Original Investigation

Association of Azithromycin With Mortality and Cardiovascular Events Among Older Patients Hospitalized With Pneumonia

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IMPORTANCE Although clinical practice guidelines recommend combination therapy with macrolides, including azithromycin, as first-line therapy for patients hospitalized with pneumonia, recent research suggests that azithromycin may be associated with increased cardiovascular events.

OBJECTIVE To examine the association of azithromycin use with all-cause mortality and cardiovascular events for patients hospitalized with pneumonia.

DESIGN Retrospective cohort study comparing older patients hospitalized with pneumonia from fiscal years 2002 through 2012 prescribed azithromycin therapy and patients receiving other guideline-concordant antibiotic therapy.

SETTING This study was conducted using national Department of Veterans Affairs administrative data of patients hospitalized at any Veterans Administration acute care hospital.

PARTICIPANTS Patients were included if they were aged 65 years or older, were hospitalized with pneumonia, and received antibiotic therapy concordant with national clinical practice guidelines.

MAIN OUTCOMES AND MEASURES Outcomes included 30- and 90-day all-cause mortality and 90-day cardiac arrhythmias, heart failure, myocardial infarction, and any cardiac event. Propensity score matching was used to control for the possible effects of known confounders with conditional logistic regression.

RESULTS Of 73 690 patients from 118 hospitals identified, propensity-matched groups were composed of 31 863 patients exposed to azithromycin and 31 863 matched patients who were not exposed. There were no significant differences in potential confounders between groups after matching. Ninety-day mortality was significantly lower in those who received azithromycin (exposed, 17.4%, vs unexposed, 22.3%; odds ratio [OR], 0.73; 95% CI, 0.70-0.76). However, we found significantly increased odds of myocardial infarction (5.1% vs 4.4%; OR, 1.17; 95% CI, 1.08-1.25) but not any cardiac event (43.0% vs 42.7%; OR, 1.01; 95% CI, 0.98-1.05), cardiac arrhythmias (25.8% vs 26.0%; OR, 0.99; 95% CI, 0.95-1.02), or heart failure (26.3% vs 26.2%; OR, 1.01; 95% CI, 0.97-1.04).

CONCLUSIONS AND RELEVANCE Among older patients hospitalized with pneumonia, treatment that included azithromycin compared with other antibiotics was associated with a lower risk of 90-day mortality and a smaller increased risk of myocardial infarction. These findings are consistent with a net benefit associated with azithromycin use.

JAMA. 2014;311(21):2199-2208. doi:10.1001/jama.2014.4304

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Pneumonia and influenza together are the eighth leading cause of death and the leading causes of infectious death in the United States.[1] Professional societies including the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) have published clinical practice guidelines for community-acquired pneumonia,[2] which recommend the use of macrolides as part of combination antimicrobial therapy for patients hospitalized with community-acquired pneumonia. Although there is observational evidence that the empirical use of macrolides is associated with improved survival after pneumonia,[3-6] there is little randomized clinical trial evidence.[7] However, there is some evidence that azithromycin is associated with QT prolongation and cardiac arrhythmias.[8,9]

A recent study evaluated all-comers in a statewide Medicaid population and found that a course of azithromycin was associated with increased risk of cardiovascular and all-cause mortality for 5 days[10] as compared with treatment with amoxicillin or ciprofloxacin. Yet it is unclear how applicable this study is for those with pneumonia, as they did not document the indications for this antibiotic nor control for important comorbid conditions (eg, cancer, respiratory disease) and social factors (eg, drug abuse, nursing home residence) and included only patients receiving Medicaid. Another recent study of Danish patients aged 18 to 64 years prescribed azithromycin for any indication did not find an association with increased cardiovascular deaths.[11] In addition, randomized clinical trials of azithromycin to prevent cardiac events did not demonstrate an increased risk of heart disease.[12,13] Therefore, further research is critically needed to examine the safety of azithromycin in patients hospitalized with community-acquired pneumonia, a group with potentially the most to gain or lose from its use.

To address this need, the aim of this study was to assess the association of azithromycin use and outcomes within 90 days of hospital admission, including cardiovascular events (heart failure, myocardial infarction, cardiac arrhythmias) and mortality, for patients 65 years and older who were hospitalized with pneumonia. We were particularly interested in describing any potential harms associated with azithromycin use in the context of its benefits.

Methods

For this population-based cohort study, we used data from the Veterans Administration (VA) health care system administrative and clinical databases. These databases are the repositories of clinical data from more than 150 VA hospitals and 850 outpatient clinics. The institutional review boards of the University of Texas Health Science Center at San Antonio and VA North Texas Health Care System approved this study with a waiver of informed consent.

