Study protocol: Assessment of low-dose ASA discontinuation risk associated with concomitant PPI use during the first year of ASA therapy for secondary prevention.

BACKGROUND

We propose to use The Health Improvement Network database (THIN) to provide new data on the risk of low-dose ASA discontinuation associated to PPI concomitant use during the first year of ASA therapy in a cohort of patients using ASA for secondary prevention of cardiovascular and cerebrovascular events.

STUDY OBJECTIVES

1- To estimate the one year risk of discontinuation of use of low-dose ASA associated to PPI concomitant use versus non-use, crude and adjusted by confounding.

2- To estimate the one year risk of discontinuation of use of low-dose ASA associated to PPI concomitant use stratified by age and sex,.

3- To evaluate other predictors of discontinuation of low-dose ASA during the first year of ASA therapy.

METHODS

Design

A retrospective cohort study using data from the THIN database in the UK.

Source population:

THIN database, which contains computerized information entered by general practitioners in the UK (1). Data on about 4 million patients are systematically recorded 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. An additional requirement for participating practices is recording of the indication for new courses of therapy. 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 (2,3).

Source cohort

This study cohort was identified in a previous study using this database (4). We identified all individuals recorded in THIN once they met all following criteria: , one year enrollment with the general practitioner, one year since first computerized prescription and being 50-84 years old. We excluded

patients with a recorded diagnosis of cancer before that date (beginning date). We also removed 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).

Study cohort of low-dose ASA users (≥2Rx) in secondary prevention

The study cohort will be comprised by new users of low-dose ASA (75–300 mg/day) for secondary prevention of cardiovascular or cerebrovascular disease who receive at least 2 prescriptions of ASA from to . We excludef ASA users with a record of ASA use ever before start date (date of first ASA Rx during follow-up), a history of alcohol abuse or alcohol-related disease, or a recorded diagnosis of cancer.

Follow up of the study cohort to ascertain discontinuation

We followed up the study cohort from 1 day after start date until the earliest of the following endpoints (stop date):

1. Discontinuation of ASA therapy (defined as a period of ≥ 90 days after the last prescribed course of ASA had been completed during which no repeat prescription was issued),
2. Cancer, alcohol abuse or alcohol-related disease,
3. Reaching the age of 85 years,
4. Death,
5. One year since start date,
6. The end of

PPI exposure definition

Cohort members will be classified into 3 mutually exclusive subcohorts according to PPI exposure during the follow-up:

1. Non-exposure to PPI will be defined as patients never receiving PPI during the entire follow-up.
2. Continuous exposure to PPI will be defined as use of PPI from start date (this includes both patients already exposed to PPI before start date as well as starting PPI together with ASA therapy) uninterruptedly (30 days gap of ASA-free was permitted) until stop date.
3. Intermittent exposure to PPI when the pattern of use of PPI during follow-up will not qualify as continuous exposure.

Cohort members will be also grouped according to the initial indication of low-dose ASA treatment:

1. IHD
2. Unstable angina
3. MI
4. CVD

Baseline characteristics

Other exposures of interest will be collected at start date and will include age, sex, body mass index, life-style factors (smoking, alcohol level use), morbidity (including gastrointestinal and cardiovascular diseases among others), co-medication (other antiplatelet drugs (clopidogrel and dipyridamole), warfarin, NSAIDs, PPIs, anti-H2s, digoxin, drugs prescribed for atrial fibrillation or other cardiovascular diseases) and use of health care services (number of general practitioners visits, referrals and hospitalizations).

We will categorize use of other medications according to 3 mutually exclusive time windows at start date: current, past and non-users.

Current will refer to users on start date or during the week prior to start date.

Past will refer to users exposed between 1 years and 1 week before start date.

N*on-use* will be defined as no use of the drug of interest in the year before start date.

Statistical analysis

We will estimate incidence rate of ASA discontinuation during the first year of low-dose ASA treatment (number of individuals who discontinue ASA during follow-up divided by the total person-time of follow-up), according to PPI exposure. Also, we will produce cumulative incidence rates using Kaplan-Meier survival analysis by PPI subcohort, overall as well as stratified by age groups and sex.

We will run Cox regression models and compute the hazard ratios (HRs) of discontinuation and their 95% confidence intervals (95%CI) associated with continue versus non-exposure to PPI. These estimates will be adjusted for age, sex and ASA indication. Additionally, we will evaluate other independent risk factors for discontinuation among baseline characteristics to control for confounding.

References:

1. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. Informatics in Primary Care 2004;12:171-7.
2. NHS Terminology Service: http://www.connectingforhealth.nhs.uk/terminology/readcodes. 2006.
3. Multilex Drug Data File: http://www.firstdatabank.co.uk/products/multilex/. 2006.
4. Martin-Merino et al Discontinuation of low dose acetylsalicylic acid therapy in UK primary care: incidence and predictors in patients with CV outcomes. Pragmatic and Observational research 2012:3:1-9.