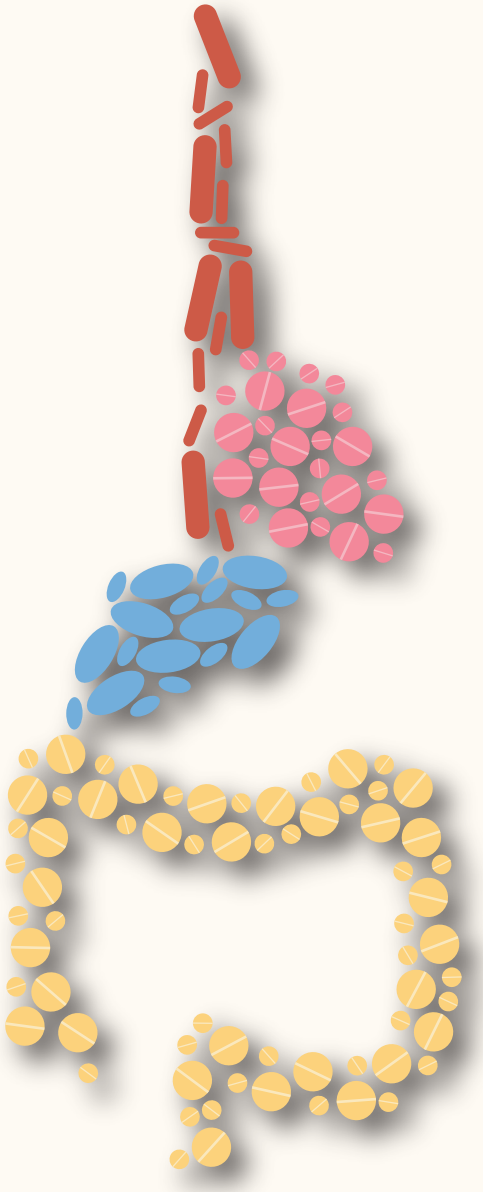
Effects of Non-Steroidal Anti-Inflammatory Drugs on the Gastrointestinal and Cardiovascular System

Gwen M.C. Masclee



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Effecten van NSAID's op het maag-darm stelsel en cardiovasculaire systeem

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CONTENTS

SECTION 1

General Introduction

INTRODUCTION

The following paragraphs provide an introduction to and brief background of the topic of this thesis. The introduction elaborates on two drug classes that are the main drugs investigated in this thesis, namely non-steroidal anti-inflammatory drugs, also known as NSAIDs, and proton pump inhibitors, which are abbreviated as PPIs.

Non-steroidal anti-inflammatory drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are derivatives from acetylsalicyl acid, a drug that is also known as aspirin. The first NSAID that has been developed was ibuprofen. Ibuprofen was used for the first time in 1968 for its analgesic and anti-inflammatory properties.[1] Since then many other NSAIDs have been developed and their use in the general population has gained a lot in popularity. In Europe, NSAIDs account for 7.7% of all drug prescriptions[2] and the annual prevalence of NSAID use is estimated at around 20%.[3] This translates to around 2.6 million subjects in the Netherlands that received NSAID prescriptions from their physician in 2013 (Figure 1). You may wonder why these drugs are one of the world's most frequently prescribed drugs? This question is relatively easy to answer, since NSAIDs have analgesic, antipyretic and anti-inflammatory actions. Subsequently, NSAIDs can be given for a wide range of indications of diseases to treat, such as in the treatment of rheumatoid arthritis or other inflammatory conditions.[5, 6] NSAIDs also have an important role in the management of pain. The first step in pain management includes the use of non-opioid drugs, such as paracetamol as this is very effective in many painful conditions. When paracetamol treatment is not sufficiently effective, NSAIDs may be considered as second treatment option.

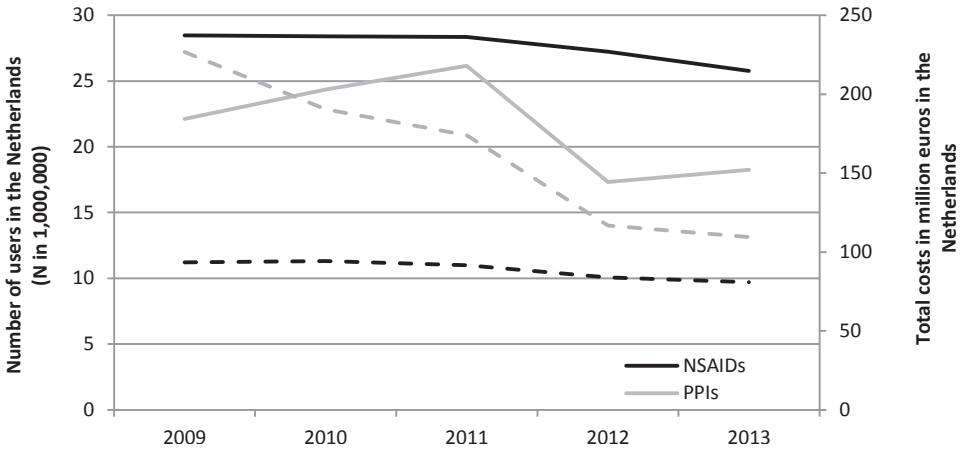

Figure 1. Number of users (solid line) and total costs in millions (dashed line) of non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) in the Netherlands between 2009 and 2013.

In the general population NSAIDs such as diclofenac or ibuprofen are considered effective drugs and relative safe or even harmless. Therefore they are widely used for mild symptoms such as: headache, migraine or musculoskeletal complaints. The mechanism by which NSAIDs diminish the pain and inflammation is via inhibition of specific enzymes, the so called cyclo-oxygenase (COX) enzymes (Figure 2). One of the endproducts of these enzymes are prostaglandins, which play an important role in pain, thrombocyte aggregation and thrombosis. They are also responsible for the production of a protective mucus layer in the stomach.[7-9] There are various isoforms of the COX-enzymes, but the most frequently studied are COX-1 and COX-2 enzyme. The COX-1 enzyme is among others responsible for production of thromboxane A_2 for platelet function and production of prostacyclin for stomach endothelium protection. COX-1 is present in most body tissues. The other isoform, COX-2 enzyme, is responsible for the perception and regulation of pain. Generally, COX-2 is present in some tissues, but during an inflammatory process the enzyme is present in other tissues as well.

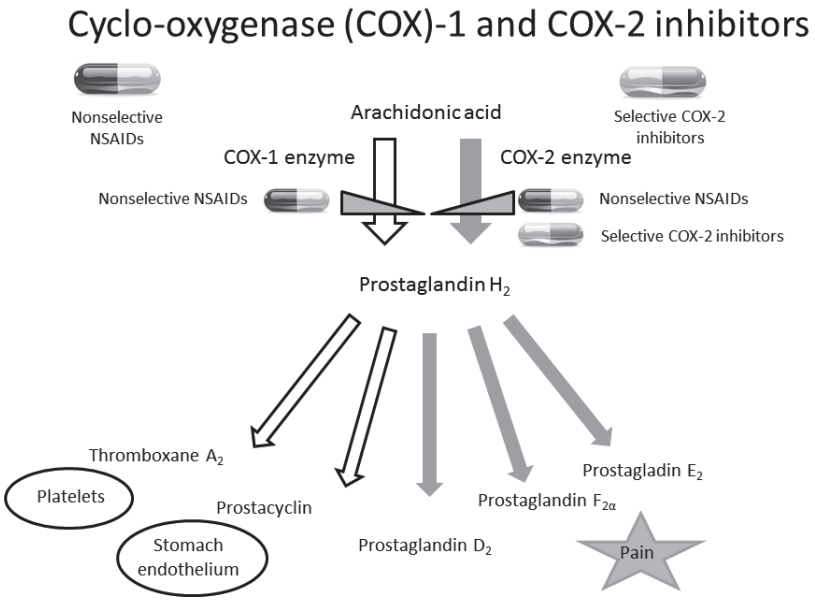

Figure 2. Mechanism of action of cyclo-oxygenase inhibitors.

Now, given the underlying mechanisms of these enzymes, it becomes clear that the traditional nonselective (ns) NSAIDs such as ibuprofen, naproxen and diclofenac, inhibit both forms of cyclo-oxygenase enzymes. However, this results in gastrointestinal vulnerability and may lead to stomach bleeding. This was one of the key reasons for development of NSAIDs that specifically inhibited the COX-2 enzyme only, and thus should be safer for the stomach; the selective COX-2 inhibitors, such as celecoxib, etoricoxib, rofecoxib and valdecoxib.[10, 11]

Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are one of the most commonly used drugs worldwide. After introduction on the market of omeprazole in 1988, the use of PPIs rapidly rose. In later years, more PPIs became available (in particular lansoprazole, rabeprazole, pantoprazole and esomeprazole). Their share on the market for 2014 in the Netherlands was 7% of all drug dispensings. The superiority of PPIs in the treatment of non-erosive reflux disease and erosive esophagitis as compared to treatment with histamine-2 receptor antagonists (H2RA) has been proven in various randomized clinical trials and is generally accepted.[13]

In the United States PPIs ranked ninth among the most frequently dispensed therapeutic classes in 2012. A similar rise in use of PPIs has been observed in European countries. In recent years, the total amount of units prescribed and number of persons using omeprazole is ranked within the top 5 of drugs in the Netherlands. This resulted in substantial expenditures, where PPIs accounted for $10.0 billion in 2012 in the United States and 110 million Euros in the Netherlands in 2013 (Figure 1). Although some PPIs have become available over-the-counter (OTC) in some countries, most PPIs are used on prescription.

The widespread use of PPIs is partly due to the application of PPIs for various medical conditions (Table 1). Despite the clear benefits of PPIs on upper GI safety, the minister of Health, Welfare and Sports in the Netherlands decided to exclude PPIs as part of the basic insurance and reimbursement of the costs. Nevertheless, it appeared that the number of upper GI bleedings decreased in the year following this decision.[16]

Table 1. Common indications for Proton Pump Inhibitor use.

Clinical indication of Proton Pump Inhibitor use
Gastroesophageal Reflux Disease
Peptic Ulcer Disease
Non-ulcer dyspepsia
Prophylaxis for NSAID or low-dose aspirin use
Helicobacter pylori eradication
Zollinger-Ellison syndrome
Barrett's esophagus

NSAID, non-steroidal anti-inflammatory drug

PPIs are considered relatively safe drugs because side effects are infrequent and mostly of modest severity; mainly including headache, diarrhea, constipation, nausea and rash. These occur in a small proportion of users (1% to 5%). The prolonged and potentially non-judicious use of PPIs, however, is associated with risks. Several of the adverse effects of PPIs that have been documented are pertinent to older people such as bone fractures,[17-24] pneumonia,[26-35] vitamin B_{12},[36-47] and iron absorption problems,[48-53] *Clostridium difficile* infection,[55-57]

hypomagnesemia,[58-63] and acute interstitial nephritis.[65-68] However, due to their wide use any small adverse effect of PPIs may have a considerable impact on health and morbidity in the elderly population.

NSAID-related Adverse Events

For a long time it has been known that the use of NSAIDs is associated with various unintended side effects. The severity of these side effects range from experiencing mild symptoms; such as dyspepsia or heart burning, to severe gastroduodenal ulcerations and bleeding, leading to hospitalization and potentially even death.

Gastrointestinal events

Upper gastrointestinal (GI) bleeding is still one of the most common acute diseases in the field of gastroenterology.[69] It occurs in around 50 to 60 persons out of 100,000 persons each year. When translating this to the Netherlands, around 8,000 to 9,000 patients suffer from acute upper GI bleeding each year. Although in recent years substantial improvement in the prevention and treatment of upper GI bleeding has been accomplished, the mortality rate of upper GI bleeding is still around 5%-10%.[70, 71] The most common cause of upper GI bleeding is still the use of NSAIDs, which increases the risk of upper GI bleeding around 2 to 4 fold [72, 73] and yields an annual absolute risk of upper GI bleeding of 1.36%, as based on the integration of event rates from meta-analyses and large randomized trials.[74] However, within the group of NSAIDs, the selective COX-2 inhibitors have proven in clinical trials to result less often in symptomatic upper GI ulcers or ulcer complications compared to the traditional NSAIDS.[10, 11, 75] Yet, it is important to realize that still a considerable proportion of around 3.7% to 8.9% of selective COX-2 inhibitor users continues to experience upper GI events.[76-79]

However, the effects of NSAIDs extend also beyond the duodenum. Currently, evidence is accumulating that NSAID use is also associated with injury to the small bowel and colon.[80] It appeared that there are more small bowel and colonic mucosal breaks and erosions in patients when taking NSAIDs.[81] However whether these physiological changes also translate to a clinically relevant outcome, such as hospitalization because of rectal bleeding or anemia remains unclear.[82] Since the outcomes of the lower gastrointestinal system are difficult to establish, especially when considering electronic health care records for case identification, this outcome was not assessed in the current thesis. Yet the outcome of microscopic inflammation of the colon was included. NSAIDs, and to a lesser extent PPIs, are thought to interfere with the cell-to-cell attachment.[83-88] When the bowel integrity and colonic permeability is affected, luminal antigens may enter easily the underlying layers of the intestines and elicit an immune and inflammatory reaction.[83]

Cardiovascular events

After successful release of selective COX-2 inhibitors on the market[10, 75] concerns were raised about their cardiovascular (CV) safety.[11] In 2001 a pharmaceutical company commenced a randomized clinical trial (RCT) to evaluate the efficacy of rofecoxib on the prevention of colorectal polyps, as another selective COX-2 inhibitor namely celecoxib had already been approved for this indication.[89] With the RCT the company aimed to further evaluate a prior cardiovascular safety issue of rofecoxib. The trial was terminated early when preliminary data showed an increased relative risk of adverse thrombotic cardiovascular events (including myocardial infarction and stroke) for rofecoxib. However, it took several years before regulatory decisions about the CV safety were made. In the meanwhile many patients were still taking rofecoxib, which led to many deaths. This rofecoxib scandal led to the voluntary withdrawal of the drug in 2004[11, 90] but as well to closer monitoring of newly marketed drugs. The United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) reviewed the safety of selective COX-2 inhibitors and concluded that selective COX-2 inhibitors increased the risk of CV events, but the overall benefit-risk balance was still positive.[93] They recommended to avoid selective COX-2 inhibitors in patients with ischemic heart disease, stroke or peripheral arterial disease.[89, 94, 95] However, subsequently signals regarding the increased arterial thrombosis risk for use of the traditional nonselective NSAIDs arose, particularly when they were used at high doses and for long-term.[96, 97] The Committee for Medicinal Products for Human use concluded in 2006 that there was insufficient evidence to conclude on a thrombotic risk. Therefore EMA requested a review of the safety of traditional NSAIDs as well. This led to the initiation of the Safety Of Non-Steroidal Anti-Inflammatory Drugs (SOS)-project which aimed to assess the gastrointestinal and cardiovascular safety of NSAIDs. Parts are described in this thesis.

GUIDELINE RECOMMENDATIONS

Physicians prescribing NSAIDs to patients are faced with mainly two issues: 1) identification of patients at high-risk of developing adverse events; and 2) the selection of appropriate strategies to prevent upper GI bleeding and its complications. The clinical decision making is complex as the physician should not only balance the analgesic and anti-inflammatory potency of NSAIDs against the gastrointestinal risk profile, but also weigh the cardiovascular risk of NSAIDs for the individual patient. Several clinical guidelines have been published which aim to indicate preferred approaches for medical problems.[98-100]

Risk factors for upper GI complications have been identified in a large variety of studies and with a considerable degree of consistency. Although most risk factors are common across each guideline, some guidelines include more risk factors than others. In general the following risk factors are considered as most important factors in all guidelines: 1) a history of an upper GI event; 2) older age, above 65 years of age; and concomitant use of 3) anticoagulants; 4) corticosteroids; or 5) antiplatelets (including low-dose aspirin). Based on

these factors an arbitrarily stratification of patients being at 'low', 'moderate' or 'high' risk can be made.[99] A patient is considered at 'low' risk if there are no risk factors present, at 'moderate' risk if there are 1 or 2 risk factors present and at 'high' risk if there are more than 2 risk factors present, or if the patient had experienced an upper GI complication before. Other factors that are occasionally mentioned in guidelines include concurrent use of selective serotonin reuptake inhibitors, using high dosages of NSAIDs and having comorbid diseases as rheumatoid arthritis, heart failure and diabetes mellitus.[100]

Strikingly, despite the fact that there is very little evidence on the risk when several of these risk factors are combined it is stated in guidelines that the risk factors act cumulatively with an increasing (additive) risk when multiple risk factors are present.[100] It is however unclear whether we can simply add the risks of the separate risk factors cumulatively; or whether we should be taking some multiplicative function of additional/excess risk into account.

Possible preventive strategies for upper GI events include a concurrent prescription of a proton pump inhibitor or histamine-2 receptor antagonist to a nonselective NSAID, or to prescribe a selective COX-2 inhibitor instead of a nonselective NSAID.

As can be understood from the cardiovascular risks of NSAIDs discussed above, the cardiovascular risk of patients should be considered in the recommendation of prevention of NSAID-related upper GI complications as well. In general, patients at risk of cardiovascular events, such as those with a history of a prior cardiovascular event, diabetes, hypertension, hyperlipidemia and obesity, often receive prophylactic low-dose aspirin.[99] When considering patients receiving low-dose aspirin as 'at risk of cardiovascular events' we can summarize the recommendations for prevention of NSAID-related upper GI complications as is shown in Table 2. The area of appropriate gastroprotection in patients at risk of upper GI events is still evolving and possibly we should prescribe a selective COX-2 inhibitor with a proton pump inhibitor to patients at risk.[101, 102]

Table 2. Recommendations for prevention of NSAID-related upper GI complications according to gastrointestinal and cardiovascular risk.[99]

		Gastrointestinal risk		
		Low	**Moderate**	**High**
Cardiovascular Risk	No low-dose aspirin use *Low CV risk*	NSAID alone	NSAID + PPI	Preferably no NSAID, otherwise COX-2 inhibitor + PPI
	Use of low-dose aspirin *High CV risk*	Naproxen + PPI	Naproxen + PPI	Preferably no nsNSAID or COX-2 inhibitor

CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pum inhibitor

AIMS AND OUTLINE OF THIS THESIS

This thesis aims to provide insight into several safety and beneficial aspects of non-steroidal anti-inflammatory drug (NSAID) use and proton pump inhibitor (PPI) use on different parts of the gastrointestinal system and the cardiovascular system. The thesis is divided in seven sections.

The first section provides a general introduction to the thesis and summarizes the use of NSAIDs, PPIs and the potential complications of use.

In Section 2 we focus on the use of PPIs. PPIs are frequently used drugs as it is recommended to co-prescribe PPIs with NSAIDs in order to mitigate the risk of NSAID-related upper gastrointestinal bleeding. The use of PPIs is however not without implications. The benefits and harms of PPI use in an elderly population are discussed in *Chapter 2.1*.

In Section 3 we elaborate on two diseases of the esophagus and their relation with the use of NSAIDs and PPIs. Barrett's esophagus (BE) is characterised by replacement of the squamous epithelium of the esophagus by metaplastic columnar epithelium and considered a consequence of prolonged gastro-esophageal reflux into the lower esophagus. BE is one of the most important risk factors for subsequent development of esophageal adenocarcinoma (EAC) via a stepwise pathway of low-grade and high-grade dysplasia. How often Barrett's esophagus occurs in the general population in the Netherlands and the United Kingdom is described in *Chapter 3.1*. In this chapter we also elaborate on the frequency of development of esophageal adenocarcinoma within patients with Barrett's esophagus. Recognizing that besides the decrease in death rates of most cancers in recent years in contrast to the increased mortality for esophageal cancer, and the 5-year survival rate of subjects with esophageal cancer is only between 13% to 17%, the need for effective prevention of esophageal cancer development is warranted. There was some promising information of cancer prevention via use of PPIs and NSAIDs in patients with BE, however, it remained unclear to which extent this could be applicable to a more general population of BE. In *Chapter 3.2* we expand the knowledge by assessing whether NSAIDs and PPIs are effective in reducing the progression from Barrett's esophagus to esophageal adenocarcinoma.

The action of NSAIDs on the stomach is well-known. NSAIDs are ulcerogenic drugs and increase the risk of upper gastrointestinal bleeding, ulceration and complications. Section 4 is devoted to this topic. Upper GI bleeding has a major impact on patients' quality of life and public health care costs. Although great improvements in prevention and treatment of upper GI bleeding have been achieved in recent decades, upper GI bleeding-related morbidity and mortality remain substantial. In clinical trials the benefit of selective COX-2 inhibitors over traditional nonselective NSAIDs with respect to upper GI events was shown. After selective COX-2 inhibitors came on the market, it became clear that physicians preferentially prescribed these 'new' and 'safer' drugs to patients at higher risk of upper GI bleeding than patients who

received the traditional older nonselective NSAIDs. In observational studies using routinely prospectively collected data, it is difficult to take this channelling preference into account. In *Chapter 4.1* we assess whether we are able to address this confounding issue. When comparing two comparable groups with regard to their upper gastrointestinal risk profile, the question of whether we should prefer prescribing a traditional nsNSAID together with a gastroprotective agent or a selective COX-2 inhibitor solely is addressed in *Chapter 4.2*.

Not only NSAIDs are known to increase the risk of upper GI bleeding, use of low-dose aspirin, which is considered standard of care for cardiovascular prevention, increases the risk of upper GI bleeding up to 4-fold. Given the fact that around 30% of patients using low-dose aspirin will also use an NSAID, the risk of upper gastrointestinal bleeding may rise substantially. In clinical guidelines it is mentioned that combining certain drugs, for instance glucocorticoids and anticoagulants, with NSAIDs should be avoided. In *Chapter 4.3* we estimate the risk of upper GI bleeding when multiple drugs are used concomitantly with nsNSAIDs, selective COX-2 inhibitors or low-dose aspirin. Additionally we assess whether drugs have synergy with each other resulting in an excess risk that would not have been expected on the basis of the individual risks of upper GI bleeding.

The last organ of the gastrointestinal system that is studied in this thesis is the colon, also known as large bowel. One of the most important functions of the colon is the resorption of water from the wastes that pass through. Inflammation of the colon interferes with this process and results in decreased water resorption and ultimately diarrhea. Microscopic colitis (MC) is a condition characterized by chronic watery diarrhea, normal radiological and endoscopic appearance and microscopic inflammation of the colon. In recent years several studies reported on an increasing incidence of MC, however whether this holds for the Netherlands as well, is unknown. In *Chapter 5.1* we investigate whether the substantial increase in colonoscopies in recent decades may be charged for that. The etiology of the disease is largely unknown, but NSAIDs and PPIs may be involved in the predisposition of MC development. In *Chapter 5.2* we disentangle the effects of NSAIDs and PPIs on the colon and investigate whether the use of these drugs increases the risk of microscopic colitis, or whether they worsen symptoms of diarrhea. Continued chronic inflammation of the colon may result in conformational changes of cells in the colon. Patients with certain chronic inflammatory bowel diseases are more likely to develop colorectal neoplasia because of chronic inflammation. Whether this also holds for chronic inflammation in the context of microscopic colitis is investigated in *Chapter 5.3*.

After the increased thrombotic risk with rofecoxib, it became clear that there is more than only the gut to look for harmful effects of NSAIDs. To assess whether the thrombotic risk is also seen for other frequently used individual NSAIDs or this was specifically an effect of selective COX-2 inhibitors, in *Chapter 6.1* analysis of the risk of acute myocardial infarction for twenty-eight individual NSAID compounds is done. Summarizing the knowledge gathered from Chapters 4.1-4.3 and Chapter 6.1 you would like to assess for an individual patient given

his/her upper GI and cardiovascular risk profile which individual NSAID should be preferred over all others. Despite some guidance from the clinical guidelines, it remains difficult for a physician to tailor NSAID-therapy and to consider appropriate gastric protection for an individual patient. *Chapter 6.2* incorporates evidence on the gastrointestinal and cardiovascular risk of NSAIDs and provides an overall decision tool to assess on individual patient-level which individual NSAID is relatively the safest choice.

In the previous chapters we use and combine a variety of databases to address the research questions. In which way to consider combination of large-scale data and results is however, an area that does not have fully developed and validated methods. In the context of a common data model we compared two methods to combine results from several nested case-control studies in the SAFEGUARD project (Section 7, *Chapter 7.1*).

In the last section (Section 8), the main findings of this thesis are summarized and discussed.

Throughout this thesis a variety of data sources, study designs and exposures are being studied. In Table 3 an overview of these including the research question can be seen.

Table 3. Overview of study principles of studies described in this thesis.