Patients were eligible to be included in this study if they met the following criteria:

- Were hospitalized from October 1, 2001, through September 30, 2012.
- Had a previously validated discharge diagnosis of pneumonia: either a primary diagnosis of pneumonia/influenza (*International Classification of Diseases, Ninth Revision* [*ICD-9*] codes 480.0-483.99 or 485-487) or a secondary discharge diagnosis of pneumonia with a primary diagnosis of respiratory failure (*ICD-9* code 518.81) or sepsis (038.xx).[14]
- Were 65 years or older on the date of admission, as both cardiac events and pneumonia-related mortality are much less frequent in those who are younger than 65 years.
- Had at least 3 VA outpatient visits in the year preceding admission to ensure appropriate assessment of comorbid conditions.
- Received at least 1 outpatient medication from a VA pharmacy within 90 days prior to admission to ensure that patients were receiving medications from VA pharmacies.
- Received at least 1 dose of antimicrobial therapy within the first 48 hours of admission.
- Received antibiotic therapy concordant with the 2007 IDSA/ATS guidelines for community-acquired pneumonia.[2] Prior studies have consistently demonstrated that the use of non-guideline-concordant antibiotics is associated with increased mortality.[7,15]

We excluded patients who received a macrolide other than azithromycin or doxycycline during their hospitalization because of the small number of prescriptions. Patients on the medical wards will have received a respiratory fluoroquinolone (eg, levofloxacin, moxifloxacin, gatifloxacin, grepafloxacin, sparfloxacin, and ofloxacin) or an appropriate β-lactam plus azithromycin, while patients in the intensive care unit will have received combination therapy with an appropriate β-lactam plus fluoroquinolone or appropriate β-lactam plus azithromycin. Patients may have also received vancomycin or linezolid therapy for potential methicillin resistant *Staphylococcus aureus* infection.

If a patient was admitted more than once during the study period, only the first hospitalization was included.

Data Sources and Definitions

We used inpatient and outpatient demographic, utilization, and comorbidity data from the National Patient Care Database and the Corporate Data Warehouse. Pharmacy data were extracted from the Decision Support System, Pharmacy Benefits Management, and the Corporate Data Warehouse. Mortality information was obtained from the Vital Status file, which has been demonstrated to have a sensitivity of approximately 98% for veterans' deaths.[16] Encrypted patient identifiers linked information across these databases.

Race and ethnicity categories included white, black, Hispanic, and other/unknown. Tobacco use and smoking cessation efforts were identified using *ICD-9* codes for tobacco use (305.1, V15.82), smoking cessation clinic use, or use of medications for the treatment of nicotine dependence (Zyban, nicotine replacement, or varenicline). Alcohol abuse was defined using *ICD-9* codes 291, 303, and 305.0 and illicit drug use by *ICD-9* codes 292, 304, and 305 (excluding 305.0-305.1). We used the Charlson-Deyo comorbidity methodology to classify other preexisting comorbid conditions.[17] Priority status was used as a proxy for socioeconomic status.[18] Mild liver disease was defined with *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) codes

572.2-572.8, 456.0, 456.1, 456.20, and 456.21 and moderate disease with *ICD-9-CM* codes 571.2 and 571.4-571.6. AIDS was defined with *ICD-9-CM* codes of 042.x, 043.x, and 044.x.

To further control for potential confounding by medications, a count of unique drugs in each of the following classes was calculated for outpatient prescriptions filled within 90 days prior to presentation: statins, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, nitrates, antiarrhythmics, β-blockers, calcium channel blockers, diuretics, antiplatelet agents, anxiolytics, tricyclic antidepressants, selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor antidepressants, antipsychotics, lithium, oral antidiabetic agents, metformin, insulin, other lipid-lowering agents, digoxin, other antihypertensive agents, inhaled β-agonists, other bronchodilators, theophylline, warfarin, and oral corticosteroids. In addition, dichotomous variables were created to identify those with corticosteroid use or outpatient use of any antibiotics within 90 days prior to admission.

We classified patients as having used azithromycin if they received at least 1 dose of azithromycin during the first 48 hours after admission.

Outcomes

Primary outcomes were 30-day and 90-day mortality and cardiovascular events within 90 days of admission. Prior research has demonstrated that 30-day mortality is largely pneumonia-related while mortality between 30 and 90 days is largely comorbidity-related.[19] We identified cardiovascular events using *ICD-9* codes indicating an inpatient diagnosis of myocardial infarction, heart failure, and cardiac arrhythmia as defined previously.[20] Cardiac arrhythmias included symptomatic bradycardia, torsades de pointes, atrial fibrillation, multifocal atrial tachycardia, ventricular fibrillation or tachycardia, and cardiac arrest. Mortality was assessed through January 25, 2013.

