IMI PROTECT – Work Package 6 / negative control antibiotics and acute myocardial infarction

STUDY REPORT

Assessment of the absence of an association between antibiotics and acute myocardial infarction

Version 21 July 2014

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1. Context

The study described in this report was performed within the framework of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Work package 6 "validation on methods involving an extended audience". This work package aims to test the transferability/feasibility of methods developed in WP2 to 5 (in particular WP2 and WP5) in a range of data sources owned or managed by Consortium Partners or members of the Extended Audience.

As defined in the WP6 research plan, the aim of this study is to evaluate if the tools proposed are specific enough not to detect an association that does not exist (negative control). As proposed in the public-private US initiative Observational Medical Outcomes Partnership (OMOP) [1, 2], the drug-event pair antibiotics and acute myocardial infarction (AMI) has been selected as a negative control in this study.

2. Objectives

The aim of the study was to assess the absence of an association between antibiotics use and AMI by replicating a nested case-control design in a US claims database (Clinformatics® datamart).

The study objectives of the replication were:

- To estimate the risk of AMI associated with antibiotics exposure (users and non-users)
- To estimate the risk of AMI associated with various antibiotics classes
- To estimate the risk of AMI associated with specific individual antibiotics

3. Methods

3.1 Data Source

The proposed study was conducted in the US Clinformatics datamart database (Optum Insight® formerly Ingenix®).

Clinformatics datamart is a large US health insurance database covering United HealthCare® insurance plans including Medicaid. The records are organized into a medical file, containing claims from providers and facilities, a pharmacy file with outpatient pharmacy dispensing records, a lab test file with outpatient lab tests records and an enrolment file that provides demographic data and dates of insurance eligibility for persons in the database. All of these files are linked at the individual level by an encrypted identifier.

Diagnoses on claims are recorded using International Classification of Diseases, Ninth Revision (ICD-9) diagnosis codes. Procedures are identified using Common Procedural Terminology (CPT), ICD, and Health Care Financing Agency (HCFA) Common Procedure Coding System (HCPCS) codes. Drugs are identified by National Drug Codes (NDC) and Hierarchical Ingredient Code List (HICL) codes.

3.2 Period of valid data collection

The period of valid data collection was defined as the period from the left censoring date up to the right censoring date. The left censoring date was the date that a patient

enrolled into the database. The right censoring date was the earliest of the following: the end of the database's data collection or the date that the patients left the plan (the end of the enrolment).

3.3 Study period

The study period started in January 2004 and ended in December 2009.

3.4 Study population

The study population was comprised of patients of all ages with an active or died registration status during the study period of January 1st, 2004 to December 31st, 2009 in the Clinformatics Data Mart. Patients had to have attained one year of enrolment in the database at the beginning of the study period and patients with a history of AMI will be excluded.
All patients from the study population were followed from the start date (date of first antibiotic prescription or assigned start date) until the earliest occurrence of one of the following endpoints: outcome or end of the study period.
We ascertained patients with the first recorded occurrence of acute myocardial infarction (AMI, outcome) and the date of diagnosis will be their index date (outcome date).

3.5 Outcome definition

The outcome for this study was the first recorded occurrence of AMI. AMI is coded in the International Classification of Diseases version 9 (ICD9) as 410.- (AMI).

4. Study Design

4.1 Population-based case-control study

4.1.1 Cases and controls

All cases, detected within the study population with a first recorded occurrence of AMI during the follow-up period from January 2004 until December 2009 were identified. The date of diagnosis of AMI was considered the index date of the cases and their matched controls.

Controls were sampled from the patients at risk at the time of occurrence of the case (incident or density sampling). Thus, for a given case, potential controls are all non-cases at the time of the occurrence of the event, including future cases. Controls can therefore be cases later on. Controls were matched to cases by age (within one year), sex, and calendar date (month & year). We selected up to five controls per case.

4.1.2 Exposure definition for the case-control analysis

4.1.2.1 Exposure definition for the main analysis

We defined patients as current users if a prescription for the drugs of interest (antibiotics) lasts until the index date or ends within 14 days prior to the index date (i.e. date of onset of AMI both in cases and their matched controls).
We defined patients as past users if the prescription ends between 14 and 365 days before the index date, and non-users, if there was no prescription in the year before the index date.

We estimated the risk associated with different antibiotics drug class categorized in the following groups: tetracyclines, penicillins, cephalosporins & betalactams, macrolides, quinolones and other antibiotics. The association between the use of antibiotics and the occurrence of AMI was estimated by comparing the odds of past and current users with the odds of non-users. Non-use of antibiotics was used as reference.