Chapter	Research Topic	Design	Setting	Country	Outcome	Drugs
2.1	Use and safety of proton pump inhibitors among the elderly	Review	NA		NA	PPIs
3.1	Incidence of BE and EAC among BE patients	Cohort study	IPCI, THIN	NL, UK	BE, EAC	NA
3.2	Chemoprevention of EAC among patients with BE	Nested CCTRL study	IPCI, THIN	NL, UK	EAC	NSAIDs, statins, PPIs, SSRIs, LDA
4.1	Generating high-dimensional propensity score on unstructured information from medical records	Matched cohort study	IPCI	NL	Upper GI bleeding	NSAIDs
4.2	Selective COX-2 inhibitors or nonselective NSAIDs plus gastroprotective agents and risk of upper GI outcomes	Nested CCTRL study	CPRD, HSD, IPCI	IT, NL, UK	Upper GI bleeding and upper GI complication	NSAIDs
4.3	Concomitant use of drugs with nsNSAIDs, selective COX-2 inhibitors and low-dose aspirin and risk of upper GI bleeding	Self-controlled case series	Aarhus, ARS, HSD, Pedianet, IPCI, PHARMO, UNIMIB	DK, IT, NL, UK	Upper GI bleeding	nsNSAIDs, selective COX-2 inhibitors, LDA, corticosteroids, SSRIs, gastroprotective agents, aldosterone antagonists, calcium channel blockers, anticoagulants, antiplatelets, nitrates
5.1	Incidence of microscopic colitis in relation to number of colonoscopies	Cohort study	IPCI	NL	Microscopic colitis	NA
5.2	Risk of microscopic colitis during use of drugs	Nested CCTRL study	IPCI	NL	Microscopic colitis	NSAIDs, PPIs, SSRIs, LDA, ACE-inhibitors, beta-blockers
5.3	Risk of colorectal neoplasia in microscopic colitis	Cohort study	Denmark, PALGA	DK, NL	Colorectal polyps, adenomas and cancer	NA
6.1	Risk of acute myocardial infarction during use of individual NSAIDs	Nested CCTRL study	GePaRD, IPCI, OSSIFF, PHARMO, SISR, THIN	GE, IT, NL, UK	Acute myocardial infarction	Individual NSAID compounds
6.2	Individualized NSAID prescribing based on cardiovascular and GI risks	Decision model	GePaRD, IPCI, OSSIFF, PHARMO, SISR, THIN	GE, IT, NL, UK	AMI, IS, HF and upper GI complication	Individual NSAID compounds
7.1	Pooling of data from multiple data sources	Nested CCTRL study	BIFAP, CPRD, GePaRD, HSD, IPCI, Medicare, OSSIFF, PHARMO, SISR	GE, ES, IT, NL, UK, US	AMI	Metformin, glimepiride

AMI, acute myocardial infarction; BE, Barrett's esophagus; CCTRL, case-control; EAC, esophageal adenocarcinoma; ES, Spain; GE, Germany; GI, gastrointestinal; HF, heart failure; IS, ischemic stroke; IT, Italy; LDA, low-dose aspirin; NA, not applicable; NL, the Netherlands; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; SSRI, selective serotonin reuptake inhibitor; UK, United Kingdom; US, United States.

SECTION 2

Use and effects of Proton Pump Inhibitors in the elderly

CHAPTER 2.1

A Benefit-Risk Assessment of the Use of Proton Pump Inhibitors in the Elderly

Gwen MC Masclee, Miriam CJM Sturkenboom, Ernst J Kuipers

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ABSTRACT

Proton pump inhibitors (PPIs) are among the most commonly used drugs worldwide and their intake increases with age. Despite a relatively safe profile, a range of studies reported associations between use of PPIs and various adverse events. The most important adverse events, such as pneumonia, bone fractures, bacterial enteric infections, and diminished vitamin absorption are critically discussed in this review in the view of body of evidence, including underlying biological mechanisms, evidence of causality and consistency. Most of the reported risks are relatively small and sometimes based on inconsistent evidence. For an individual patient and particularly the elderly, it is relevant to question the indication of use and balance the benefit and potential harm of PPI therapy. This approach can minimize morbidity and reduce health care costs. In this review the use and safety of proton pump inhibitors among the elderly is described.

Use of Proton Pump Inhibitors

Proton pump inhibitors (PPIs) are one of the most commonly used drugs worldwide. After introduction on the market of omeprazole in 1988, PPI use rapidly rose. In later years, more PPIs became available (in particular lansoprazole, rabeprazole, pantoprazole and esomeprazole). The superiority of PPIs in the treatment of non-erosive reflux disease and erosive esophagitis as compared to treatment with histamine-2 receptor antagonists (H2RA) has been proven in various randomized clinical trials and is generally accepted.[13]

In the United States PPIs ranked ninth among the most frequently dispensed therapeutic classes in 2012. A similar rise in use of PPIs has been observed in European countries. In recent years, the total amount of units prescribed and number of persons using omeprazole is ranked within the top 5 of drugs in the Netherlands. This resulted in substantial expenditures, where PPIs accounted for $10.0 billion in 2012 in the United States. Although some PPIs have become available over-the-counter (OTC) in some countries, most PPIs are used on prescription.

Among the elderly, utilization patterns of PPIs are less well studied. The overall frequency of drug use is much higher among elderly as compared to the general population.[104] An Italian study showed that drugs used by elderly were in particular for acid-related disorders.[104] Around 16% of elderly subjects recorded using drugs for acid-related disorders (H2RA, PPIs and antacids).[104]

Depending on the indication, PPIs can be used both short and long-term. Short-term use of PPIs is not associated with severe, unexpected adverse effects. Obviously, safety of PPIs is more jeopardized during long-term treatment. Elderly in long-term need of PPIs form a population with frequent co-morbid disease and concomitant multi-drug use.[105] Both factors affect the risk of adverse events. A third factor that is important when assessing associations in pharmaco-epidemiology is the presence of a dose-relationship. Though causality can never be fully established in observational studies, according to Bradford-Hill criteria, the presence of a dose-relationship strongly supports a causal association; i.e. meaning that higher dosages should be associated with a greater risk than lower dosages.[106]

In this review the use and safety of PPIs in the elderly is discussed. PPIs are generally considered as safe drugs. However, a range of studies reported associations between use of PPIs and various adverse events. Some of the most relevant potential adverse events, such as pneumonia, bone fractures, bacterial enteric infections, and diminished vitamin absorption are critically discussed in this review in the view of body of evidence, including underlying biological mechanisms, evidence of causality and consistency.

Indications of PPI use in the elderly

The widespread use of PPIs is partly due to the application of PPIs for various medical conditions (Table 1). An observational study reported in 2006 that the most common indications for incident PPI use (defined as new users who did not take a PPI within the

previous 12 months) were gastroesophageal reflux disease (GERD) and non-reflux dyspepsia, accounting respectively for 27% and 25% of new prescriptions. Long-term PPI use (defined as receiving at least 3 PPI prescriptions) occurred in around 60% of patients with esophagitis Los Angeles classification grade A/B, in 75% of grade C/D esophagitis and in 70% of subjects diagnosed with Barrett's esophagus.[107] However, PPIs were prescribed only once in the majority of patients and particular for symptom relief of simple reflux.[107] Only in 6% of PPI users the indication was defined as 'other'.[107] This contrasted to an Australian study, in which 21% of PPI use was for acute gastrointestinal bleeding, and 40% for 'other' indications.[108] Age of 65 years or older is an established risk factor for upper gastrointestinal (GI) bleeding in non-steroidal anti-inflammatory drug (NSAID) users.[99] Among the elderly PPIs are therefore often co-prescribed to NSAIDs as gastroprotective measure.[109]

Table 1. Common indications for Proton Pump Inhibitor use in the elderly.

Clinical indication of Proton Pump Inhibitor use
Gastroesophageal Reflux Disease
Peptic Ulcer Disease
Non-ulcer dyspepsia
Prophylaxis for NSAID or low-dose aspirin use
Helicobacter pylori eradication
Zollinger-Ellison syndrome
Barrett's esophagus

NSAID, non-steroidal anti-inflammatory drug

Additionally, the use of low-dose aspirin (LDA; up to 325mg/day for cardiovascular prevention) is considered an indication for PPI use. It has been shown that use of LDA increases the risk of upper GI bleeding 2 to 4 fold.[73, 110-113] Clinical guidelines recommend use of PPIs in patients receiving LDA to minimize upper GI bleeding risk when one of the following risk factors is present: 1) history of peptic ulcer disease or upper GI bleeding; 2) aged 60 years or older; 3) concomitant use of corticosteroids; 4) presence of dyspepsia or GERD.[114] Following this definition, elderly using LDA should be prescribed a PPI for appropriate gastroprotection. Adherence to these recommendations however still deserves improvement.[98, 115, 116]

There is scarce evidence on the risk of upper GI bleeding during use of corticosteroids or anticoagulants, as the underlying co morbid disease or concomitant use of NSAIDs or LDA may partially explain the risk of upper GI bleeding.[72, 73, 117-119] Nevertheless, PPIs can also be considered as appropriate gastroprotective treatment in vulnerable elderly using corticosteroids or anticoagulants.

Eradication of *Helicobacter pylori* (*H. pylori*) is a common indication for short-term use of PPIs. It served as indication in 15% of PPI users.[107]

Age related changes in the stomach of the elderly

In the elderly, prostaglandin-levels decrease due to diminished conversion of arachidonic acid to prostaglandin via the cyclo-oxygenase (COX)-1 enzyme. This may result in a stomach being more prone to irritants and an increase in the risk of upper GI bleeding. This partially accounts for the recommendation that gastroprotective measures should be employed in the elderly when using NSAIDs.[99] Supporting evidence comes from experimental studies, showing that older rats expressed lower levels of COX-enzyme mRNA than younger rats and had an impaired response of prostaglandin synthesis to irritants.[120] In addition, in elderly there is a higher basal acid output in the stomach[121] resulting in lower prostaglandin concentrations in the stomach and duodenum.[122] Therefore, the stomach of the elderly is more vulnerable to exposure and toxic stimuli, such as drugs (i.e. NSAIDs, LDA). Protective measures including co-prescription of a PPI are therefore recommended to the elderly.[99]

Despite the fact that elderly patients may suffer from more pronounced esophageal mucosal injury and acid exposure than younger patients, the perception of symptom severity for heartburn is less.[123] The time to symptom perception and sensory intensity is reduced in the elderly. An age-related reduction in chemosensitivity to acid is a possible underlying mechanism. However, it has been suggested that the altered perception of esophageal pain in elderly people is the result of an ageing process rather than an acquired phenomenon resulting from disease.[124]

Thirdly, atrophic gastritis is more prevalent among the elderly, in particular among *H. pylori*-positive subjects.[125] Gastric atrophy ultimately may occur in 40-50% of *H. pylori* infected individuals. The impact of acid suppression on *H. pylori* presence and its shift from gastric antrum to corpus has been extensively discussed previously. By decreasing gastric acidity in the gastric corpus, colonization of the corpus by *H. pylori* is enhanced.[125, 126] Increased inflammation of the gastric corpus accelerates the progression to chronic atrophic gastritis.[126] Chronic atrophic gastritis increases the risk of gastric cancer. This explains the recommendation in international guidelines to consider a test-and-treat regimen for *H. pylori* infection in subjects who require long-term maintenance treatment with a PPI.[127]

Harmful use of PPIs in the elderly

Apart from the susceptibility of adverse outcomes due to long-term PPI treatment in elderly, several factors interact with each other that may lead to negative outcomes; including poor nutritional status, co morbid diseases and polypharmacy. Concerns were raised about the association between PPI use and increased mortality in institutionalized older people[128] and in patients discharged from hospitals.[129] The risk of death in the year following hospitalization increased by 51% (HR 1.51; 95%CI: 1.03-2.77) for PPI users compared to PPI non-users.[130] In another study the risk increased by 36% (HR 1.36; 95%CI: 1.04-1.77) in elderly in long-term care hospitals and by 90% (HR 1.90; 95%CI: 1.23-2.94) among elderly in acute geriatric wards and nursing homes.[129] These rates are in line with estimates from another study.[128] The

association was even stronger for use of high-dose PPIs than for use of low-dose PPIs.[130] The groups of PPI users were too small to allow for stratification of the analysis to individual PPIs, apart from esomeprazole and lansoprazole, which both demonstrated a significant increased risk of mortality.[130] Thus elderly residents who reside in long-term care hospitals or in acute geriatric wards or nursing homes may be at increased risk of mortality when using PPIs compared to non-users of PPIs.[129] Although underlying mechanism of increased mortality may be by some of the adverse events that are discussed in the current review, a potential explanation that also should be considered is that PPIs users reflect a group of older patients with complex medication regimens for multiple chronic conditions.[130, 131] This hypothesis is supported by the fact that there was no increase in mortality risk among elderly in assisted-living facilities, whereas an increase was seen for more care-dependent elderly.[129] Adherence to PPIs in the year following hospitalization was not addressed, nor nutritional status nor the causes of death.[130] In addition there is discrepancy between results from observational studies and clinical trials, which can be explained by residual confounding and confounding-by-indication or channeling; as the more diseased subjects are the ones receiving PPIs. Although residual confounding cannot be fully accounted for in observational studies, these studies reflect daily clinical practice when using primary care data. In clinical trials often the frail elderly with greater burden of polypharmacy and multimorbidity are excluded.[105, 132] As a consequence, observational studies are the only manner to study long-term safety of medication in the elderly in real-life practice. Observational studies utilizing electronic health care data from primary or secondary care are therefore particularly valuable when adverse events are unknown or considered rare.[133] Though findings of increased mortality should be replicated by others, current available studies stress the need for better attention to indications for long-term use of PPIs in the hospital setting.

Inappropriate use of PPIs in the elderly

Inappropriate use of PPIs is common, particularly among the elderly. Some studies for instance reported inappropriate PPI use in 50% to 80% of patients admitted to and discharged from geriatric and internal medicine wards.[134-136] Inappropriate use both consists of lack of a proper indication, inappropriate duration of treatment or inappropriate dosing.[137] A study from the United Kingdom showed that PPIs at maximum therapeutic dosages for more than 8 weeks are among the most frequently inappropriate medications in elderly in residential care homes.[138] Inappropriate indications may be as high as 50% of elderly admitted to nursing homes[139] and 61% of elderly admitted to a hospital.[140] Similar rates of inappropriateness were observed in other studies.[141-143] Discontinuation of PPIs after *H. pylori* eradication remains an issue, as two studies report that 50% to 60% of subjects became chronic PPI users and subsequently contributed to 75% of PPI costs in the year after eradication.[144, 145] Failure of discontinuation of PPI therapy is especially seen among the elderly (aged 65 years and over) after *H. pylori* eradication or in subjects who previously used anti-ulcer medication, or continue to use NSAIDs or aspirin.[145] As a consequence, PPI use for symptom relief may result in a substantial

proportion of subjects exposed for a long-term period. In an observational study using primary care data from the United Kingdom only 0.45% of subjects were classified as long-term users but they contributed to a large proportion of PPI-related expenditures.[146] On the other hand, step-down management of PPIs for indications such as heartburn or acid regurgitation is particularly successful among the elderly.[123, 147]

Educating and supporting physicians about the importance of reviewing the indications and duration of PPI use in elderly is relevant to reduce PPI prescription costs and maintain patients' safety. Educational programs may successfully reduce inappropriate PPI prescriptions in elderly patients during their hospital stay.[140] A randomized study among adults discharged from a hospital studied the impact of additional information in the discharge letter stressing review of PPI use after discharge compared to standard care (discharge letter without such information). This additional information did not result in higher rate of evaluation of PPI use by general practitioners (GPs).[142] Educating patients in a patient-centered programme may be an alternative,[148] although this likely will be less successful in the elderly who often use various drugs and may not be completely accurate about the need and use of all drugs they use. A study assessing the potential strategies to reduce PPI prescription in the UK and the associated costs identified a number of strategies that were used by GPs: 1) not starting PPIs; 2) dose reduction; 3) therapeutic substitution from PPIs to other anti-acid agents; 4) therapeutic switching to a cheaper brand of PPI; 5) self-regulation by encouraging patients to experiment with lowering dosages of PPI, or taking it as necessary, or any combination of these strategies.[149] Although some patients may return to the initial PPI dose prescribed, almost 50% of patients reduced their PPI intake to a minimum and thus reduced health care costs and presumably improved patients' safety.[149] PPI dose reduction can be achieved in the elderly population, if the prescribing physician is encouraged to regularly, such as in every visit, review the medication list of the elderly. Adequate recommendations and clear documentation of the indication for PPI use in discharge letters may help clinicians in reducing inappropriate and prolonged PPI use and decrease polypharmacy among the elderly.[143] Thus there is considerable evidence to encourage both patients, but also doctors to regulate PPI indication and duration of use.

Adverse events with use of PPIs

PPIs are considered relatively safe drugs because side effects are infrequent and mostly of modest severity; mainly including headache, diarrhea, constipation, nausea and rash. These occur in a small proportion of users (1% to 5%). The prolonged and potentially non-judicious use of PPIs however is associated with risks. Several of the adverse effects of PPIs that have been documented are pertinent to older people. Because PPIs are among the most commonly used drugs, any small adverse effect of PPIs may have a considerable impact on health and morbidity in the elderly population. Some of the most important PPI-related adverse events in the elderly will be discussed in this review and are summarized in Table 2.

Table 2. Potential adverse events during Proton Pump Inhibitor use, supporting evidence and precautions.

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Drug interaction with clopidogrel	Not applicable	Competitive inhibition of CYP 2C19 by PPIs impairing the conversion of clopidogrel to its active substance and thereby affecting the platelet inhibition function	Low strength (risk estimates < 2)	Inconsistent	Association due to confounding by indication and residual confounding.	For any small risk remaining, bypass competitive inhibition via different timings of intake.
Drug interaction with low-dose aspirin (LDA)	Not applicable	Decreased gastric acidity limits the lipophylicity of LDA and thereby reduces the passive absorption of LDA across the gastric mucosal membrane	Low strength (risk estimates < 2)	Inconsistent	Conflicting evidence, association may be due to confounding	No profound evidence for an interaction between LDA and PPIs that allows changing guideline recommendations to avoid concomitant use of these agents.
Drug interaction with levothyroxine	Not applicable	Decreased absorption of thyroxine in the jejunum and ileum	Low strength (risk estimates < 2)	Inconsistent	Short term follow-up (6 weeks) /monitoring of TSH levels	Limited evidence for an interaction, however if present: preferentially long-term use of PPIs (≥ 6 months) predisposes. Separate administration (4-6hours) is recommended.
Bone fractures	Cumulative 1-year incidence of hip fractures: Women -70-74 years : 500 per 100,000 persons - 80-84 years: 1,000 per 100,000 persons Men: -70-74 years: 300 per 100,000 persons -80-84 years: 500 per 100,000 persons	Several mechanisms: 1. Decreased calcium absorption 2. Blocking repair mechanism of micro fractures 3. Hypergastrinemia leading to parathyroid hyperplasia and increased parathyroid hormone levels	Low strength (risk estimates < 2)	Inconsistent	- No dose- or duration-responses observed. - Association likely influenced by prevalence of polypharmacy and co morbid diseases among the elderly	Fractures occur likely in elderly subjects that are already more prone to fractures due to co morbid diseases. Consider lowering the dose and shorter the duration of use and evaluating risk factors for osteoporosis.

Table 2. Potential adverse events during Proton Pump Inhibitor use, supporting evidence and precautions (*continued*).

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Pneumonia	Annual incidence: - 25-44 per 1,000 persons for non-institutionalized elderly -33-114 per 1,000 persons for elderly in residential care	By suppression of the gastric acid environment bacterial and viral colonization may occur	Low to moderate strength (risk estimates < 2 - 4)	Inconsistent	No duration response observed. Confounding by indication and protopathic bias likely present	A very small effect of PPIs on pneumonia may remain present but will have very little impact on clinical practice.
Vitamin B12 absorption	Widely varying prevalences of vitamin B12 deficiency reported (3-40%). At least 5-15% of elderly (over 65 years of age) affected.	Several mechanisms: 1. Hypochlorhydria resulting in diminished release of protein-bound vitamin B12 2. Decreased secretion of intrinsic factor 3. Gastric bacterial overgrowth due to achlorhydria 4. Decreased bioavailability of vitamin B12 via small bowel bacterial overgrowth in blind loops of duodenum and jejunum	Low strength (risk estimates < 2)	Inconsistent	No data on effect of PPIs on other sensitive measures of vitamin B12 deficiency (MMA or homocysteine)	*H. pylori* infection aggravates impaired vitamin B12 absorption. Monitoring of vitamin B12 levels every 1 or 2 years during long-term PPI therapy is not recommended, but may be considered in subjects at risk.
Iron absorption	Prevalence anemia -women ≥65 years: 10.2% - men ≥65 years 11% Prevalence iron deficiency anemia: -4% of elderly patients	Diminished non-heme iron absorption	Unknown	Inconsistent	Lack of clinical and observational studies providing evidence on association of PPI-iron absorption among the elderly	In the elderly with iron deficiency demanding increased iron absorption or iron supplementation, PPI therapy may retard replenishment of the iron storage. No data is available on routinely monitoring of iron levels, but this may be considered every 1-2 years in subjects at risk.

Table 2. Potential adverse events during Proton Pump Inhibitor use, supporting evidence and precautions (*continued*).

Adverse event	Background incidence	Biological mechanism	Strength of association	Consistency of evidence	Limitations of studies	Conclusions/precautions
Clostridium difficile infection	Incidence: 22 cases per 100,000 persons in the general population. Age≥65 years increases the risk up to 16-fold.	Several mechanisms: 1. Conversion of spore-forming *C.difficile* to a vegetative form able to survive in the enteric lumen 2. Promoting of small intestinal bacterial overgrowth affecting the commensal intestinal microbiota	Moderate strength (risk estimates ≈2-3)	Inconsistent	- Uncontrolled confounding for severity of illness or other co morbid diseases - PPIs may act as an intermediate factor for antibiotic therapy - Limited data on dose- and duration effects	Considering advancing age as independent risk factor, with PPIs as potential risk factor, clinicians should be aware of CDI risk when prescribing PPIs to the elderly. They should test for *C.difficile* presence in the elderly when they present with diarrhea using a low test threshold
Other enteric infections (*Salmonella spp., Campylobacter spp.*)	Incidence in the elderly: -*Campylobacter* infection: 15.3 cases per 100,000 persons - *Salmonella* infection: 17.2 cases per 100,000 persons	Diminished gastric acid barrier defense allowing survival of bacterial organisms	Moderate strength (risk estimates ≈2-4)	Inconsistent	Limited evidence on clearly defined PPI exposure and duration	- No definite conclusions from the current available data - Reconsider the indication of PPI use, particularly among the elderly presenting with diarrhea
Hypomagnesemia	Prevalence: -36% of elderly in long-term care facilities affected	Poorly understood	Unknown	Inconsistent	Limited data	Scarce data on the association of PPIs and hypomagnesemia but this may be due to absence of evidence
Acute interstitial nephritis (AIN)	No background incidence numbers known. Estimated that AIN accounts for 6-8% of renal failure cases.	- Idiosyncratic reaction - Due to reduced peritubular blood flow, longer exposure time of renal interstitium to PPIs	Unknown	Inconsistent	Limited data	Not sufficient evidence for causal relation, but a small association may remain present. Given the devastating effects and poor prognosis of late diagnosis, clinical awareness is required

Abbreviations: LDA, low-dose aspirin; CDI, Clostridium difficile infection; AIN, acute interstitial nephritis.

Search Strategy

An extensive literature search in PubMed was performed using defined keywords and synonyms (i.e., proton pump inhibitors, drug effects, drug prescriptions, polypharmacy, drug toxicity, adverse events, pneumonia, *Clostridium difficile*, gastrointestinal bacterial infections, fractures, vitamin B12 deficiency, iron deficiency) for each of the adverse events of interest. Original and review articles were considered eligible for this current review. Review articles were first and subsequently related original articles extracted to cover the current available literature for each outcome separately. No systematic approach was considered as for each adverse event separately systematic reviews have been published and the current review provides an expert opinion review.

Drug metabolism

There are differences across the various PPIs with respect to bioavailability, peak plasma levels, acid dissociation constant (pKa), excretion and route of metabolization. The latter may subsequently affect the clinical efficacy and interaction with other drugs in certain patient groups. Hepatic cytochrome P-450 (CYP) enzymes are responsible for metabolization of PPIs, with CYP2C19 being the most important enzyme. Omeprazole, rabeprazole, pantoprazole and esomeprazole are primarily metabolized by CYP2C19, whereas lansoprazole is mainly metabolized by CYP3A4. Gene polymorphisms affect the activity of CYP2C19. Genotypes with lower enzymatic activity of CYP2C19 are most prevalent in Asian populations. In contrast, this slow metabolizer phenotype is present in less than 5% of the Caucasian population.[150-153] The vast majority of Caucasians are rapid metabolizers. Plasma levels of PPIs depend on the CYP metabolism, and as such, differences in metabolization result in different clinical efficacy with an inverse relation between metabolizer status and acid suppressive effect.[153-156] It has been demonstrated in several studies that the efficacy of for instance omeprazole and rabeprazole differed across individuals according to CYP2C19 genotypes. Treatment for *H. pylori* infection was more successful in patients with a slow metabolizer phenotype.[151, 152, 154] Similar different success rates across individual PPIs were seen for treatment of GERD.[152, 157] The CYP2C19 dependent action of PPIs indicates that the majority of Caucausians may benefit from higher dosages of PPIs, which should lead to more successful treatments.[158] Nevertheless, if subjects are slow-metabolizers and take concomitant drugs which interfere with CYP2C19 metabolism, increasing dosages of PPIs increase the risk of adverse events and drug interaction.

Drug-drug interaction

All PPIs increase the gastric pH. This impairs the absorption of several drugs. These drugs include antimycotics for systemic use (i.e. ketoconazole, itraconazole, posoconazole),[159] digoxin, nifedipin, tyrosin kinase inhibitors (i.e erlotinib),[160] antiretroviral drugs,[161]

phenytoin,[159] diazepam,[159] didanosine, methadone and aspirin. After the absorption of PPIs into the systemic circulation, some inhibit various components of the CYP enzyme in the liver and intestine, in particular CYP2C19 and CYP3A4. As discussed above, CYP2C19 genetic polymorphisms affect PPI metabolism. The effect of these polymorphisms thus may also affect metabolization of other drugs by CYP2C19. Therefore, interaction between PPIs and other drugs differs across individuals. Given the fact that rabeprazole depends less on CYP2C19 metabolization, CYP2C19 genotypes have less effect on rabeprazole plasma levels and clearance. However, it remains controversial whether the risk of drug-drug interaction among PPIs is highest for omeprazole and lowest for rabeprazole and pantoprazole.[153, 155, 156] Although drug-drug interactions may have deleterious effects, most of the interactions are uncommon and clinically irrelevant. Some of the drug-drug interactions with PPIs are discussed below.