Statistical Analyses

For the primary analyses, we used propensity score matching to balance measured confounders between groups (azithromycin vs no azithromycin). Logistic regression was used to create the propensity score, and then nearest-number matching with a caliper of 0.0001 with no replacement was performed.[21] We selected candidate variables that we believed would be potentially associated with severity of illness (eg, intensive care unit [ICU] admission, use of mechanical ventilation) or outcomes (eg, age, nursing home status, prior cardiac disease). Variables included in the propensity score are displayed in **Table 1** and **Table 2**, and eFigures 1 and 2 in the Supplement demonstrate the overlap between the groups before and after matching. Odds ratios (ORs) were calculated to determine the association between azithromycin use and the outcomes using conditional logistic regression models with robust standard errors. To analyze time to event for mortality and cardiovascular outcomes by receipt of azithromycin, we used Kaplan-Meier plots to display the survivor functions and assessed statistical significance using the log-rank test.

For secondary analyses, we used generalized linear mixed-effect models with the patient's hospital as a random effect to examine the association of azithromycin with the outcomes of interest in several populations (**Table 3**). We included the similar covariates in these models that were used to derive the propensity score.

We performed instrumental variable logistic regression using the 2-stage residual inclusion (2SRI) approach.[22] Modern utilization of instrumental variables has prominently been used to handle the issue of omitted variable bias.[23] When this problem exists, the treatment variable is said to be endogenous, or correlated with the error. The underlying principal behind the use of instrumental variables is to separate the portion that is uncorrelated with the error and use it to estimate the treatment effect. The chosen instrumental variable was proportion of patients receiving azithromycin in each hospital, which we calculated by dividing the number of patients receiving inpatient azithromycin by the total number of eligible patients at each hospital. To verify the instrumental variable, we tested and found a strong relationship between the instrumental variable and azithromycin use (OR, 75.9; 95% CI, 68.2-84.4) using bivariable logistic regression (eFigure 3 in the Supplement). Likewise, we tested and found no relationship between the instrumental variable and dependent variables (all $P \geq .05$) using multiple logistic regression (eFigures 4-5 in the Supplement).

The first-stage model of the 2SRI analysis regressed azithromycin use on the instrumental variable, adjusting for all covariates in Table 1 and Table 2. From this model, we obtained residuals, which were then added as a covariate in the second-stage model. The second-stage model separately regressed each outcome on azithromycin use, adjusting for first-stage residuals and all covariates. We then calculated the average marginal effect of azithromycin use for each outcome, using bootstrapping with replacement in 1000 replications to obtain 95% confidence intervals. Average marginal effects are calculated by using the observed values of variables for each unique observation (as opposed to the mean value for each variable across all observations or representative values) to create observation-specific effects. These effects are then averaged across all observations.

Statistical significance was defined as a 2-tailed P value of ≤.05. Stata version 12 (StataCorp) or SAS version 9.3 (SAS Institute) were used for all analyses.

Results

There were 73 690 patients from 118 hospitals who met the inclusion criteria (eFigure 1 in the Supplement). Patients' mean age was 77.8 years (95% CI, 77.7-77.8), 52.6% (95% CI, 52.2%-52.9%) of patients were married, 98.3% (95% CI, 98.2%-98.4%) were male, and 15.9% (95% CI, 15.7%-16.2%) were admitted to the ICU. The median duration of follow-up was 461 days (interquartile range [IQR], 138-979). Overall, 20.0% (95% CI, 19.7%-20.3%) of the patients died and 43.1% (95% CI, 42.8%-43.5%) had a cardiac event within 90 days of admission. There were 38 787 patients who received

Table 1. Demographic and Hospitalization Characteristics of Propensity-Matched Azithromycin Users and Nonusers Hospitalized With Pneumonia

