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

First published: 11/01/2017

Last updated: 30/01/2025

Study Finalised

Administrative details

EU PAS number

EUPAS17206

Study ID

39503

DARWIN EU® study

No

Study countries

United States

Study description

The purpose of this observational study is to examine the effects of azithromycin use on cardiovascular (CV) mortality. This observational study was preceded by four recently published retrospective cohort studies by Ray et al. (2012), Svanstrom et al. (2013), Rao et al. (2014), and Mortensen et al. (2014), which examined this, or a related research question. These studies have produced conflicting results, but taken together suggest a possible association between azithromycin use and acute CV risk, most notably in patients with pre existing CV risk at baseline. An additional observational study with sufficient power is required to further assess the potential CV signal. This observational study will be conducted in the Veterans Health Administration (VHA) database, as it closely resembles the study cohort in Ray et al. (2012), and will have sufficient power within high baseline CV risk subgroups, a population of particular interest for this research question.

Study status

Finalised

Contact details

Study institution contact

Vera Frajzyngier vera.frajzyngier@pfizer.com

Study contact

vera.frajzyngier@pfizer.com

Primary lead investigator

Vera Frajzyngier

Primary lead investigator

Study timelines

Date when funding contract was signed
Planned: 05/08/2016

Actual: 05/08/2016

Study start date
Planned: 31/03/2017

Actual: 12/04/2017

Date of final study report
Planned: 28/02/2020

Actual: 19/02/2020

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Pfizer

Study protocol

A0661211_PROTOCOL _02DEC2016.doc.pdf (2.36 MB)

A0661211_PROTOCOL_V3_Amendment 2_CLEAN_19JUL2019.doc.pdf (2.06 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

EU RMP category 3 (required)

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

This observational study will investigate acute effects of azithromycin use on cardiovascular mortality in comparison to amoxicillin-clavulanate, among patients with a respiratory or ear, nose or throat (ENT) infection indication of use.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Study drug International non-proprietary name (INN) or common name

AZITHROMYCIN

AMOXICILLIN

Population studied

Short description of the study population

This study will be conducted among veterans enrolled in the VHA.

Patients must meet the following inclusion criteria to be eligible for inclusion in the study:

Inclusion Criteria:

1. Dispensation of an outpatient or inpatient prescription for azithromycin or amoxicillin between 01 Jan 2000 and 31 Dec 2014. If a patient had more than one prescription dispensing within this period, each exposure will be counted separately (thus, individuals may contribute multiple prescription dispensings to the analysis), and the index date of each exposure will be identified as the first day the exposure meets the inclusion criteria. The second prescription fill will be excluded if it occurs <10 days from the first dispensing.
2. Only oral prescription dispensings will be included (not intravenous or ophthalmic) and amoxicillin-clavulanate prescription dispensings will also be included in the amoxicillin group.
3. Patients with regular use of VHA medical care, defined as at least two outpatient (excluding emergency department [ED], as ED visits may not be

considered regular) or inpatient encounters in the one year prior to index antibiotic prescription dispensing will be included. The encounters must be separated by >30 days (for inpatient, by admission date), and at least one must be within 6 months prior to the index antibiotic prescription dispensing. This will ensure that patients have ongoing health care encounters, particularly near the index date, and regularly receive their healthcare from VHA facilities, rather than outside facilities, which may be financially covered/ reimbursed by the VHA, but will not be captured in the VHA EMR system.

Patients meeting any of the following criteria will not be included in the study:
Exclusion Criteria:
1. Missing date of birth or gender.
2. Age < 30 or >74 years on the index date (the date of the index antibiotic prescription dispensing).
3. Not enrolled in/disenrolled from VHA benefits during the 365 days prior to the index date. This criterion ensures capture of potential confounders and effect measure modifiers.
4. No pharmacy dispensings (other than the index antibiotic) during the one year prior to the index date. This criterion ensures patients use VHA to fill prescriptions.
5. More than one type of study antibiotic prescribed on the index date, or within 10 days prior (ie, wash-out period).
6. Residing in a nursing home or other residential institution on the index date or at any time in the preceding 365 days, except for stays of <30 days following hospital discharge. Since the VHA contains data only on VHA-paid nursing homes and nursing home residency in patients with Medicare, this definition also
includes inferred nursing home stays. Inferred nursing home stays will be defined as 2 or more outpatient encounters in the year leading up to the index

prescription dispensing date with procedure codes indicating nursing home place of service separated by at least 28 days. It also includes external cause of injury diagnosis code indicating place of residence was an institution. This criterion considers that the cause of death information recorded on death certificates, and therefore the NDI, within a nursing home setting may be less accurate.

Age groups

- Adults (18 to < 46 years)
- Adults (46 to < 65 years)
- Adults (65 to < 75 years)

Estimated number of subjects

4.100.000

Study design details

Outcomes

Cardiovascular death, Non-cardiovascular death

Data analysis plan

The analysis will generate cumulativeincidences and estimate hazard ratios (HR) and risk differences (RD) for CV and non-CV death occurring within 10 days of azithromycin and amoxicillin-clavulanate dispensing for a respiratory or ENT indication of use, stratified by indication. Event rates will be further compared among those with either a prior history of CV disease or a high CV mortality risk score. Inverse probability of treatment weights (IPTW) will be used to control confounding, variables that are imbalanced after weighting will be included as covariates in the regression model. Standard meta-analytic techniques will be used to pool HR and RD estimates for the respiratory and ENT indication of use

populations.

Documents

Study results

a0661211-report-body.pdf (4.2 MB)

Study, other information

a0661211-abstract.pdf (562.9 KB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No