STUDY PROPOSAL

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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BACKGROUND

Clopidogrel is a thienopyridine with platelet inhibitory properties that selectively inhibits adenosine diphosphate (ADP)-induced platelet aggregation with no direct effects on arachidonic acid metabolism (1). Although clopidogrel also can inhibit platelet aggregation induced by collagen and thrombin, these inhibitory effects are abolished by increasing the agonist concentration and, therefore, are likely to reflect blockade of ADP-mediated amplification of the platelet response to other agonists. Clopidogrel is a prodrug that suffers in vivo hepatic transformation mediated mainly by cytochrome P-450 isoenzymes to generate an active metabolite, that irreversibly inhibits the platelet $P2Y_{12}$ ADP receptor. The active metabolite of clopidogrel has a pharmacodynamic pattern quite similar to that of aspirin, in causing the cumulative inhibition of platelet function on repeated daily administration of low doses with platelet function returning to normal 7 days after the last dose of clopidogrel. This also justifies the once-daily regimen of clopidogrel despite its short half-life in the human circulation. Clopidogrel, along with aspirin therapy, is now widely used around the world to prevent thrombotic events in patients with acute coronary syndromes and after coronary artery stenting.

The inhibition of gastric acid secretion is a key therapeutic target for peptic ulcer, gastro esophageal reflux disease (GERD) and nonsteroidal anti-inflammatory drug–induced gastropathy among other acid-related diseases. Currently this is mainly achieved by blocking the effects of acid secretagogues through the use of irreversible H+/K+-ATPase inhibitors commonly referred to as proton pump inhibitors (PPIs). PPIs are potent acid suppressants and are the one drug class most widely used. All of them undergo extensive hepatic biotransformation.

The isoenzyme CYP2C19 seems to be one of the determinants of the pharmacodynamic response to clopidogrel (2,3), and is also involved in the metabolism of PPIs (4), though other CYP isoenzymes (CYP2C9: used in the

metabolism of NSAIDs such as naproxen, ibuprofen or celecoxib) have been reported as affecting platelet responsiveness to clopidogrel (3). In a recent randomized, double-blind, placebo-controlled study (5), the authors suggest a potential clopidogrel–omeprazole drug interaction at the CYP2C19 level. In their study of patients undergoing elective coronary stenting, co-administration of omeprazole with clopidogrel was associated with significantly higher platelet P2Y12 reactivity as measured by a flow cytometry assay employing monoclonal antibodies specific for vasodilator-stimulated phosphoprotein phosphorylation (VASP-P): all clopidogrel patients were also taking aspirin. These results support the findings from their prior observational study (6). In another pharmacodynamic study addressing the interaction between PPIs and clopidogrel, the authors found no association with esomeprazole and pantoprazole (7). At the same time, two observational studies have reported an increased risk of myocardial infarction (MI)/acute coronary syndrome (ACS) among concomitant users of clopidogrel and PPI (8,9). A third observational study using a population-based registry of MI patients reported that the use of omeprazole, or any other proton-pump inhibitor, had no effect on the clinical response (death from any cause, nonfatal stroke, or myocardial infarction) to clopidogrel over one year follow-up (10).

The current study protocol is designed with the aim to address methodological shortcomings in published epidemiological studies, in particular the absence of data on the occurrence of cardiovascular (CV) and upper gastrointestinal (UGI) events in one single population through:

- Evaluating both CV and GI risks in the same population-based cohort (not only CV as in published studies)
- Controlling for differences in "base-line risk" between study groups i.e. to allow adjustment for relevant confounding factors like smoking habits lacking in published observational studies
- Providing information on life style factors like BMI, alcohol use lacking in published observational studies

- Optimizing selection of truly population-based datasources to allow for evaluation of dual clopidogrel and acetylsalisylic acid (ASA) treatment (extensive over-the counter use of ASA not accounted for in published studies)

This study proposal will address separetely the risk of two outcomes in a cohort of patients discharged after a hospitalization for acute serious coronary heart disease:

1) Acute myocardial infarction (AMI) and coronary heart disease death (CHD death)

2) Upper gastrointestinal bleed (UGIB)

In order to improve the power of the study, we will run the same protocol in two primary care databases in the UK: GPRD (General Practice Research Database) and THIN (The Health Improvement Network). We wil only count practices providing data to both schemes.

STUDY OBJECTIVES

PART ONE: ACUTE MYOCARDIAL INFARCTION / CORONARY HEART DISEASE DEATH

1- To estimate the risk of AMI/CHD death associated with use of clopidogrel: dose and duration-response.

2- To examine whether the risk of AMI/CHD death among users of clopidogrel varies according to concomitant use of PPIs.

3- To estimate the risk of AMI/CHD death associated with use of aspirin/clopidogrel: dose and duration-response.

3- To examine whether the risk of AMI/CHD death among users of aspirin/clopidogrel varies according to concomitant use of PPIs.

PART TWO: UPPER GASTROINTESTINAL BLEED

1- To estimate the risk of UGIB associated with use of clopidogrel: dose and duration-response.

2- To examine whether the risk of UGIB among users of clopidogrel varies according to concomitant use of PPIs.