Variables	Azithromycin, No. (%) (n = 31 863)	No Azithromycin, No. (%) (n = 31 863)	*P* Value	Standardized Difference
Age, mean (SD), y	77.8 (7.4)	77.8 (7.4)	.33	−0.008
Men	31 296 (98.2)	31 299 (98.2)	.93	−0.001
Race				
White	26 107 (81.9)	26 099 (81.9)	.93	0.001
Black	3498 (11.0)	3518 (11.0)	.80	−0.002
Hispanic	1768 (5.6)	1754 (5.5)	.81	0.002
Married	16 715 (52.5)	16 680 (52.4)	.78	0.002
Nursing home residence	360 (1.1)	380 (1.2)	.44	−0.006
Socioeconomic proxy[a]				
VA priority group 1	6894 (21.6)	6833 (21.4)	.58	0.005
VA priority group 2-6	21 761 (68.3)	21 878 (68.7)		−0.008
VA priority group 7-8	3208 (10.1)	3152 (9.9)		0.006
Calendar year of hospital admission				
2001	618 (1.9)	615 (1.9)	>.99	0.001
2002	2625 (8.2)	2639 (8.3)		−0.002
2003	2982 (9.4)	2947 (9.3)		0.004
2004	2501 (7.9)	2493 (7.8)		0.001
2005	2517 (7.9)	2525 (7.9)		−0.001
2006	2380 (7.5)	2421 (7.6)		−0.005
2007	2758 (8.7)	2766 (8.7)		−0.001
2008	3206 (10.1)	3200 (10.0)		0.001
2009	3215 (10.1)	3206 (10.1)		0.001
2010	3369 (10.6)	3342 (10.5)		0.003
2011	3315 (10.4)	3333 (10.5)		−0.002
2012	2377 (7.5)	2376 (7.5)		0.000
ICU admission	4970 (15.6)	4950 (15.5)	.83	0.002
Invasive mechanical ventilation	1660 (5.2)	1693 (5.3)	.56	−0.005
Vasopressors	1270 (4.0)	1263 (4.0)	.88	0.001
Comorbid conditions				
Tobacco use	12 661 (39.7)	12 639 (39.7)	.86	0.001
Alcohol abuse	1418 (4.5)	1420 (4.5)	.97	−0.000
Illicit drug abuse	444 (1.4)	454 (1.4)	.74	−0.003
Myocardial infarction	2264 (7.1)	2236 (7.0)	.66	0.003
Heart failure	8179 (25.7)	8149 (25.6)	.78	0.002
Peripheral vascular disease	5310 (16.7)	5313 (16.7)	.97	−0.000
Chronic obstructive pulmonary disease	16 513 (51.8)	16 458 (51.7)	.66	0.003
Rheumatologic disease	944 (3.0)	941 (3.0)	.94	0.001
Mild liver disease	137 (0.4)	146 (0.5)	.59	−0.004
Peptic ulcer disease	965 (3.0)	947 (3.0)	.68	0.003
Dementia	1469 (4.6)	1474 (4.6)	.92	−0.001
Diabetes	11 058 (34.7)	11 059 (34.7)	.99	−0.000
Diabetes with complications	3518 (11.0)	3559 (11.2)	.60	−0.004
Moderate liver disease	288 (0.9)	303 (1.0)	.53	−0.005
Hemiplegia	349 (1.1)	344 (1.1)	.85	0.002
Renal disease	5407 (17.0)	5434 (17.1)	.77	−0.002
Any prior malignancy	7942 (24.9)	7906 (24.8)	.73	0.003
Metastatic solid tumor	1147 (3.6)	1167 (3.7)	.65	−0.003
Hematologic malignancy	856 (2.7)	834 (2.6)	.59	0.004
AIDS	68 (0.2)	67 (0.2)	.93	0.001

Abbreviations: ICU, intensive care unit; VA, Department of Veterans Affairs.

[a] Priority status was used as a proxy for socioeconomic status.[18]

Table 2. Medication Use Among Propensity-Matched Azithromycin Users and Nonusers Hospitalized With Pneumonia

	Median No. of Patients (IQR)			
	Azithromycin (n = 31 863)	No Azithromycin (n = 31 863)	*P* Value	Standardized Difference
Antipsychotics	0 (0-0)	0 (0-0)	.83	0.002
Antiplatelet agents	0 (0-0)	0 (0-0)	.91	−0.001
Anticonvulsants	0 (0-0)	0 (0-0)	.93	0.001
SSRIs/SNRIs	0 (0-0)	0 (0-0)	.85	0.001
TCAs	0 (0-0)	0 (0-0)	.82	−0.002
Anxiolytics	0 (0-0)	0 (0-0)	.74	0.003
Statins	0 (0-1)	0 (0-1)	.64	0.004
ARBs	0 (0-0)	0 (0-0)	.96	−0.000
ACE inhibitors	0 (0-1)	0 (0-1)	.91	0.001
Antiarrhythmics	0 (0-0)	0 (0-0)	.81	0.002
β-Blockers	0 (0-1)	0 (0-1)	.65	0.004
Calcium channel blockers	0 (0-1)	0 (0-1)	.57	0.004
Diuretics	0 (0-1)	0 (0-1)	.98	0.000
Oral antidiabetics	0 (0-0)	0 (0-0)	.99	0.000
Other lipid-lowering medications	0 (0-0)	0 (0-0)	.71	0.003
Other antihypertensive medications	0 (0-0)	0 (0-0)	.84	0.002
Nitrate antianginal medications	0 (0-0)	0 (0-0)	.59	0.004
Other bronchodilators	0 (0-1)	0 (0-1)	.73	0.003
β-Agonists	0 (0-1)	0 (0-1)	.61	0.004
Theophyllines	0 (0-0)	0 (0-0)	.87	0.001
Metformin, No. (%)	2394 (7.5)	2370 (7.4)	.72	0.003
Insulin, No. (%)	3542 (11.1)	3550 (11.1)	.92	−0.001
Digoxin, No. (%)	2600 (8.2)	2582 (8.1)	.79	0.002
Warfarin, No. (%)	3738 (11.7)	3729 (11.7)	.91	0.001
Lithium, No. (%)	72 (0.2)	69 (0.2)	.80	0.002
Corticosteroids, No. (%)	6340 (19.9)	6333 (19.9)	.94	0.001
Antibiotics within 90 d prior to hospitalization, No. (%)	9986 (31.3)	9921 (31.1)	.57	0.004

Abbreviations: ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers; IQR, interquartile range; SSRIs/SNRIs, selective serotonin reuptake inhibitors/serotonin–norepinephrine reuptake inhibitors; TCAs, tricyclic antidepressants.

combination antimicrobial therapy including azithromycin while 34 903 patients received other guideline-concordant antimicrobial therapies. eTable 1 in the Supplement shows the key characteristics by use of azithromycin.

