STUDY PROTOCOL

ASSOCIATION BETWEEN LOW DOSE ACETYLSALICYLIC ACID AND PROTON PUMP INHIBITORS AND RISK OF ACUTE MYOCARDIAL INFARCTION OR CORONARY HEART DISEASE DEATH

Nested case control analyses in a cohort of patients with acute serious coronary heart disease

The analyses are based on a previous protocol "A pharmacoepidemiological study on the interaction between clopidogrel and proton pump inhibitors and the risk of acute myocardial infarction, coronary heart disease death and upper gastrointestinal bleeding in the GPRD and THIN databases"

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1. INTRODUCTION

We propose to utilize a cohort of individuals hospitalized for a serious acute coronary event and who were alive one month after the qualifying hospitalization to assess the impact of concomitant current use of PPI and low dose ASA on myocardial infarction (MI)/coronary heart disease (CHD) death outcomes. The study cohort emanates from an ongoing AstraZeneca-sponsored study aiming at assessing a potential interaction between clopidogrel and PPIs and the risk of acute myocardial infarction and CHD death.

This available cohort will be used to assess the impact of concomitant use of PPI and low dose ASA on the risk of MI/CHD deaths. A nested case control analysis will be performed in the cohort of patients with acute serious coronary heart disease**.**

2. BACKGROUND

In a recent pharmacoepidemiology study the association between aspirin and PPI exposure and cardiovascular (CV) outcomes was investigated (Charlot et al 2010). The authors concluded that in aspirin-treated patients with recent myocardial infarction concomitant treatment with PPIs was associated with increased risk of adverse CV events. The study was performed in a population-based cohort, identified through individual-level linkage of nation-wide registries in Denmark, and included 20 390 subjects receiving aspirin but not clopidogrel, who survived 30 days after a first-time myocardial infarction between1997 and 2006. Composite CV events occurred in 1151 (25.2%) patients receiving PPIs and in 894 (18%) patients not receiving PPIs, adjusted hazard ratio (HR, 95% CI), 1.72 (1.56-1.89). At this point in time the Charlot et al study has been reported as an abstract only.

We propose to utilize the available cohort of patients with acute serious CHD to assess the impact of concomitant use of PPI and low dose ASA on MI/CHD death outcomes. From a methodological perspective this study would add value to the information provided by Charlot et al by providing data on:

1. A population-based cohort of patients with acute serious CHD with complete follow-up and validated outcomes.

2. The database captures life style CV risk factors such as smoking, alcohol use and body mass index that are known predictors of CV recurrences (not available in the registries in Denmark used by Charlot et al)

3. Most low dose ASA for secondary cardiovascular prevention in the UK is based on prescriptions (i.e. not OTC) and low dose ASA use is therefore close to completely captured in the database.

4. All prescription medications are completely recorded, including information on indication for new courses of therapy.

5. Treatment patterns of antiplatelet drugs among a cohort of individuals after an episode of serious acute coronary disease.

3. OBJECTIVES

To estimate the risk of MI/CHD death associated with use of monotherapy low dose ASA (single antiplatelet) as well as concomitant use of monotherapy low dose ASA and proton pump inhibitors (PPIs).

4. METHODS

4.1 Design

A nested case-control analysis in a retrospective cohort study with prospective data recording will be performed using The Health Improvement Network (THIN) and General Practice Research Database (GPRD).

The case ascertainment and selection of controls are based on the original protocol assessing the impact of concomitant current use of PPI and clopidogrel on MI/CHD death outcomes. The nested case control analyses estimating a potential interaction between concomitant use of low dose ASA and PPI and risk of MI/CHD deaths will be performed in this cohort.

4.2 Source Population

THIN is a computerized medical research database that contains systematically recorded data on more than 3 million UK primary care patients. It is representative of this population with regard to age, sex, and geographic distribution, and has been validated for use in pharmacoepidemiological research (Lewis et al 2007). GPRD includes about 7% of the UK population, and it is also age-, gender-, and geographically representative. Data from approximately 4.5 million patients are systematically recorded by participating general practitioners and sent anonymously to GPRD. GPRD collects and organizes this information in order to be used for research projects. The validity of GPRD has been demonstrated in previous studies (Garcia Rodriguez and Perez Gutthann 1998, Jick et al 2003).