4.1.2.2 Exposure definition for the secondary analysis

We defined patients as current users if a prescription for the drugs of interest (antibiotics) lasts until the index date or ends within 30 days prior to the index date (i.e. date of onset of AMI both in cases and their matched controls).
We defined patients as past users if the prescription ends between 30 and 365 days before the index date, and non-users, if there was no prescription in the year before the index date.

4.1.3 Statistical Analyses

We computed odds ratios (OR) and 95% confidence intervals of first occurrence of AMI (see outcome definition) associated with current use of antibiotics (as a group and different classes and individual drugs when possible) as compared to non-use with conditional logistic regression. Age, sex, calendar year, and other variables (see Covariates) were introduced in the model to control for potential confounding. Also, dose and duration-relationships was examined. Separate analyses were done using only definite cases in a first step and definite and probable cases as a second step. Several strategies to select confounders were compared to assess the impact of the selection method on the results. For the analysis, the effect of core variables other than those used to match cases and controls was examined by constructing a series of bivariate models. Likelihood Ratio tests was used to compare models. We also fitted a full model, including all of the potential confounders.

We constructed different regression models, first including general confounders (age, sex, BMI, alcohol, smoking). And in a second step we also fitted a full model including all other potential confounders (comorbidities and drugs).

5. Results

5.1. Population, antibiotics used and incidence of AMI

5.1.1 Characteristics of study participants

Table 1 shows baseline characteristics of the study participants.

Table 1 : Baseline characteristics of study participants

	All patients (%) N = 19, 589,333
Gender (men)	49.7
Age group	
<18	24.5
18-29	16.9
30-49	34.9
50-64	18.5
>65	5.1
Arterial embolism and thrombosis	0.0
Atherosclerosis	0.2
Diabetes mellitus	3.3
Diabetic retinopathy	0.1
Disorders of lipoid metabolism	9.7
Glycosuria	0.0
Hypertensive disease	8.7
Ischemic heart	1.4
Impaired glucose tolerance test(oral)	0.0
Occlusion of cerebral arteries	0.1
Overweight and obesity	1.4
Peripheral vascular disease, unspecified	0.3
Polyneuropathy in diabetes	0.1
Secondary diabetes mellitus	0.0
Transient cerebral ischemia	0.1
Antithrombotic drugs	1.3
Lipid lowering drugs	7.6
NSAR	0.0
antidiabetics	3.1
cardiovascular drugs	12.7
corticosteroids for systemic use	8.0
drugs for obstructive airway diseases	7.7

5.1.2 Antibiotics used in study participants

A total 35.1% of participants used at least one antibiotic during the study period. Regarding antibiotic drug classes, the most frequently used classes were penicillins (14.9% of users) and macrolides (10.6% of users) (Table 2).

Table 2 : Distribution of antibiotics used in study participants (N=19,589,333)

	All patients (%)
Any antibiotics	35.1
Penicillins	14.9
Macrolides	10.6
Cephalosporins	6.1
Tetracyclines	2.5
Quinolones	1.0
Others	0.1

5.1.3 Incidence of AMI in study participants

The total person-time of the period of the observation of the cohort was 31,286,268.26 person-years. Overall the incidence of AMI was 1.61 per 1,000 person-years, 2.07 in men and 1.17 in women, respectively.

Table 3: Incidence rate of AMI in study participants, Clinformatics Datamart Database, (2004/01 – 2009/12)

	total	men	women
Number of cases	50,286	31,532	18,754
Number of patients	19,589,333	9,732,982	9,856,351
Follow-up (person-years)	31,286,268.26	15,209,378.31	16,076,889.95
Rate (per 1,000 p-ys)	1.61 (1.59, 1.62)	2.07 (2.05, 2.10)	1.17 (1.15, 1.18)

5.2. Case-control analyses

5.2.1 Characteristics of cases and controls

According to the definition, 50,286 cases were identified in the US Clinformatics Data Mart database between January 2004 and December 2009, and 251,366 controls were selected and matched on age at the index date and sex.

The mean age at index date was around 62.4 years and 37.3% were women. The characteristics of the cases and controls and the antibiotics they used are summarized in tables 4, 5 and 6.

