion (0.2%); ventilator (0.7%); cardiogenic shock (5.1%); intra-aortic balloon pump (2.0%); COPD (37.2%); glucocorticoid therapy (41.7%); hypertension (78.6%); diabetes (40.4%); carotid artery disease (10.3%); and HF (49.1%). Follow-up cardiac medications and procedures were relatively well balanced between groups with the exception of PCI, which was lower in AZM vs control (5.2% vs 8.1%) (see **Table 1** for group-specific summaries). The subgroup of the full cohort that was examined for short-term outcomes contained 16,266 patients (AZM, n = 2,718; control, n = 13,548) (Supplemental Table 3).

The HF-free at baseline cohort contained 1,530 patients exposed to AZM and 7,650 controls. Baseline characteristics were well-balanced between the AZM and control groups, with overall characteristics including: (mean age 63.4 ± 14.4 years); sex (55.3% male); region (36.3% South); CCI score (mean 5.2 ± 3.0); index MI length of stay (mean 4.5 ± 4.3 days); NSTEMI (48.9%); index MI year (18.2% in 2011); renal failure (14.0%); septic shock (3.4%); blood transfusion (0.2%); ventilator (0.3%); cardiogenic shock (2.5%); intra-aortic balloon pump (1.4%); COPD (31.8%); glucocorticoid therapy (42.9%);

hypertension (73.2%); diabetes (34.6%); and carotid artery disease (7.4%). Follow-up cardiac medications and procedures were relatively well balanced between groups with the exception of PCI, which was lower in AZM vs control (8.2% vs 2.1%) (see **Table 2** for group-specific summaries). The subgroup of the HF-free at baseline cohort for 30-day analyses contained 8,512 patients (AZM, n = 1,411; control, n = 7,101) (Supplemental Table 4).

LONG-TERM OUTCOMES. In the AZM group, a rate of 4.1 subsequent MIs per 100 person-years was observed compared to 2.5 subsequent MIs per 100 person-years in the control group. As seen in the **Central Illustration**, the Kaplan-Meier survival estimates of time to subsequent MI were lower in the AZM group vs the control group starting within the first 6 months postindex MI through the 5 years postindex. At 5 years, the probability of subsequent MI was 15.3% in AZM compared to 9.7% in control (**Central Illustration**). After adjusting for baseline stroke, postindex cardiac medications and procedures, and CCI, the rate of subsequent MI was significantly higher in the AZM group vs control (HR: 1.36 [95% CI: 1.06-1.74], $P = 0.0172$) (**Table 3**).

In the HF-free at baseline cohort, the AZM group had 14.8 incident HF diagnoses per 100 person-years vs 12.6 in the control group.

The time to incident HF was observed to be shorter in the AZM group vs control beginning less than 1 year following index MI (**Figure 1**). At 5 years, the probability of incident HF was 39.8% in the AZM group compared to 35.5% in control (**Figure 1**). This increased rate of incident HF was not statistically significant in the AZM group vs control after adjusting for baseline stroke, postindex cardiac medications and procedures, and CCI (HR: 1.18 [95% CI: 0.95-1.46], $P = 0.1390$) (**Table 3**).

In both cohorts, no variables had SMDs of >10% after propensity score matching (Supplemental Table 2), and therefore only the CCI score was included as a time-varying covariate in the models.

