NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: The Acute Effects of Azithromycin Use on Cardiovascular Mortality, as Compared with Amoxicillin-Clavulanate in Veterans.

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Rationale & Background:

The study examined the acute effects on cardiovascular (CV) mortality of azithromycin use in comparison to amoxicillin-clavulanate use among patients with a respiratory or ear-nose-throat (ENT) infection, for which these antibiotics are commonly indicated. The possible association between an increased acute risk of CV death and treatment with azithromycin over other antibiotics, including amoxicillin (with and without clavulanate), has been a recurrent topic of research following initial findings reported by Ray et al. (2012), who also suggested that attributable risk might be highest in persons with a high baseline risk.[1] Subsequent observational studies, including by Svanström et al. (2013),[2] Rao et al. (2014),[3] Mortensen et al. (2014),[4] Trifirò et al. (2017),[5] and Chou et al. (2015),[6] have also investigated similar potential associations with inconsistent and largely negative results.

A qualitative assessment of these past studies reveals critical limitations, including potential conflation of effects by patients' use of multiple antibiotics in a short period of time, missing antibiotic indication information, a lack of adjustment for covariates occurring close to the index antibiotic dispensing, poor balance of baseline characteristics between comparator groups even after adjustment, and channeling of azithromycin use into high-risk indications. Addressing such limitations is crucial to accurately assess whether azithromycin is associated with an increased risk of CV death as compared to amoxicillin-clavulanate for a respiratory or ENT infection indication.

Research Question & Objectives:

This observational study investigated acute effects on CV mortality of azithromycin use relative to amoxicillin-clavulanate use among patients with a respiratory or ENT infection indication. The study was conducted using the US Veterans Health Administration (VHA) database.

Primary Objective:

The study estimated the hazard ratios (HRs) and risk differences (RDs) of CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days of dispensed prescription for a respiratory or ENT infection indication.

Subgroup analyses:

1. CV death among those with a history of CV disease.

2. CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.

Secondary Objective:

The study also estimated the HRs and RDs of non-CV death for azithromycin users as compared to amoxicillin-clavulanate users among persons 30-74 years of age within 1-5 and 6-10 days of dispensed prescription, for a respiratory or ENT infection indication.

Subgroup analyses:

1. Non-CV death among those with a history of CV disease.

2. Non-CV death among those with high baseline CV mortality risk as defined by a CV mortality risk score.

Study design:

Retrospective cohort study.

Setting:

This study included veterans enrolled in the VHA who received an outpatient prescription dispensing for azithromycin or amoxicillin-clavulanate during 2000 to 2014 for a respiratory or ENT infection indication. Dispensings were the unit of observation for this study.

Subjects and study size, including dropouts:
For the respiratory indication, 629,345 azithromycin dispensings and 168,429 amoxicillin-clavulanate dispensings were included in the study; for the ENT indication, 143,783 azithromycin dispensings and 203,142 amoxicillin-clavulanate dispensings were included. These final sample sizes were achieved after applying the study eligibility criteria and trimming the propensity score used for confounding adjustment. This total sample size allowed for the minimum detectable HR of 2.09 for CV death within 1-5 days and an HR of 2.28 for CV death within 6-10 days with 90% power.

Variables and data sources:
Variables:

- Exposures: Antibiotic prescription dispensing for azithromycin or amoxicillin-clavulanate.

- Outcomes: CV death (primary outcome), non-CV death (secondary outcome), and cardiac death (only considered for sensitivity analysis).

- Key covariates: Statistical analyses adjusted for: CV conditions and medications (CV medications were assessed on the date of antibiotic dispensing, and within 1-7 days, 8-30

days, and 31-365 days prior to antibiotic dispensing); demographic factors (age, gender, race/ethnicity, marital status); frailty index; other baseline medical comorbidities (e.g., respiratory, neurologic, and psychiatric conditions); other baseline non-CV medications (e.g., opioids and psychiatric drugs, assessed on the day of antibiotic dispensing, and within 1-7 days, 8-30 days, and 31-365 days prior to antibiotic dispensing); baseline health care utilization variables (e.g., number of CV-related office visits, emergency department [ED] visits assessed on the day of antibiotic dispensing, and within 1-7 days, 8-30 days, and 31-365 days prior to antibiotic dispensing); and CV mortality risk score.