Clopidogrel

Some years ago a possible interaction of clopidogrel with PPIs associated with an increased risk of cardiovascular (CV) events gained a lot of public attention and concern. In 2009 both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) recommended to restrict concurrent use of PPIs and clopidogrel.[164] A detrimental interaction between these drugs was suggested by several clinical and observational studies.[165] Clopidogrel is an inactive prodrug that requires metabolization and activation to its active thiol metabolite. The latter targets and irreversibly inhibits the ADP P2Y12 receptor to achieve effective platelet inhibition.[166] In the liver, metabolization is achieved by several CYP isoenzymes, of which CYP2C19 is the main contributor. PPIs may influence this process. As PPIs can competitively bind to the catalytic site of this enzyme, they can impair the conversion of clopidogrel to its active substance and thereby affect the platelet inhibition function. A recent meta-analysis showed that there is no differential risk of CV events across individual PPIs, arguing against a suggested differential effect of omeprazole or pantoprazole on CYP2C19 inhibitions platelet function and pharmacokinetic data.[167]

Nevertheless, the studies that showed an association between concurrent PPI and clopidogrel therapy and an increased risk of recurrent acute myocardial infarction (MI) were subject to considerable confounding by indication[168] (i.e. those subjects at increased risk of recurrent MI were more likely to receive clopidogrel instead of another platelet aggregation inhibitor compared to those subjects with a lower risk of recurrent acute MI). When the issue of confounding by indication was addressed (by comparing current use of clopidogrel plus current use of PPI not only to current clopidogrel without PPI use but also with current clopidogrel plus past use of PPIs) - current PPI use was compared with past PPI use - the association between PPI use and increase risk of recurrent MI during clopidogrel disappeared. This suggests that the observed association between current PPI use and recurrent acute MI, is likely the result of residual confounding[169] or bias.[165] If however, any small effect remains to be truly present, a solution would be to use both drugs on varying timings as the half-life of PPIs range from within 1 hour up to 2 hours and clopidogrel 6 hours. Even though the half-life of

drugs in elderly might be prolonged, competitive inhibition can be by-passed by different timings of drug intake.

Low-dose aspirin

It has been suggested that the bioavailability of low-dose aspirin (LDA) may be reduced by PPIs, resulting in reduced inhibition of platelet aggregation. There is debate whether the possible interaction has a significant clinical effect, i.e. leads to more CV events. An observational study among patients experiencing a first-time MI when using PPI concomitantly with LDA found an increase in risk of recurrent MI, stroke or death from cardiovascular causes in concomitant PPI users.[170] However, several other studies did not find evidence for such an effect,[171, 172] nor demonstrated an increase in risk of non-fatal MI or coronary death events.[173] The conflicting results from observational studies may be explained by differences in study design such as differences in start of LDA (within 30 days after first-time MI vs. any time after CV event), exposure definition (daily assessment of concomitant use of PPIs and LDA vs. claimed PPI prescription). Nevertheless, the current available data thus do not provide evidence that guideline recommendations on concomitant PPI and LDA use in patients at high risk of CV and GI events should be changed.

Levothyroxine

Orally ingested thyroxine is absorbed for 60% to 80%, which occurs in the jejunum and ileum. The absorption is optimal when the stomach is empty. Patients with jejuno-ileal bypass surgery or bowel resection are in need of higher doses of levothyroxine after surgery.[174] It was shown that thyroid-stimulating hormone (TSH) suppression decreased in patients with atrophic gastritis and *H. pylori* infection.[175] Both of these observations emphasize the importance of gastric acid in the absorption of thyroxine.[176] Previously it was demonstrated that calcium- and aluminium-containing antacids increase TSH and/or decrease thyroxine (T4) levels in patients previously stabilized on levothyroxine substitution.[177] It has therefore been recommended to administer levothyroxine and anti-acid agents at least 4 hours separately from each other. Whether this also holds for PPIs has been under debate in recent studies. In two studies initiation of PPI therapy (omeprazole and lansoprazole) resulted in an increase in TSH levels after 2 months, which required increasing doses of levothryoxine up to 37% in order to suppress TSH.[175, 178] Others did not demonstrate such interaction between PPIs (esomeprazole and pantoprazole) and levothyroxine, likely due to the short period of follow-up (6 weeks),[179, 180] in which changes of hormone levels may not be expected.[181] Although gastric acidity is important for the absorption of levothyroxine, findings on the interference with proton pump inhibitors are inconsistent. The evidence is limited and indicates that long-term use of PPIs (≥ 6 months) may predispose to drug-interaction. Patients with hypothyroidism receiving levothyroxine may need additional thyroid function tests after start of PPI therapy, particularly if symptoms of hypothyroidism emerge. The precise underlying

pharmacokinetic mechanism remains unknown, however separate administration of levothyroxine and PPIs by 4 to 6 hours is currently recommended.

Effects on Bone Metabolism and Fractures

Fractures, in particular hip fractures, are common in the elderly and are a major cause of morbidity and mortality in the elderly worldwide.[182, 183] The annual incidence of fractures among subjects aged 50 years and over is estimated at 0.38% for women, and 0.25% for men.[184] The incidence of hip fracture may be as high as 6.2% and 4.9% among female and male elderly nursing home residents, respectively. At the age of 80 years every one out of five women and at the age of 90 every one of two women has developed a hip fracture.[185] Age related modifications in bone density and bone strength affect the likelihood of a fracture in the elderly. There were concerns that PPI use may exacerbate the age related bone modifications and subsequently increase the risk of fractures.

A proposed mechanism of PPIs resulting in increased risk of fractures is the inhibition of bone resorption and calcium malabsorption. This was demonstrated both in vitro[186, 187] and in vivo[188] and consequently resulted in decreased bone turnover. Calcium absorption decreases with advancing age (fractional calcium absorption decreases with 5.6% from women aged 69-74 years to women aged 85 years and over) and is dependent on several interacting factors, such as intake of calcium supplements and food.[189] PPIs have been suggested to significantly decrease calcium absorption, although this study was performed in elderly women taking omeprazole and under fasting conditions.[190]
In addition, profound acid suppression by PPI therapy may indirectly cause hypergastrinemia (via suppression of somatostatin release).[191] This in turn may stimulate the parathyroid glands leading to hyperplasia and hypertrophy of the parathyroid glands and increased parathyroid hormone (PTH) levels up to 28%.[188] Again, this will result in inappropriate rates of bone resorption and weakening of the bone.

If the calcium absorption is indeed impaired during long-term PPI use, it could contribute to the development of osteoporosis by bone mineral loss. However, this theory is disputed by a study from Targownik *et al.* which did not show an association between chronic PPI use and bone mineral density (BMD) loss.[192] Four other studies also could not find any association between PPI therapy and BMD, as PPI users had very similar BMD to non-users of PPIs.[193-196] One study among adult patients (18 to 56 years) with GERD demonstrated that PPI treatment was associated with a lower BMD.[197] A second study, among a small group of community dwelling older subjects (65 years or older) showed that PPI use was inversely associated with trabecular BMD, which is an early marker of osteoporosis.[198] A possible association between PPI use and fracture could therefore be related to factors of osteoporosis, at least in subjects that already are predisposed to osteoporosis.

An alternative mechanism of PPIs causing fractures would be an effect of PPIs on the central nervous system (such as dizziness, visual disturbances) which may result in falls and

possibly an increase in fracture incidence. However, this hypothesis was disputed by a nested case-control study on 20,000 subjects who had a fall recorded in their primary care record.[199]

Studies on the risk of PPI-related fractures show conflicting results. Some demonstrated an association between chronic use of PPIs and risk of hip fracture[17, 24] or fractures in general (including hip, wrist, vertebral).[22, 23] Reported risks (relative risks or odds ratios) ranged from 1.18 (95% confidence interval (CI): 1.12-1.43) to 4.55 (95% CI: 1.68-12.29).[17, 22-24] Yet, these studies included a mixture of fracture types. Other studies could not confirm these positive associations, and moreover, only some were able to demonstrate a dose-response effect[24] or a duration-effect.[17, 21, 22] When exploring cause-effect associations, the presence of a dose- and duration-effect supports a causal-relation.[19] In addition, if the mechanism of fractures is through the antisecretory effect, one might also expect to see an increased risk of fractures for other acid suppressant medications, such as H2RAs. However while some studies indeed showed that H2RAs increased the risk of fractures,[22, 24] a case-control study in contrast reported that H2RAs protected against fractures.[23] An overall OR of 1.08 (95%CI: 1.00-1.18) for fractures overall was observed during H2RA use.[18] When comparing PPIs with H2RA directly, the risk of fractures was increased during PPI use (hazard ratio 1.34; 95%CI: 1.14-1.38).[18, 193]

Several methodological issues may have biased these studies. Firstly, many of the studies were not able to address confounding factors such as the use of calcium supplements, vitamin D or tobacco and alcohol intake. Secondly, the low magnitude of the observed associations, the lack of a dose- and duration-response and the inability to address and control for important confounding factors may have influenced any reported association between PPIs and bone fractures. Despite the conflicting results and methodological issues from studies, the FDA announced on May 25, 2010 to change the labeling information of PPIs and indicate a possible increased risk of fracture when using PPIs. After systematically reviewing the literature, the Canadian Association of Gastroenterology did not support the FDA statement and stated that in the light of uncertainty about the magnitude of risk, clinicians should consider whether a lower dose or shorter duration of PPI therapy would adequately treat the patient's condition.[20]

Nevertheless, when summarizing the available data, a possible increased risk of fractures of hip, wrist and spine in patients using PPIs cannot be ruled out. The risk depends on duration and dose of use, though at which threshold of dose and duration is unknown and may differ across individuals. There remains uncertainty about the magnitude of risk, therefore, clinicians should consider in patients receiving PPI therapy to lower the dose and shorten the duration, while evaluating risk factors for osteoporosis before routinely prescribing PPIs.

Pneumonia

The gastric acid barrier is an important defense mechanism against pathogen invasion through the gastrointestinal tract. Suppression of gastric acid, may increase the susceptibility to microbial colonization. From studies in mechanically ventilated subjects,[31] we know that use of

acid-suppressive drugs facilitates intestinal pathogen colonization from the stomach to the lower respiratory tract.[34] Aspiration of gastric contents, which occurs rather frequently among the elderly, may then promote respiratory tract infection.[32]

Although several studies provided evidence to support an association between PPI use and the risk of community-acquired pneumonia,[27] the overall results were inconsistent. The observed odds ratios in observational studies for PPI use ranged from 0.63 to 1.80; and for H2RA use from 1.10 to 2.00.[27] In absolute terms these risks are considered modest given the fact that relative effects were estimated. When pooling the relative risk estimates from randomized clinical trials for PPI or H2RA use combined, the risks ranged from 0.12 up to 5.00.[27] However, the latter should be interpreted with caution, as risks of drug-related adverse events cannot be well studied using data from clinical trials because of selective patient inclusion in trials.[133] Careful monitoring of drug safety relies on monitoring of events in 'real life practice'. Observational studies utilizing electronic health care data from primary or secondary care are therefore particularly valuable when side effects are unknown or considered rare.[133]

Furthermore, the studies performed suffer from important limitations. As the largest increase in risk was seen shortly after start of use of PPIs (within 2 weeks) without any duration-response relation - which supports the causality of the effect - , confounding and protopathic bias likely affected the results. Confounding by indication occurred as GERD symptoms were a predominant indication for PPI use, while GERD also acts as independent risk factor for pneumonia.[26] Protopathic bias occurred by misclassification of early signs of pneumonia (including non-specific chest symptoms and discomfort) as GERD. A way to mitigate against bias from unmeasured confounding is to restrict the study population to PPI users without GERD as indication for PPI use. This particular design has been used by Filion *et al.*, including four databases from Canada with people aged 66 years and over.[28] Indeed they showed that the proposed hypothesis of an association between PPIs and hospitalization for community acquired pneumonia disappeared when applying a restricted study population.[28] In addition, there was no increase in the risk when comparing younger individuals with older individuals – in fact the opposite was observed.[30] Neither was the risk of PPI-related pneumonia different for subjects aged younger than 60 years of age compared to subjects aged 60 years and over.[33]

In mechanically ventilated patients the risk of aspiration pneumonia is increased due to gastroesophageal reflux by the presence of nasogastric tubes. PPIs do not have any preventive effect on aspiration pneumonia, apart from the effect of PPIs on the gastric volume.[35]

Although there is no evidence to support the risk of community-acquired pneumonia in the elderly, caution should be taken in elderly at increased risk for infection and for whom pneumonia may be an important cause of morbidity and mortality, or in those with asthma or chronic obstructive lung disease.[29] Due to decreased immune responses elderly patients often suffer from more severe infection. Despite the fact that a very modest effect of PPIs on

pneumonia may remain present, even considering the drawbacks of the studies, the impact in clinical practice is very limited.

Vitamin B12 absorption

Vitamin B12, a water-soluble vitamin, is ingested via food in a protein-bound state. Gastric acid is essential to release the vitamin from the proteins in the food. Vitamin B12 then binds to intrinsic factor and eventually is absorbed in the ileal part of the small intestine. Inhibition of gastric acid secretion by PPIs may therefore reduce the bioavailability of dietary vitamin B12. Deficiency of vitamin B12 may have devastating effects, ranging from anemia to neurological (peripheral neuropathy) or psychiatric diseases (dementia, sensory ataxia).[201]

Four mechanisms may explain PPI-associated vitamin B12 malabsorption. Firstly, in hypochlorhydria state (when there is a deficit in acid- and pepsin-availability) the protein-bound vitamin B12 may not be adequately released. Secondly, long-term PPI use may result in a decrease of intrinsic factor secretion. Thirdly, achlorhydria may cause gastric bacterial overgrowth. This may accelerate vitamin B12 deficiency development by production of vitamin B12 analogs that compete with absorption and use of vitamin B12. Nevertheless, gastric bacterial overgrowth has not been associated with nutritional consequences. Fourthly, profound acid suppression may decrease the bioavailability of vitamin B12 via small bowel bacterial overgrowth in blind loops of the duodenum and jejunum.[202]

The decrease in absorption of protein bound vitamin B12 was first observed for H2RA treatment in a small group of patients.[45] This effect was also seen for PPI use. In particular, a clinical study showed that the vitamin B12 absorption-rate decreased from 3.2% to 0.9% in healthy male volunteers when using daily 20 mg omeprazole for 2 weeks.[39] This observation was confirmed by others.[42, 43] When using a higher dose of omeprazole (40mg) vitamin B12 absorption decreased further.[39] Causality of the association was supported as a duration-effect was observed in another study.[46] It was shown that PPI use (with a mean duration of 4.5 years among the 111 omeprazole users) was inversely associated with vitamin B12 levels. Thus with longer PPI use serum levels of vitamin B12 were lower. [46]

A case-control study among patients aged 65 years and over identified from a geriatric primary care setting, showed that the odds of vitamin B12 deficiency was 4.45 (95% CI: 1.47-13.34) times higher for current long-term PPI users (using at least 12 months PPIs/H2RAs) compared to non-users.[47] A study on older subjects (aged 60 to 102 years) from an ambulatory geriatric clinic − including a total of 141 PPI users − showed that individuals having used PPIs for a longer period had a lower serum B12 level. This trend was particularly true for those subjects that did not use vitamin B12 supplementation (n=107).[37] The results of this study should be interpreted with care as no effect over time can be concluded from a cross-sectional study.

It is important to realize that elderly patients compared to younger patients already have a higher background vitamin B12 deficiency-risk. Elderly frequently have a borderline vitamin B12 status. One would therefore expect the effect of PPIs on vitamin B12 level to be

more pronounced in the elderly, particularly given the fact that around 5% to 15% of the elderly suffer from decreased vitamin B12 levels.[38, 40] While a normal diet usually contains substantially more vitamin B12 than is needed, in the elderly the functional reserve is diminished because vitamin B12 absorption is decreased. It is postulated that malabsorption is the most important factor in development of vitamin B12 deficiency in the elderly, rather than diminished secretion of intrinsic factor. This is probably related with the development of atrophic gastritis and hypochlorhydria with advancing age, again reducing the levels of acid and pepsin and subsequent release of protein-bound vitamin B12 to its unbound state. Other factors may interfere in this process, such as *H. pylori* infection.[36] In a Dutch study *H. pylori* positive GERD patients had a significant drop in vitamin B12 level during omeprazole treatment, whereas in *H. pylori* negative GERD patients no influence on vitamin B12 level was seen.[44]

In a subgroup of patients use of PPIs may worsen the potential decrease in vitamin B12 level. This concerns patients with higher plasma levels of PPIs, as occurs in patients with a slow CYP2C19 metabolizer status. It was shown that CYP2C19 polymorphisms affected vitamin B12 levels during long-term (>1 year) treatment with omeprazole 20 mg daily, with lower vitamin B12 levels for subjects heterozygous for mutated *CYP2C19* alleles as compared to homozygous for wild type alleles.[41] In clinical practice, genotyping of CYP2C19 is not standard of care.

There are however quite some gaps in the current knowledge. Vitamin B12 itself serves as a coenzyme in the conversion of methyl malonyl coenzyme A (MMA) to succinyl coenzyme A and of homocysteine to methionine. More sensitive measures to assess a vitamin B12 deficit therefore are elevated levels of either MMA or homocysteine.[203] No studies so far have examined the effect of PPIs or H2RAs on these indicators. This may be relevant because alarming neuropsychiatric disorders may occur, even despite normal levels of serum vitamin B12. Such severe outcomes are however very rare. Yet, given the frequent occurrence of lower vitamin B12 levels and the reversible aspect of symptoms by early detection of vitamin B12 deficiency, regular testing and monitoring of vitamin B12 levels in elderly every 1 or 2 years – if PPI therapy is continued – may be considered, but is not considered routine practice.[204] Particularly *H. pylori* positive patients or those with long-term higher PPI dose treatment may be assessed as the decrease in vitamin B12 levels may be more explicit.[36, 41, 44] Once vitamin B12 deficiency is diagnosed in a patient, levels can be orally or parenterally supplemented. Furthermore, when the deficiency might be a complication from long-term use of PPIs, attention should be paid to the indication, dose and potential discontinuation of the PPI.

Iron absorption

Iron is present in food as heme or non-heme iron. Gastric acid is involved in the process of non-heme iron absorption as is known from studies where the addition of gastric acid improved the absorption in patients with achlorhydria.[205, 206] First, it facilitates the dissociation of iron salts from food but also reduces ferric iron to ferrous iron, which is more soluble.

Secondly, it facilitates complex forming with sugars and amines for enhanced absorption in the duodenum.

Subsequently one may expect that reducing gastric acid by PPI use, particularly over a prolonged period, may result in reduced iron absorption. However, there is only little evidence on the occurrence of iron-deficiency anemia during PPI use. It has been shown that in Zollinger-Ellison patients, who are provided continuous long-term PPI treatment, omeprazole did not decrease body iron stores and did not result in iron deficiency.[53] However, the 'negative results' of this study may not be generalizable to or true for the general population or the elderly. In addition, in a small group of hereditary hemochromatosis patients (n=7) (which results in excessive accumulation of iron in parenchymal cells of e.g. the liver and pancreas), PPI use reduced non-heme iron absorption by 50%.[52] Still, whether these effects are also present under non-hemochromatosis circumstances and to which extent they might accelerate iron deficiency among the elderly remains unknown. It is clear that the iron-binding capacity decreases with aging and is affected by factors such as malnutrition and chronic disease, which are more prevalent in the elderly.[50]

Yet, in the elderly with iron deficiency demanding increased iron absorption or iron supplementation, PPI therapy may retard replenishment of the iron storage. Since iron deficiency is the second most common cause of anemia in the elderly, any effect of PPIs may have clinically significant impact by worsening angina and congestive heart failure, prolonged hospitalization, leading to falls and fractures.[48, 49] There are no data available on the timing of testing and monitoring of iron levels in elderly using PPI therapy long-term, if monitoring is considered. Testing of iron levels every 1-2 years, during long-term PPI therapy may be considered in subjects at risk of iron-deficiency. It is however more important that the clinician is aware of the slight increased risk of iron deficiency during long-term PPI therapy.

Bacterial enteric infections

Many studies have examined the association between PPIs and bacterial enteric infections. The most commonly investigated organism is *Clostridium difficile* (*C. difficile*).

Clostridium difficile

C. difficile is a Gram-positive anaerobic spore-forming bacterium. Colonization of the intestinal tract occurs via the fecal-oral route and is facilitated by disruption of the commensal intestinal microbiota for instance due to antimicrobial therapy. The organism is capable of producing exotoxins responsible for symptomatic *C. difficile* infection (CDI): toxin A, a powerful enterotoxin; and toxin B, a potent cytotoxin (Figure 1). Both toxins bind to receptors on intestinal epithelial cells and can cause disruption of the actin cytoskeleton and impairment of tight junctions. Furthermore, they are cytotoxic and lead to the production of pro-inflammatory cytokines.[51, 207] It is well known that the elderly represent a particular risk group prone for CDI. This is partly due to the high prevalence of risk factors for *C. difficile* among the

elderly; such as chronic comorbid diseases, residence in hospitals or nursing homes and the dominant risk factor: antibiotic therapy (particularly fluorquinolones, clindamycin, broad spectrum penicillins and cephalosporins).[208, 209] A potential additional risk factor that should be added to the list is PPI use (Figure 2).

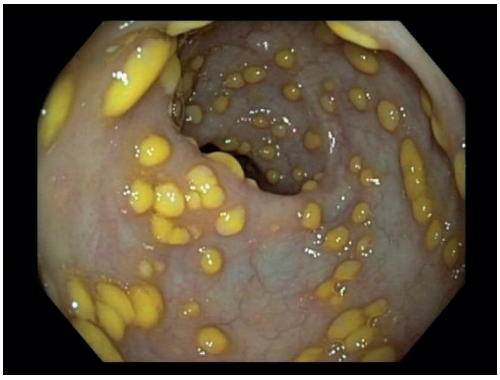

Figure 1. Endoscopic image of the colonic wall with irregular yellow pseudomembranes consistent with pseudomembranous colitis caused by *Clostridium difficile*.

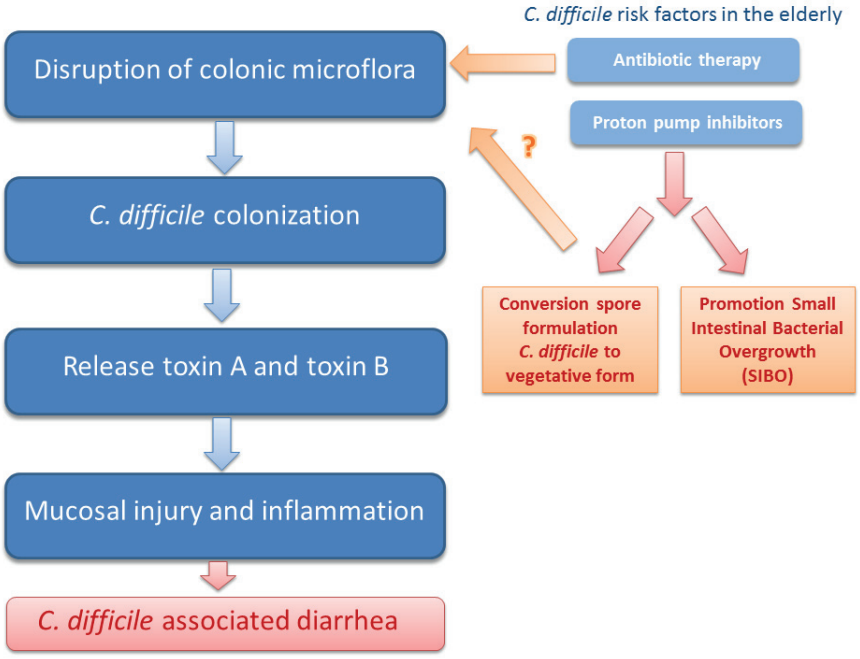

Figure 2. Pathophysiology of Proton Pump Inhibitor - related *Clostridium difficile* infection.

PPIs may facilitate conversion of spore-formulation *C. difficile* to its more virulent vegetative form which survives in the enteric lumen. These *C. difficile* spores are easily spread between patients and in particular in hospitals or nursing homes. The vegetative *C. difficile* may be harmless but may also return to a toxin-producing strain causing *C. difficile* associated diarrhea. A normal enteric flora is the most important protective factor against CDI; it is therefore not surprising that antibiotic therapy, disrupting the commensal intestinal microbiota, increases the risk of CDI. PPIs may also interfere in this process, as it was suggested that PPIs promote small intestinal bacterial overgrowth, at least in subgroups of patients (such as *H. pylori* infected subjects or irritable bowel syndrome patients), including the elderly.[210] In fact, in 2012 the FDA issued a warning that PPIs may predispose to CDI.[54]

Several reviews and meta-analyses on currently available studies have been conducted. One systematic review of the risk of enteric infection in patients taking acid suppression included 19 observational studies (case-control and cohort studies) and showed that the odds ratio of CDI when using acid suppression in general was estimated at 1.95 (95% CI: 1.48-2.58).[57] When looking at PPI use separately (n=126,999 patients) the odds ratio was 2.05 (1.47-2.85) and for H2RA use only 1.48 (95% CI: 1.06-2.06). Two recent meta-analyses confirmed this association.[55, 56] In the review by Janarthanan *et al.* a summary risk estimate of 1.69 was observed (when considering case-control studies only (n=17) a risk estimate of 2.31 was observed, and for cohort studies only (n=6) a risk estimate of 1.48).[55] Kwok *et al.* included 42 studies (using broader inclusion criteria) and provided a pooled estimate of PPI use (OR 1.74; 95% CI 1.47-2.85) compared to non-use of PPI.[56] Interestingly, Kwok *et al.* also pooled the risk estimates of studies that evaluated PPI use in patients with recurrent CDI, resulting in a pooled OR of 2.51 (95%CI 1.16-5.44).[56] All three reviews however, are affected by substantial differences between the results of the included studies as the measure of heterogeneity (I2) was 92%,[55] 78%[57] and 85%[56] (0% representing no heterogeneity between studies, and a greater value representing substantial heterogeneity).