3- To estimate the risk of UGIB associated with use of aspirin/clopidogrel: dose and duration-response.

3- To examine whether the risk of UGIB among users of aspirin/clopidogrel varies according to concomitant use of PPIs.

METHODS

Design

A retrospective cohort study with nested case-control analyses will be performed using data from the databases GPRD and THIN in the UK.

Data sources

GPRD contains computerized information entered by general practitioners in the U.K. Data on over 3 million patients are systematically recorded and sent anonymously to the Medicines and Healthcare Products Regulatory Agency (MHRA), which collects and organizes this information for use in research projects. The computerized information includes demographics, details from general practitioner's visits, diagnoses from specialist's referrals and hospital admissions, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer.

THIN covers about 5% of the UK population, and is age-, gender-, and geographically representative. Data from approximately 4 million patients are systematically recorded by participating general practitioners and sent anonymously to THIN. THIN collects and organizes this information in order to be used for research projects. The computerized information includes demographics, details from general practitioner's visits, diagnoses from specialist's referrals and hospital admissions, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer.

The READ classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs in both databases.

Ascertainment of study cohort

Follow up will start on the first day after once an individual meets the criteria of at least one year enrollment with the general practitioner, one year since first computerized prescription and being 50-84 years old. That date will be their start date1. We will exclude patients with a recorded diagnosis of cancer before start date1. We will also remove from the source population all persons aged 70 and above with a follow-up longer than one year and less than 2 health contacts during their total follow-up

(proxy for incomplete data recording). Follow-up will end on the first of the following:

1. The date of a qualifying event; which is a hospitalization for acute serious coronary heart disease: defined as acute myocardial infarction, revascularization of the coronary arteries, or unstable angina.
2. The attainment of age 85;
3. The date of recorded diagnosis of cancer;
4. The date of death;
5.

We will review computer profiles of all persons identified with a serious coronary heart disease (free text comments will not be requested at this stage) and will retain as our study cohort all patients with documented evidence of hospitalization for acute serious coronary heart disease and who are alive one month after the qualifying hospitalization (start date2).

AMI and CHD death: case ascertainment and validation

We will follow-up all study cohort members from start date2 until the earliest occurrence of one of the following endpoints:

1. The date of a code suggesting a hospitalization for acute myocardial infarction
2. The attainment of age 85;
3. The date of recorded diagnosis of cancer;
4. The date of death;
5.

We will manually review computerized profiles of all patients with a code suggesting MI as well as deceased patients: free text comments will be requested before reviewing patient profiles. All patient personal identifiers will be suppressed. At this stage, we will exclude patients not admitted to a hospital and patients with a hospitalization for a non IHD event in the previous month. For a random sample of 100 potential cases of AMI in each

database, we will send a questionnaire to the GPs in order to confirm the diagnosis of AMI and request all information available in their office related to the episode of AMI including hospital discharge letters, electrocardiograms (ECGs), or results from myocardial serum enzyme levels . To validate cases we will use the adapted international standardised diagnostic criteria for acute myocardial infarction (11,12). We will apply the same methods of case ascertainment and validation for AMI as described in our two recent studies, one using the GPRD (13) and the second with THIN (14). In these two studies, we obtained a confirmation rate close to 95 % among the requested random sample of patients considered cases after the manual review. If based on the information from the questionnaire and medical records, 90% or more are confirmed as cases of AMI, we will not request information for all remaining potential cases.

Also, we will review all deaths and consider a patient as dying from coronary heart disease (CHD) when there is a) postmortem evidence of fresh MI, b) a recent coronary artery occlusion or ante-mortem evidence of CHD in the absence of another cause of death, or c) recorded CHD as the underlying cause of death.We will consider as cases of CHD death patients who died from CHD before reaching the hospital as well as fatal AMI (patients dying within the first 30 days after the occurrence of AMI).

UGIB: case ascertainment and validation

In addition to cancer we will remove from our study cohort for UGIB ascertainment all individuals with a reorded history of oesophageal varices, Mallory-Weiss disease, alcoholism, chronic liver disease or coagulopathies prior to start date2. Then, we will follow-up all study cohort members from start date2 until the earliest occurrence of one of the following endpoints:

1. The date of a code suggesting an episode of UGIB
2. The attainment of age 85;
3. The date of excluision factor occurrence: codes for cancer, oesophageal varices, Mallory-Weiss disease, alcoholism, chronic liver disease or coagulopathies.
4. The date of death;
5.