- Key effect measure modifiers: History of prior CV disease in baseline and baseline CV mortality risk as measured by a CV mortality risk score.

Statistical methods:

The study used proportional hazards analyses with inverse probability of treatment weighting (IPTW) to estimate the relative risk of CV death, non-CV death, and cardiac death (as a sensitivity analysis) associated with azithromycin versus amoxicillin-clavulanate. Specifically, HRs for azithromycin vs. amoxicillin-clavulanate were estimated using a Cox proportional hazards model. Binomial regression was used to estimate RDs comparing azithromycin to amoxicillin-clavulanate for the primary and secondary outcomes. Risks (cumulative incidences) were reported for the primary analysis as the number of outcome events divided by the number of treatment episodes at risk. All analyses were conducted separately for respiratory and ENT indications.

Data were also pooled across indications using standard meta-analytic techniques. Pooled regression analyses were also performed, using a Cox proportional hazards model with a random effect to adjust for indication to provide a single overall estimate for the study. A pooled RD was estimated using a GEE model that included an indicator variable for each indication stratum.

Sensitivity analyses were conducted using a risk period of 1-10 days following the index antibiotic dispensing. Sensitivity analyses considering cardiac death, dispensings to Priority Group 1 veterans [patients who are the highest priority for VHA care due to the highest levels of service-connected disability, ensuring they are more likely to receive all of their care from a VHA facility], dispensings to patients age ≤65 years, etc. were also conducted.

Data source: This study used data from the VHA's Corporate Data Warehouse (CDW), an integrated electronic medical record (EMR) system with a centralized data warehouse that contains information on all outpatient visits, hospital stays, treatments, dispensed prescriptions, and laboratory results as well as billing and benefits information of veterans who seek care at a VHA facility. The CDW only includes information on care received within a VHA facility. In combination with CDW data, the study also used data from the United States (US) National Death Index (NDI) to verify cause of death.

Results:

Respiratory indication

For the respiratory indication, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.12 (95% CI: 0.63, 2.00) within 1-5 days and 0.65 (95% CI: 0.36, 1.16) within 6-10 days. The HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.26 (95% CI: 0.77, 2.07) within 1-5 days and 1.05 (95% CI: 0.60, 1.86) within 6-10 days.

The RD of CV death for azithromycin compared to amoxicillin-clavulanate was 11 (95% CI: -43, 64) per million dispensings within 1-5 days and -39 (95% CI: -98, 20) per million dispensings within 6-10 days. The RD of non-CV death for azithromycin compared to amoxicillin-clavulanate was 26 (95% CI: -27, 80) per million dispensings within 1-5 days and 5 (95% CI: -47, 57) per million dispensings within 6-10 days.

ENT indication

For the ENT indication, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 0.46 (95% CI: 0.09, 2.30) within 1-5 days and 0.70 (95% CI: 0.22, 2.29) within 6-10 days. The HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 2.18 (95% CI: 0.36, 13.14) within 1-5 days and 1.24 (95% CI: 0.27, 5.64) within 6-10 days.

The RD of CV death for azithromycin compared to amoxicillin-clavulanate was -16 (95% CI: -46, 14) per million dispensings within 1-5 days and -14 (95% CI: -60, 31) within 6-10 days. The RD of non-CV death for azithromycin compared to amoxicillin-clavulanate was 11 (95% CI: -16, 39) per million dispensings within 1-5 days and 5 (95% CI: -32, 41) per million dispensings within 6-10 days.

Pooled analyses across indications

After applying standard meta-analytic techniques to pool results across indications, the HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.00 (95% CI: 0.55, 1.81) within 1-5 days and 0.66 (95% CI: 0.39, 1.11) within 6-10 days. The HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.31 (95% CI: 0.81, 2.12) within 1-5 days and 1.07 (95% CI: 0.63, 1.83) within 6-10 days.