As mentioned before, antibiotic use is the dominant risk factor for CDI. Concomitant use of PPIs and antibiotics may confer an even greater risk than what may be expected based on the risks of each drug alone. This has been shown in a meta-analysis, where the excess risk of CDI during concomitant use of PPIs and antibiotics was estimated at 19%.[56] In other words, the risk of CDI was 19% higher than expected, and increases with 1.96 respectively 1.75 times for concomitant use of PPIs and antibiotics compared to use of PPIs or antibiotics alone. It is important to realize that statistically significant interaction does not directly imply biological drug synergism.[212]

That acid suppression decreases the gastric defense barrier is supported by the fact that a higher odds ratio of *C. difficile* infection is observed with more pronounced acid suppression during PPI use than during H2RA therapy.[57] More importantly, there may be uncontrolled confounding in the studies, as they could not adjust for severity of illness or other co morbid diseases. This is particularly important as the co-morbid disease itself may increase the susceptibility of CDI and given the fact that PPIs may be preferentially prescribed to patients with more severe co-morbid disease.[168] Secondly, PPIs may be an intermediate

factor or a proxy for antibiotic therapy. Although the association of PPIs with pneumonia is definitely not certain, it can also not be ruled out. Therefore, if PPIs would act in such a way, the subsequent use of antibiotics for PPI-induced pneumonia may be the underlying explanation for the association of PPIs with CDI. Thirdly, there is limited data on a dose- and duration-relation of PPIs with CDI.

Adequately performed systematic reviews and meta-analyses generally are able to provide the strongest possible evidence when individual studies may have produced conflicting evidence. Though given the risk of bias within studies that are included in reviews and meta-analyses, the latter may produce spurious summary result estimates if many studies with a high risk of bias are included. This could be the case of the reviews discussed above. Nevertheless, considering that PPIs and advancing age both are independent risk factors for CDI, results from the studies should alert clinicians when prescribing PPIs to the elderly and lower the threshold for testing for *C. difficile* when elderly on PPI treatment suffer from diarrhea.

Other bacterial enteric infections

Decreased gastric acidity may also increase the risk of other bacterial enteric infections, such as *Salmonella spp.* and *Campylobacter spp* infection. Both bacteria are acid sensitive organisms that cannot survive at a low pH.[213] There are however limited data on these infections during PPI use, let alone among the elderly. Current available studies show that the odds ratios for *Salmonella* infections range widely from 2.6 to 11.2 for gastric acid-suppressive agents (PPIs and H2RAs combined), while for PPIs only the odds ratios were, depending on the strain of *Salmonella* species, between 4.2 and 8.3.[214] The same authors conclude in another study that the odds ratio of PPIs for *Campylobacter* infection was 4.5 (95% CI: 3.3-6.1) and for *Salmonella* infection 4.3 (95% CI: 2.9-6.5) when adjusting for age, sex, degree of urbanization and educational level.[215] The study is however biased as a definition on PPI exposure (such as determination of PPI use either by interview or prescription; or the division into current versus past use) was lacking. A case-control study using primary care data from the United Kingdom provided evidence to support the association of PPIs on bacterial infections. The outcome was gastroenteritis caused by several specific bacteria (*Salmonella, Campylobacter, Shigella, Clostridium* or other bacteria) that was proven by fecal culture. Current PPI exposure (defined as exposure to PPIs within one week before the date of bacterial gastroenteritis) regardless of PPI treatment duration, showed a risk estimate of 2.9 (95% CI: 2.5-3.5), which was higher than that of H2RA use (relative risk 1.1; 95% CI: 0.9-1.4). They also demonstrated a dose and duration effect.[216]

In view of the limited evidence on the risk of bacterial infections during PPI use, and specifically among the elderly, no definite conclusion can be drawn. However, this should prompt clinicians in reconsidering the indication of PPI use among the elderly and particularly when the elderly present with diarrhea. Enteropathogenic bacterial stool testing is easy and can prevent substantial morbidity of bacterial gastroenteritis among the elderly. Thus when an

elderly person on long-term PPI treatment presents with diarrhea, the possibility of enteric bacterial infection, caused by *C. difficile, Salmonella spp.* or *Campylobacter spp.* should be considered.

Other adverse events

There are some more rare PPI-related adverse events mentioned in the literature. Two of these will be discussed in this section, namely hypomagnesemia and interstitial nefritis.

After publication of two cases of hypomagnesemic hypoparathyroidism associated with PPI use,[59] several case series have been reported on the association between PPI use and hypomagnesemia.[58, 60-63] This concerned the FDA to publish a warning in 2011.[64] The underlying mechanism remains poorly understood and might act via hereditary predisposition such as mutations in ion channels for active magnesium transport. Theoretically, PPI-induced hypochlorhydria may reduce mineral absorption and cause mineral deficiency. However, there is no evidence that PPIs inhibit magnesium absorption.[217] Despite detrimental consequences of severe hypomagnesemia on neuromuscular and cardiovascular functions, no studies or reports have documented the clinical consequences of PPI related hypomagnesemia. Whether the effects of PPIs on magnesium levels are mainly applicable to the elderly is unclear, but hypomagnesemia during PPI use seems to be more common in co-users of diuretics, a combination of drugs which is more common in elderly.[218]

The second rare adverse event is acute interstitial nephritis (AIN). AIN is characterized by renal injury due to inflammation and edema of the renal interstitium. This can eventually lead to acute renal failure. Drug use is the most common cause of AIN, accounting for around 60% of cases.[66] Most frequently reported drugs causing AIN are antibiotics, NSAIDs and diuretics. If drug-induced AIN is diagnosed in an early stage and the drug is withdrawn promptly, a poor prognosis (as severe as requiring renal transplantation) can be prevented. Many case reports in the context of PPI use have been published in the last decade.[67] However, the evidence to support an association between PPIs and AIN is very concise. PPI-induced AIN is an idiosyncratic drug reaction to the drug or its metabolite and has so far not been related to time of exposure or dose of the drug.[67] Besides, PPI-induced AIN is a rare disease, with a precautionary estimated incidence of 1 per 12,500 person-years.[68] Case reports and case series do not allow measuring or controlling for confounding or for drawing conclusions on causality of the association. This is particularly important, since other concomitantly used drugs may have been the cause of AIN. Nevertheless, given the reduced peritubular blood flow among the elderly, the renal interstitium is exposed for a longer time to PPIs. This may result in the elderly being more prone for PPI-related renal damage. Although 45% of the elderly have a poor metabolizer phenotype for omeprazole, neither CYP2C19 poor metabolizer phenotype or genotype is a risk factor for AIN.[65] So far, there is insufficient evidence to establish a causal relationship, but any small association may be present. Therefore, clinical suspicion and awareness of renal adverse effects among the elderly with a poor renal function and using PPIs is required.

Conclusions

Proton pump inhibitors are nowadays among the most widely drugs. The efficacy of PPIs for various medical conditions has led to its wide-scale use. In turn, due to its relative safety profile, the overuse of PPIs both in terms of prolonged use and use for inappropriate indications is substantial and particularly among the elderly residing in hospitals or nursing homes. There have been several risks associated with PPIs, such as fractures, bacterial enteric infections and vitamin deficiencies which may be especially relevant for the elderly. There is no profound evidence to support an interaction between PPIs and clopidogrel or low-dose aspirin. Long term use of PPIs may predispose to drug-interaction with levothyroxine and may be avoided by separate administration. Uncertainty remains about the magnitude of risk of fractures during PPI therapy, therefore, clinicians should consider in patients receiving PPI therapy to lower the dose and shorten the duration, while evaluating risk factors for osteoporosis before routinely prescribing PPIs. There is no conclusive evidence that PPIs increase the risk of community acquired pneumonia. Routine testing for *Helicobacter pylori* in subjects starting on long-term PPI therapy is not recommended, but should be considered in long-term users (>12 months). Severe outcomes due to vitamin B12 deficiency occur rarely. In *H. pylori* positive patients or those with long-term higher PPI dose treatment the decrease in vitamin B12 levels may be more explicit. PPIs may retard replenishment in the elderly resulting in iron deficiency in the elderly. Monitoring of vitamin B12 and iron levels is not recommended, but may be considered every 1-2 years in subjects at risk of vitamin B12- or iron-deficiency. Bacterial enteric infection by *C. difficile, Salmonella spp., Campylobacter spp., s*hould be considered when elderly subjects on long-term PPI therapy present with diarrhea. The risks reported in studies are modest and there are many limitations when interpreting the results. Considering the rarity of the outcomes even in absence of PPIs and the fact that the studies risks are relative to the underlying baseline risk, doubling a small risk remains a modest effect in absolute sense. The relevant question to ask nowadays is probably not so much how large the potential risk for an adverse event during or due to PPI use might be, but whether the elderly patient has the proper indication for continued use of the PPI. Properly balancing the indication, benefits and harms of PPI therapy on an individual level can substantially minimize avoidable risk, morbidity and reduce health care costs.

2

SECTION 3

NSAIDs and PPIs in the context of Barrett's esophagus and Esophageal Adenocarcinoma

CHAPTER 3.1

The incidence of Barrett's esophagus and esophageal adenocarcinoma in the United Kingdom and the Netherlands is levelling off

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ABSTRACT

BACKGROUND

Barrett's esophagus (BE) is a risk factor for esophageal adenocarcinoma (EAC). Several studies report increasing incidences of BE with substantial variation.

AIM

Aim of this study was to determine age- and sex-stratified incidence rates (IR) of BE and EAC.

METHODS

Cohort study using two primary care databases in the United Kingdom (UK) and the Netherlands (NL) (2000- 2012). BE and EAC cases were identified using disease-specific READ codes (UK) and free-text search with manual validation (NL). Age-and sex-specific incidence rates (IRs) were calculated for both BE and EAC.

RESULTS

From the study population of 6,885,420 subjects in UK we identified 12,312 incident BE and 40 (0.3%) subsequent incident EAC cases. There were 1,383 incident BE, and subsequent 5 (0.4%) incident EAC cases among the 1,487,191 subjects in NL. The IR of BE increased linearly with age: 15.6/100,000 PYs (UK) and 23.7/100,000 PYs (NL) for patients aged 40-44 years, increasing to 85.6/100,000 PYs (UK) and 87.0/100,000 PYs (NL) for 70-74 years. In both UK and NL, IR of BE was 2 to 4 times higher in males than females across all age groups. With respect to calendar time, the IR of BE increased by 35% (UK) and 41% (NL) from 2000 to 2003, after which IRs remained stable until 2012.

CONCLUSION

Incidence rates of BE in the UK and NL increased until 2003, but levelled off thereafter. Around 0.3% of patients with BE developed EAC at least one year after BE diagnosis. These findings may help tailor endoscopic surveillance strategies among patients with BE.

INTRODUCTION

Barrett's esophagus (BE) is characterised by replacement of the squamous epithelium of the esophagus by metaplastic columnar epithelium and considered a consequence of prolonged gastro-esophageal reflux into the lower esophagus.[219, 220] BE is an important risk factor for the development of EAC via a stepwise pathway of low-grade and high-grade dysplasia.[219, 220] It is estimated that the risk of EAC is increased by approximately 30 to 125 fold in persons with BE.[221] Endoscopic surveillance for EAC among patients with BE is therefore recommended.[222]

Several studies reported increasing incidence rates (IRs) of BE,[223-226] although these vary widely, from 23 to 62 cases per 100,000 person-years (PYs).[223, 226] A single-center Dutch study observed an increase in the prevalence of BE from 2.6% to 4.7% between the 1990s and 2004.[225] A study in Northern Ireland showed an 159% increase from 24 to 62 cases per 100,000 PYs between the periods of 1993-1997 and 2002-2005.[223] The rise in incidence may partially be explained by a 'true' increase of BE and partially by better clinical awareness of physicians resulting in more gastroscopies.[227, 228]

The increase in incidence of BE goes hand in hand with a similar marked increase in EAC incidence in the USA and Western Europe, at a more rapid rate than any other type of malignancy.[229] Several studies report estimates of EAC IR among BE patients ranging between 1.2-6.5 EAC cases per 1,000 PYs [230-232] to 6.6 per 100 patient-years.[233] In general, the increased incidence of EAC is observed mostly in males below 60 years of age.[226] There is, however, significant heterogeneity across performed studies since study populations differed substantially.[231] Most studies are based on selected patients in hospitals or specialty clinics rather than being population-based.[234, 235] The currently available population-based studies report data only until 2009.[223, 226, 231, 232, 236]

The aim of our study was to determine the incidence of BE in the general population in the Netherlands and in the United Kingdom and to determine the risk of EAC among patients diagnosed with BE.

METHODS

Data sources

Two European population-based primary care registries served as data source: 1) The Health Improvement Network (THIN) database from the United Kingdom (UK)[237] and 2) the Integrated Primary Care Information database (IPCI) from the Netherlands (NL).[238] Both databases contain prospectively collected data as part of routine care representing real-life practice. In both countries, all citizens are registered with a primary care practitioner, who acts as a gatekeeper to secondary and tertiary medical care. THIN collects anonymised information on >3 million active patients from >400 participating practices, IPCI contains >1.5 million active patients from 340 practices. For each individual patient all relevant medical information from primary

and secondary care are documented in the electronic record. This information includes demographics, diagnoses and drug prescriptions.

THIN employs the READ clinical terminology system for coding medical diagnosis and symptoms,[239] whereas IPCI employs the International Classification for Primary Care.[240] Information on drug use is captured in THIN using the MULTILEX product dictionary and British National Formulary (BNF) codes, whereas in IPCI drugs are coded according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification.[242]

Study Design and Population

A dynamic population-based retrospective cohort study was conducted, in which we included patients aged ≥18 years. At least one year of available healthcare data prior to study entry was required in order to assess patient's medical history and to discriminate between prevalent and incident BE cases. Follow up started on 1 January 2000; date of reaching 18 years of age; or the date that one year of valid data was accrued within the database, whichever came later.

Follow up ended on date of occurrence of study outcome (BE or EAC); date of transfer out of the general practitioner's (GP) practice; death; or 31st of December 2011 (THIN) or 2012 (IPCI), whichever was earliest.

Patients with esophageal or stomach cancer at any time before study entry were excluded. Patients with a diagnosis of stomach cancer within 6 months after BE diagnosis date were also excluded.

Outcome Definition

Barrett's esophagus

In THIN, incident BE cases were identified using corresponding READ codes (Supplementary Table 1).[239] To explore outcome misclassification, we performed sensitivity analyses including additional evidence supporting the BE diagnosis. In the first sensitivity analysis we defined a case of BE as a subject with a BE record confirmed on at least two occasions, or when the clinical record contained additional evidence based on a prescription of a gastroprotective agent (GPA) (proton pump inhibitors, histamine 2 receptor antagonists or misoprostol). The prescription had to be recorded within 3 months prior to or after the date of BE diagnosis ('*case definition 2*'). In the second sensitivity analysis we included also procedure codes for diagnostic gastroscopy within 1 year prior, or up to 1 year after BE diagnosis ('*case definition 3'*).

As the ICPC coding system does not contain a specific code for Barrett's esophagus (BE), case identification in IPCI was based on free-text search of clinical narratives (including synonyms for BE such as 'Barrett', 'intestinal metaplasia', 'columnar epithelium') in combination with relevant (but less specific) codes. An iterative search was performed using relevant key words in appropriate sections of the clinical narratives to distinguish between affirmative and negative mentions of items included in the criteria for BE. Automatic case

identification as such would yield a positive predictive value of only 44%; therefore, we validated all cases by manual review of the medical records to ensure that the cases analysed were all confirmed cases of BE and to confirm the date of diagnosis. Cases were included when: 1) a record of a BE diagnosis; and 2) additional evidence consisting of either a gastroscopy or histology report confirming BE diagnosis were present. We performed sensitivity analysis including only histologically confirmed BE cases.

BE cases were classified as incident if the date of BE diagnosis occurred after inclusion in the study cohort and classified as prevalent if the date of BE diagnosis occurred prior to study entry.

Esophageal Adenocarcinoma

In THIN, EAC cases were identified by two algorithms, one specific and one less specific algorithm (for detailed information see Supplementary Table 1). In IPCI, all patients with a record of ICPC codes D77.1 (malignant neoplasia of the esophagus) and D77.0 (malignant neoplasia of the digestive tract—not specified), or with a record by free text search including word combinations of 'esophagus', 'cancer', 'carcinoma', 'malignancy' or 'neoplasia' manually validated for confirmation of EAC diagnosis, date of diagnosis and the type of carcinoma (squamous cell-, adeno-, or other types of carcinoma). EAC cases were considered incident if the date of diagnosis occurred after inclusion into the BE cohort and was at least 12 months after BE diagnosis. Cases occurring within one year from BE diagnosis were considered to be already existent at BE diagnosis date and in relation to the BE diagnostic work-up.

Gastroscopies

Since endoscopic confirmation is necessary for the diagnosis of BE, changes in the rate of gastroscopies may change the incidence rate of BE as well. We therefore determined the IR of BE with the number of gastroscopies as denominator. We identified in THIN all gastroscopies using pertinent READ codes, whereas in IPCI an extended automated search using free text search in medical records was performed. Key words including 'gastroscopy', 'duodenoscopy' and synonyms were used and negations or referrals for gastroscopies were automatically excluded. Gastroscopies performed after the date of BE or EAC diagnosis were not considered, thereby excluding surveillance gastroscopies for either BE or EAC. In order to prevent overestimation of the number of gastroscopies during which BE could be detected (such as several gastroscopies performed during hospitalization for upper GI bleeding) gastroscopies performed within three months of the previous one were excluded. We compared the number of gastroscopies to the rate of gastroscopies per capita from a national register recording all procedures from all hospitals in NL.[244]

Statistical analysis

IR of BE and of EAC with 95% confidence intervals (95% CI) were estimated by dividing the number of incident cases by the number of person-years (PYs) at-risk within the study

population. The IR of BE in relation to number of gastroscopies performed was calculated by dividing the number of BE cases by the number of gastroscopies performed in the study population. This analysis was done stratified on calendar year, sex and age group. Time trends of incidence of BE were evaluated from 2000 to 2012 by regression analysis (R^2) using the method of least squares, where a value 1 indicates a perfect fit, and by joint point analysis.
Using multivariate Poisson regression we calculated relative risks of developing BE while adjusting for age and sex. Survival analysis was performed to estimate the 1-year risk of EAC since incident BE diagnosis.

RESULTS

Study population

The source population comprised 8,372,611 persons (UK: 6,885,420; NL: 1,487,191) contributing to 48,918,172 person years (PYs) (UK: 44,505,240; NL: 4,412,932) of follow-up during the study period.

Figure 1 illustrates the composition of the study cohorts. We identified 12,312 (THIN) and 1,383 (IPCI) incident BE cases. In IPCI, after manual validation of the 4,978 potential BE patients (Figure 1) 2,171 (44%) were classified as definite cases (both prevalent and incident) of whom histological confirmation was seen in 1,338 (62%) cases. From the BE cases 1,383 were incident and histological confirmation was available for 701 cases.
Cases were more frequently male (UK: 63% and NL: 62%). Mean age at BE diagnosis was significantly lower in men than in women, both in UK: 63.3 years (SD 13.6) vs. 67.5 years (SD 13.7), and NL: 59.7 years (SD 13.3) vs. 63.8 years (SD 13.2).

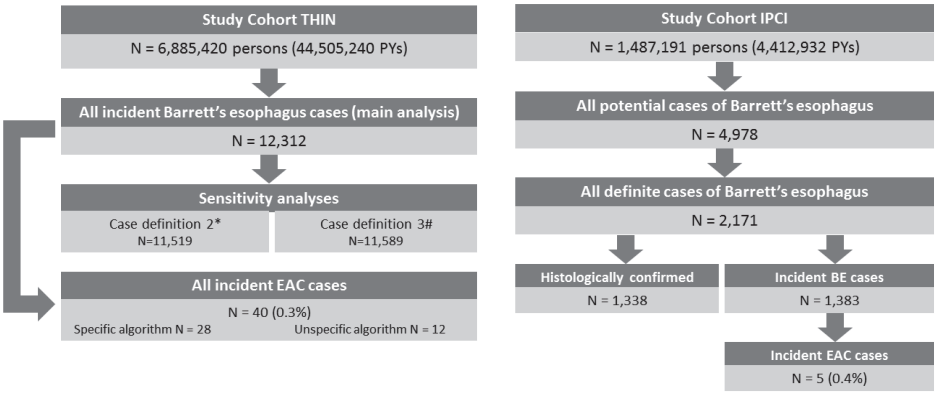

Figure 1. Flowchart of study cohort in the United Kingdom and the Netherlands.

** Case definition 2: incident BE subjects included who had at least two times BE diagnosis mentioned or additional support from a prescription of a gastroprotective agent (GPA) (proton pump inhibitors, histamine 2 receptor antagonists or misoprostol) that had to be recorded within 3 months prior up to 3 months after the date of BE diagnosis.*
 # Case definition 3: Additional to case definition 2 we also included procedure codes for diagnostic gastroscopy within 1 year prior or up to 1 year after BE diagnosis.

Incidence rate of Barrett's esophagus

The IR of BE in the UK was 27.7/100,000 PYs and in the Netherlands 31.4/100,000 PYs (Table 1). In the UK the IR of BE increased linearly with age: from 15.6/100,000 PYs for patients 40-44 years of age up to 85.6/100,000 PYs for patients aged 70-74 years (Figure 2, R^2=0.993). The IR remained stable hereafter; the IR of BE in NL showed the same linear increase from 23.7/100,000 PYs for patients aged 40-44 years to 87.0/100,000 PYs for those aged 70-74 years (R^2=0.939). IR remained stable thereafter for those aged 75 years or older. Across all age groups the IR of BE was higher for males than for females: 2 to 4 times in UK, and 2 to 3 times in NL.

Table 1. Incidence rates of BE in the United Kingdom and the Netherlands per 100,000 person-years and gastroscopies.

	THIN (United Kingdom)				
	No of BE cases	**No of Person-Years (PYs)***	**No of gastroscopies**	**BE/100,000 PYs (95% CI)**	**BE/1,000 gastroscopies (95% CI)**
Overall	12,312	44,505,240	386,185	27.7 (27.2 - 28.2)	31.9 (31.3 - 32.4)
Age (years)					
< 40	546	21,347,680	62,826	2.6 (2.3 - 2.8)	8.7 (8.0 - 9.4)
40-60	3,751	12,873,488	130,862	29.1 (28.2 -30.1)	28.7 (27.8 - 29.6)
> 60	8,015	10,284,072	192,497	78.0 (76.2 - 79.7)	41.6 (40.8 - 42.5)
Calendar year					
2000	723	3,409,933	24,873	21.2 (19.7 - 22.8)	29.1 (27.0 - 31.2)
2001	834	3,446,739	28,059	24.2 (22.6 - 25.9)	29.7 (27.7 - 31.7)
2002	954	3,496,061	30,836	27.3 (25.6 - 29.1)	30.9 (29.0 - 32.9)
2003	1,019	3,555,199	31,788	28.7 (26.9 - 30.5)	32.1 (30.1 – 34.0)
2004	986	3,629,212	32,634	27.2 (25.5 - 28.9)	30.2 (28.4 - 32.1)
2005	958	3,679,156	31,549	26.0 (24.4 - 27.7)	30.4 (28.5 - 32.3)
2006	1,009	3,736,764	32,769	27.0 (25.4 - 28.7)	30.8 (28.9 - 32.7)
2007	992	3,784,897	33,010	26.2 (24.6 - 27.9)	30.1 (28.2 - 31.9)
2008	1,150	3,858,063	35,128	29.8 (28.1 - 31.6)	32.7 (30.9 - 34.6)
2009	1,190	3,919,243	35,881	30.4 (28.7 - 32.1)	33.2 (31.3 – 35.0)
2010	1,170	3,974,886	35,148	29.4 (27.8 - 31.2)	33.3 (31.4 - 35.2)
2011	1,327	4,015,087	34,510	33.1 (31.3 - 34.9)	38.5 (36.4 - 40.5)
2012					
Sex					
Male	7,811	22,142,206	173,735	35.3 (34.5 - 36.1)	40.6 (44.0 - 45.9)
Female	4,501	22,363,032	212,450	20.1 (19.5 - 20.7)	21.2 (20.6 - 21.8)

** Number of person-years by year may not add up to overall number due to truncation of decimals.*

Table 1. Incidence rates of BE in the United Kingdom and the Netherlands per 100,000 person-years and gastroscopies (*continued*).

			IPCI (The Netherlands)		
	No of BE cases	**No of Person-Years (PYs)***	**No of gastroscopies**	**BE/100,000 PYs (95% CI)**	**BE/1,000 gastroscopies (95% CI)**
Overall	1,383	4,409,995	87,635	31.4 (29.7 - 33.0)	15.8 (14.9 - 16.6)
Age (years)					
< 40	83	2,164,425	16,061	3.8 (3.1 - 4.7)	5.2 (4.2 - 6.4)
40-60	544	129,871	32,111	41.9 (38.5- 45.5)	16.9 (15.6 - 18.4)
> 60	756	946,799	39,463	79.8 (74.3 - 85.7)	19.2 (17.9 - 20.6)
Calendar year					
2000	23	87,187	960	26.4 (17.2 - 38.9)	24.0 (16.0 - 35.7)
2001	29	84,393	1,018	34.4 (23.5 - 48.7)	29.5 (20.7 - 41.8)
2002	28	82,542	956	33.9 (23.0 - 48.3)	30.3 (21.2 - 43.2)
2003	32	86,193	1,264	37.1 (25.9 - 51.7)	25.3 (18.0 - 35.5)
2004	24	88,701	1,464	27.1 (17.8 - 39.6)	16.4 (11.0 - 24.3)
2005	28	92,030	1,570	30.4 (20.7 - 43.3)	17.8 (12.4 - 25.7)
2006	14	67,970	1,222	20.6 (11.8 - 33.6)	12.3 (7.5 - 20.2)
2007	38	147,402	2,423	25.8 (18.5 – 35.0)	16.1 (11.8 - 21.9)
2008	113	361,775	6825	31.2 (25.9 - 37.4)	16.6 (13.8 - 19.9)
2009	176	592,740	11,941	29.7 (25.5 - 34.3)	14.9 (12.9 - 17.2)
2010	268	758,719	15,832	35.3 (31.3 - 39.7)	16.0 (14.2 - 18.1)
2011	289	925,060	18,908	31.2 (27.8 – 35.0)	13.6 (12.1 - 15.4)
2012	307	994,892	23,252	30.9 (27.5 - 34.5)	11.4 (10.1 - 12.8)
Sex					
Male	856	2,159,543	40,104	39.6 (37.0 - 42.4)	21.3 (20.0 - 22.8)
Female	527	2,250,452	47,531	23.4 (21.5 - 25.5)	11.1 (10.2 - 12.1)

** Number of person-years by year may not add up to overall number due to truncation of decimals.*

With respect to calendar time, in the UK IR of BE increased by 35% from 21.2/100,000 (95%CI: 19.7-22.8) PYs in 2000 to 28.7/100,000 (95%CI: 26.9-30.5) PYs in 2003. In the NL the IR increased by 41% from 26.4/100,000 (95%CI: 17.2-38.9) PYs in 2000 to 37.1/100,000 (95%CI: 25.9-51.7) PYs in 2003. In both UK and NL, the IR remained fairly stable after 2003 up to 2011 (Table 1). Joint point analysis showed that the average percentage change after 2002 in the UK was 1.08, which was significantly different from the period before 2003.