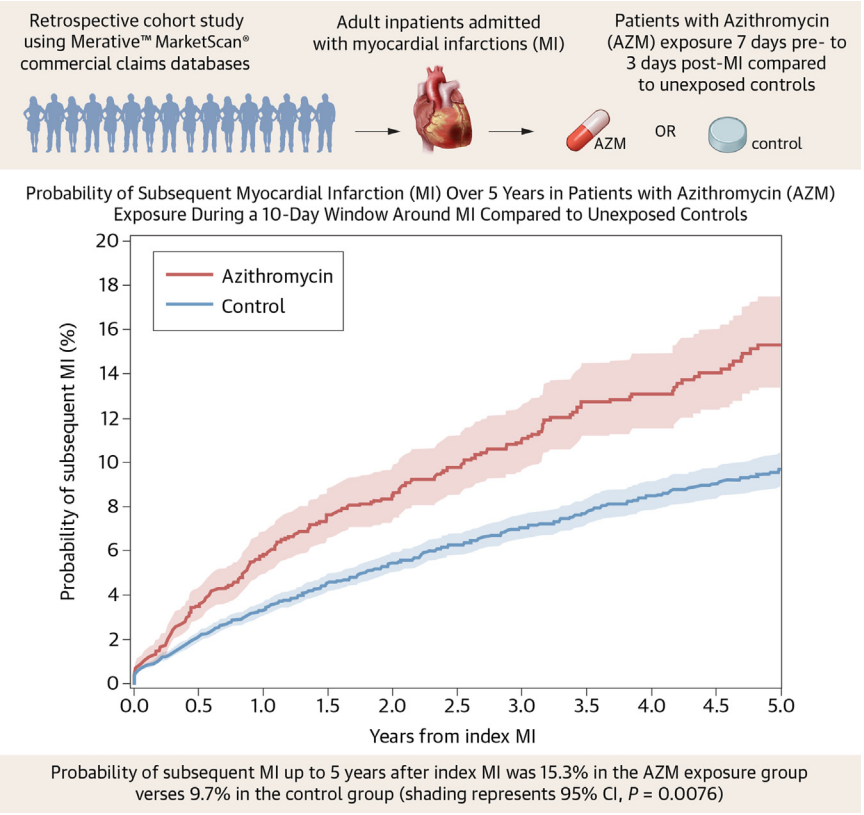
SHORT-TERM OUTCOMES. The odds of each 30-day outcome were significantly higher in the AZM group vs control (OR all-cause readmission: 1.34 [95% CI: 1.17-1.55], $P < 0.001$; MI-related readmission: 1.68 [95% CI: 1.35-2.08], $P < 0.001$; MI-sequelae-related readmission: 1.42 [95% CI: 1.20-1.69], $P < 0.001$; and MI readmission: 1.80 [95% CI: 1.20-2.70], $P = 0.0045$ (**Table 4**). Among the HF-free at baseline cohort, the odds of 30-day incident HF were significantly higher in the AZM group vs control (OR: 1.64 [95% CI: 1.36-1.97], $P < 0.001$) (**Table 4**).