Similar results were obtained from random effects Cox proportional hazards regression analyses. The HR of CV death for azithromycin compared to amoxicillin-clavulanate was 1.07 (95% CI: 0.64, 1.80) within 1-5 days and 0.67 (95% CI: 0.40, 1.13) within 6-10 days. The HR of non-CV death for azithromycin compared to amoxicillin-clavulanate was 1.26 (95% CI: 0.79, 2.00) within 1-5 days and 1.07 (95% CI: 0.63, 1.82) within 6-10 days.

The RD for CV death from meta-analysis of pooled results across indications comparing azithromycin to amoxicillin-clavulanate was -10 (95% CI: -36, 17) per million dispensings within 1-5 days and -23 (95% CI: -59, 13) per million dispensings within 6-10 days. The RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 14 (95% CI: -10, 39) per million dispensings within 1-5 days and 5 (95% CI: -25, 35) per million dispensings within 6-10 days.

Similar results were seen when pooling data across indications for a single RD estimate from GEE model that included an indicator term for indication; the RD for CV death comparing

azithromycin to amoxicillin-clavulanate was 5 (95% CI: -33, 43) per million dispensings within 1-5 days and -30 (95% CI: -73, 13) per million dispensings within 6-10 days. The RD for non-CV death comparing azithromycin to amoxicillin-clavulanate was 20 (95% CI: -19, 59) per million dispensings within 1-5 days and 5 (95% CI: -33, 43) per million dispensings within 6-10 days.

Sensitivity analyses

Results of various subgroup and sensitivity analyses generally confirmed the above results. This includes the sensitivity analyses using a 1-10 day outcome assessment window, which supported the conclusions seen in the separate 1-5 and 6-10 day windows, and analyses of cardiac death.

Discussion: In this study of over 1 million dispensings of azithromycin versus amoxicillin-clavulanate for respiratory indications and ENT indications (assessed separately), there is no evidence of an increased risk of CV death. The lack of evidence disfavoring azithromycin extends to non-CV death and cardiac death (assessed in a sensitivity analysis) within 1-5 and 6-10 days of antibiotic dispensings. This conclusion also persists in subgroups with higher risk of baseline CV death and across sensitivity analyses, including when the 1-10 day outcome window was assessed.

This study focused on respiratory or ENT indications, which account for most azithromycin use in the VHA system. Since the indications themselves are expected to be associated with different risks of CV death, and influence the choice of azithromycin over amoxicillin-clavulanate, analyses were conducted in parallel for the two indication groups and combined using meta-analysis.

Residual confounding is always a remaining concern for retrospective, observational studies. To the extent possible, this study attempted to address concerns about sources of bias via study design and statistical methods. Since there is no known biological or clinical mechanism associated with azithromycin that may increase risk of non-CV death, the null findings for non-CV death further confirmed that residual confounding was unlikely to impact results of this study.

The study was prompted by findings from Ray et al. (2012) who reported a small absolute increase in CV deaths during 5 days of azithromycin therapy. Though Ray et al. (2012) hypothesized that azithromycin may increase the risk of CV death, potentially due to QT prolongation resulting in ventricular arrhythmia and sudden cardiac death (SCD), their data could not establish a specific causal mechanism for this finding. In addition, while Ray et al. (2012) found a small increase in risk of CV death associated with azithromycin, this was not found in the current study. Similar to Ray et al. (2012), the present study excluded patients with serious illnesses, included a summary measure of CV mortality risk and a frailty index, and used propensity score-based methods for confounding control. However, the study also made improvements to the methodology employed by Ray et al. (2012). Specifically, key strengths of the design and analysis of the present study are: (1) empirical choice for the antibiotic comparator of amoxicillin-clavulanate; (2) restriction of the study population to dispensings with respiratory and ENT indication; (3) application of an antibiotic washout period of 60 days prior to index to minimize conflation of effects from other antibiotics; (4) use of NDI-coded CV death

as the study outcome; (5) validation of the algorithm used to identify antibiotic indication; (6) stratification by baseline risk for CV death based on history of CV disease and a CV mortality risk score; (7) inclusion of concurrent, recent past, and distant past measures of baseline characteristics; (8) inclusion of a frailty index; and (9) use of IPTW for confounder control.

The results of this study are consistent with some and contrast with other published studies that have examined similar research questions. However, the rigorous design and statistical analysis implemented in this study allow it to present strong evidence that there is no meaningful relationship between azithromycin and CV death.

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