We then calculated the IR of BE per 1,000 gastroscopies. In the UK, IR of BE per 1,000 gastroscopies increased by 32% from 29.1 in 2000 up to 38.5 in 2011 (Figure 3 and Table 1). In NL IR of BE increased from 24.0/1,000 gastroscopies in 2000 to 30.3/1,000 in 2002 and decreased thereafter to 11.4 in 2012. The decrease in IR of BE per gastroscopies was slightly

more pronounced for subjects aged 60 years and over in NL but not in the UK. However, similar trends in the IR of BE across age groups in the UK and NL were observed (Figure 3). Multivariable Poisson regression showed that a male subject had a 2.8-fold increased risk of BE, compared to a female subject of the same age. The risk of BE diverged significantly between males and females from the age of 35-39 years (data not shown).

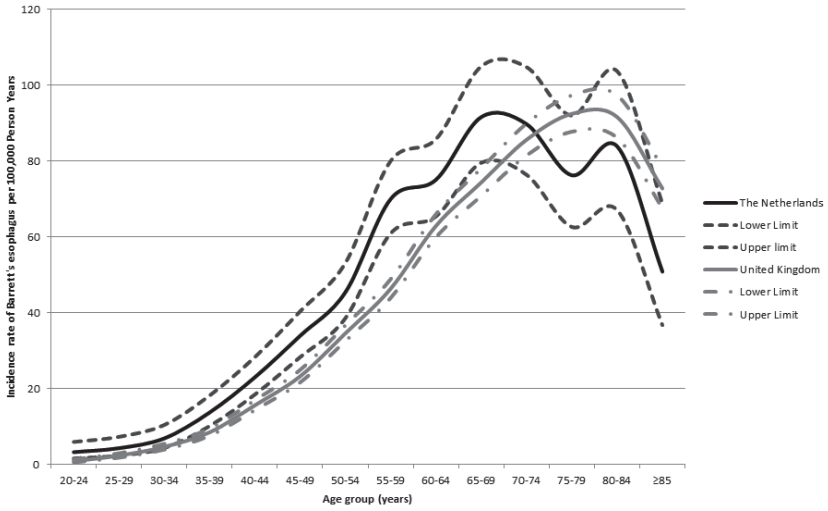

Figure 2. Incidence Rates of BE in the United Kingdom and the Netherlands by age group.

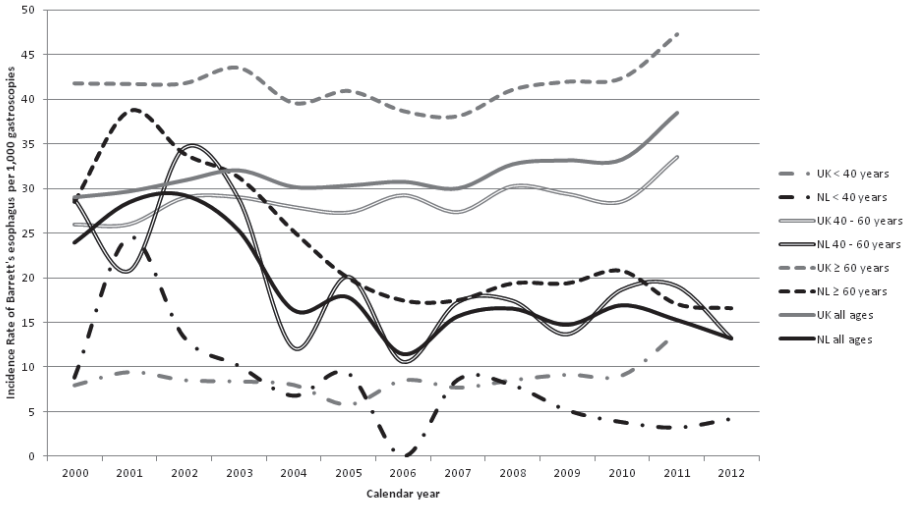

Figure 3. Incidence Rate of BE in the United Kingdom and the Netherlands per 1,000 gastroscopies over all ages and by age groups.

Esophageal adenocarcinoma

From the BE cases, we identified 40 (0.3%) incident EAC cases in the UK and 5 (0.4%) incident EAC cases in the NL. Forty-five patients in the UK (0.4%) and 2 patients in NL (0.1%) were diagnosed with EAC within one year of BE diagnosis and were considered prevalent EAC and therefore excluded in the analysis. Mean age of BE diagnosis in the incident EAC cases was 67.0 years (SD 10.3) and mean time from BE diagnosis until EAC diagnosis was 4.2 years (SD 2.5).

In NL, incident EAC cases were diagnosed with BE at a mean age of 63.5 years (SD 11.3) and mean time to EAC diagnosis was 3.5 years (SD 0.8). The overall IR of EAC was 22.6/100,000 PYs in UK and 80.1/100,000 PYs in NL. In 2000 the IR of EAC was 8.9/100,000 PYs and increased 4-fold up to 38.1/100,000 PYs in 2010. Time from BE until EAC diagnosis is shown in Figure 4. The one-year risk of EAC after BE diagnosis, excluding EAC cases within one year after BE diagnosis, was 0.086% (95% CI: 0.04 – 0.17) overall, 0.11% (95% CI: 0.05-0.23) for males and 0.06% (95% CI: 0.02-0.24) for females.

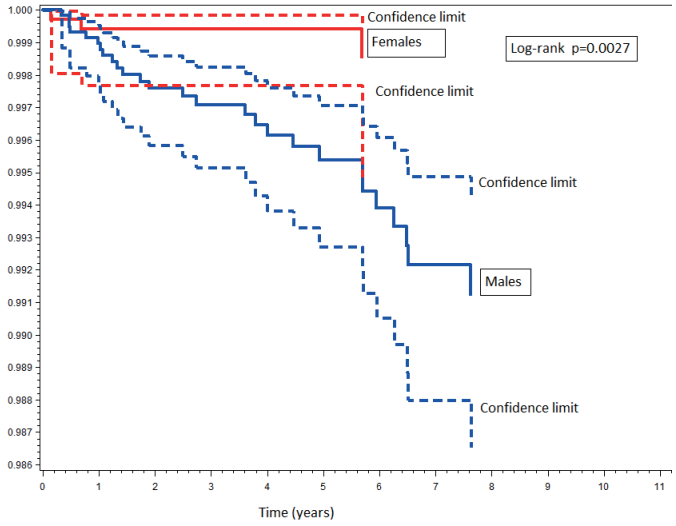

Figure 4. Survival curve from BE diagnosis until EAC diagnosis excluding the one year after BE diagnosis.

Sensitivity analyses

We employed different BE definitions in THIN as sensitivity analyses. No differences in the IRs was observed when the three case definitions were compared (Figure 1 & Figure 5). IR of BE was 26.0/100,000 PYs by applying *case definition 3* (cases with a BE record confirmed on at least two occasions; evidence derived from a GPA-prescription or gastroscopy letter). IR was 25.9/100,000 PYs by applying *case definition 2* (only GPA prescription as evidence).

As we might have overestimated the number of BE cases in NL, we performed a sensitivity analysis including only histologically confirmed cases. Among these, IR showed similar, although slightly lower, estimates with an overall incidence of 15.2/100,000 PYs. IR increased from 3.3/100,000 PYs among subjects aged 30-34 years to 48.3/100,000 PYs for those aged 70-74 years. Over time IR remained fairly stable from 13.8/100,000 PYs in 2000 and 12.6/100,000 PYs in 2012.

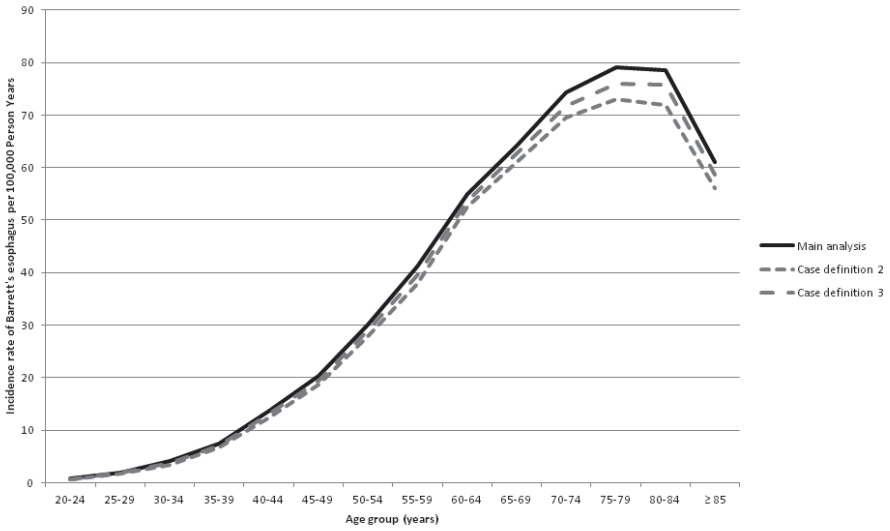

Figure 5. Incidence Rates of BE in United Kingdom with different case definitions.

Main analysis: all incident BE subjects included. Case definition 2: incident BE subjects included who had at least two times BE diagnosis mentioned or additional support from a prescription of a gastroprotective agent (GPA) (proton pump inhibitors, histamine 2 receptor antagonists or misoprostol) that had to be recorded within 3 months prior up to 3 months after the date of BE diagnosis. Case definition 3: Additional to case definition 2 we also included procedure codes for diagnostic gastroscopy within 1 year prior or up to 1 year after BE diagnosis.

DISCUSSION

This study showed that the incidence of Barrett's esophagus increased in the beginning of the millennium both in the United Kingdom and the Netherlands, but levelled off after 2003. In contrast, the IR of EAC continued to increase until now, although among BE patients, incident EAC occurred in only 0.3% of BE patients, demonstrating a one-year risk of 0.09%. This persistent increase may reflect the long lag time between BE and progression to high-grade dysplasia and EAC. In other words, the current increase in EAC incidence may reflect the increase in BE incidence that happened a decade ago.

Our data are consistent with a previous Dutch study that showed an increase in BE incidence between 1996 up to 2003, most pronounced in young males below 60 years of

age.[226] This increase was not explained by a rise in gastroscopies performed.[226] These findings were confirmed by another Dutch study using a nationwide registry of pathology records.[224] A population-based study from Northern Ireland also observed that the increase in BE was not explained by a rise in gastroscopies and truly increased over the period of 1993 up to 2005.[223] However, from 2003 onwards, we could not confirm such a linear rise in incidence of BE anymore. A levelling off of the BE incidence trend was already observed by Coleman *et al.* [223] They found a decline in the increase between four time periods; from 1993-1997 to 1998-2001 the increase was 94%, but from 1998-2001 to 2002-2005 the increase was only 34%. [223]

In the late 1990s, dyspepsia guidelines alerted clinicians to suspect BE more readily in symptomatic subjects. Indeed, referrals for gastroscopy increased, although the proportion of symptomatic subjects remained more or less stable until mid-2000s.[224] Additionally in 1996 the Dutch GP guidelines restricted referral indications for gastroscopy to subjects with alarm symptoms or recurrent dyspepsia.[246] This restriction was included in the UK guidelines (NICE) eight years later, in 2004[26] after which a gradual decline in referrals has been noted.[248] This explains the difference in BE incidence per gastroscopy over calendar time between the NL, which decreased from 2000 onwards, and the UK, which showed an increase.

One explanation why there is a levelling of the incidence of BE could be a birth cohort effect. Another is that better and earlier diagnosis and treatment of GERD and dyspepsia may have resulted in fewer patients developing BE. Increased awareness of clinicians may have resulted in an initial increase in incidence of BE, this effect was more pronounced in the late 1990s and early 2000s since guidelines at that time recommended gastroscopy for indications as dyspepsia and GERD. As was shown before, the incidence of BE increased tremendously and was already expected to level off at a certain point.[223] As a large proportion of EAC occurs via the stepwise pathway of BE via dysplasia towards EAC, an effect of the incidence of BE is also expected to impact the incidence of EAC. As we observed that the levelling off occurred after 2003, we expect that the incidence of EAC will also level off, but due to the decade long lag time between BE and development of EAC, any effect of this is likely to appear in the next 10 to 15 years.

To study the risk of incident EAC after BE diagnosis, a relatively long follow-up time from the first Barrett's cell to the final carcinoma progression is needed. Although BE is a well acknowledged risk factor for development of EAC, the absolute risk remains fairly low. The most recent meta-analysis showed an annual risk of 0.6% of EAC among all BE subjects,[231] whereas another meta-analysis estimated an 0.33% annual risk for non-dysplastic BE subjects,[249] very similar to an annual risk of 0.39% when including only high-quality studies.[230] Though an Irish population-based study estimated the annual EAC risk at 0.13%,[236] the ten-year risk of EAC is 5%.[250] We found a one-year risk of 0.09%, lower than the ones reported in meta-analyses, because of differences in characteristics of the data sources; primary care databases may be limited by underreporting of carcinoma cases. Additionally we could not retrieve segment-length or dysplasia status at time of BE diagnosis. This may have resulted in classifying subjects as BE whereas histology may not support BE diagnosis.

It is difficult to identify the 'true' IR of a disease that is present in symptomatic and asymptomatic subjects and diagnosed by gastroscopy and may be complicated by diagnostic work-up in symptomatic subjects only. Depending on the type of data used, each study faces challenges. Clinical endoscopic studies may suffer from biased retrieval of cases using symptom-based questionnaires leading to remarkably high IR of BE.[235, 251] Population-based studies are challenged by the lack of detail from histology reports, which is particularly true for routinely collected GP data without free text in medical records,[223] whereas studies using nation-wide registries lack clinical characteristics.[224] Nevertheless, we believe the sensitivity analysis including only histologically confirmed BE cases is representative of the true incidence of BE. In only 12% of cases BE diagnosis was negated and when theoretically considering the subjects in which we had no information on histology (26%) also were negated, the sensitivity analysis would likely reflect the true incidence of BE. On the other hand, when considering this 26% as being histologically confirmed, the true IR of BE would be 12% lower than our main analysis.

Strengths of the current study include the scale and setting as we combined primary healthcare data from two European countries. Whereas previous studies may have suffered from selection of Barrett's patients in referral centers, we were able to estimate the IR of BE in the general population.

We acknowledge the following limitations. First of all, although both data sources provide a representative sample of the country specific population, under-recording of BE and EAC cases cannot be ruled out. However, GPs participating in both data sources are instructed to code all medical diagnoses and symptoms electronically. In IPCI we encountered different results depending on software systems, as some are richer in free text information than others. This is relevant considering that the ICPC coding system does not contain a specific code for Barrett's esophagus. Nevertheless, as for BE endoscopic surveillance is needed, it is very unlikely that a GP has not recorded a BE diagnosis in the patient's medical record. Misclassification of BE might have occurred, due to miscoding by GPs. We mitigated this by performing sensitivity analyses, including additional evidence (including histology) to support the diagnosis. We might have underestimated the number of gastroscopies. Therefore we used the national information system recording all procedures in all hospitals from the Netherlands to validate the number of gastroscopies per capita in the Netherlands.[244] From 2007 till 2011 the national numbers confirmed the slight underreporting of gastroscopies in IPCI, though without large differences.

In conclusion, the incidence rate of Barrett's esophagus in the United Kingdom and the Netherlands has increased substantially in both males and females at the beginning of the millennium but has remained stable since then. The rise in incidence was not explained by an increase in gastroscopies. Around 0.3% of BE patients are diagnosed with esophageal adenocarcinoma at least one year after diagnosis of BE, demonstrating a one-year risk of 0.09%. The observed current increase in the EAC incidence among BE patients probably reflects the increase in the incidence of BE a decade ago.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Corresponding Read codes for identification of Barrett's esophagus and esophageal adenocarcinoma in THIN database.

READ code	Description of code		READ code	Description of code	Event
J101611	Barrett's oesophagus				BE
J102500	Barrett's ulcer of oesophagus				BE
J10y600	Barrett's oesophagus				BE
B102.00	Malignant neoplasm of abdominal oesophagus				Specific algorithm EAC
B105.00	Malignant neoplasm of lower third oesophagus				Specific algorithm EAC
B106.00	Malignant neoplasm, overlapping lesion of oesophagus				Specific algorithm EAC
B10y.00	Malignant neoplasm of other specified part of oesophagus				Specific algorithm EAC
B10z.00	Malignant neoplasm of oesophagus NOS				Specific algorithm EAC
B110100	Malignant neoplasm of gastro-oesophageal junction of stomach				Specific algorithm EAC
B110111	Malignant neoplasm of gastro-oesophageal junction				Specific algorithm EAC
B10..00/B10z.11	Malignant neoplasm of oesophagus / Oesophageal cancer	Combined with:	BBB2.00	Adenocarcinoma with squamous metaplasia	Unspecific algorithm EAC*
			BB57.00	Adenocarcinoma, intestinal type	
			BB53.00	Adenocarcinoma, metastatic, NOS	
			BB5..11	Adenocarcinomas	
			BB5z.00	Adenoma or adenocarcinoma NOS	

*BE, Barrett's esophagus; EAC, esophageal adenocarcinoma. * Recording of the combination of the two codes should have occurred within 1 year of each other.*
In THIN, we applied two algorithms to identify esophageal adenocarcinoma cases. In the first algorithm we used READ codes specific for EAC. In the second algorithm we identified cases with a record of esophageal cancer and an additional record of adenocarcinoma within one year of the diagnosis of esophageal cancer. This second search algorithm would identify EAC as we assumed that a histological confirmation of the type of esophageal carcinoma will be recorded after the detection of the cancer in the first letter to the GP.

CHAPTER 3.2

NSAIDs, statins, low-dose aspirin and PPIs and the risk of esophageal adenocarcinoma among patients with Barrett's esophagus, a population-based case-control study

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ABSTRACT

BACKGROUND

Non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs), low-dose aspirin and statins may decrease the risk of esophageal adenocarcinoma (EAC) among patients with Barrett's esophagus (BE). However, previous studies did not adequately address bias and confounding.

AIM

Our objective was to estimate the risk of EAC among patients with BE exposed to NSAIDs, PPIs, low-dose aspirin and statins.

METHODS

We conducted a case–control study nested within a BE cohort. From two primary care databases (the United Kingdom (UK) and the Netherlands (NL)) we identified cases being adults ≥18 years of age with EAC or high-grade dysplasia (HGD) diagnosis ≥1 year after BE diagnosis. Controls were matched on age, sex, year of BE diagnosis and database. Drug use was assessed from BE diagnosis until matching date. Adjusted ORs with 95% CI were calculated by conditional logistic regression.

RESULTS

Within the BE cohort (n=15,134), 45 EAC (UK: 40, NL: 5) and 12 HGD cases (NL: 12) were identified. ORa for EAC during NSAID use was 1.2 (95% CI 0.6 to 2.5) and during statin use for >3 years 0.5 (95% CI 0.1 to 1.7). When including HGD cases (n=57), ORa for NSAID use was 0.9 (95% CI 0.5 to 1.8) and for statin use >3 years 0.5 (95% CI 0.1 to 1.7). Higher doses of statins showed lower estimates for EAC and HGD, though not statistically significant. Low-dose aspirin and PPIs did not significantly decrease the risk of EAC and HGD.

CONCLUSION

In this population-based nested case-control study, use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of HGD and EAC among patients with BE. These findings indicate that for an unselected group of patients with BE chemoprevention by use of drugs to reduce progression to HGD and EAC should not be directly considered as routine care.

INTRODUCTION

Barrett's esophagus (BE) is a premalignant condition in which the squamous epithelium of the esophagus is replaced by metaplastic columnar epithelium.[252] BE is considered a consequence of prolonged gastro-esophageal reflux[222] and is the most important risk factor for development of esophageal adenocarcinoma (EAC) via a stepwise pathway of low-grade and high-grade dysplasia. It is estimated that the risk of EAC is increased by approximately 30 to 125-fold in persons with BE,[221] and occurs in a small proportion of patients with BE yearly.[253] Endoscopic surveillance for BE is therefore recommended.[222]

In recent decades, the incidence of BE increased, accompanied by a marked increase in EAC incidence in the USA and Western Europe.[249, 254] However, estimates of EAC incidence among patients with BE vary substantially.[230, 231, 233, 255] Generally, gastrointestinal cancers account for 25% of all cancers and approximately 4.9% of all deaths worldwide.[35] Death rates of most cancers decreased in recent years in contrast to the 3% increase in death rates of all esophageal cancers (squamous cell carcinoma as well as adenocarcinoma) among males.[35] The age-standardised mortality rate for esophageal cancer overall is 5.1 per 100,000 persons.[254] The need for effective prevention of esophageal cancer, in general, is therefore warranted, particularly given the low 5-year survival rate of 13% to 17%.[36]

Several studies reported that use of non-steroidal anti-inflammatory drugs (NSAIDs), low-dose aspirin, statins and proton pump inhibitors (PPIs) may decrease the risk of EAC among patients with BE.[14, 163, 245, 258-263] However, these studies were based on small, selected samples of EAC cases. PPIs are considered standard care for symptom relief in patients with BE, thus it was suggested that PPIs may decrease the risk of progression to high-grade dysplasia (HGD) or EAC.[245] In contrast, other studies showed an increase in risk of EAC with PPI use, probably because the underlying treatment indication may be a risk factor for EAC rather than that PPIs being harmful for EAC among patients with BE.[259, 264] Nevertheless, one cannot directly assume that PPIs, which are efficacious for treatment of erosive esophagitis, will also be beneficial in the pathway from BE to EAC development. Two meta-analyses both including nine observational studies showed that the risk of esophageal cancer[258] and HGD/EAC[265] among those who frequently use NSAIDs or aspirin was significantly lower compared with never users.[258] However, studies included in the earlier meta-analysis did not specifically include patients with BE. A pooled analysis on individual patient data confirmed the significant reduction in risk of EAC in BE patients with NSAID prescriptions.[266] Two case-control studies observed an association between use of NSAIDs[259] and statins,[259, 267] and the risk of EAC among patients with BE. Generalisation and extrapolation of results from the latter studies to the general population is, however, difficult as both studies were performed in US veterans.[259, 267] Additionally, there was no adjustment for important risk factors of EAC progression such as alcohol use and smoking.[259] Nevertheless, a recent systematic review and meta-analysis showed a risk reduction in development of esophageal cancer in general and EAC among patients with BE who took statins.[268]

Causality of an apparent association is generally supported by a dose-duration relationship.[162] However, studies to date neither reported a clear exposure definition free of recall bias [14, 260, 266] nor conducted dose-duration analyses. Finally, concerns have been raised about publication bias of these studies on chemoprevention of EAC in BE patients.[262]

Thus, to what extent NSAIDs, low-dose aspirin, statins and PPIs may reduce the risk of EAC among patients with BE in clinical practice remains unknown. Therefore, we conducted a matched case-control study to evaluate the risk of EAC among patients with BE associated with use of NSAIDs, low-dose aspirin, statins and PPIs.

METHODS

Data sources

Two European population-based general practice registries served as data sources: 1) The Health Improvement Network (THIN) from the UK (1996-2011)[237] and the 2) Integrated Primary Care Information database (IPCI) from the Netherlands (NL, 1996–2012).[238] Both databases contain prospectively collected data that represent real-life practice. In the UK and in NL, all citizens are registered with a general practitioner (GP), who acts as a gatekeeper to secondary and tertiary medical care. THIN collects anonymised data on more than 3 million active patients from over 400 participating general practices, IPCI contains over 1.5 million active patients from 340 practices. For each individual patient all relevant medical information, from primary and secondary care, as well as additional information, including demographics and drug prescriptions, is documented in the medical record. Both data sources comply with European Union guidelines on the use of medical data for research.

THIN employs the READ clinical terminology system for coding medical diagnosis and symptoms,[239] whereas IPCI uses the International Classification for Primary Care (ICPC).[240] Information on drug prescriptions is captured in THIN with the Multilex product dictionary and British National Formulary (BNF) codes, whereas in IPCI, information on drug prescriptions is coded according to the WHO's Anatomical Therapeutic Chemical (ATC) classification.[242] The Scientific and Ethical Advisory Boards of both databases approved the study. Identification of the source and study population has been described previously.[255]

Source population

The source population consisted of all patients aged ≥18 years who contributed data to the database between 1 January 1996 and 31 December 2011 (THIN) or March 2013 (IPCI). At least 1 year of available data prior to study entry were required to assess patient's medical history for exclusion criteria and risk factors. Follow-up started on 1 January 1996, or the date of reaching 18 years of age, or the date that 1 year of valid data were accrued within the database, whichever came later. Follow-up ended on the date of occurrence of study outcome

(EAC), date of transfer out of the GP's practice, death, or last data drawn, whichever was earliest.