TABLE 2 Patient Characteristics in Matched Heart Failure-Free Cohort

	Overall (N = 9,180)	AZM (n = 1,530)	Control (n = 7,650)
Total observation, y (sum)	17,021.1	2,819.8	14,201.3
Age, y	63.4 ± 14.4	63.7 ± 14.6	63.6 ± 13.9
Male	5,076 (55.3%)	846 (55.3%)	4,230 (55.3%)
Region			
Northeast	1734 (18.9%)	289 (18.9%)	1,445 (18.9%)
North Central	3,000 (32.7%)	500 (32.7%)	2,500 (32.7%)
South	3,330 (36.3%)	555 (36.3%)	2,775 (36.3%)
West	1,056 (11.5%)	176 (11.5%)	880 (11.5%)
Unknown	60 (0.7%)	10 (0.7%)	50 (0.7%)
Baseline comorbidities			
CCI	5.2 ± 3.0	5.2 ± 2.8	5.2 ± 3.0
Cancer	2,630 (28.6%)	464 (30.3%)	2,166 (28.3%)
Chronic kidney disease	942 (10.3%)	161 (10.5%)	781 (10.2%)
Diabetes	3,172 (34.6%)	529 (34.6%)	2,643 (34.5%)
End-stage renal disease	181 (2.0%)	23 (1.5%)	158 (2.1%)
Hypertension	6,720 (73.2%)	1,110 (72.5%)	5,610 (73.3%)
Hyperlipidemia	1,215 (13.2%)	180 (11.8%)	1,035 (13.5%)
Stroke	1,511 (16.5%)	221 (14.4%)	1,290 (16.9%)
Peripheral artery disease	699 (7.6%)	103 (6.7%)	596 (7.8%)
Glucocorticoid therapy	3,942 (42.9%)	658 (43.0%)	3,284 (42.9%)
IBD	160 (1.7%)	23 (1.5%)	137 (1.8%)
Neuromuscular disease	2 (0.0%)	1 (0.1%)	1 (0.0%)
COPD	2,923 (31.8%)	482 (31.5%)	2,441 (31.9%)
Carotid artery disease	680 (7.4%)	109 (7.1%)	571 (7.5%)
Index MI event variables			
Index MI year			
2010	1,326 (14.4%)	221 (14.4%)	1,105 (14.4%)
2011	1,674 (18.2%)	279 (18.2%)	1,395 (18.2%)
2012	1,404 (15.3%)	234 (15.3%)	1,170 (15.3%)
2013	1,092 (11.9%)	182 (11.9%)	910 (11.9%)
2014	1,086 (11.8%)	181 (11.8%)	905 (11.8%)
2015	780 (8.5%)	130 (8.5%)	650 (8.5%)
2016	930 (10.1%)	155 (10.1%)	775 (10.1%)
2017	888 (9.7%)	148 (9.7%)	740 (9.7%)
Index MI event length of stay, days (mean ± SD)	4.5 ± 4.3	4.5 ± 4.3	4.4 ± 4.3
Renal failure	1,284 (14.0%)	216 (14.1%)	1,068 (14.0%)
Septic shock	316 (3.4%)	56 (3.7%)	260 (3.4%)
Cardiogenic shock	231 (2.5%)	41 (2.7%)	190 (2.5%)
Intra-aortic balloon pump	126 (1.4%)	24 (1.6%)	102 (1.3%)
Blood transfusion	17 (0.2%)	4 (0.3%)	13 (0.2%)
Ventilator	24 (0.3%)	7 (0.5%)	17 (0.2%)
NSTEMI	4,485 (48.9%)	748 (48.9%)	3,737 (48.8%)
Pneumonia at index	1,232 (13.4%)	406 (26.5%)	826 (10.8%)
Follow-up cardiac medications and procedures			
ACE inhibitor	590 (6.4%)	100 (6.5%)	490 (6.4%)
Angiotensin II receptor blocker	514 (5.6%)	86 (5.6%)	428 (5.6%)
Beta-blocker	1,253 (13.6%)	207 (13.5%)	1,046 (13.7%)
Immunosuppressant	98 (1.1%)	18 (1.2%)	80 (1.0%)
P2Y12 inhibitor	538 (5.9%)	82 (5.4%)	456 (6.0%)
Statin	1,374 (15.0%)	223 (14.6%)	1,151 (15.0%)
PCI	285 (3.1%)	125 (8.2%)	160 (2.1%)
CABG	108 (1.2%)	58 (3.8%)	50 (0.7%)

AZM = azithromycin; CABG = coronary-artery bypass grafting; CCI = Charlson comorbidity index; COPD = chronic obstructive pulmonary disease; IBD = inflammatory bowel disease; NSTEMI = non-ST-elevation myocardial infarction; PCI = percutaneous coronary intervention.

CENTRAL ILLUSTRATION **Azithromycin Exposure in a 10-Day Window of Myocardial Infarction and Cardiovascular Outcomes**



Gusovsky A, et al. JACC Adv. 2024;3(11):101337.

Kaplan-Meier survival curves illustrating the probability of subsequent myocardial infarction (MI) (95% CIs shaded) up to 5 years in those with azithromycin (AZM) exposure in a 10-day window around MI compared to unexposed matched controls. After adjusting for baseline stroke, MI medications and procedures, and patient severity, probability of subsequent MI in the AZM group was 1.36 times that of unexposed matched controls ($P = 0.0172$).

In both cohorts, no variables had an SMD of >10% after propensity score matching (Supplemental Table 2), and therefore no additional variables were included for adjustment in the models.

SENSITIVITY ANALYSIS. When excluding patients with pneumonia at index, the rate of subsequent MI was still significantly higher in the AZM group vs control (HR: 1.43 [95% CI: 1.08-1.90], $P = 0.0128$) (Supplemental Table 5).

