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

STUDY PROTOCOL

The risk of myocardial infarction not associated with the use of antibiotics
A study using a US database

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1. Context of PROTECT Workpackage 6 studies

The study described in this protocol is 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 workpackage 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 aims of this study are to evaluate if the tools proposed are specific enough not to detect an association not existing. As proposed in the public-private US initiative Observational Medical Outcomes Partnership (OMOP), the drug-event pair antibiotics and myocardial infarction has been selected as a known absence of association.

2. Objectives

We propose to assess the absence of association between antibiotics use and myocardial infarction by replicationg a nested case-control design in a US claims database (LabRx).

The study objectives of the replication are:

- To estimate the risk of myocardial infarction associated with antibiotics exposure (users and non-users)
- To estimate the risk of myocardial infarction associated with various antibiotics classes
- To estimate the risk of myocardial infarction associated with specific individual antibiotics
- To assess the effect of dose and duration of use for specific individual antibiotics

The secondary objectives are

- To replicate the analysis using a population-based case-control design

3. Methods

3.1 Data Source

The proposed study will be conducted in the US Invision datamart database (Optum Insight® formerly Ingenix®).

Main characteristics of these databases that summarised below:

Invision Data Mart (US)
Invision 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 enrollment 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 is defined as the period from the left censoring date up to the right censoring date. The left censoring date is the date that a patient enrolled into the database. The right censoring date is the earliest of the following: the date a patient died, the end of the database's data collection, or the date that the practice left the database.

3.3 Study period

The study period will start in January 2004 and end in December 2009. Information on the use of antibiotics and occurrence of myocardial infarction will be obtained from claims data where prescription and diagnosis data are recorded.

3.4 Source population

The source population will be 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 Invision Data Mart. Patients must have attained one year of enrolment in the database at the beginning of the study period.

3.5 Study population

3.5.1 Primary population

From the aforementioned primary source population, two study cohorts will be selected:

- the first cohort will include all patients who received at least one antibiotic prescription during the study period. For this cohort, the date of first prescription of an antibiotic after meeting the eligibility criteria (entry date) defines the start of follow-up (start date), for the exposed cohort.

- the second cohort will be selected from the same source population among patients who have not received an antibiotic prescription during the study period and in the year before the entry date (date when the patient meet the eligibility criteria and enter in the study). We will select a random sample of these patients not exposed to antibiotics ("non users") frequency-matched by age, sex and calendar date (month and year, if possible) of database enrolment to the cohort of antibiotic users. For these patients, we will assign a quarter frequency-matched to the cohort of antibiotic users over all the study period and then a date corresponding to the middle of the assigned quarter. This assigned date will be used as the start of follow-up (start date).

3.5.2 Secondary population

For the purpose of a population-based case-control study, all subjects from the aforementioned source population will be considered as secondary study population.

3.6 Outcome definition

All patients from the study population will be followed from the start date (date of first antibiotic prescription or assigned start date in the comparison cohort) until the earliest occurrence of one of the following endpoints: a code from table 1 (outcome), death or end of the study period.

We will ascertain patients with the first recorded occurrence of myocardial infarction (outcome) and the date of diagnosis will be their index date (outcome date). For these patients, patient profiles from the claims/electronic data will be collected.

The outcome for this study is the first recorded occurrence of acute myocardial infarction. Acute Myocardial Infarction is coded in the International Classification of Diseases version 9 (ICD9) as 410.- (Acute myocardial infarction).

4. Study Design

4.1 Nested case-control study

4.1.1 Cases and controls

All cases, detected within both study cohorts (exposed and non-exposed to antibiotics) with a first recorded occurrence of myocardial infarction during the follow-up period from January 2004 until December 2009 will be identified. The date of diagnosis (myocardial infarction) will be considered the index date of the cases and their matched controls. Separate analyses will be done using only definite cases in a first step and definitive and probable cases in a second step.

Controls will be 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 will be matched to cases by age (within on year), sex, and calendar date (month & year). We will select up to five controls per case.