Of the 73 690 patients we identified who met the study criteria, the propensity-matched group was composed of 63 726 patients: 31 863 azithromycin users and 31 863 matched nonusers. Table 1 and Table 2 show the balance between key variables after propensity matching. There were no significant differences between groups for any of the key characteristics. The median duration of follow-up was 466 days (IQR, 140-998).

Outcomes

In the propensity-matched cohort, 90-day mortality was 17.4% (95% CI, 17.0%-17.9%) for azithromycin users as compared with 22.3% (95% CI, 21.8%-22.7%) for nonusers ($P < .001$). For any cardiovascular event, 43.0% (95% CI, 42.5%-43.6%) of the azithromycin users had at least 1 vs 42.7% (95% CI, 42.2%-43.2%) of nonusers ($P = .38$). For myocardial infarction, 5.1% (95% CI, 4.8%-5.3%) of the azithromycin users had at least 1 vs 4.4% (95% CI, 4.2%-4.6%) of nonusers ($P < .001$). Cardiac arrhythmias occurred within 90 days in 25.8% (95% CI, 25.3%-26.2%) of azithromycin users and 26.0% (95% CI, 25.5%-26.5%) of nonusers ($P = .52$). Heart failure occurred in 26.3% (95% CI, 25.8%-26.8%) of azithromycin users and 26.2% (95% CI, 25.7%-26.7%) of nonusers ($P = .73$).

Both 30-day mortality (OR, 0.76; 95% CI, 0.73-0.80) and 90-day mortality (OR, 0.73; 95% CI, 0.70-0.76) were significantly lower for azithromycin users. **Figure 1** shows mortality and demonstrates that those who received azithromycin had significantly lower mortality ($P < .001$). We found an increased odds of myocardial infarction among those who received azithromycin (OR, 1.17; 95% CI, 1.08-1.25). However, there was no significant increase in any cardiac event (OR, 1.01; 95% CI, 0.98-1.05), cardiac arrhythmia (OR, 0.99; 95% CI, 0.95-1.02), or heart failure (OR, 1.01; 95% CI, 0.97-1.04). **Figure 2** shows time to any cardiac events after admission and demonstrates that azithromycin users had significantly higher numbers of cardiac events ($P = .01$).

Secondary Analyses

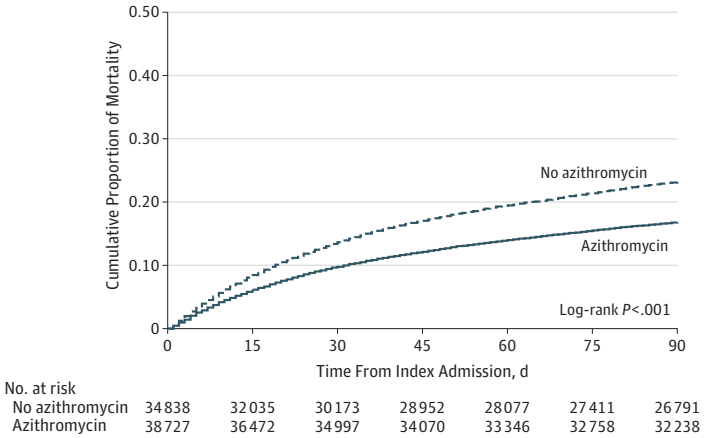
Using the entire cohort (N = 73 690), we examined key subgroups that might be at increased risk for death and cardiovascular events (eg, history of diabetes) or whose results might

Table 3. Secondary Analysis of the Association of Azithromycin With Mortality and Cardiovascular Outcomes