In both databases participating primary care practitioners (PCPs), who have been trained to record their patient´s information in a standard manner and have agreed to supply it anonymously for research purpose, record data prospectively as part of their routine patient care, including demographics and life style factors (e.g. alcohol use, body mass index (BMI) and smoking status), consultation rates, referrals, hospital admissions, laboratory test results, diagnoses, prescriptions ordered by the PCPs, and a free text section, and send it to THIN and GPRD, respectively for use in research projects. Prescriptions issued by PCPs are recorded automatically in the database. The Read classification is used to code specific diagnoses (Stuart-Buttle et al 1996), and a drug dictionary based on data from the MULTILEX classification is used to code drug prescriptions (First Data Bank 2010). As some practices contribute their information both to THIN and GPRD, we ascertained the practices common to both databases and have used their information only once in order not to have duplicate data in our dataset.

4.3 Case Ascertainment

THIN and GPRD were used to identify individuals aged 50–84 years with documented evidence of hospitalization for acute serious coronary heart disease (MI, revascularization of coronary arteries or unstable angina) and who were alive one month after the qualifying hospitalization . Study subjects were required to have been enrolled with their PCP for at least 1 year and to have a computerized prescription history of at least 1 year before the start of the study. Patients were excluded from the study if they had a diagnosis of cancer. Patients aged ≥ 70 years with a follow-up longer than 1 year were excluded from the study cohort if they had fewer than two recorded consultations with a PCP during their entire follow-up (proxy for incomplete and invalid data recording).

All individuals in the study were followed up from day 30 after the hospitalization for acute serious coronary disease until the first of the following endpoints: The date of a code suggesting a hospitalization for acute myocardial infarction, cancer, reaching the age of 85 years, death, or the end of the study period . The final study cohort of 42,542 patients was followed up for a mean of 3.5 years.

During the study period, patients with an entry of MI were identified through read codes The profiles of these patients, including the free-text comments, were reviewed manually by epidemiologists at CEIFE, to ascertain the number of cases with a new diagnosis of MI or of death due to CHD. All patient personal identifiers were suppressed and information on drug use was removed to allow for a blinded revision of patient profiles. Doubtful cases were reviewed by two researchers and agreement was reached. Patients were not retained as MI cases if they were not admitted to hospital after the ischemic event (patients who were admitted to an emergency department and discharged on the same day were also excluded); were admitted to hospital for any reason other than cardiovascular disease in the month before the MI; or were admitted to hospital for any reason other than cardiovascular disease and had an MI during hospitalization.

In addition, the profiles of patients censored as death during the follow-up were reviewed manually (free text comments were not requested for these patients) according to the same procedure as described above to identify those who had died from CHD.

In recent studies applying the same methods of case ascertainment and validation for MI a confirmation rate close to 95% was obtained among the requested random sample considered cases after the manual review (Garcia Rodriguez et al 2004, Garcia Rodriguez et al 2008).

4.4 Selection of Controls

A total of 10,000 age-, sex- and calendar-year-matched controls were sampled from the pool of our two original study cohorts (THIN=27,715 and GPRD=14,827): 6500 controls from THIN and 3500 from GPRD. Selection of controls in both datasets was based on the weight of their respective follow up contribution during the study period. This was done by generating a random date from within the study period for each member of the study population. If the random date for a study member was included in the follow-up period, that person was marked as an eligible control and the random date was used as their index date. The same exclusion criteria were applied to controls as to cases.

4.5 Characterization of Exposure Groups and assessment of Cardiovascular and Gastrointestinal Risk Factors

The following potential confounders were ascertained:

Demographics; age (50-64, 65-74,75-84 years), sex and calendar year (2000-2002; 2003-2004; 2005-2006, 2007-2008). We calculated the follow-up time interval between start date and index date and subsequently categorized it into 5 time periods: first month; 2 to 3 months; 4 to 6 months; 7 to 12 months and longer than 1 year.

Life style factors; Body mass index (calculated from recorded height and weight; weight in kg / (height in metres2) was ascertained prior to index date. Standard cut points were used to classify subjects as underweight (BMI less than 20), normal weight (BMI 20-25), overweight (BMI 25 to 29.99) or obese (BMI $\geq$30 kg/m2). Smoking status was categorized into current smoker, past smoker, never smoker. Missing demographic data were assessed as a separate category. Most recent value before index date was ascertained for each study subject.