Definition of Barrett's esophagus

Patients with BE were identified using diagnosis codes; in THIN using corresponding READ codes (see Supplementary Table 1 in Chapter 3.1).[239] In IPCI, each potential BE case was manually validated to confirm the histological diagnosis of BE and the date of first diagnosis or mentioning of BE in the clinical record. Patients were excluded if they had a history of esophageal cancer any time before BE diagnosis and if they had a history of gastric cancer within 6 months after BE diagnosis. In IPCI, we could utilise free text from the medical record to assess the Barrett segment length and grade of dysplasia.

Definition of esophageal adenocarcinoma

In THIN, EAC cases were identified by READ codes (see Supplementary Table 1 in Chapter 3.1). In IPCI, all patients with a record of ICPC codes D77.1 (malignant neoplasia of the esophagus) and D77.0 (malignant neoplasia of the digestive tract—not specified), or with a record from free text search including word combinations of 'esophagus', 'cancer', 'carcinoma', 'malignancy' or 'neoplasia' were identified. Similar to BE, all potential cases were manually validated for confirmation of the EAC diagnosis, date of first diagnosis and the type of carcinoma (squamous cell-, adeno-, or other types of carcinoma). Early cancer (HGD) was identified in IPCI also, but could not be assessed in THIN.

We only considered incident HGD or EAC cases: that is, if the date of diagnosis occurred after inclusion into the BE cohort and was at least 12 months after BE diagnosis. Cases occurring within 1 year from BE diagnosis were considered to be already existent at BE diagnosis date and in relation to the BE diagnostic work-up.

Cases and controls selection

Two nested case–control studies were conducted assessing the risk of EAC for use of four drugs (NSAIDs, PPIs, statins and low-dose aspirin); one including only EAC cases and a second case–control study including HGD cases from IPCI as well.

Cases were adults diagnosed with EAC ≥12 months after BE diagnosis, because cases occurring within 1 year of BE diagnosis were considered to be existent and related to BE diagnostic work-up (eg, missed EAC at BE diagnosis). Index date was defined as date of first reporting of EAC diagnosis during follow-up. Controls were members of the incident BE cohort who did not develop EAC up to matching date. Controls were matched by incidence density sampling on age (±5 years), sex, year of BE diagnosis (±1 year) and database. We matched on year of BE diagnosis in order to account for any influence of guideline changes in endoscopic surveillance over calendar time.

Drug exposure

Drug exposures of interest included four drug groups: NSAIDs, PPIs, statins and low-dose aspirin. They were assessed in terms of outpatient prescriptions for NSAIDs (including high-dose aspirin, ie, >325 mg/day), PPIs, statins and low-dose aspirin (up to 325 mg/day) from BE diagnosis until EAC diagnosis. In order to compare the OR of NSAIDs, PPIs and statins to other drugs, we considered another group of medications, which served as control. Antidepressants (selective serotonin re-uptake inhibitors (SSRIs)) are currently not known to be either positively or negatively associated with EAC.

Duration of prescriptions was calculated based on the prescribed quantity and dosing regimen. As the most likely preventive effect of drugs on cancer progression is through a cumulative mechanism, we calculated all duration and defined daily dose (DDD) values from date of BE diagnosis until index date. Duration was classified according to never use (reference category), cumulative use of less than 1 month, between 1 and 12 months, >12 months (or if applicable 1–2 years; 2–3 years and >3 years). Considering that PPIs are indicated as treatment for patients with BE, duration was classified as 0–6 months (reference category), 6–12 months, 1–2 years and >2 years. Dose of exposure was classified using the ratio of prescribed daily dose compared with DDD using quartiles into categories (<0.8, 0.8–1.2, ≥1.2 DDD per day). As there is no DDD for low-dose aspirin, dose analysis was not performed for use of low-dose aspirin.

Potential confounders

We considered as potential confounders: concurrent diagnosis of esophagitis or gastritis within 1 year before BE diagnosis; hiatal hernia; smoking habits (non-smoker, ex-smoker, current smoker) and alcohol abuse (never, current, past).

Statistical analyses

Baseline characteristics of cases and controls were described per database and compared using univariate conditional logistic regression. To estimate the risk of HGD and EAC among patients with BE, matched and adjusted odds ratios (ORa) with 95% confidence intervals (CIs) were calculated using conditional logistic regression for both databases separately and as a pooled analysis on patient-level pooled data.

Potential confounders were included in the adjusted analysis (ORa) if they resulted in a change of more than 10% of the initial estimate. Time since BE diagnosis was forced into the adjusted model.

Subsequent analyses included dose-duration analyses. The risk of EAC and HGD-EAC was also assessed for concomitant use of NSAIDs, low-dose aspirin, statins and/or PPIs. Use of PPIs only was considered as reference category considering that PPIs are standard therapy for BE. All analyses were performed using SAS V.9.2 (Cary, North Carolina, USA).

Power Calculation

Given an exposure prevalence of NSAIDs of 30%, statins of 22% or 36%, PPIs of 87% or 52% and low-dose aspirin of 25% among controls and a correlation of 0.5 between exposed and unexposed patients we have 80% power (with a type 1 error of 5%) to detect a true OR of EAC of 0.34 for NSAIDs, around 0.38–0.40 for statins, around 0.32–0.45 for PPIs and 0.29 for low-dose aspirin, which would be in concordance with previous studies.

RESULTS

Study population

From the source population of 7,570,765 subjects in the UK and 1,496,276 subjects in NL we identified 13,696 and 1,438 incident BE cases, respectively. Men accounted for 63% (UK) and 62% (NL) of patients with BE. Mean age at BE diagnosis was 64.8 (SD 13.8) years in the UK and 61.2 (SD 13.4) years in NL.

In the UK, we identified 40 incident EAC cases within the BE cohort (0.3%) to whom we could match 656 controls. Median number of controls per case was 17 (interquartile range (IQR): 9-23). In NL we identified five incident EAC cases among the BE cohort (0.3%). These were matched to 76 control subjects, with a median of 5 controls per case (IQR: 4-6). In addition, we identified 12 HGD cases, resulting in a second case-control set of 17 cases (5 EAC+12 HGD) matched to 753 controls (median 44 controls; IQR: 6-61). Figure 1 shows a flowchart of the study population.

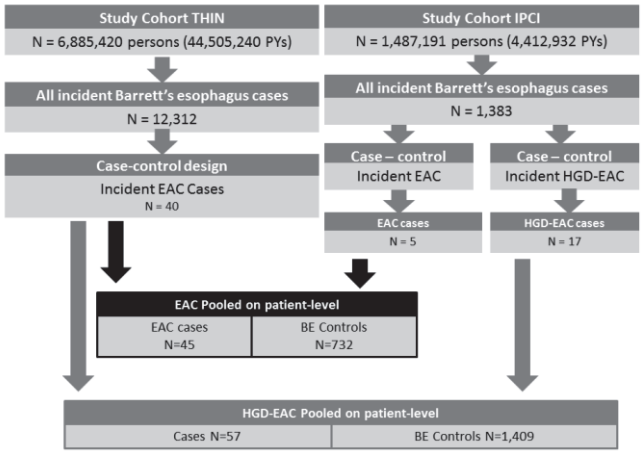


Figure 1. Flowchart of Barrett's esophagus and Esophageal Adenocarcinoma cases in the United Kingdom and the Netherlands.

BE, Barrett's esophagus; EAC, esophageal adenocarcinoma; HGD, high-grade dysplasia; THIN, The Health Improvement Network; IPCI, Integrated Primary Care Information; PYs, person years.

Table 1 provides baseline characteristics of cases and controls. In the UK a larger proportion of cases had a body mass index (BMI) over 25 kg/m²; 68% of cases and 59% of controls. In NL, the BMI of only one case within 1 year of EAC diagnosis was available (21.3 kg/ m²). Controls had a mean BMI of 28.7 kg/m² (SD 4.7) in NL. Presence of esophagitis or gastritis at time of BE diagnosis was more often seen in controls than in cases. In the UK, a hiatal hernia was more often present among cases, whereas the opposite was found in NL. In the UK, EAC cases were more likely to be current smokers than controls (OR 3.3; 95%CI: 1.4-8.0), as seen in NL though not significantly. Mean time from BE diagnosis until EAC diagnosis was 4.2 (SD 2.5) years in the UK and 3.5 (SD 0.8) years in NL.

Drug exposure

Table 2 provides characteristics of drug use from BE diagnosis until index date for cases and controls per database. Statins were used by 30% and 0% of EAC cases; and by 36% and 22% of controls in the UK and NL, respectively. PPIs were used by EAC cases for a mean of 4.1 years (UK) and 2.3 years (NL), and by controls for 2.9 years (UK) and 1.9 years (NL). SSRIs were used by 12.5% of EAC cases in UK for a mean duration of 1 year, and by 7.6% of controls for a mean duration of 1.7 years. Low-dose aspirin was used by 26% of BE subjects in the UK and 6% of patients with BE in NL.

Risk of Esophageal Adenocarcinoma

To estimate the risk of EAC with use of NSAIDs, PPIs, statins and low-dose aspirin, a nested case–control study was conducted. From the adjusted model, on patient-level pooled data, exposure to NSAIDs and PPIs did not provide a significant decrease in the risk of EAC (Table 3); for statins a non-significant effect was seen (ORa 0.7; 95% CI 0.4 to 1.5). This was seen in both databases separately as well (data not shown).

For NSAID use, ORs ranged between 1.1 and 1.4 for all duration categories; regarding dose-analysis, no difference in risk was found between higher and lower dosages (Table 4). Although not significant, a dose-duration-response was seen for statins, with lower OR for longer duration of use compared with non-use of statins. Statin use ≥1.2 times higher compared to the recommended DDD resulted in an OR of 0.7 (95%CI: 0.2-2.3). For PPIs an increase in OR was seen with prolonged duration, in the matched and in the adjusted analyses. PPIs used at highest dose showed an OR for HGD-EAC of 0.9 (95% CI: 0.3-2.3). The ORs varied for duration categories of SSRIs. No dose-response was seen for SSRI use. Use of low-dose aspirin provided ORs below 1 for EAC for matched and adjusted analysis, when considering the exposure at any time between BE diagnosis and EAC diagnosis; however the 95% confidence limits still included the 1. When considering duration analysis, the adjusted model provided for the prolonged duration of use (> 1 year) an OR of 0.9 (95%CI 0.4-2.1).

Concomitant use of drugs of interest did not decrease the risk of EAC (Table 5) compared to use of PPIs only, probably due to the smaller number of cases.

Table 1. Baseline Characteristics of Esophageal Adenocarcinoma Cases and High-grade Dysplasia Cases in the United Kingdom and Netherlands.

		United Kingdom				The Netherlands			
		EAC Case N (%)	Control N (%)	OR (95% CI)	P-value	HGD-EAC Case N (%)	HGD-EAC Control N (%)	OR (95% CI)	P-value
	Total	40 (100)	656 (100)			17 (100)	753 (100)		
	EAC					5 (29.4)			
	HGD					12 (70.6)			
Sex	male	33 (82.5)	597 (91)			11 (65)	524 (70)		
	female	7 (17.5)	59 (9)			6 (35)	229 (30)		
Mean age at index date (SD)		71.2 (10.4)	70.2 (9.0)			68.8 (8.2)	66.4 (8.8)		
Age group (years)	< 50	1 (2.5)	14 (2.1)			0 (0)	17 (2.3)		
	51-65	8 (20)	149 (23)			6 (35)	338 (45)		
	66-80	25 (62.5)	434 (66)			10 (59)	364 (48)		
	> 80	6 (15)	59 (9)			1 (5.9)	34 (4.5)		
Body Mass Index (kg/m2) mean (SD)		27.7 (4.1)	26.9 (4)	1.1 (1.0-1.1)	0.210	28.9 (6.8)	26.4 (7.4)	1.1 (0.9-1.3)	0.500
BMI categories	18-25	10 (25)	202 (31)			1 (5.9)	85 (11)		
	<18	0 (0)	7 (1.1)	-		0 (0)	22 (2.9)	-	
	>25-30	19 (47.5)	269 (41)	1.5 (0. 7-3.3)	0.329	2 (12)	156 (21)	1.3 (0.1-14.7)	0.995
	>30-35	7 (17.5)	89 (14)	1.8 (0.7-5.0)	0.246	0 (0)	73 (9.7)	-	
	>35	1 (2.5)	31 (4.7)	0.8 (0.1-7.0)	0.866	1 (5.9)	14 (1.9)	6.1 (0.3-112.1)	0.993
	missing	3 (7.5)	58 (8.8)	1.0 (0.3-3.8)	0.992	13 (76)	403 (54)	2.0 (0.3-16.5)	0.994
Esophagitis at BE diagnosis	no	39 (97.5)	629 (95.9)			14 (82)	525 (70)		
	yes	1 (2.5)	27 (4.1)	0.6 (0.1-4.7)	0.633	3 (18)	228 (30)	0.5 (0.1-1.8)	0.299
Gastritis at BE diagnosis	no	38 (95)	621 (94.7)			13 (76)	582 (77)		
	yes	2 (5)	35 (5.3)	1.2 (0.3-5.2)	0.808	4 (24)	171 (23)	1.5 (0.5-4.9)	0.516
Hiatal Hernia at BE diagnosis	no	33 (82.5)	579 (88.3)			8 (47)	268 (36)		
	yes	7 (17.5)	77 (11.7)	1.7 (0.7-4.0)	0.259	9 (53)	485 (64)	0.7 (0.2-2.0)	0.487
Excessive alcohol use	never	17 (42.5)	370 (56)	Ref		17 (100)	713 (94.7)	-	
	current	22 (55)	276 (42)	**2.0 (1.0-3.0)**	**0.048**	(0)	40 (5.3)		
	past	1 (2.5)	10 (1.5)	2.8 (0.3-23.4)	0.345				
Smoking	never	14 (35)	322 (49)	Ref		9 (53)	380 (50.5)	Ref	
	current	9 (22.5)	70 (11)	**3.3 (1.4-8.0)**	**0.009**	8 (47)	373 (49.5)	1.5 (0.5-4.5)	0.443
	past	17 (42.5)	264 (40)	1.7 (0.8-3.7)	0.155				

Table 1. Baseline Characteristics of Esophageal Adenocarcinoma Cases and High-grade Dysplasia Cases in the United Kingdom and Netherlands (*continued*).

		United Kingdom				The Netherlands			
		EAC Case N (%)	Control N (%)	OR (95% CI)	P-value	HGD-EAC Case N (%)	HGD-EAC Control N (%)	OR (95% CI)	P-value
	Total	40 (100)	656 (100)			17 (100)	753 (100)		
Index year	1998	1 (2.5)	7 (1.1)			1 (5.9)	5 (0.7)		
	2000	1 (2.5)	12 (1.8)			1 (5.9)	4 (0.5)		
	2001	3 (7.5)	24 (3.7)			1 (5.9)	7 (0.9)		
	2002	2 (5)	10 (1.5)			2 (12)	9 (1.2)		
	2003	2 (5)	15 (2.3)			1 (5.9)	3 (0.4)		
	2004	4 (10)	94 (14)						
	2005	7 (17.5)	128 (20)						
	2006	1 (2.5)	20 (3)						
	2007	2 (5)	30 (4.6)			1 (5.9)	22 (2.9)		
	2008	6 (15)	107 (16)			1 (5.9)	66 (8.8)		
	2009	4 (10)	72 (11)			1 (5.9)	49 (6.5)		
	2010	4 (10)	85 (13)			2 (12)	163 (22)		
	2011	3 (7.5)	52 (7.9)			5 (29.4)	374 (50)		
	2012					1 (5.9)	51 (6.8)		
***Helicobacter pylori* infection**	no	40 (100)	603 (91.9)	-	-	17 (100)	714 (94.8)	-	
	yes	0 (0)	53 (8.1)			0 (0)	39 (5.2)		

Table 2. Exposure characteristics of cases and controls in the United Kingdom and the Netherlands.

		United Kingdom		Netherlands	
		EAC Case	**Control**	**HGD-EAC case**	**HGD-EAC control**
		N = 40	N = 656	N = 17	N = 753
NSAIDs	Exposed - N	11	148	2	102
	Mean duration of use in days (SD)	205 (373)	218 (348)	18 (4)	49 (111)
	Mean cumulative DDD (SD)	223 (393)	232 (383)	9 (2)	31 (79)
	Median duration of use in days (IQR)	40 (20-178)	56 (28-203)	18 (15-20)	15 (10-60)
	Median cumulative DDD (IQR)	40 (30-223)	56 (28-208)	9 (7-10)	10 (5-30)
Statins	Exposed – N	12	236	3	123
	Mean duration of use in days (SD)	648 (569)	996 (913)	570 (289)	409 (300)
	Mean cumulative DDD (SD)	466 (353)	1,000 (1,258)	560 (191)	383 (331)
	Median duration of use in days (IQR)	616 (109-966)	728 (350-1,386)	450 (360-900)	330 (180-629)
	Median cumulative DDD (IQR)	504 (110-775)	625 (243-1,248)	450 (450-780)	270 (158-480)
PPIs	Exposed – N	36	570	10	389
	Mean duration of use in days (SD)	1,500 (1,134)	1,071 (978)	615 (462)	442 (372)
	Mean cumulative DDD (SD)	1,425 (1,247)	1,060 (1,123)	576 (402)	661 (1,636)
	Median duration of use in days (IQR)	1,481 (644-2,017)	766 (392-1,458)	471 (240-1,020)	315 (180-630)
	Median cumulative DDD (IQR)	1,223 (644-1,772)	700 (364-1,428)	471 (300-719)	360 (180-840)
SSRIs	Exposed - N	5	50	0	15
	Mean duration of use in days (SD)	369 (280)	613 (705)	-	743 (669)
	Mean cumulative DDD (SD)	366 (283)	843 (1,430)	-	737 (670)
	Median duration of use in days (IQR)	252 (252-504)	381 (90-840)	-	600 (180-1,740)
	Median cumulative DDD (IQR)	252 (252-504)	339 (90-896)	-	596 (180-1,740)
Low-dose Aspirin	Exposed - N	10	173	1	47
	Mean duration of use in days (SD)	796 (606)	804 (733)	360	391 (301)
	Mean cumulative DDD (SD)*	-	-		-
	Median duration of use in days (IQR)	672 (448-1,344)	600 (280-1,096)		270 (180-540)
	Median cumulative DDD (IQR)	-	-		-

** Low-dose aspirin (≤325 mg/day) has no DDD value.*

DDD, defined daily dose; SSRIs, selective serotonin re-uptake inhibitors; NSAIDs, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; IQR, interquartile range; SD, standard deviation.

Table 3. Risk of Esophageal Adenocarcinoma and High-grade Dysplasia-Esophageal Adenocarcinoma by drug class by duration on data pooled on patient-level.

Exposure	Duration category	EAC						HGD-EAC					
		Case N (%)	Control N (%)	ORmatched (95% CI)	P-value	ORadjusted* (95% CI)	P-value	Case N (%)	Control N (%)	ORmatched (95% CI)	P-value	ORadjusted* (95% CI)	P-value
Total N		**45**	**732**					**57**	**1,409**				
NSAID	None	32 (71)	566 (77)	Ref		Ref		44 (77)	1,159 (82)	Ref		Ref	
	Yes	13 (29)	166 (23)	1.3 (0.6-2.5)	0.492	1.2 (0.6-2.5)	0.532	13 (23)	250 (18)	1.0 (0.5-1.9)	1.000	0.9 (0.5-1.8)	0.876
	≤ 1 m	6 (11)	65 (9)	1.4 (0.6-3.6)	0.454	1.4 (0.6-3.5)	0.471	6 (11)	121 (9)	1.1 (0.4-2.6)	0.882	1.0 (0.4-2.5)	0.967
	>1 m-1 y	5 (9)	72 (10)	1.2 (0.4-3.1)	0.768	1.1 (0.4-3.0)	0.817	5 (9)	98 (7)	0.9 (0.3-2.4)	0.836	0.8 (0.3-2.3)	0.737
	>1 y	2 (4)	29 (4)	1.2 (0.3-5.3)	0.837	1.1 (0.3-5.2)	0.859	2 (4)	31 (2)	1.1 (0.2-4.7)	0.934	1.0 (0.2-4.6)	0.970
Statins	None	33 (73)	479 (65)	Ref		Ref		42 (74)	1050 (75)	Ref		Ref	
	Yes	12 (27)	253 (35)	0.8 (0.4-1.5)	0.432	0.7 (0.4-1.5)	0.412	15 (26)	359 (25)	0.9 (0.5-1.7)	0.720	0.9 (0.5-1.7)	0.673
	≤ 1 m	1 (2)	6 (1)	2.1 (0.2-20.4)	0.511	2.0 (0.2-20.1)	0.561	1 (2)	7 (0)	2.2 (0.2-20.6)	0.487	2.1 (0.2-20.5)	0.520
	>1 m-1 y	3 (7)	62 (8)	0.9 (0.3-3.2)	0.908	1.0 (0.3-3.4)	0.971	4 (7)	128 (9)	0.9 (0.3-2.8)	0.914	1.0 (0.3-2.8)	0.951
	> 1 y-2 y	4 (9)	66 (9)	0.9 (0.3-2.7)	0.848	0.9 (0.3-2.6)	0.824	5 (9)	90 (6)	1.1 (0.4-2.9)	0.868	1.1 (0.4-2.8)	0.907
	> 2 y-3 y	1 (2)	30 (4)	0.6 (0.1-4.9)	0.651	0.6 (0.1-4.7)	0.629	2 (4)	41 (3)	1.2 (0.3-5.3)	0.828	1.1 (0.2-4.9)	0.897
	> 3 y	3 (7)	89 (12)	0.5 (0.1-1.7)	0.259	0.5 (0.1-1.7)	0.239	3 (5)	93 (7)	0.5 (0.1-1.8)	0.276	0.5 (0.1-1.7)	0.253
PPIs	0 to ≤ 6 m	5 (11)	103 (14)	Ref		Ref		11 (19)	450 (32)	Ref		Ref	
	Yes	40 (89)	629 (86)	1.1 (0.4-3.0)	0.814	1.1 (0.4-2.8)	0.911	46 (81)	959 (68)	1.0 (0.5-2.2)	0.917	0.9 (0.4-2.0)	0.855
	7 - ≤ 12 m	6 (13)	169 (23)	1.9 (0.5-6.6)	0.502	2.0 (0.5-7.0)	0.299	7 (12)	158 (11)	1.7 (0.6-4.6)	0.293	1.7 (0.6-4.5)	0.312
	13-≤ 24 m	9 (20)	151 (21)	1.8 (0.6-5.4)	0.672	1.7 (0.6-5.3)	0.328	10 (18)	227 (16)	1.7 (0.7-4.2)	0.255	1.6 (0.6-3.9)	0.326
	> 24 m	5 (11)	162 (22)	2.1 (0.8-5.6)	0.476	1.9 (0.7-5.2)	0.207	27 (47)	377 (27)	1.7 (0.7-4.0)	0.204	1.5 (0.7-3.6)	0.327
SSRIs	None	40 (89)	679 (93)	Ref		Ref		52 (91)	1,344 (95)	Ref		Ref	
	Yes	5 (11)	53 (7)	1.7 (0.6-4.7)	0.281	1.7 (0.6-4.6)	0.310	5 (9)	65 (5)	1.6 (0.6-4.2)	0.356	1.5 (0.6-4.1)	0.390
	≤ 1 m	0 (0)	3 (0)	-	0.992	-	0.992	0 (0)	3 (0)	-	0.988	-	0.988
	>1 m-1 y	3 (7)	23 (3)	2.6 (0.7-9.2)	0.142	2.5 (0.7-8.9)	0.155	3 (5)	28 (2)	2.4 (0.7-8.6)	0.165	2.4 (0.7-8.4)	0.175
	>1 y	2 (4)	27 (4)	1.2 (0.3-5.5)	0.778	1.2 (0.3-5.4)	0.815	2 (4)	34 (2)	1.1 (0.2-4.9)	0.888	1.1 (0.2-4.7)	0.931
Low-dose Aspirin													
	None	35 (78)	553 (76)	Ref		Ref		46 (81)	1,189 (84)	Ref		Ref	
	Yes	10 (22)	179 (24)	0.9 (0.4-1.8)	0.702	0.8 (0.4-1.8)	0.662	11 (19)	220 (16)	0.9 (0.4-1.9)	0.799	0.9 (0.4-1.8)	0.764
	≤ 6 m	2 (4)	33 (5)	1.0 (0.2-4.2)	0.954	1.0 (0.2-4.3)	0.970	2 (4)	49 (3)	0.9 (0.2-3.7)	0.840	0.9 (0.2-3.8)	0.847
	>6 m-1 y	0 (0)	26 (4)	-		-		1 (2)	36 (3)	-		-	
	>1 y	8 (18)	120 (16)	1.0 (0.4-2.2)	0.920	0.9 (0.4-2.1)	0.844	8 (14)	135 (10)	0.9 (0.4-2.1)	0.867	0.9 (0.4-2.1)	0.805

** Adjusted for duration of follow-up since BE diagnosis. BE, Barrett's esophagus; HGD, high-grade dysplasia; NSAID, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; EAC, esophageal adenocarcinoma; SSRIs, selective serotonin reuptake inhibitors; m, months; y, year.*

Risk of High-Grade Dysplasia or Esophageal Adenocarcinoma

In NL, we were able to retrieve HGD cases as well. When including these in the case definition, the effects were attenuated but in the same direction as the case-control study including EAC cases only. There was no significant decrease in the risk of HGD-EAC for exposure to NSAIDs, statins, PPIs and low-dose aspirin in the adjusted analysis (Table 3). For NSAIDs, the OR increased with use of higher dosages (Table 4). Again, for statins a duration-response relationship with the longest duration yielding the lowest ORa (0.5; 95% CI: 0.1-1.7) and an inverse association with increasing dose was observed, though none significant. For low-dose aspirin, PPI and SSRI use, no dose-response effects were shown.

The risk of HGD-EAC was 13% lower for concomitant use of NSAIDs+PPIs (ORa 0.9; 95%CI:0.3-2.2) (Table 5). None of the associations were statistically significant.