	Events per No. of Azithromycin Users	Events per No. of Nonusers	Odds Ratio (95% CI)
Entire cohort (N = 73 690)	(n = 38 787)	(n = 34 903)	
30-Day mortality	3848	4819	0.77 (0.73-0.81)
90-Day mortality	6582	8152	0.73 (0.70-0.76)
Any CV event (90 d)	16 873	14 895	1.02 (0.99-1.06)
Heart failure (90 d)	10 163	9176	1.03 (0.99-1.07)
Myocardial infarction (90 d)	1948	1523	1.11 (1.03-1.20)
Cardiac arrhythmia (90 d)	10 303	9002	0.99 (0.95-1.03)
No prior outpatient antibiotics (n = 50 930)	(n = 27 249)	(n = 23 691)	
30-Day mortality	2638	3155	0.78 (0.73-0.83)
90-Day mortality	4486	5329	0.74 (0.71-0.78)
Any CV event (90 d)	11 895	10 066	1.02 (0.97-1.06)
Heart failure (90 d)	7076	6207	0.996 (0.95-1.05)
Myocardial infarction (90 d)	1394	1023	1.13 (1.03-1.24)
Cardiac arrhythmia (90 d)	7350	6012	1.02 (0.97-1.07)
Prior cardiac disease (n = 21 280)	(n = 10 951)	(n = 10 329)	
30-Day mortality	1230	1648	0.74 (0.67-0.80)
90-Day mortality	2112	2720	0.72 (0.67-0.77)
Any CV event (90 d)	8153	7561	1.04 (0.97-1.11)
Heart failure (90 d)	6585	6091	1.05 (0.98-1.11)
Myocardial infarction (90 d)	1099	883	1.15 (1.04-1.27)
Cardiac arrhythmia (90 d)	4257	3954	0.97 (0.91-1.03)
History of diabetes (n = 26 280)	(n = 13 800)	(n = 12 480)	
30-Day mortality	1311	1637	0.79 (0.73-0.86)
90-Day mortality	2200	2779	0.74 (0.69-0.79)
Any CV event (90 d)	6704	5953	1.04 (0.98-1.10)
Heart failure (90 d)	4519	4039	1.06 (0.997-1.13)
Myocardial infarction (90 d)	811	639	1.12 (0.99-1.25)
Cardiac arrhythmia (90 d)	3707	3260	1.002 (0.94-1.07)
Admitted to ICU (n = 11 731)	(n = 5919)	(n = 5812)	
30-Day mortality	1517	1774	0.88 (0.81-0.97)
90-Day mortality	2111	2563	0.78 (0.72-0.85)
Any CV event (90 d)	3572	3358	1.11 (1.02-1.20)
Heart failure (90 d)	2132	2002	1.11 (1.01-1.21)
Myocardial infarction (90 d)	370	314	1.16 (0.98-1.38)
Cardiac arrhythmia (90 d)	2381	2238	1.04 (0.95-1.13)
Mechanical ventilation required (n = 4012)	(n = 2022)	(n = 1990)	
30-Day mortality	784	843	0.93 (0.81-1.07)
90-Day mortality	1037	1163	0.81 (0.70-0.93)
Any CV event (90 d)	1237	1123	1.24 (1.08-1.43)
Heart failure (90 d)	753	669	1.20 (1.04-1.40)
Myocardial infarction (90 d)	105	76	1.42 (1.01-1.98)
Cardiac arrhythmia (90 d)	788	763	0.98 (0.85-1.13)
Female only (n = 1279)	(n = 638)	(n = 641)	
30-Day mortality	54	81	0.61 (0.40-0.93)
90-Day mortality	97	123	0.73 (0.52-1.04)
Any CV event (90 d)	245	239	1.04 (0.78-1.38)
Heart failure (90 d)	155	147	1.17 (0.83-1.65)
Myocardial infarction (90 d)	16	20	0.80 (0.36-1.79)
Cardiac arrhythmia (90 d)	150	142	1.02 (0.74-1.39)

Abbreviations: CV, cardiovascular; ICU, intensive care unit.

Figure 1. Survival Curves by Azithromycin Use vs Nonuse

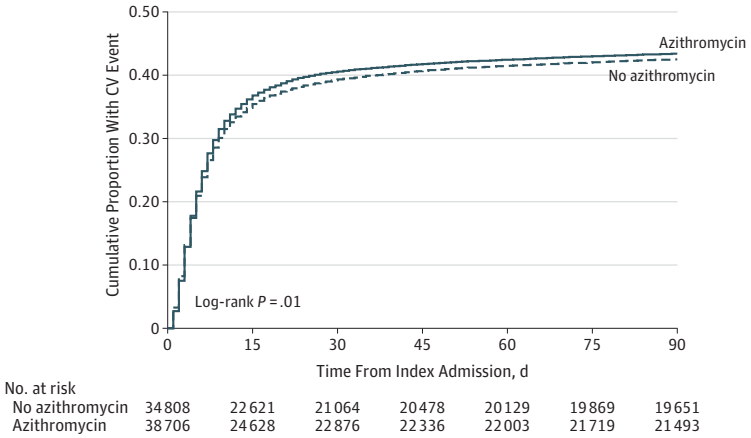


No. at risk

No azithromycin	34838	32035	30173	28952	28077	27411	26791
Azithromycin	38727	36472	34997	34070	33346	32758	32238

Not included in this analysis were 125 patients who died on the same day as admission.