DISCUSSION

Our findings show that exposure to AZM within a 10-day window of an MI was associated with an increased risk of subsequent MI up to 5 years and cardiac-related hospital utilization in 30 days, even with adjustment for cardiac medications and procedures postindex MI. Incident HF up to 5 years was not significantly different between AZM and controls, although short-term (30 days) incident HF was significantly higher in the AZM group.

This is the first study to examine outcomes on multiple timeframes following the receipt of AZM close to the time of an MI. Because existing literature demonstrated inconsistency regarding the exposure-outcome relationship of AZM and cardiac outcomes, particularly in populations with differing severity, this study fills a unique gap.[10,11,26,27] Studies by Svanstrom et al (2012) and Patel et al (2020) contradicted the basis of the Food and Drug Administration warning, showing no increased risk of cardiac events associated with AZM. As expected, conflicting findings may have created ambiguity on the safety of AZM and cardiac outcomes for clinicians.[10,11,26,27] The

Svanstrom et al study examined a Danish population of relatively young (<65 years old) and healthy (no hospitalizations in the past month) adults. In addition to generalizability limitations with a Danish cohort, their study does not examine a cardiac-impaired or at-risk population, nor does it take into account the timing of AZM receipt around the time of an MI.

The Patel et al study uses the same data source as the present study (Merative MarketScan databases); however, the populations in that study were defined by AZM or amoxicillin prescriptions regardless of other comorbidities including recent MI. Because of the broad efficacy of these therapies to treat acute respiratory infections, which are common among otherwise healthy individuals, the Patel et al study captured many healthy patients, unlike the present study. Subanalyses of their higher-risk subgroups indicated that, among patients with history of syncope/cardiac dysrhythmias/nonspecific chest pain, or baseline cardiovascular disease, those exposed to AZM did not have significantly higher odds of short-term cardiac events compared to amoxicillin.[10] This finding provides important context for the interpretation of our results. We distinguish our study from Patel et al by a) including an unexposed control group (vs amoxicillin exposure), and b) the precision timing of AZM receipt (vs no timing requirement). Therefore, we hypothesize that the timing of AZM therapy around the time of an MI could be an important contributing factor.

It is important to note that the AZM group in the full-matched cohort had a higher proportion of patients with evidence of pneumonia diagnosis at index MI than control (35.3% vs 16.0%). Thus, suspected or confirmed pneumonia likely drove some AZM exposure, as AZM is a first-line therapy for the treatment of community-acquired pneumonia. To ensure results regarding long-term subsequent MI were not explained by pneumonia during the index MI, we performed a sensitivity analysis excluding patients with pneumonia at index MI event from both AZM and control groups, and the results were sustained. These findings provide further assurance that the results reported are not confounded by a pneumonia infection at the time of the index MI.

Both cohorts in this analysis had >30% COPD at baseline. Given COPD exacerbation and MI may present with similar symptoms (shortness of breath, etc.) in some cases, there is a possibility that some MI patients in this study were, in reality, miscategorized as patients with COPD exacerbations. However, the validity of MI ICD codes has been proven to be equally as accurate in categorizing MI patients compared to the interpretation of electrocardiogram results.[28]

TABLE 3 Results from Cox Proportional Hazard Models for Azithromycin Exposure Around Time of Myocardial Infarction and Subsequent Myocardial Infarction and Incident Heart Failure Diagnosis Up to 5 Years

	Subsequent MI (N = 18,066)		Incident HF (N = 9,180)	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
AZM vs no AZM	**1.36 (1.06-1.74)**	**0.0172**	1.18 (0.95-1.46)	0.1390
CCI (time-varying)	**1.14 (1.1-1.18)**	**<0.0001**	**1.20 (1.17-1.23)**	**<0.0001**
Baseline stroke	0.84 (0.64-1.1)	0.1974	1.16 (0.94-1.44)	0.1706
Ace inhibitor	0.9 (0.56-1.44)	0.6666	1.02 (0.73-1.41)	0.9221
Angiotensin II receptor blocker	0.75 (0.46-1.24)	0.2664	0.84 (0.58-1.20)	0.3324
Beta blocker	0.74 (0.47-1.17)	0.1951	1.24 (0.90-1.70)	0.1857
Immunosuppressant	1.47 (0.71-3.02)	0.2978	0.99 (0.54-1.82)	0.9752
P2Y12 inhibitor	**1.82 (1.17-2.82)**	**0.0074**	1.15 (0.83-1.60)	0.3991
Statin	0.69 (0.44-1.08)	0.1051	**0.51 (0.37-0.70)**	**<0.0001**
CABG	0.68 (0.39-1.19)	0.1758	1.23 (0.63-2.38)	0.5459
PCI	0.69 (0.42-1.14)	0.1447	**0.35 (0.15-0.78)**	**0.0103**