Comorbidity; Diabetes, MI, unstable angina, angina, cerebrovascular disease, COPD, GERD, and peptic ulcer antecedent (which includes dyspepsia, gastritis, uncomplicated peptic ulcer and complicated peptic ulcer). Comorbidity was ascertained prior to start date.

Concomitant medication; Antihypertensives, statins, nitrates, clopidogrel, NSAIDs, oral corticosteroids, and oral anticoagulants. We also collected polytherapy – number of prescribed

different drugs (other than ASA) in the 30 days prior to the index date (0-2, 3-5, 6-9, 10-14, 15 or more).

4.6 Exposure definition

For antihypertensives, statins, NSAIDs, oral steroids, warfarin and nitrates, medication use was classified into four categories: *current use*, when the supply of the most recent prescription lasted until the index date or ended in the 6 days before the index date; *recent use*, when the supply of the most recent prescription ended 7–90 days before the index date: *past use*, when the most recent prescription ended 91–365 days before the index date; or *non-use*, when there was no recorded use of the relevant medication in the 365 days before the index date.

For low dose aspirin, clopidogrel PPI and H_2RA the medication use was categorized as follows: *current users* when the supply of the most recent prescription lasted until the index date; *recent use*, when the supply of the most recent prescription ended 7–90 days before the index date; *past use*, when the supply of the most recent prescription ended 91–365 days before the index date or non-use, when there was no recorded use of the relevant medication in the 365 days before the index date.

Current users of low dose ASA, PPIs, H_2RAs were subdivided into two mutually exclusive groups: *users at start date* (either on the respective medication already prior to start date or starting within the 30 days after start date) and *users after start date* (initiating the therapy after the first 30 days since start date so not exposed at start date).

Those categories were further subdivided into two mutually exclusive groups according to the pattern of *continuous use* during their person-time contribution in the study period. First a time interval between stop date and first Rx date (date of the first recorded prescription during the study period: note for those who started before the start date and had supply days at start date, we used the start date to compute the time interval) was computed. Then, from this time interval the duration of treatment of the respective medication was subtracted (duration was computed summing the days corresponding to consecutive prescriptions allowing for a free interval gap no greater than 30 days). All individuals with a difference greater than zero were considered as non-continuous users: all others were considered continuous users.

4.7 Statistical analysis

A nested case–control analysis will be performed to assess potential risk factors for MI/CHD deaths using unconditional logistic regression. In this analysis all patients ascertained with MI/CHD death will be used as cases. The control group comprises the random sample of 10,000 subjects frequency-matched by age (+/- one year), sex and calendar year (described in section 4.4). Under our study design of incidence density sampling, the OR is an unbiased estimator of the incidence rate ratio (RR) (Rothman 2002).

To determine the association between study outcome and current use of low dose ASA with or without concomitant PPI, we will run unconditional logistic regression models and compute the odds ratio (OR) and their 95% confidence intervals (95%CI). The estimate will be adjusted for the frequency-matched variables (age, sex, calendar year), time to event and other variables defined in section 4.5 with at least one subject in each category.

The effect of PPIs on the association between low dose ASA and MI/CHD death will be examined using the above mentioned adjusted regression model. The interaction between the use of PPI and monotherapy low dose ASA will be studied by comparing the risk among users of monotherapy low dose ASA (not exposed to clopidogrel in the year prior) versus the risk among concomitant users of monotherapy low dose ASA and PPI. The primary evaluation will assess the association between continuous current use of PPI and ASA started at the same time. Further exploration of the effect associated with different patterns of PPI and low dose ASA data will be conducted, as necessary. Statistical analyses will be performed using Stata package version 11.0 (StataCorp LP, College Station, TX, USA).

5. PROJECT FORMALITIES AND TIMELINES

The estimated delivery date of final analyses and study report is .

5.1 Good Pharmacoepidemiology Practices

This study was performed in accordance with the Guidelines for Good Pharmacoepidemiology Practices (2007). The study protocol was approved by an ethics review board: ISAC (Independent Scientific Advisory Committee) for the GPRD study and Multi-centre Research Ethics Committee (MREC) for the THIN study.

6. REFERENCES

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