International Journal of Cardiology 248 (2017) 376–381

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Incidence of colorectal cancer in new users and non-users of low-dose aspirin without existing cardiovascular disease: A cohort study using The Health Improvement Network

Lucía Cea Soriano [a,b,*,1], Montse Soriano-Gabarró [c,2], Luis A. García Rodríguez [d,3]

[a] Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
[b] Department of Preventive Medicine and Public Health, Faculty of Medicine, Complutense University of Madrid, Spain
[c] Epidemiology, Bayer AG, Berlin, Germany
[d] Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain

ARTICLE INFO

Article history:
Received 14 March 2017
Received in revised form 12 May 2017
Accepted 13 June 2017

Keywords:
Colorectal cancer
Incidence
Cardiovascular disease
Aspirin
Observational
General population

ABSTRACT

Background: Evidence regarding the chemo-protective effects of aspirin has influenced expert opinion in favour of low-dose aspirin use in certain patient populations without cardiovascular disease (CVD). The effects of aspirin in reducing the incidence of colorectal cancer (CRC) may be a large contributor to this favourable risk–benefit profile of low-dose aspirin in primary CVD prevention.
Methods: Using The Health Improvement Network, we estimated the incidence of CRC in individuals free of CVD and either prescribed or not prescribed prophylactic low-dose aspirin. Two cohorts – new-users of low-dose aspirin (N = 109,426) and a comparator cohort of non-users (N = 154,056) at start of follow-up – were followed (maximum 13 years) to identify incident CRC cases. Individuals with a record of CVD, cancer or low-dose aspirin prescription before start of follow-up were excluded.
Results: 2330 incident cases of CRC occurred; 885 in the aspirin cohort and 1445 in the comparator cohort, after mean follow-ups of 5.43 years and 5.17 years, respectively. Incidence rates of CRC per 10,000 person-years (95% confidence interval) were 14.90 (13.95–15.92) in the aspirin cohort and 18.15 (17.24–19.12) in the comparator cohort; incidence rate ratio 0.82 (0.76–0.89) adjusted for age, sex and primary care practitioner (PCP) visits in the previous year. Lower incidence rates were seen in the aspirin cohort for all strata evaluated (gender, age group and number of PCP visits in the previous year) except those aged ≥80 years.
Conclusion: Among most individuals without established CVD, initiation of low-dose aspirin is associated with a reduced incidence of CRC.

1. Introduction

The effectiveness of low-dose aspirin in the prevention of ischaemic cardiovascular events is well established [1–3]. There is also a growing body of evidence regarding a potential role for aspirin in chemoprotection, particularly in reducing the incidence and mortality of colorectal cancer (CRC) when used in patients either with or without known CVD [4–10]. This accumulation of evidence has led experts to favour use of low-dose aspirin in the primary CVD prevention setting in either broad [11] or more specific [12,13] patient populations, the latter largely dependent on the individual's CVD and bleeding risk profile.

Data on CRC that have informed these recommendations have arisen mainly from post-hoc analysis of cardiovascular randomized controlled trial data, [4,14–16] which may have excluded many patients that would use aspirin in the real world. We conducted an observational cohort study to estimate the incidence of CRC among new users of low-dose aspirin versus a comparator cohort of non-users of low-dose aspirin in individuals without known CVD in the general population. To help inform risk–benefit decisions in certain patient groups, we also

* Corresponding author at: Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante 28, 28004 Madrid, Spain.
E-mail addresses: luciaceife@gmail.com, tlcea@ucm.es (L. Cea Soriano).

[1] Lucía Cea Soriano contributed to the study design, the acquisition of data, the analysis and interpretation of the data, review of the manuscript, and the decision to submit the manuscript for publication.
[2] Montse Soriano-Gabarró contributed to the study concept, the interpretation of the data, review of the manuscript, and the decision to submit the manuscript for publication.
[3] Luis A. García Rodríguez contributed to the study concept, the study design, the acquisition of data, the analysis and interpretation of the data, review of the manuscript, and the decision to submit the manuscript for publication.

http://dx.doi.org/10.1016/j.ijcard.2017.06.052
0167-5273/

estimated incidence rates of CRC according to age group, gender and general health status/level of comorbidity.