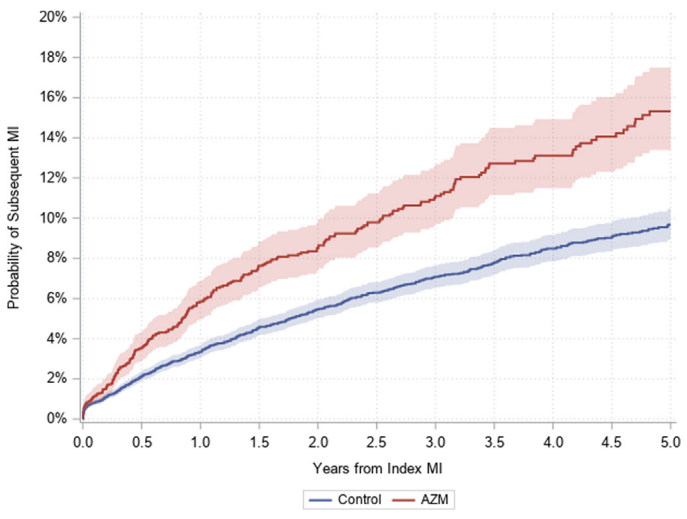
Summary of Cox proportional hazards models examining the association between AZM vs control and events of interest (subsequent MI and incident HF), presenting variable names and corresponding hazard ratios with 95% CIs and *P* values. *P* values <0.05 are **bolded**.

AZM = azithromycin; CABG = coronary-artery bypass grafting; CCI = Charlson comorbidity index; HF = heart failure; HR = hazard ratio; MI = myocardial infarction; PCI = percutaneous coronary intervention.

This, in combination with matching on COPD at baseline, provides us with confidence that the results reported in the present study are less subject to misclassification bias.

The therapeutic potential of AZM as an immunomodulator has been investigated for multiple conditions, most notable in therapy to counteract the

FIGURE 1 Time to Incident Heart Failure (HF) by Azithromycin (AZM) vs Control Kaplan-Meier Survival Curves Illustrating the Probability of Incident HF Up to 5 Years in the AZM vs Control Groups With Shaded 95% CIs



MI = myocardial infarction.

TABLE 4 Results From Logistic Regression Models for 30-Day Outcomes

	All-Cause Readmission (n = 16,266)		MI-Related Readmission (n = 16,266)		MI-Sequelae-Related Readmission (n = 16,266)		MI Readmission (n = 16,266)		Incident HF (n = 8,512)	
	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value	OR (95% CI)	*P* Value
AZM vs control	1.34 (1.17-1.55)	<0.001	1.68 (1.35-2.08)	<0.001	1.42 (1.20-1.69)	<0.001	1.80 (1.20-2.70)	0.0045	1.64 (1.36-1.97)	<0.001

Summary of logistic regression models examining the association between AZM vs control and events of interest (all-cause readmission, MI-related readmission, MI-sequelae-related readmission, and incident HF), presenting odds ratios with 95% CIs and *P* values.

AZM = azithromycin; HF = heart failure; MI = myocardial infarction; OR = odds ratio.

immunopathology of COVID-19.[29] Modulating inflammation with AZM has been shown to be effective in patients with panbronchiolitis,[30,31] bronchiolitis obliterans syndrome,[32,33] COPD,[34,35] and cystic fibrosis.[36-38] Additionally, investigations of the impact of AZM for other conditions that include inflammation as part of the pathophysiology, including MI, have been conducted using animal models. At the cellular level, this effect shifts macrophage activation away from inflammation and more toward a regulatory setpoint,[39,40] and in several animal models of inflammatory disease, it significantly decreases neutrophil influx.[18,19,41,42] These animal studies highlight the importance of studying the exposure of AZM around the time of cardiac insult using real-world data to further evaluate the potential effects of the drug. Due to the therapeutic index, we anticipated a beneficial effect, knowing the risk of cardiotoxicity may exist. The present findings indicate that while AZM may have immunomodulatory activity, the therapeutic benefit is significantly outweighed by the risk of cardiotoxicity in this high-risk population.