Figure 2. Time to First Cardiac Event by Azithromycin Use vs Nonuse



No. at risk

No azithromycin	34808	22621	21064	20478	20129	19869	19651
Azithromycin	38706	24628	22876	22336	22003	21719	21493

Cardiovascular events were myocardial infarction, heart failure, and cardiac arrhythmia. Not included in this analysis were 176 patients who had a cardiovascular event on the same day as admission.

Table 4. Results of Instrumental Variable Analyses

	Second-Stage Azithromycin Coefficient in Logit (Bootstrapped 95% CI)	Adjusted Predicted Probability		Average Marginal Effect of Azithromycin (Bootstrapped 95% CI)
		Azithromycin Users (Bootstrapped 95% CI)	Nonusers (Bootstrapped 95% CI)	
30-Day mortality	−0.56 (−0.71 to −0.41)	0.09 (0.09 to 0.10)	0.15 (0.14 to 0.16)	−0.05 (−0.07 to −0.04)[a]
90-Day mortality	−0.60 (−0.73 to −0.47)	0.16 (0.16 to 0.17)	0.25 (0.24 to 0.26)	−0.08 (−0.10 to −0.07)
Any CV event	−0.02 (−0.14 to 0.08)	0.43 (0.42 to 0.44)	0.43 (0.42 to 0.44)	−0.004 (−0.02 to 0.02)
Heart failure	−0.27 (−0.41 to −0.15)	0.25 (0.24 to 0.25)	0.28 (0.27 to 0.29)	−0.04 (−0.06 to −0.02)
MI	0.71 (0.47 to 0.95)	0.06 (0.06 to 0.07)	0.03 (0.03 to 0.04)	0.03 (0.02 to 0.04)
Arrhythmia	0.08 (−0.04 to 0.21)	0.27 (0.26 to 0.28)	0.26 (0.25 to 0.27)	0.01 (−0.01 to 0.03)

Abbreviations: CV, cardiovascular; MI, myocardial infarction.

[a] Sample interpretation: azithromycin users had a 5% lower probability of 30-day mortality than nonusers.

be partially confounded (those with prior antibiotic use). Table 3 summarizes these results. Results were similar to the propensity-matched analyses except that for a few outcomes, the results were no longer statistically significant. For female patients (n = 1279), there was a protective association but no significant association with cardiac events even though the ORs were similar to other subgroups. Ten-day mortality and cardiovascular outcomes were similar to those found in the overall analysis for differing subgroups (eTable 2 in the Supplement).

In the instrumental variable analyses (**Table 4**), it was found that azithromycin users had a 5% lower probability of 30-day

mortality than nonusers (95% CI, −7% to −4%) and an 8% lower probability of 90-day mortality than nonusers (95% CI, −10% to −7%). There were no statistically significant differences in any cardiac events or arrhythmias, but there was a significant increase in the probability of myocardial infarction of 3% for azithromycin users (95% CI, 2% to 4%). In contrast to the other findings, in these analyses we found a decrease in the probability of heart failure for azithromycin users of 4% (95% CI, −6% to −2%).

Discussion

In this national cohort study of veterans hospitalized with pneumonia, azithromycin use was consistently associated with decreased mortality and a slightly increased odds of myocardial infarction. This study supports the current IDSA/ATS guidelines for community-acquired pneumonia[2] that recommend the use of azithromycin as part of combination therapy for patients hospitalized with pneumonia.

Although we found a survival benefit, we also observed that azithromycin was associated with a significant but small increase in the odds of myocardial infarction as compared with other guideline-concordant therapies. To put the balance of benefits and harms in context, based on the propensity-matched analysis, the number needed to treat with azithromycin was 21 to prevent 1 death within 90 days, compared with a number needed to harm of 144 for myocardial infarction. This corresponds to a net benefit of around 7 deaths averted for 1 nonfatal myocardial infarction induced.

These results also partly confirm the findings of Ray et al[10] that azithromycin is associated with increased odds of cardiovascular events. They found that azithromycin users, as compared with nonantibiotic users (hazard ratio [HR], 2.88; 95% CI, 1.79-4.63) or amoxicillin users (HR, 2.49; 95% CI, 1.38-4.50) had an increased risk of cardiovascular death. Yet the risk of cardiovascular death was similar for those who received the respiratory fluoroquinolone levofloxacin (HR, 1.27; 95% CI, 0.66-2.47), which is another guideline-concordant option for the treatment of pneumonia. In addition, their study did not document whether patients actually had an appropriate indication for antibiotic therapy.

These findings are consistent with previous research that suggests that azithromycin causes QT prolongation,[8,9] which may lead to cardiac arrhythmias. Despite this potential increased risk of arrhythmias and myocardial infarction, azithromycin lacks the appreciable drug-drug interactions seen with other macrolide antibiotics; it is considered the safest of all macrolide antibiotics from a cardiac perspective.[24] We are unsure how azithromycin would lead to heart failure or myocardial infarction except for demand ischemia/cardiac dysfunction. In addition, it is important to note that numerous studies have demonstrated that many patients hospitalized with pneumonia have some type of cardiac event at the time of hospitalization or soon after.[20,25,26] Therefore, it is difficult to differentiate between cardiac events secondary to azithromycin use vs effects of the underlying infection.