2. Methods

2.1. Data source

We used data from The Health Improvement Network (THIN), a primary care database of anonymized patient electronic medical records (EMRs) in the United Kingdom (UK). Almost all of the UK population are registered with a primary care practitioner (PCP) and THIN currently covers approximately 6% of the UK population [17]. The database is representative of the UK population with regards to age, sex and geographic distribution, and has been validated for use in pharmacoepidemiologic research [18,19]. Almost 600 general practices throughout the UK have contributed data to THIN [17]. Participating PCPs record information prospectively as part of their routine patient care, and regularly send their data anonymously to THIN for use in research projects. Patient information is entered using Read codes or as free text. Read codes are the standard clinical terminology used in UK general practice, supporting detailed clinical encoding of diagnoses, symptoms, laboratory tests and results, therapeutics, surgical procedures and demographics [20]. Prescriptions are entered using Gemscript codes based on the National Health Service's (NHS) dictionary of medicines and devices [21] and are automatically recorded upon issue. Information from secondary care is communicated back to the PCP and entered in the database retrospectively. PCPs may also maintain paper files with laboratory data, hospital discharge summaries, consultant letters and other patient-specific information, which can be obtained by requesting copies of paper files and/or through surveys of PCPs without breach of confidentiality. For a subset of THIN practices, data can be linked at the patient level to Hospital Episode Statistics (HES) [22]. Hospital Episode Statistics contain clinical and administrative data on hospital episodes (admissions and visits), which are collected from UK NHS hospitals and linked to International Classification of Diseases-10 codes. The study protocol was approved by an independent scientific review committee for THIN (reference number 14-088A1).

2.2. Identification and follow-up of the study cohorts

The study design is illustrated in Fig. A.1. The source population comprised individuals in THIN aged 40–84 years between 1 January 2000 and 31 December 2009 who met the following eligibility criteria: at least 2 years registration with the PCP, at least 1 year since the beginning of their computerized prescription history, at least one encounter/visit recorded in the previous 3 years. Individuals were excluded if they had a prescription for low-dose aspirin (75 or 300 mg; tablets available in the UK) or a diagnosis of cancer any time before study entry. Individuals aged 70 years or more with a follow-up longer than 1 year and with fewer than two recorded consultations with a PCP during their entire follow-up (a proxy for incomplete and/or invalid data recording) were also excluded.

From the source population we identified a cohort of new users of low-dose aspirin (N = 170,336) with the date of first low-dose aspirin prescription set as the start of follow-up (start date). We then matched each member of the low-dose aspirin cohort to an individual from the source population still free of low-dose aspirin on the start date; matching was by age, sex, calendar year and number of PCP visits (0–1, 2–4, 5–9, 10–19 or ≥20 in the previous year) – these individuals comprised the comparator cohort (N = 170,336). We then excluded from both cohorts individuals with a record of CVD before the start date (i.e. secondary prevention population) to leave only those eligible for primary prevention of CVD. To do this, we used an automated computer algorithm that searched individuals' medical records in THIN for Read codes suggestive of CVD (codes included those for myocardial infarction, unstable angina, revascularization procedures, cerebrovascular disease, peripheral artery disease and ischaemic heart disease unspecified) any time before the start date and up to 30 days after the start date, and then designated individuals with such codes to the secondary prevention population. All remaining individuals who did not have a relevant Read code to suggest they had existing CVD were designated to the primary CVD prevention population. In the low-dose aspirin cohort, 109,426/170,336 (64.2%) individuals were assigned to the primary CVD prevention cohort (i.e. were assumed to be taking low-dose aspirin for primary CVD prevention). In the comparator cohort, 154,056/170,336 (90.4%) were assigned to the primary CVD prevention cohort (i.e. were assumed to be CVD free, and eligible for, but not receiving low-dose aspirin for primary CVD prevention).