DISCUSSION

In this population-based case–control study nested within a cohort of patients with BE, statin use may decrease the risk of EAC and HGD by up to 50%. PPIs did not reduce the risk of HGD and EAC, however, only when used at highest dose (eg, at least 1.2 times the recommended daily dose) a non-significant reduction may be present. In this unselected group of patients with BE, use of low-dose aspirin or NSAIDs was not associated with a decrease in risk of EAC. This is the first population-based study that looked at the preventive effect of these four different drugs used individually and also concomitantly.

The mechanism of EAC prevention is possibly related to inhibition of cyclo-oxygenase (COX)-2 production. Elevated levels of COX-2 in esophageal epithelial cells have been observed in BE, and noted to increase with disease progression from BE to EAC.[200] In experimental studies, COX-2 inhibitors inhibited the growth of BE cells, potentially through suppression of basic fibroblast growth factor.[269] Another study confirmed that the end product of COX-2 conversion (prostaglandin E2) is reduced in patients with BE without HGD when using esomeprazole combined with higher doses (up to 325 mg/day) of cardiovascular aspirin.[270]

Statins exert antineoplastic properties in several ways. By inhibition of the 3-hydroxy-3-methylglutanyl coenzyme A (HMG-CoA) reductase enzyme, subsequent modulation of growth signal transduction, cellular proliferation and cell death is achieved, which affects different organs.[4] In EAC cells particularly, statins inhibit cell proliferation and induce apoptosis[271] and limit the metastatic potential by reducing intracellular adhesion molecules.[272] However, statins also inhibit COX-2 expression in BE cells.[273]

Table 4. Risk of Esophageal Adenocarcinoma and High-grade Dysplasia-Esophageal Adenocarcinoma by drug class by daily dose on data pooled on patient-level.

Drug exposure	Dose category	EAC only				HGD-EAC			
		Case N(%)	Control N(%)	ORmatched (95% CI)	P-value	Case N(%)	Control N(%)	ORmatched (95% CI)	P-value
Total		45 (100)	732 (100)			57 (100)	1,409 (100)		
NSAID	None	32 (71)	566 (77)	Ref	-	44 (77)	1,159 (82)	Ref	-
	<0.8 DDD/day	3 (7)	39 (5)	1.1 (0.3-3.7)	0.909	3 (5)	107 (8)	0.6 (0.2-2.2)	0.475
	≥0.8 - < 1.2 DDD/day	4 (9)	74 (10)	0.9 (0.3-2.5)	0.783	4 (7)	84 (6)	0.8 (0.3-2.3)	0.633
	≥1.2 DDD/day	6 (13)	53 (7)	2.2 (0.8-5.6)	0.111	6 (11)	59 (4)	1.9 (0.8-5.0)	0.160
Statin	None	33 (73)	479 (65)	Ref	-	42 (74)	1,050 (75)	Ref	-
	<0.8 DDD/day	8 (18)	126 (17)	0.9 (0.4-2.2)	0.880	9 (16)	174 (12)	1.0 (0.5-2.1)	0.959
	≥0.8 - < 1.2 DDD/day	1 (2)	49 (7)	0.3 (0.05-2.6)	0.305	2 (4)	62 (4)	0.7 (0.2-3.1)	0.637
	≥1.2 DDD/day	3 (7)	78 (11)	0.7 (0.2-2.3)	0.519	4 (7)	123 (9)	0.8 (0.3-2.4)	0.731
PPI	None	5 (11)	103 (14)	Ref	-	11 (19)	450 (32)	Ref	-
	<0.8 DDD/day	9 (20)	168 (23)	0.9 (0.3-3.0)	0.914	11 (19)	196 (14)	1.1 (0.4-2.8)	0.910
	≥0.8 - < 1.2 DDD/day	23 (51)	315 (43)	1.2 (0.4-3.4)	0.723	27 (47)	454 (32)	1.1 (0.5-2.6)	0.768
	≥1.2 DDD/day	8 (18)	146 (20)	1.1 (0.4-3.6)	0.822	8 (14)	309 (22)	0.9 (0.3-2.3)	0.813
SSRI	None	40 (89)	679 (93)	Ref	-	52 (91)	1,344 (95)	Ref	-
	<0.8 DDD/day	1 (2)	8 (1)	3.0 (0.4-25.4)	0.317	1 (2)	8 (1)	3.0 (0.3-25.1)	0.321
	≥0.8 - < 1.2 DDD/day	4 (9)	32 (4)	2.3 (0.7-7.1)	0.149	4 (7)	44 (3)	2.0 (0.7-6.0)	0.218
	≥1.2 DDD/day	0 (0)	13 (2)	-	0.987	0 (0)	13 (1)	-	0.987

DDD, defined daily dose; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma; NSAID, non-steroidal anti-inflammatory drugs; PPIs, proton pump inhibitors; SSRIs, selective serotonin reuptake inhibitors.

Table 5. Risk of Esophageal Adenocarcinoma and High-grade Dysplasia-Esophageal Adenocarcinoma for concomitant drug exposure of NSAIDs, low-dose aspirin, statins and PPIs.

			EAC only			
Drug exposure#	Case N (%)	Control N (%)	ORmatched (95% CI)	P-value	ORadj model* (95% CI)	P-value
Total	45 (100)	732 (100)				
PPI only	19 (42)	284 (39)	Ref	-	Ref	-
No NSAID or LDA or statin or PPI	3 (7)	65 (9)	0.9 (0.2-3.2)	0.837	0.9 (0.3-3.4)	0.919
NSAID + PPI	6 (13)	72 (10)	1.2 (0.5-3.2)	0.700	1.1 (0.4-3.0)	0.773
Statin + PPI	5 (11)	85 (12)	1.0 (0.4-2.9)	0.963	1.0 (0.3-2.8)	0.988
LDA + PPI	3 (7)	30 (4)	1.4 (0.4-5.5)	0.597	1.3 (0.4-5.2)	0.655
LDA + PPI + Statin						
NSAID + LDA + Statin + PPI	4 (9)	41 (6)	1.2 (0.4-3.8)	0.744	1.2 (0.4-3.8)	0.760

			HGD-EAC			
Drug exposure#	Case N (%)	Control N (%)	ORmatched (95% CI)	P-value	ORadj model* (95% CI)	P-value
Total	57 (100)	1,409 (100)				
PPI only	22 (39)	441 (31)	Ref	-	Ref	-
No NSAID or LDA or statin or PPI	9 (16)	407 (29)	1.0 (0.4-2.4)	0.947	1.1 (0.4-2.8)	0.839
NSAID + PPI	6 (11)	124 (9)	0.9 (0.4-2.4)	0.898	0.9 (0.3-2.2)	0.774
Statin + PPI	7 (12)	143 (10)	1.2 (0.5-3.1)	0.630	1.2 (0.5-3.0)	0.674
LDA + PPI	3 (5)	42 (3)	1.3 (0.4-4.9)	0.691	1.2 (0.3-4.7)	0.742
LDA + PPI + Statin	2 (4)	104 (7)	0.4 (0.1-1.7)	0.202	0.4 (0.1-1.7)	0.198
NSAID + LDA + Statin + PPI	4 (7)	43 (3)	1.2 (0.4-3.9)	0.727	1.2 (0.4-3.8)	0.745

 # Numbers do not add up due to drug exposure categories with only one exposed case, not shown in the Table.

** Adjusted for duration of follow-up since BE diagnosis.*

BE, Barrett's esophagus; HGD, high-grade dysplasia; EAC, esophageal adenocarcinoma; NSAID, non-steroidal anti-inflammatory drugs; LDA, low-dose aspirin; PPI, proton pump inhibitor.

Contrasting to other studies, we did not observe a significant preventive effect of NSAIDs, low-dose aspirin and statins with respect to the risk of HGD-EAC. [14, 258, 266, 274] Based on the biological mechanisms, combined use of statins and NSAIDs or statins with low-dose aspirin may be expected to result in a greater risk reduction compared to either drug alone. We did not observe NSAIDs or low-dose aspirin with statins combined resulting in a significant risk reduction of EAC. This may be due to several reasons. First, despite our large BE cohort, the number of identified cases was smaller. Although we may have not have identified all potential EAC cases from the database, in a case– control study this is not necessary to obtain unbiased estimates. However, it limited the power of the study and resulted in statistically non-significant results. For assessment of concomitant drug exposure, in particular, we did not reach statistical significance due to the lack of power, though this was not the primary aim of the study.

Our nesting cohort included all incident BE patients from the general population, and by matching on duration since BE diagnosis and excluding patients with prevalent BE, we removed any effect of selective survival bias, disease severity[275] or time window bias,[276] as those patients with BE with a longer follow-up are more likely to develop HGD or EAC. By doing so, observing any spurious association was avoided. Second, we mitigated against immortal time bias[277] by defining the exposure period from BE diagnosis up to matching date, thus avoiding an overestimation of the preventive effect. The estimates from our study are likely more generalisable to the daily clinical practice in the general population, also including patients with less severe BE, that is, those with a shorter BE segment. A potential preventive effect of NSAIDs might therefore be only observed within selected high-risk subgroups. Thirdly, the inability to show a significant decrease in HGD and EAC risk for drug use may be explained by the distinct exposure definition that we applied. Contrasting with others [14, 274], we classified exposure cumulatively and performed dose-duration-analyses rather than assessing drug exposure at a single moment. This, however, also limited the analyses by creating multiple exposure categories. Drug exposure changes over time, especially in the long time taken to develop cancer. Assessment of exposure on a fixed moment will result in bias that exaggerates the effect downwards; showing a protective effect while actually it has no effect.[276] A pooled analysis of observational studies demonstrated an inverse association between the risk of HGD-EAC and use of NSAIDs.[266] A prospective cohort study also showed a decreased hazard ratio of HGD-EAC for use of NSAIDs and statins, however, the study results were influenced by immortal time bias.[15, 261] In that study, the majority of cases included HGD cases. In line with the other Dutch study,[261] when we included HGD cases the risk of HGD-EAC was lower than including EAC cases only. The preventive effect is possibly achieved in premalignant stage of dysplasia-development rather than of adenocarcinoma. It is, however, difficult to disentangle drug exposure effects in three different risk periods: induction (dysplasia), latent (between dysplasia and cancer) and disease period (cancer). Ideally, this requires knowledge on exact timing of the first aberrant Barrett's cell and subsequent stages towards HGD and EAC develop. The fourth explanation for not observing a preventive effect may be the exposure prevalence. Regarding NSAID exposure prevalence, we could not capture over-the-counter use of NSAIDs. During the study period NSAIDs and PPIs were reimbursable in the Netherlands and United Kingdom, and thus we assume that over-the-counter use of NSAIDs and PPIs did not confound the results to a great extent. Prevalence of PPI (81%) and statin (26%) exposure in our study is, however, comparable to other studies and is therefore unlikely to have limited our power.[261, 278]

A large prospective US cohort study showed a tremendous protective effect of NSAIDs on EAC risk.[274] However, NSAID exposure was assessed in a personal interview and classified very broadly by NSAIDs used at least once a week for 6 months.[274] If the preventive effect of NSAIDs would be as high as reported (up to 80%), a duration and dose response effect is to be expected. This study failed to demonstrate an inverse association between duration of NSAID use and the risk of EAC. In fact, the opposite was observed; the most protective effect was seen for the shortest duration,[274] contradicting a causal association.[162, 279]

A pooled analysis also could not demonstrate that prolonged duration of NSAID use was associated with a lower risk of EAC.[266] Additionally, heterogeneity between studies was observed,[266] which emphasizes the controversy around clinically effective chemoprevention with NSAIDs.

The preventive effect of statins is shown in several studies,[14, 261] yielding a risk reduction of EAC up to 48% for statin use >1 year.[259] However, in a meta-analysis, the risk reduction of EAC among patients with BE was only seen when studies were included that assessed drug exposure by patient interview, which may be prone to recall bias, whereas the risk reduction was not significant, including studies that assessed drug exposure by use of prescription/dispensing data in electronic medical records.[268] Also, for statins, the most pronounced effect was seen when HGD was included.[260] Results from the latter study should be interpreted with caution as drug exposure was classified by self-report as 'ever' instead of a duration classification. A recent case-control study, using a GP database from the UK, showed that statins may also decrease the risk of EAC and esophagogastric junctional adenocarcinoma in the general population.[280] The chemopreventive action of statins was more pronounced when combined with low-dose aspirin in a previous study.[14] It could be that the preventive effect of statins is explained by other risk factors common to statin users and patients with EAC, such as cardiovascular risk factors or lifestyle changes: smoking, exercise and weight.[280] Also it may be that patients with BE died from vascular diseases rather than of cancer-related causes or before HGD or EAC developed.[281] In our study, statin users were less likely to be current smokers, were of older age and were more often men. However, whether lifestyle changes due to comorbid cardiovascular diseases and initiating statin therapy may have resulted in healthier behavior, and subsequent EAC risk reduction, is open to debate.

Strengths of the current study include the scale and setting by combining healthcare data from two European countries with comparable GP databases and applying a common study protocol and drug exposure definition. The nested case–control design in a well-defined population representing the general population minimised selection bias. While previous studies may have suffered from recall bias or the lack of detailed drug prescription data, we were able to estimate the risk of HGD and EAC within patients with BE during drug use in the general population. Although our analysis may be limited by the small number of cases in the dose–duration analyses, partly due to the fact that we only included incident cases (diagnosed ≥1 year after BE diagnosis), our study is unlikely to suffer from biases (immortal time bias, time window bias) and confounding (disease severity) by matching on important risk factors. Matched and adjusted analyses were in line with each other suggesting that there was little confounding.

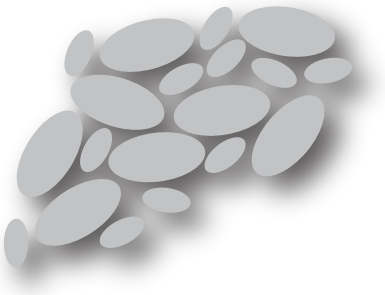
A limitation of the study is the lack of detailed pathology information on the Barrett segment length and grade of dysplasia, as is current practice for risk stratification of patients with BE. This may have resulted in misclassification of BE and EAC. However, the 1-year risk of EAC after BE diagnosis, excluding EAC cases within 1 year after BE diagnosis, was 0.086% (95% CI: 0.04–0.17) in the current study,[255] which is similar to other population-based studies.[232, 236, 253] Because we could not verify the diagnosis of BE against a clinical prespecified standard and

did not review biopsy specimens, it is also possible that we inadvertently included patients at very low risk of developing EAC. In the Dutch database, we could search through the medical records and noted that 8% had a segment length <2 cm, 13.7% between 2 and 3 cm, 11.8% longer than 3 cm, whereas for 60% of BE controls the length was not mentioned. Regarding the grade of dysplasia at time of BE diagnosis, 45% of controls had no dysplasia; there was low-grade dysplasia in 6% of BE subjects, indefinite for dysplasia in 1.8%, whereas no information on dysplasia grade was available in 46% of controls. Of the cases that developed HGD or EAC, 24% had a prior histology report of low-grade dysplasia. In the Dutch database we could utilise all free text entered in the medical record, enabling us to look for more detailed information in clinical letters, resulting in higher proportion of risk factors, such as presence of esophagitis and a hiatal hernia at time of BE diagnosis as compared with the UK database, in which we relied on diagnosis codes. We tried to address confounding-by-indication and time-window bias by matching on age, sex and year of BE diagnosis.[276] This is seen by the fact that individual risk factors did not increase the risk of EAC and adjustment for these confounders did not change the estimate by ≥10%. The observation that PPIs appear to increase the risk of EAC is explained by the treatment indication being a risk factor for EAC, reverse causation and the phenomenon of 'channeling', where high-risk patients are being prescribed PPIs whereas low-risk patients with lower doses or not at all,[168, 259, 264, 280, 282] a phenomenon often seen with PPIs and upper gastrointestinal bleeding.[283] It could also be that the effect of PPIs is apparent after minimally 2 years of use,[245, 259] an observation that was not significant in our study.

In conclusion, in this population-based nested case-control study, use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of HGD and EAC among patients with Barrett's esophagus. These findings indicate that for an unselected group of patients with BE, chemoprevention by use of drugs to reduce progression should not be considered directly as routine care.

SECTION 4

NSAIDs and the risk of Upper Gastrointestinal Bleeding



CHAPTER 4.1

Generating and evaluating a propensity model using textual features from electronic medical records

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Miriam CJM Sturkenboom, Jan A Kors, Martijn J Schuemie

Submitted.

ABSTRACT

BACKGROUND

Propensity score (PS) methods are commonly used to control for confounding in comparative effectiveness studies. Electronic health records (EHRs) contain much unstructured data that could be used as proxies for potential confounding factors.

AIM

To assess whether the unstructured information can also be used to construct PS models that would allow to properly deal with confounding.

METHODS

In a cohort study of new users of non-steroidal anti-inflammatory drugs (NSAIDs) from the Dutch Integrated Primary Care Information (IPCI) database, we identified all patients who experienced an upper gastrointestinal (GI) bleeding. We used a large-scale regularized regression to fit two PS models using all structured and unstructured information in the EHR. We calculated hazard ratios (HRs) to estimate the risk of upper GI bleeding among selective cyclo-oxygenase-2 (COX-2) inhibitor users compared to nonselective NSAID (nsNSAID) users.

RESULTS

The crude hazard ratio of upper GI bleeding for COX-2 inhibitors compared to nsNSAIDs was 0.50 (95% confidence interval 0.18-1.36). Matching only on age resulted in an HR of 0.36 (0.11-1.16), and of 0.35 (0.11-1.11) when further adjusted for sex. Matching on PS only, the first model yielded an HR of 0.42 (0.13-1.38), which reduced to 0.35 (0.96-1.25) when adjusted for age and sex. The second model resulted in an HR of 0.42 (0.13-1.39), which dropped to 0.31 (0.09-1.08) after adjustment for age and sex.

CONCLUSION

PS models can be created using unstructured information in EHRs. An incremental benefit was observed by matching on PS over traditional matching and adjustment for covariates.

INTRODUCTION

Electronic health records (EHRs) are primarily used for routine medical care, but secondary use of EHR data for observational research is becoming increasingly popular especially in studying of drug effects postmarketing.[284] In this era data is used to generate information on drug safety and effectiveness in a cost-efficient way and by exploiting actual care patterns, which differ largely from experimental settings.[285-288] In an experimental setting such as in randomized clinical trials, the choice for a treatment is randomized, which would take care of potential confounding by indication.[289] In actual care the treatment decision is usually influenced by measurable patient characteristics such as medical history, concomitant drug intake but also by personal prescriber preferences, which cannot be measured easily. This phenomenon of preferential prescribing is also known as channeling and may lead to confounding by indication.[290, 291] A well-known example of channeling is the preference of doctors to prescribe selective cyclo-oxygenase-2 inhibitors (COX-2 inhibitors) over nonselective (ns) non-steroidal anti-inflammatory drugs (NSAIDs) to patients at risk of developing upper gastrointestinal (GI) bleeding, as the COX-2 inhibitors were developed on purpose to mitigate the GI effects of NSAIDs.[243, 292] Although clinical trials showed that selective COX-2 inhibitors are 'safer' than nsNSAIDs in relation to upper GI bleeding,[293] observational studies showed no large differences between the rate of upper GI bleeding between COX-2 inhibitor and nsNSAIDs, possibly due to residual confounding by indications arising from channeling.[294] In order to obtain unbiased estimates in observational studies this confounding must be dealt with. However, it is challenging to capture all relevant confounders in the EHR databases because information is not primarily recorded for research purposes. Moreover, often relevant information is recorded in EHRs in an unstructured way.[295, 296]

Attempts to construct methods that deal with confounding have resulted in the propensity score method. The propensity score is an estimated conditional probability of receiving one particular treatment over another given a set of measured covariates.[297] It can be regarded as a comprehensive way to look at channeling. Propensity score methods can be used to control for the unbalance between the treatment groups in order to estimate the comparative effectiveness of treatments.[297] Four different methods of using the propensity to reduce confounding have been described[298]: (1) matching on propensity score; (2) stratification on the propensity score; (3) inverse probability of treatment weighting using the propensity score; (4) and covariate adjustment using the propensity score. Typically, all variables related to either the outcome and/or exposure are included in the propensity score model,[299, 300] sometimes these variables are not the exact confounding factors but proxies thereof. [301] Yet, identifying appropriate proxies in large EHRs is challenging. Schneeweiss *et al*.[302] proposed a high-dimensional propensity score (hd-PS) algorithm to empirically identify a large number of relevant covariates, with high prevalence, to control for confounding. In a case study on selective COX-2 inhibitors and nsNSAIDs using claims data in the USA, application of the hd-PS algorithm to control for confounding was found to produce an effect estimate for the risk of upper GI complications between selective COX-2 inhibitors and

nsNSAIDs that was comparable to the one found in randomized trials.[296] The hd-PS model is constructed by using many covariates of which some could serve as proxies for unobserved factors that otherwise may not be considered. Typically, only structured information such as diagnostic or procedure codes that is available in the claims databases, are included in the model. Electronic health records comprise much unstructured data and we propose that this information could also be used as proxies for potential confounding factors.

The aim of this study was therefore to assess whether unstructured text in EHRs can be used to construct a propensity score model that would allow to properly deal with confounding. We assessed the performance of propensity score models in addressing confounding by indication using as an example the association between selective COX-2 inhibitors and nonselective NSAIDs in relation to upper gastrointestinal bleeding.

METHODS

Data source

We used the Dutch Integrated Primary Care Information database (IPCI),[238] a population-based general practice (GP) EHR database. This database contains prospectively collected routine care data representing real-life practice. In the Netherlands, all citizens are registered with a GP, who acts as a gatekeeper to secondary and tertiary medical care. IPCI contains over 1.8 million patients from 340 GP practices. For each individual person, all relevant medical information from primary and secondary care is documented in the medical record. Apart from patient demographics, the recorded information in the EHRs contains medical notes (including symptoms, physical examination, assessments and diagnoses), drug prescriptions, laboratory results, referrals for hospitalization or specialist care, and hospital discharge summaries. In the IPCI database, drug prescriptions are coded using the Z-index, but are recoded according to the Anatomical Therapeutic Chemical (ATC) classification for research purposes.[242] Diagnoses are coded according to the International Classification for Primary Care (ICPC).[240] Almost 60% of the medical record are clinical narratives, which do not contain coded information, but contain important information such as patient-reported symptoms and notes from the GP.

Selection of NSAID cohort

We created a cohort of all new adult (≥18 years) users of NSAIDs between 1996 and 2013. Patients had to be enrolled for at least one year in the database in order to be eligible for cohort entry. ATC codes used for NSAID exposure are presented in Supplementary Table 1. Within the NSAID cohort we selected all episodes of NSAID use. A new NSAID episode was created if the following criteria were met: (a) at least six months of data available before NSAID exposure, (b) no prescription of any nonselective NSAID or selective COX-2 inhibitor in the previous six months, and (c) no mentioning of drug names, in the free-text, corresponding

with NSAID-related ATC codes in the previous six months. An NSAID episode continued when consecutive NSAID prescriptions started before or within 30 days of the end of the duration of the previous prescription. The duration of a prescription was calculated by dividing the prescribed quantity by daily dose regimen. The end of the episode was defined as the end of the last NSAID prescription. The episode selection is illustrated in Figure 1. Episodes were classified as an nsNSAID or selective COX-2 inhibitor episode based on the first prescription in that episode being an nsNSAID or a selective COX-2 inhibitor, respectively. If a patient switched between exposure (from selective COX-2 inhibitor to nsNSAID or vice versa) the duration of the NSAID episode was ended at the switch of the exposure. A patient could have multiple NSAID episodes, but only if the above mentioned criteria were met.

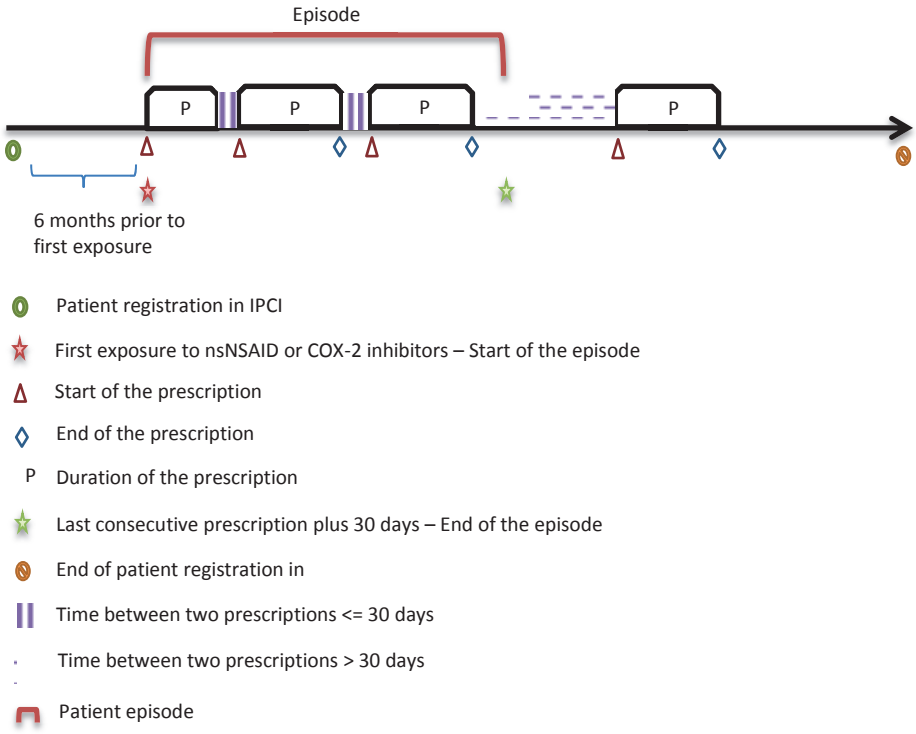

Figure 1. Episode selection.