This study's results raise the question: why would azithromycin be associated with a mild increased odds of cardiac events but decreased odds of mortality? The beneficial effects of azithromycin, and of macrolides in general, as compared with other guideline-concordant antibiotic regimens for pneumonia may be due less to their antimicrobial properties but more to their effect on immune function. Previous studies have demonstrated that macrolides have significant anti-inflammatory effects.[27-30] The efficacy of macrolides as immune modulators is demonstrated when used in the treatment of diffuse panbronchiolitis. This autoimmune lung condition had a 70% 5-year mortality rate until long-term erythromycin therapy was found to reduce mortality to less than 20%.[31-33] Macrolide antibiotics are also now being used in a variety of respiratory diseases as immunomodulatory agents, including cystic fibrosis, bronchiectasis, post-lung transplant obliterative bronchiolitis, and asthma.[34,35] Unfortunately, there is little research to our knowledge of short-term administration of macrolides so this is only a hypothesis.

Numerous studies have demonstrated that combination therapy with a β-lactam plus macrolide is superior to β-lactam–only therapy in community-acquired pneumonia.[3-5,36-39] Therefore, the current ATS/IDSA clinical practice guidelines for community-acquired pneumonia recommend that if a β-lactam is used that it be combined with macrolides, fluoroquinolones, or doxycycline, depending on the site of care.[2] Other smaller observational studies of severe pneumonia suggest that combination antibiotic therapies with macrolides have superior outcomes to fluoroquinolones alone or other combination therapies including fluoroquinolones.[40-44] One study demonstrated that patients who received a β-lactam plus fluoroquinolone had significantly higher mortality than those who received a β-lactam plus macrolide (OR, 2.71; 95% CI, 1.2-6.1).[41]

There were a number of limitations in this study. This older VA patient population had only a small number of female patients, so although there were no significant associations with any cardiac events, we believe that the outcomes are similar to those for the entire population. This analysis was restricted to those 65 years and older because younger patients are at lower risk for both cardiac events and pneumonia. Another limitation was reliance on *ICD-9* diagnosis of cardiovascular events rather than clinical information, which particularly may affect the diagnosis of heart failure. Not infrequently there is clinical confusion about whether patients have heart failure, pneumonia, or both. We are unable to determine the extent to which these conditions may have been improperly differentiated. However, due to the definition of pneumonia used in this study, treating physicians most likely believed that pneumonia was present and that there would be no bias toward or against azithromycin use.

In addition, although the *ICD-9* codes that were used have been previously validated in other populations, they have not been in VA administrative data. Also, the outcomes were assessed retrospectively and we lacked Medicare data to ascertain non-VA events, so some cardiac events were not detected, but we do not believe there would be differential

ascertainment between treatment groups. Next, we were unable to assess the duration of azithromycin therapy because of the design of the study database. In addition, we did not examine specific causes of death; however, previous studies have documented poor correlation between death certificate data and actual cause of death.[45] Furthermore, prior to propensity matching, the patients exposed to azithromycin did have a number of small but significant differences from unexposed patients (eTable 1 in the Supplement), suggesting that the patients treated with azithromycin may have been less severely ill. Our propensity matching was successful in producing 2 groups with similar measured characteristics, so we are confident that we at least have appropriately accounted for these measured factors; however, it remains possible that unmeasured confounders could potentially bias these results.

Conclusions

Among older patients hospitalized with pneumonia, treatment that included azithromycin compared with other antibiotics was associated with a lower risk of 90-day mortality (number needed to treat of 21) in exchange for a smaller increased risk of cardiac events (number needed to harm of 144 for myocardial infarction). These findings are consistent with a net benefit associated with azithromycin use in patients hospitalized for pneumonia.

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Administrative, technical, or material support: Mortensen, Pugh, Frei, Good.
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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Copeland reported having received grants from the National Institute of Nursing Research, the Veterans Health Administration, and Xenex Corp. Dr Metersky reported having been a speaker/consultant for Pfizer until 2011. Dr Frei reported having received grants from Bristol-Myers Squibb, Ortho-McNeil Janssen, Pfizer, and Forest. No other disclosures were reported.

Funding/Support: This study was supported by a grant from the National Institute of Nursing Research (R01NR010828), and Dr Restrepo was supported by the National Heart, Lung, and Blood Institute (K23HL096054). This material is the result of work supported with resources and the use of facilities at the VA North Texas Health Care System.

Role of the Sponsor: The funding sources had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer: The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs, National Institute of Nursing Research, or the National Institutes of Health.

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