2.3. Follow-up to identify incident cases of CRC

Both cohorts were followed from the start date until the earliest of the following: a Read code for CRC, a record of cancer other than CRC, age 90 years, death, or the end of the follow-up period (31 December 2011). The EMRs of all patients with a Read code suggestive of CRC (N = 2930), including free-text comments, were manually reviewed while masked to aspirin exposure. Potential incident cases of CRC had been validated in a previous study [23] where we manually reviewed the medical records of all potential cases with a Read code for CRC in THIN, and also validated through linkage to HES data (for patients in practices linked to HES) and via questionnaires to GPs for a sample of patients [24]. The index date was designated as the date of first CRC-related symptom, screening or diagnostic procedure or surgery, whichever came first. In cases where the index date was unclear – for instance, when patients presented several times to their PCP with non-specific symptoms – an external gastroenterologist was consulted to ascertain the most likely index date.

2.4. Ascertainment of data on patient characteristics (both cohorts)

We ascertained the age of individuals at the start date, and lifestyle factors (body mass index [BMI], smoking and alcohol intake) any time before the start date using the most recent value/status. Morbidities, including traditional CVD risk factors, digestive, respiratory, central nervous system, metabolic, and articular disorders, were considered present when this information was recorded in the database any time before the start date. We also extracted information on medication use, which was classified into the following three categories: *current use*, when supply of the most recent prescription lasted until the start date or ended within 90 days before the start date; *past use*, when supply of the most recent prescription ended more than 90 days before the start date; and *non-use*, when there was no recorded use any time before the start date. The number of different medications in the month before the start date was categorized into the following three groups: 0–1, 2–4 and ≥5.

2.5. Statistical analysis

Characteristics of the two study cohorts at the start of follow-up were described using frequency counts and percentages for categorical variables, and means with standard deviation for continuous variables. Incidence rates with 95% confidence intervals (CIs) were calculated for both cohorts, overall and stratified by age, sex and number of PCP visits in the year before start of follow-up (as a proxy for general health status). We also calculated absolute differences in risk of CRC between the two study cohorts and incidence rate ratios (IRRs) with 95% CIs.

3. Results

3.1. Baseline characteristics of the study cohorts

Frequency distributions of characteristics of the two study cohorts at the start of follow-up are shown in Table 1 for demographics, lifestyle factors and healthcare use and in Fig. 1 and Table A.1 for morbidities and medications. Although the matching of individuals in the two cohorts was performed before restricting to individuals free of CVD at the start date, the distribution of gender, age and previous PCP visits were comparable in the two primary CVD prevention study cohorts; mean age was 63.0 years in both cohorts. The distribution of current smokers and alcohol consumption was similar in the two cohorts, but obesity (BMI ≥ 30 kg/m^2) was more frequent in the low-dose aspirin cohort than in the non-exposed comparator cohort; mean BMI was 28.6 kg/m^2 in the low-dose aspirin cohort and 26.9 kg/m^2 in the comparator cohort. Traditional risk factors – hypertension, diabetes, gout, obesity, deep vein thrombosis (DVT), pulmonary embolism (PE), atrial fibrillation (AF) and heart failure – were all more prevalent in the low-dose aspirin cohort than in the comparator cohort, which was expected as these conditions are factors influencing the decision to prescribe low-dose aspirin among individuals free of established CVD. Seventy six percent of the low-dose aspirin cohort had at least one of the following comorbidities compared with 48% in the comparator cohort: hypertension, hypercholesterolaemia, diabetes, DVT, AFT, heart failure or obesity. The frequency of gastrointestinal disorders, such as dyspepsia, uncomplicated peptic ulcer, complicated peptic ulcer and gastro-oesophageal reflux disease was similar between the two cohorts. As expected, use of medications indicated for metabolic syndrome conditions, such as antihypertensive medications, statins and oral antidiabetics, in the month before the start of follow-up was substantially higher in the low-dose aspirin cohort compared with the comparator cohort; 66.1% of the aspirin cohort were current users of at least one of these classes of drugs compared with 38.1% in the comparator cohort. Use of non-steroidal anti-inflammatory drugs, respiratory drugs and acid-suppressing drugs was slightly higher in the low-dose aspirin cohort. A high level of polypharmacy was slightly more common among the low-dose-aspirin cohort.

3.2. Incidence of CRC

A total of 885 incident cases of CRC occurred in the low-dose aspirin cohort over a mean follow-up of 5.43 years (median 5.13 years) and 1445 cases occurred in the non-user comparator cohort over a mean follow-up of 5.17 years (median 4.90 years). Incidence rates of CRC