Table 4 : Characteristics of cases (N=50,286) and controls (N= 251,366)

		Cases n = 50,286	Controls n = 251,366
Gender	Female (%)	37.3	37.3
Age (years)	Mean (SD)	62.4 ± 14.3	62.3 ± 14.3
Comorbidities	Diabetes mellitus (%)	19.7	9.6
	Disorders of lipoid metabolism (%)	31.2	25.0
	Hypertension (%)	19.7	9.6
	Ischemic heart disease (%)	19.0	6.8
	Cerebrovascular accident (%)	2.4	1.1
Treatments	Antithrombotic drugs (%)	13.8	6.3
	Lipid lowering drugs (%)	33.7	24.2
	Antidiabetics (%)	16.5	8.3
	Cardiovascular drugs (%)	55.2	38.5
	Corticosteroids for systemic use (%)	15.5	12.2
	Drugs for obstructive airway diseases (%)	11.0	10.3

Table 5 : Antibiotics use with the 14 days definition of current exposure

		Cases n = 50,286 %	Controls n = 251,366 %
Any antibiotic	Current user *	6.8	4.5
	Past user **	45.9	40.8
Penicillins and betalactams	Current user	2.1	1.6
	Past user	21.0	18.4
Macrolides	Current user	2.3	1.3
	Past user	19.2	16.3
Cephalosporins	Current user	1.5	0.9
	Past user	13.5	10.8
Tetracyclines	Current user	0.6	0.5
	Past user	5.3	4.6
Quinolones	Current user	0.4	0.2
	Past user	3.0	2.5
Other antibiotics and combinations	Current user	0.2	0.0
	Past user	0.3	0.2

*Current user:] 0; 14 days]; ** Past user:] 14; 365 days]

Table 6 : Antibiotics use with the 30 days definition of current exposure

		Cases n = 50,286 %	Controls n = 251,366 %
Any antibiotic	Current user *	11.4	8.2
	Past user **	41.2	37.1
Penicillins and betalactams	Current user	3.7	3.1
	Past user	19.3	17.0
Macrolides	Current user	3.9	2.5
	Past user	17.6	15,2
Cephalosporins	Current user	2.6	1.7
	Past user	12.4	10.0
Tetracyclines	Current user	1.1	1.0
	Past user	4.7	4.2
Quinolones	Current user	0.6	0.4
	Past user	2.8	2.3
Other antibiotics and combinations	Current user	0.2	0.0
	Past user	0.3	0.2

*Current user:] 0; 30 days]; ** Past user:] 30; 365 days]

5.2.2 Crude and adjusted odd ratios per antibiotic class: main analysis

Table 7 shows the ORs of AMI any and for specific types of antibiotics with times windows: 15 days. Compared to non-use as the reference, current and past use of any

antibiotics was associated with AMI with adjusted ORs of 1.51 (95%CI 1.44-1.58) and 1.11 (95%CI 1.09-1.13), respectively.
Current and past use of penicillins, cephalosporins and macrolides were also associated with occurrence of AMI.

Table 7: Adjusted odds ratios of AMI for antibiotics user groups with the 14 days definition of exposure

	Cases n= 50,286 %	Controls n=251,366 %	Crude OR (95% CI)	Adjusted OR (95% CI)*
Any antibiotics				
current	6.8	4.5	1.84 (1.76 to 1.92)	1.51 (1.44 to 1.58)
past	45.9	40.8	1.32 (1.29 to 1.35)	1.11 (1.09 to 1.13)
Penicillins and beta lactams				
current	2.1	1.6	1.34 (1.25 to 1.44)	1.15 (1.07 to 1.24)
past	21.0	18.4	1.19 (1.16 to 1.22)	1.06 (1.03 to 1.08)
Macrolides				
current	2.3	1.3	1.92 (1.79 to 2.06)	1.73 (1.61 to 1.86)
past	19.2	16.3	1.24 (1.21 to 1.27)	1.12 (1.09 to 1.15)
Cephalosporin				
current	1.5	0.9	1.80 (1.66 to 1.96)	1.52 (1.40 to 1.66)
past	13.5	10.8	1.30 (1.26 to 1.34)	1.10 (1.07 to 1.13)

* adjusted by co-morbidities (atherosclerosis, diabetes mellitus, disorders of lipoid metabolism, hypertension, ischemic heart, cerebrovascular accident) and drugs (antithrombotic drugs, lipid lowering drugs, antidiabetics, cardiovascular drugs, corticosteroids for systemic use, drugs for obstructive airway diseases);
current use [0; 14] days and past use [14; 365] days

5.2.3 Crude and adjusted odd ratios per antibiotic class: secondary analysis

Table 8 shows the ORs of AMI any and for specific types of antibiotics with times windows: 30 days. Compared to non-use as the reference, current and past use of any antibiotics was associated with AMI with adjusted ORs of 1.38 (95%CI 1.33-1.43) and 1.10 (95% CI 1.08-1.12), respectively.
Current and past use of penicillins, cephalosporins and macrolides were also associated with AMI.
Results of the secondary analysis did not differ from results of the primary analysis.