We will manually review computerized profiles of all patients with a code suggesting UGIB: free text comments will be requested before reviewing patient profiles. All patient personal identifiers will be suppressed. At this stage, we will exclude patients with a hospitalization for a non UGI event in the previous month. We will consider a patient to be a case of UGIB when no exclusion criterion is found, the specific site of the bleed/perforation is located in the stomach or duodenum or the clinical diagnosis is peptic ulcer, and the patient has been referred to a consultant or admitted to hospital. We will classify cases according to the source of the bleed/perforation into gastric and duodenal. Subjects with any of the exclusion criteria mentioned above in the 2 months after the date of case detection (index date), and subjects with the source of the bleed/perforation in the esophagus or lower gastrointestinal tract will be excluded. The date of first objective sign of the bleed episode will be considered as index date. To validate the case status based on the review of computerized patient profiles, we will send the general practitioners for a random sample of 100 potential UGIB cases in each database, a questionnaire and a request to send all the information related to that event. We will apply the same methods of case ascertainment

and validation for UGIB as described in two of our studies, one using the GPRD (15) and the second with THIN (16). In these two studies, we obtained a confirmation rate close to 95 % among the requested random sample of patients considered cases after the manual review. If based on the information from the questionnaire and medical records, 90% or more are confirmed as cases of UGIB, we will not request information for all remaining potential cases.

Statistical analysis

Two separate nested case-control analyses will be performed to better estimate the effect of clopidogrel as well as the contribution of concomitant use of PPIs to the risk of each of our three study outcomes (AMI/CHD death, UGIB). We will use all confirmed cases and the date of admission to hospital or onset of study outcome will be used as index date among cases. A date comprised during the study period will be generated at random for each study cohort member. All persons with a random date included in their person-time period of observation (between start date2 and end of follow-up) will be eligible as controls, and this date will be used as their index date. Finally, we will randomly sample a group of 5,000 controls frequency-matched by age (+/- one year), sex and calendar year: two control groups will be sampled, one for each study outcome. We will examine the distribution of personal characteristics, concomitant medication and comorbidities among controls according to the exposure to clopidogrel with and without PPIs.

To determine the association between study outcome and current use of clopidogrel as compared to non-use, we will run unconditional logistic regression models and compute the odds ratios (ORs) and their 95% confidence intervals (95%CI). Owing to the selection process of controls, ORs are unbiased estimates of rate ratios in the underlying study cohort. All estimates will be adjusted for the frequency-matched variables (age, sex, calendar year), follow-up time (interval between start date2 and index date),

BMI, GP visits, referrals, smoking, hyperlipidemia, alcohol intake, townsend score (socioeconomic indicator), AMI, angina, unstable angina, cerebrovascular disease, diabetes, rheumatoid arthritis, COPD and use of anticoagulants, antihypertensives, oral steroids, aspirin and NSAIDs. The effect of PPIs on the association between clopidogrel and outcome of interest will be examined in the above mentioned adjusted model. If numbers permit, the interaction with individual PPIs will be evaluated.

The interaction between two factors (a and b) will be studied by estimating the Relative Excess Risk due to Interaction (RERI) (17) in order to identify departures from additivity [$RERI=RR_{factors\ a\ and\ b} - (RR_{factor\ a} + RR_{factor\ b} - 1)$]. A value of RERI = 0 indicates additivity of effects (no interaction), superadditivity (or synergism) if greater than 0, and subadditivity (or antagonism) if lower than 0. The interaction between the use of acid-suppressing drugs and clopidogrel will also be studied by stratification according to use of acid-suppressing drugs.

Exposure definition

The GPs record in the computer the name, dose, frequency, and number of pills prescribed. Exposure to study drugs will be categorized as: "current," when the supply of the most recent prescription lasted until index date or ended in the month before the index date; "recent," when it ended between one month and one year before the index date; "past," when it ended between one one and two years before the index date; and "non-use," when there was no recorded use in the two years before the index date. A secondary analysis will consider current when the supply of the most recent prescription lasted until index date or ended in the week before the index date.

Duration of use will correspond to the sum of days included in the time period of "consecutive" prescriptions: two prescriptions are considered "consecutive" when the time interval between the end of supply of the first

one and the beginning of supply of the second one is less than two months. We will categorize treatment duration into three groups: duration no greater than one month, duration between one month and one year, and duration greater than one year. Clopidogrel dose will be either 75 mg or 150 mg daily. Specific cutoff values for PPI dose (in mg) will be as follows: omeprazole 20, esomeprazole 40, lansoprazole 30, pantoprazole 40, rabeprazole 20, cimetidine 800, famotidine 40, nizatidine 300, ranitidine 300. Doses less than the cut-off value will be grouped under low doses, doses equal to the cut-off value under medium doses and doses greater than the cut-off value under high doses.

Power calculation

We expect to identify a cohort of patients discharged alive after an hospitalization for acute serious coronary heart disease in the vicinity of 25,000. This cohort will contribute an average of 4 years of follow-up resulting into 100,000 person-years. Assuming an annual incidence of 2% for MI/CHD death and 1% for UGIB, the expected number of cases will be 2,000 and 1,000 respectively. Accordingly, the number of exposed cases to clopidogrel would be 800 and 400 assuming a prevalence of clopidogrel use of 40%. If we assume that 40% of users of clopidogrel will be prescribed concomitantly PPI, these sample sizes will permit to detect a relative risk of 1.25 for MI/CHD and a relative risk of 0.75 for UGIB with a power greater than 80%, a 5% one-sided alpha error and a control/case ratio of 5.

Good Pharmacoepidemiology Practices

This study will be performed in acordance with the Guidelines for Good Pharmacoepidemiology Practices (2007) (18). The study protocol will have to be 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.

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