The large sample size and use of a well-defined patient population with concurrent MI are notable strengths of this study. This approach allowed for a robust analysis of the impact of AZM in a high-risk patient group with MI. Additionally, we adjusted for potential confounding factors, such as demographic characteristics, relevant baseline comorbidities, and indicators of index MI severity, which enhances the validity of the findings. As such, our findings have significant implications for clinical practice, suggesting that caution should be exercised when prescribing AZM to patients with a history of MI. However, additional research is needed to corroborate these findings and investigate the underlying mechanisms of the observed association.

STUDY LIMITATIONS. Despite its strengths, this study has some limitations. First, this study uses commercial insurance claims data, which records medical information primarily for the purposes of billing. Second, results should be interpreted with caution given that mortality data was not available. Patients were followed up to 5 years or disenrollment, which includes the possibility of lost-to-follow-up due to death. However, the number of patients remaining enrolled in the study does not vary greatly between comparator groups at any time through the 5-year follow-up period (approximately 68% remained; see Appendix 6). We interpret this limited variability as partial evidence of similar rates of lost-to-follow-up, though we cannot be certain of any differential mortality rates. A future direction includes an examination of mortality in this and other claims datasets. Next, MI severity is not directly available through laboratory results (eg, troponin, left ventricular ejection fraction, number of vessels, etc); however, we aimed to adjust for this by matching several variables examined during the index MI event (eg, cardiogenic shock) as a proxy for MI severity. Nonetheless, the inability to measure MI severity directly remains a limitation of this analysis. Next, the composite short-term outcome MI-related hospitalization included multiple diagnoses that may have indicated the hospitalization was cardiac-related, including chest pain. Although chest pain is often benign,[43] we chose to include it in the composite outcome as it is an important symptom to monitor, particularly in the 1 month following an MI event.[44] However, we explored five 30-day outcomes, all of which significantly favored the control group. Merative MarketScan claims databases do not contain patient race or ethnicity information, which could be an associated factor that we were not able to adjust for. All patients in Merative MarketScan claims are commercially insured, and therefore the findings of this study may not be generalizable to other populations. Additionally, AZM exposure was identified using National Drug Codes and HCPCS codes, and any other receipt of AZM was not accounted for, as it is not available in claims data. This study spans the transition from ICD-9-CM to ICD-10-CM, which were both used in this study. However, it should be noted that Panozzo et al

found that the incidence and prevalence of MI were similar across the two coding eras.[45] Lastly, the dose of AZM was not considered for this study. Examining the dose-response of AZM on the outcomes is important to elucidate its true influence and is a future direction of this work.

CONCLUSIONS

In this retrospective matched cohort study, we found increased risk of subsequent MI within 5 years among patients exposed to AZM around the time of their first MI compared to unexposed controls. Furthermore, the odds of all-cause readmission, MI-related readmission, MI-sequelae-related readmission, and incident HF were significantly increased 30 days post-MI in patients exposed to AZM compared to unexposed controls. When needed, alternative therapies to AZM should be considered for patients with a history of or at risk for MI. These findings highlight the importance of careful considerations when prescribing AZM to patients with a history of risk of MI and present a potential opportunity to develop drug delivery strategies that improve the therapeutic index of the drug by harnessing the immunomodulatory potential of AZM while reducing the off-target cardiac toxicity. More research should be done to examine the temporal association between AZM exposure and clinical outcomes such as MI and mortality as an outcome using other sources of data.

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Drs Feola, Venditto, and Abdel-Latif are the founders of Bluegrass Pharmaceuticals, which focuses on immune modulation with macrolide derivatives. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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APPENDIX For Supplemental Tables, please see the online version of this paper.