Table 8 : Adjusted odds ratios of AMI for antibiotics user groups with the 30 days definition of exposure

	Cases n= 50.286 %	Controls n=251.366 %	Crude OR (95% CI)	Adjusted OR (95% CI)*
Any antibiotics				
current	11.4	8.2	1.67 (1.62. 1.73)	1.38 (1.33. 1.43)
past	41.2	37.1	1.30 (1.28. 1.33)	1.10 (1.08. 1.12)
Penicillins and beta lactams				
current	3.7	3.1	1.27 (1.20. 1.34)	1.09 (1.03. 1.15)
past	19.3	17.0	1.19 (1.16. 1.22)	1.06 (1.03. 1.09)
Macrolides				
current	3.9	0.4	1.69 (1.61. 1.78)	1.54 (1.46. 1.63)
past	17.6	15.2	1.23 (1.19. 1.26)	1.11 (1.08. 1.14)
Cephalosporin				
current	2.6	1.7	1.62 (1.52. 1.73)	1.36 (1.27. 1.46)
past	12.4	10.0	1.29 (1.25. 1.33)	1.09 (1.06. 1.13)

* adjusted by co-morbidities (atherosclerosis, diabetes mellitus, disorders of lipoid metabolism, hypertension, ischemic heart, cerebrovascular accident) and drugs (antithrombotic drugs, lipid lowering drugs, antidiabetics, cardiovascular drugs, corticosteroids for systemic use, drugs for obstructive airway diseases)
Current use]0; 30] days and past use]30; 365] days

6. Discussion

This study showed that the adjusted odds ratio were slightly higher than 1, 1.51 for current use of any antibiotic and around unity (1.11) for past use.

While the association between bacterial infections and AMI is well established (3, 4), studies evaluating the association between antibiotics and AMI provided contradictory results. Most of the studies using either a case-control or a cohort design or meta-analyses found no association between antibiotic use (macrolides, tetracyclines or quinolones) with risk estimates varying between 0.91 and 1.65 (5 - 10). One cohort study showed a positive and significant association between macrolides and quinolones use (OR 1.10 (95% CI 1.04- 1.16) and OR 1.20 (95% CI 1.13-1.26), respectively) (11). Finally, other studies found a protective effect of tetracyclines and quinolones on occurrence of AMI or in secondary prevention of coronary artery disease (12, 13). Lastly, within the project OMOP, Ryan et al reported in a paper findings from a series of assessments of risk identification methods to determine their ability to correctly identify ‘true’ drug–adverse event outcome associations and drug–adverse outcome negative controls as ‘not associated’. They also observed variability of results on the association between antibiotics: erythromycins, sulfonamides, tetracyclines and AMI that were classified as a negative control (14).

The observed results may be partly explained by unmeasured confounding. Smoking status and BMI were not available and were not adjusted for in the analysis. An indication bias may also be considered as acute infections are indeed associated with occurrence of AMI (3, 4) but information about the indication for antibiotics prescriptions were not available, nor information on efficacy of the prescribed antibiotics that may be used after failure of previous treatments. Moreover, another unmeasured potential confounder to be considered is influenza virus infection that is associated with both an increased risk of AMI occurrence (15, 16) and a secondary bacterial infection (17) whereas vaccination against influenza has a protective effect (18).

7. Conclusion

This study observed an association between antibiotics and AMI, which has been known to be non-existent (negative control).

8. References

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9. Appendices

Table 9: ICD9 codes of major comorbidities

ICD9 codes	DISEASES
401-405	HYPERTENSIVE DISEASE Excludes: that complicating pregnancy. childbirth. or the puerperium (642.0-642.9) that involving coronary vessels (410.00-414.9)
410-414	ISCHEMIC HEART DISEASE 410 Acute myocardial infarction 411 other acute and subacute forms of ischemic heart disease 412 Old myocardial infarction 413 Angina pectoris 414 Other forms of chronic ischemic heart disease
440	Atherosclerosis
443.9	Peripheral vascular disease. unspecified
444	Arterial embolism and thrombosis
434	Occlusion of cerebral arteries
435	Transient cerebral ischemia
250	Diabetes mellitus
249	Secondary diabetes mellitus Includes: diabetes mellitus (due to) (in) (secondary) (with): drug-induced or chemical induced infection
791.5	Glycosuria
357.2	Polyneuropathy in diabetes
363	Diabetic retinopathy
790.22	Impaired glucose tolerance test (oral)
278	Overweight and obesity
272	Disorders of lipoid metabolism

Table 10: Confounding drugs

Drugs affecting sympathetic and parasympathetic nervous system	
	Drugs for obstructive airway diseases
	Corticosteroids for systemic use
Drugs given for the treatment of diseases closely associated with an increased AMI risk	
	Antidiabetics
	Lipid-lowering drugs (e.g. statins. fibrates)
	Cardiovascular drugs
	Antithrombotic drugs (e.g. ASS).
	Antiobesity preparations
	Drugs used in nicotine dependence
Further Drugs possibly influencing the risk for AMI	
	NSAR