4.1.2 Exposure definition for the case-control analysis

We will define patients as current users if a prescription for the drugs of interest lasts until the index date or ends within 30 days prior to the index date (i.e. date of onset of acute myocardial infarction both in cases and their matched controls). We will use a window of 14 and 30 days as a secondary definition of current use.

We will define 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.

The association between the use of antibiotics and the experience of acute myocardial infarction will be estimated by comparing the odds of past and current users with the odds of non-users. Non-use of antibiotics will be used as baseline. We will study the effect of dose and duration of treatment among current users.

Duration of use will be defined by the treatment period covering consecutive prescriptions. Prescriptions will be considered consecutive when less than 30 days elapse between them.

We will estimate the risk associated with different antibiotics drug class categorized in the following groups: Tetracyclines, penicillins, cephalosporins & betalactamics, macrolids, quinolones and other antibiotics.

4.1.3 Statistical Analyses

We will compute odds ratios (OR) and 95% confidence intervals of first occurrence of acute myocardial infarction 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) will be introduced in the model to control for potential confounding. Also, dose and duration-relationships will be examined. Separate analyses will be done using only definite cases in a first step and definite and probable cases as a second step. Several strategies to select confounders will be 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 will be examined by constructing a series of bivariate models. Likelihood Ratio tests will be used to compare models. We will also fit a full model, including all of the potential confounders.

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

4.2 Population-based case-control study

4.1.1 Cases and controls

All cases, detected within the secondary study population with a first recorded occurrence of acute myocardial infarction during the follow-up period from January 2004 until December 2009 will be identified. The date of diagnosis (acute myocardial infarction) will be considered the index date of the cases and their matched controls. Separate analyses will be done using only definite cases in a first step and definitive and probable cases in a second step.

Controls will be 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 will be matched to cases by age (within on year), sex, and calendar date (month & year). We will select up to five controls per case.

4.1.2 Exposure definition for the case-control analysis

We will define patients as current users if a prescription for the drugs of interest lasts until the index date or ends within 30 days prior to the index date (i.e. date of onset of acute myocardial infarction both in cases and their matched controls). We will use a window of 14 and 30 days as a secondary definition of current use.
We will define 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.

The association between the use of antibiotics and the experience of acute myocardial infarction will be estimated by comparing the odds of past and current users with the odds of non-users. Non-use of antibiotics will be used as baseline. We will study the effect of dose and duration of treatment among current users.

Duration of use will be defined by the treatment period covering consecutive prescriptions. Prescriptions will be considered consecutive when less than 30 days elapse between them.

We will estimate the risk associated with different antibiotics drug class categorized in the following groups: Tetracyclines, penicillins, cephalosporins & betalactamics, macrolids, quinolones and other antibiotics.

4.1.3 Statistical Analyses

We will compute odds ratios (OR) and 95% confidence intervals of first occurrence of acute myocardial infarction (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) will be introduced in the model to control for potential confounding. Also, dose and duration-relationships will be examined. Separate analyses will be done using only definite cases in a first step and definite and probable cases as a second step. Several strategies to select confounders will be 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 will be examined by constructing a series of bivariate models. Likelihood Ratio tests will be used to compare models. We will also fit a full model, including all of the potential confounders.

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5. Covariates and potential confounders

The following variables were considered for adjustment as ‘control variables’ in the multivariate model:

- age and sex
- BMI
- Smoking
- Alcohol consumption
- Comorbidities and classical risk factors (see list of codes in table 1)
    - Vascular diseases
    - Hypertensive diseases
    - Cardiac diseases
    - Any history of angioplasty or coronary bypass surgery prior to the current MI.
    - Patients reporting a history of hospitalisation or diagnosis of MI prior to the current MI
    - Chronic ischemic heart disease

    - Any history of heart failure
    - Non cardiac ischemic diseases
    - Any history of stroke
    - Atherosclerosis
    - Metabolic diseases
    - Diabetes
    - Impaired glucose tolerance
    - Lipid disorders
- Drug confounders (see list in table 2)
    - Drugs affecting sympathetic and parasympathetic nervous system
    - Drugs given for the treatment of diseases closely associated with an increased AMI risk
    - Further Drugs possibly influencing the risk for AMI

Table 1: 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 2: 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