Selection of Upper Gastrointestinal bleeding patients

Within the cohort of new NSAID users we identified all potential subjects who experienced an upper gastrointestinal (GI) bleeding via an automated search.[303] Upper GI bleeding was defined as all forms of ulcer complications such as bleeding, perforation, or obstruction. The entire medical record of all potential upper GI bleeding patients was extensively reviewed to ensure the diagnosis and the date of onset. Any other cause of upper GI bleeding (such as

variceal bleeding or Mallory Weiss bleeding) was excluded. The date of upper GI bleeding was determined as the date of first mentioning of symptoms leading to the upper GI bleeding diagnosis or if this date was unknown, the date of diagnosis.

Propensity score model

A propensity model was fitted using all information (structured and unstructured) in the EHR. To reduce the number of potential variables we first converted all text to lowercase after which we removed special characters, words not starting with a letter or a digit, stop words (such as *de*, *het* – the article *the* in English), and punctuation. All unique words (also known as unigrams) in the 6 months prior to cohort entry were extracted and used as textual features (potential covariates). We tested two methods to limit the number of covariates that would be included in the regression. The first method generated models using covariates of which the frequency in the cohort was above a certain threshold, e.g., 1,000 without any further selection. In the second method, we generated a model using covariates that were associated with the outcome. The chi-square test was used to select covariates that were statistically significantly associated with the outcome (p-value less than 0.05).

The selected features were subsequently used in a large-scale regularized regression using a LaPlace prior[304] with the hyperparameter of 0.01 to construct a propensity model for each method. The advantage of using a regularized regression is that it can handle high-dimensional data.[305] A flowchart depicting the process of propensity score model generation (for methods 1 and 2) is presented in Figure 2.

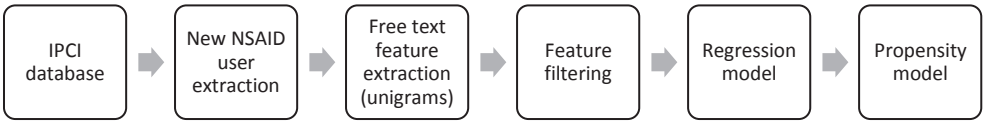

Figure 2. Flowchart showing the process of generating a propensity score model from unstructured free text.

We used three-fold cross-validation[306] to evaluate the predictive accuracy of the two models. The data set was randomly divided in three equally-sized subsets or folds. In three cross-validation runs, each time, the model was successively trained on two folds and tested on the third fold. For each cross-validation run, an area under the receiver operating characteristic curve (AUC) was calculated. The averaged AUC was used as the overall performance measure.

One-to-many propensity score matching

The propensity score was used to account for the preferential prescribing of selective COX-2 inhibitors to patients at high-risk of developing an upper GI bleeding[294]. In this study, we used the greedy one-to-many matching as described by Rassen *et al.*[307]:

1. For each selective COX-2 inhibitor user the difference in PS with all nsNSAID users was computed
2. Starting with the lowest difference, each selective COX-2 inhibitor user was matched with one nsNSAID user. Once an nsNSAID user was matched, he or she was precluded from further matching. A caliper of 0.01 was used, meaning no matches were made if the difference in PS was greater than 0.01.
3. After all selective COX-2 inhibitor users were matched with one nsNSAID user, the process was repeated until all new nsNSAID users were matched to new selective COX-2 inhibitor users or there was no match possible.

The algorithm ensured that all selective COX-2 inhibitor users were matched with at least one nsNSAID user if such a match was available within the caliper.

Statistical Analysis

To estimate the risk of upper GI bleeding among selective COX-2 inhibitor users compared to nsNSAID users we calculated hazard ratios with their corresponding 95% confidence intervals (CIs) using Cox proportional hazard regression. We conducted the analysis for four datasets: 1) a crude comparison (unmatched); 2) matched on age (± 2 years) and adjusted for sex and exposure to low-dose aspirin; 3) matched on PS with covariate frequency above 1,000 and then adjusted for age, sex, and exposure to low-dose aspirin; and 4) matched on PS with covariates having an association with the outcome and then adjustment for age, sex, and exposure to low-dose aspirin.

RESULTS

NSAID cohort

From the source population of more than 1.8 million patients we identified 518,768 new users of NSAIDs based on ATC codes. We then processed the unstructured free-text in the entries of the new users to identify mentioning of drug names corresponding with NSAID-related ATC codes. In total, 36,188 new users were removed because either an nsNSAID or selective COX-2 inhibitor drug was mentioned in the free-text in the six months preceding first NSAID exposure. This resulted in 482,580 new NSAID users in the study cohort. Out of these, 459,701 (95%) were nsNSAID users and 22,879 (5%) were selective COX-2 inhibitor users. Within the

NSAID cohort we retrieved 11,994 potential upper GI bleeding patients. After reviewing the medical records we retained 1,048 upper GI bleedings.

The average duration of episodes for initiators of selective COX-2 inhibitors was 94 days and 66 days for initiators of nsNSAIDs. Baseline characteristics of initiators of selective COX-2 inhibitors and nsNSAIDs are shown in Table 1. Most of the episodes of selective COX-2 inhibitors and nsNSAIDs were started after the year 2004.

Propensity model

In total, we extracted 2,762,326 covariates (i.e., unique words) from approximately 2.4 million entries in the 6 months prior to NSAID episodes from the medical records of 482,580 new NSAID users. Table 2 shows the performance of the propensity models built using different covariates selection methods. The first model used all covariates with a frequency of 100 or more in the cohort, which resulted in 95,078 unique covariates entered into the model. Increasing the frequency to 1,000 resulted in a reduction of the number of covariates to 27,619. The number of covariates further reduced when frequency was increased to 5,000. The performance of the models in terms of their predictive accuracy was comparable. The predictive performance of the propensity model that was built using 3,650 covariates that had an association with the outcome according to the chi-square test. This resulted in an AUC of 70.59. The performance of the propensity model that included only the established confounders resulted in an AUC of 66.27. The number of covariates in the models however were only 111.

Risk of upper gastrointestinal bleeding

The crude hazard ratio of upper GI bleeding for selective COX-2 inhibitors compared to nsNSAIDs was 0.50 (95% 0.18-1.36) (Table 3). When matched on age, the hazard ratio of selective COX-2 inhibitor use compared to nsNSAID use was 0.36 (95% CI: 0.11-1.16). Further adjusting for sex and exposure to low-dose aspirin resulted in HR of 0.35 and 0.36 respectively. Matching on PS only, using one-to-many matching with a covariate frequency above 1,000, yielded a hazard ratio of 0.42 (95% CI: 0.13 – 1.38). Subsequent adjustment for age resulted in a hazard ratio of 0.36 (95% CI: 0.10 – 1.22). Matching on PS with covariates associated with outcome gave a hazard ratio of 0.42 (95% CI: 0.13 – 1.39). Adjusting for age reduced the ratio to 0.32 (95%: 0.09 – 1.09). The top 25 covariates, in terms of their weights (beta values), from both propensity score models are presented in Supplementary Table 2-3.

Table 1. Baseline characteristics of initiators of selective COX-2 inhibitors and nonselective NSAIDs.

Characteristics	%	
	Selective COX-2 initiators (n=22,879)	nsNSAID initiators (n=459,701)
Age (mean)	57.7	47.9
Male	36.5	43.2
Female	63.5	56.8
Exposure to low-dose aspirin	2.8	1.1
Age (years)		
≤ 30	6.5	17.3
31 – 40	8.4	16.1
41 – 50	17.7	22.4
51 – 60	22.4	19.7
61 – 70	20.8	13.8
71 - 80	15.9	7.7
> 80	8.3	3.0
Calendar year of treatment initiation		
before 2003	0.1	10.8
2003	1.4	2.0
2004	3.1	1.9
2005	1.6	1.9
2006	1.5	1.3
2007	2.6	2.3
2008	7.3	6.7
2009	11.5	12.3
2010	15.6	16.4
2011	22.7	20.6
2012	30.7	22.7
2013	1.9	1.1
Upper GI risk factors		
Use of antiplatelets	6.3	3.2
Use of anticoagulants	3.2	1.3
Use of gastroprotective agents	23.4	11.8
Other comorbidities		
Dyspepsia	0.2	0.2
Smoking	0.5	0.5
Heart failure	0.4	0.2
Diabetes mellitus	0.5	0.3
Concomitant use of other medications		
Selective serotonin reuptake inhibitors	4.4	3.3
Spironolactone	0.7	0.3
Calcium channel blockers	7.2	3.7

Table 2. Predictive performance of different hd-PS models built using covariates with different frequencies in the data set.

	PS Model	Number of covariates	AUC*
Method 1	Covariate frequency ≥ 100	95,078	72.27
	Covariate frequency ≥ 1,000	27,619	72.32
	Covariate frequency ≥ 5,000	11,699	72.17
Method 2	Covariates selected using Chi-square test (independent of frequency)	3,650	70.59

** AUC, area under the Receiver Operating Characteristic curve.*

Table 3. Hazard ratios with 95% confidence intervals (CI) comparing selective COX-2 inhibitors with nsNSAIDs.

Matching	Adjustment	Hazard ratio	95% CI
Unmatched	None	0.50	0.18 – 1.36
Age	None	0.36	0.11 – 1.16
	Sex	0.35	0.11 – 1.18
	Sex, Aspirin	0.36	0.11 – 1.18
Propensity Score covariate frequencies > 1,000	None	0.42	0.13 – 1.38
	Age	0.36	0.10 – 1.22
	Sex	0.39	0.12 – 1.30
	Age, Sex	0.35	0.96 – 1.25
	Sex, Aspirin	0.39	0.12 – 1.32
Propensity Score covariates based on association test	None	0.42	0.13—1.39
	Age	0.32	0.09—1.09
	Sex	0.43	0.13—1.42
	Age, Sex	0.31	0.09 – 1.08
	Sex, Aspirin	0.43	0.13—1.42
	Age, Sex, Aspirin	0.31	0.09 – 1.10

For (a) Unmatched -crude, (b) Matched on age only and then adjusting for sex and similar exposure to low-dose aspirin (c) Matched on PS only and then adjusting on age, sex, and similar exposure to low-dose aspirin (d) Matched on PS built using covariates selected with chi-square test and then adjusting on age, sex, and similar exposure to low-dose aspirin.

DISCUSSION

In this study, we generated a propensity model using unstructured information from electronic healthcare records (EHR). We tested different methods to construct this and demonstrated the feasibility to do so as well as its performance. Since electronic health records are now widely available for secondary use, we need to develop methods and test performance of these methods for use in epidemiological evaluations such as drug effects.

Our method to generate a propensity score model is substantially different from the high-dimensional propensity score (hd-PS) approach proposed by Schneeweiss et al.[302] The hd-PS algorithm that was developed for claims data uses structured information such as diagnostic codes, in-patient procedure codes, and drugs dispensed. In each identified data dimension, the highest ranked codes are selected to enter in the hd-PS model. Our method is different since we used as the basis unstructured text to generate propensity models, using a large-scale regularized regression, without pre-identified data dimensions. Several methods other than logistic regression such as data-adaptive and classification trees have been proposed for fitting a propensity model.[305] To reduce the number of 'meaningless' features, we needed various textual data cleaning steps. We subsequently extracted all unigrams from the cleaned free-text, which served as potential covariates. Here we applied different approaches, to look at the impact of our choices. In the first method, the most-frequent covariates in the cohort were selected to enter the propensity score model. Since the covariates were selected merely on the basis of their frequency in the cohort, this method is

prone to include covariates that may actually be instrumental variables. Instrumental variables have an association with the exposure but not with the outcome except through their effect on exposure. If covariates are included that are not true confounders, the variance increases and sometimes a small amount of bias may be introduced.[103, 308-310] In order to mitigate the potential to include covariates that are instrumental variables we included covariates with a significant association with the outcome to the propensity score model in the second method we applied.[310]

We used three-fold cross-validation to evaluate the predictive performance of each generated model. The propensity models generated using covariates with only high frequency in the cohort performed better. This may be due to the presence of some instrumental variables which can result in a decrease in performance (mean squared error) but increase in predictive performance.[311] Increasing the frequency threshold for covariate selection reduced the number of covariates that entered into the propensity score model but the performance of the models was still comparable. This suggests that the performance of the models was mostly based on a few covariates with high occurrence in the text. Reducing the number of covariates reduced the computation time needed to fit the model. By selecting covariates with an association with the outcome we significantly reduced the total number of covariates without greatly affecting the performance. The propensity models generated using covariates with only high frequency in the cohort performed better than the one where association with the outcome was verified. This may be due to the presence of some instrumental variables which can result in an increase in predictive performance.[305] We used another propensity model for the comparison purposes where only the established confounders age, sex, and exposure to low-dose aspirin were included. The predictive performance of this model was lower than the other two models which were generated from the free-text covariates. The second method, where covariate association with the outcome was verified, showed large decrease in the hazard ratios after further adjustments.

Whereas previous studies have constructed the hd-PS with structured information, such as ICD and READ codes across different data dimensions in different sources,[296, 301, 302, 312] large proportions of information may be unstructured. We showed that this unstructured free-text can be used to construct propensity models. A high number of removals (7%) from the cohort based on a drug mentioned in the free-text indicates the importance of processing unstructured free-text instead of only relying on the structured information such as prescription tables containing ATC codes.

Our study also has several limitations. First, by including covariates based on their frequencies we might have selected covariates that are not necessarily related to the outcome or the exposure, which could introduce bias.[299, 313] Second, since we only used unigrams, covariates like '*congestive heart failure'* cannot be recognized as such. Instead it will be recognized as individual words '*congestive' 'heart'* and '*failure'* which might lead to over- and underestimation of some covariates. Like previous studies using hd-PS methods, we also used the known association between NSAIDs and upper GI bleeding as an example. It is unclear whether our findings regarding the PS generated from unstructured free-text apply to other

treatment-outcome pairs. Since the PS algorithm in general relies on the information present in the cohort, a similar approach using a different data set might have different results even when using the known example of NSAID-upper GI bleeding.

The majority of selective COX-2 inhibitor episodes started after the year 2004, the period after the withdrawal of rofecoxib from the market because of cardiovascular risks.[11] This may explain the strong protective effect of selective COX-2 inhibitors in the crude analysis which we would expect, but is different from previous observational studies that were done more closely to the introduction of selective COX-2 inhibitors.[296, 301, 302, 312] Since most of our patients started after the contra-indications were introduced, channeling towards high risk patients was less of an issue.[314]

In conclusion, our study showed that PS models can be created using unstructured information in electronic healthcare records. This is useful for database studies using a large amount of unstructured free-text as in EHRs. We observed a small incremental benefit by matching on PS over traditional matching and adjustment for covariates. Better methods for extracting meaningful covariates from the free-text may be required for effective proxy adjustment via propensity scores.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. List of ATC codes used for NSAID exposure assessment.

ATC code	Name	Type of NSAID
M01AA*	butylpyrazolidines	nonselective NSAID
M01AB*	Acetic acid derivatives	nonselective NSAID
M01AC*	Oxicams	nonselective NSAID
M01AE*	Propionic acid derivatives	nonselective NSAID
M01AG*	Fenamates	nonselective NSAID
M01AH01	Celecoxib	Selective COX-2 inhibitor
M01AH03	Valdecoxib	Selective COX-2 inhibitor
M01AH04	Parecoxib	Selective COX-2 inhibitor
M01AH05	Etoricoxib	Selective COX-2 inhibitor
M01AH06	Lumiracoxib	Selective COX-2 inhibitor

**all drugs from this group are included.*

Supplementary Table 2. Top 25 covariates by their weights selected by the regression model (covariates frequency > 1000).

Rank	Unigram	Translation	Beta value
1	dh*	Diakonesse huis (type of hospital)	0.565
2	rrzit	Blood pressure measurement in sitting position	0.548
3	nabehandeling	Follow-up treatment	0.532
4	school	School	0.430
5	orthopaedisch	Orthopedic	0.376
6	specialistische	Specialist/Specialistic	0.360
7	bacteri	Bacteria	0.334
8	tonsillen	Tonsils	0.326
9	acne	Acne	0.319
10	rfe*	Reason for Encounter	0.312
11	tonsillitis	Tonsillitis	0.303
12	bloedafname	Blood sampling	0.287
13	nvgb*	Patient did not appear at appoint, no message	0.285
14	origineel	Original	0.282
15	menstruatie	Menstruation	0.279
16	arthroscopie	Arthroscopy	0.241
17	housenumber	“House number”	0.238
18	bloedbeeld	Complete blood test	0.236
19	waarneming	Observation	0.225
20	ref*	Reference/referral	0.225
21	abnormaal	Abnormal	0.223
22	n89	ICPC Code N89 (Migraine)	0.217
23	glu*	Glucose	0.203
24	assistent	Assistant	0.202
25	spastische	Spastic	0.201

** Abbreviations, might have other meanings as well depending on the context.*

Supplementary Table 3. Top 25 covariates by their weights selected by the regression model (chi-square test).

Rank	Unigram	Translation	Beta value
1	rrzit	Blood pressure measurement in sitting position	0.675
2	dh*	Diakonesse huis (type of hospital)	0.656
3	school	School	0.545
4	izh*	Hospital	0.413
5	rfe*	Reason for Encounter	0.376
6	tonsillen	Tonsils	0.369
7	acne	Acne	0.357
8	cvx*	Cervix	0.347
9	declareren	Declare	0.345
10	menstruatie	Menstruation	0.343
11	tonsillitis	Tonsillitis	0.309
12	ref*	Reference/referral	0.306
13	diak*	Diakonesse huis (type of hospital)	0.295
14	erythro	Erythrocyte	0.264
15	kindergeneeskunde	Pediatrics	0.263
16	bultje	Bump	0.254
17	exfoliatieve	exfoliation	0.248
18	intensieve	Intensive	0.247
19	arthroscopie	Arthroscopy	0.240
20	fp		0.236
21	asdrukpijn	Axial pressure pain	0.234
22	bevalling	Delivery	0.234
23	zwanger	Pregnant	0.230
24	regulair	Regular	0.224
25	zelfcontrole	Self-control	0.214

** Abbreviations, might have other meanings as well depending on the context.*

4

CHAPTER 4.2

Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice?

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ABSTRACT

BACKGROUND

Two strategies for prevention of upper gastrointestinal (GI) events for nonselective (ns)NSAID users are replacement of the nsNSAID by a cyclo-oxygenase-2 (COX-2)-selective inhibitor or co-prescription of a gastroprotective agent (GPA).

AIM

Aim was to identify whether and in whom either of these strategies should be preferred in daily practice.

METHODS

A nested case-control study was conducted using three European primary care databases. We selected a cohort including all naive nsNSAID+GPA (≥ 80% GPA adherence) and COX-2 inhibitor users (without GPA use) aged ≥50 years. Cases with an upper GI event (i.e. symptomatic upper GI ulcer or bleeding (upper GI bleeding)) were matched to cohort members without an upper GI event on age, sex and number of individual upper GI risk factors (i.e. upper GI event history, age≥65 years, concomitant use of anticoagulants, antiplatelets, or glucocorticoids) and calendar time. Conditional logistic regression analysis was used to calculate odds ratios (ORs) with 95% confidence intervals (CI), while adjusting for potential confounders.

RESULTS

Within the NSAID cohort (n=617,220), 398 upper GI event cases were identified. The risk of upper GI events was equivalent for COX-2 inhibitor and nsNSAID+GPA (≥80% adherence) users (OR: 1.02; 95%CI:0.77-1.37). In concurrent glucocorticoid users, the risk of upper GI events was significantly elevated for nsNSAID+GPA (≥80% adherence) compared to COX-2 inhibitor users (OR: 9.01; 95%CI:1.61-50.50).

CONCLUSION

The risk of upper GI events was similar in nsNSAID+GPA (≥80% adherence) and COX-2 inhibitors users. In patients concurrently using glucocorticoids a significant increase in the risk of upper GI events for nsNSAID+GPA users was observed and COX-2 inhibitors should be preferred.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently prescribed by both general practitioners and medical specialists, and serve as key pharmacological agents in the management of arthralgic and inflammatory conditions. Multiple epidemiologic studies and prospective clinical outcome trials have characterized the risk of NSAID-related gastrointestinal (GI) complications, which include upper gastrointestinal (GI) ulcers and bleeding. To mitigate the increased risk among long term NSAID users, guidelines have been developed and strategies are recommended [99, 100, 315, 316] including prescription of cyclo-oxygenase (COX)-2-selective inhibitors or concurrent use of gastroprotective agents (GPAs), such as proton pump inhibitors (PPIs). Although both preventive strategies aim to reduce the incidence of upper GI events, the risk of such complications is not eliminated; a considerable proportion of NSAID plus GPA users (6.3% to 8.5%) and COX-2 inhibitor users (3.7% to 8.9%) continues to experience upper GI events. [76-79]

Defining which of the two preventive strategies is preferred in terms of upper GI safety has been the scope of recent studies. Most of the randomized clinical trials showed no superiority for one of the preventive strategies over the other. [76-78, 317] Only one large randomized clinical trial showed a beneficial effect in favor of celecoxib.[82] In this 6 month trial patients randomized to celecoxib, as compared to the combination of diclofenac and omeprazole, had a reduced rate of clinically significant overall gastrointestinal events when a composite endpoint was considered (events from both the upper and lower GI tract). Looking at the upper gastrointestinal tract specifically, this head to head comparison demonstrated similar rates for upper gastrointestinal bleeding. [82] Extrapolation of the previously described body of literature to guide clinicians in the care of the general population has several limitations. Many of the prospective randomized clinical studies have included patients using supra-therapeutic doses of COX-2 inhibitors or included a selected group of high-risk patients (i.e. those with a recent upper GI event).[76-78, 82] Alternatively in some of the prospective trials, the presence of co-morbid diseases such as ischemic heart disease, peripheral arterial disease[82], or congestive heart failure [78] were considered as exclusion criterion, thereby preferentially selecting patients at lower risk of upper GI events. Additionally, the exclusion of patients with frequently used co-medication (e.g. low-dose aspirin [78], anticoagulant agents [77, 78] and corticosteroids [77]) in some of the studies might be an important issue, considering that the use of low-dose aspirin clearly influences the efficacy of upper GI protection in COX-2 inhibitors. [73, 318] Finally, as a consequence of protocol driven inclusion of patients with recent or past upper GI bleeding and in some studies, the recruitment of patients from hospital-setting [78, 82] or endoscopy centers [76, 77], a substantial number of enrolled subjects may have had NSAID-associated complications and as such a higher risk.

Apart from the clinical studies, one population-based cohort study concluded that COX-2 inhibitors alone were not superior to nonselective (ns)NSAID combined with PPI in the prevention of hospitalization for a perforated or bleeding ulcer.[319] This observation was confirmed in an observational case-control study, using a population-based claims-database in

Canada, in which both gastroprotective strategies were similarly effective in the prevention of NSAID-related upper GI events, but it did not address the lack of adherence to PPIs.[101] However, we and others have demonstrated that in real life, GPA adherence during nsNSAID use is an important factor to consider when evaluating and comparing the effectiveness of different gastroprotective strategies. If the NSAID and PPI are given as separate medications non- or low adherence to GPAs is often seen[320] and associated with significantly increased risk of nsNSAID-related upper GI events. [294, 321, 322]

Thus, whether COX-2 inhibitors and nsNSAIDs plus GPA are similarly effective in preventing incident NSAID-related upper GI events in daily clinical practice including patients both at high- and low-risk is still unknown. Therefore, we conducted a case-control study to compare the risk of upper GI events between COX-2 inhibitor users and nsNSAID users, who were highly GPA adherent (at least 80% adherence to GPAs), making use of population-based primary health care data from three European countries. As COX-2 inhibitors might be preferentially prescribed to specific patient groups, we restricted to nsNSAID users who were highly GPA adherent (at least 80% adherence to GPAs).

METHODS

Description of data sources

Three similar European population-based primary care registries served as data sources: 1) the General Practice Research Database (GPRD) from the United Kingdom (UK, 1998–2008), 2) the Integrated Primary Care Information database (IPCI) from the Netherlands (1996–2007), and 3) the Health Search/CSD Longitudinal Patient Database (HSD) from Italy (2000–2007). In these three countries, all citizens are registered with a primary care practice, which acts as a gatekeeper to secondary and tertiary medical care. For each individual patient all relevant medical information from primary and secondary care, as well as additional information, including demographics and drug prescriptions, is recorded in the health care medical record. All three registries comply with European Union guidelines on the use of medical data for research. The protocol of the present study was approved by the Medical Ethics Committee of each database. We have previously shown the validity to combine and to compare data from these databases.[102, 294] For GPRD, the READ dictionary was used to identify medical diagnosis and symptoms, whereas the International Classification for Primary Care[240] and the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM)[323] were used for that purpose in IPCI and HSD, respectively. In IPCI and HSD information on drug prescription was coded according to the Anatomical Therapeutic Chemical (ATC) classification.[242] In GPRD information on drugs is captured with MULTILEX product dictionary and British National Formulary (BNF) codes.

Determination of NSAID cohort

The identification of the source population and NSAID cohort has been described elsewhere.[294] In brief, a source population was identified within each database by inclusion of patients from start of the study period, 50 years of age or the date that one year of valid data within the database was available, whichever was the most recent. The one-year period prior to inclusion in the source population was required for valid assessment of baseline characteristics and inclusion and exclusion criteria at the time of NSAID prescription. We identified a cohort of all new users (i.e. no NSAID prescriptions within 6 months prior to inclusion) of either COX-2 inhibitors or nsNSAIDs (excluding the fixed combination of diclofenac with misoprostol) was identified. Exclusion criteria were history of gastrointestinal tract cancer, alcohol abuse, chronic liver disease, inflammatory bowel disease, or coagulopathy. Within the cohort of new users, all episodes of NSAID use were determined and defined as consecutive NSAID prescriptions with intervening gaps not exceeding the duration of the previous NSAID prescription (Figure 1). The duration of an NSAID episode was calculated by dividing the prescribed quantity by daily dose regimen (GPRD/IPCI) or the indication-specific defined daily dose (HSD). The end of an NSAID episode was defined as the end of the duration of the last NSAID prescription within that episode or the end of follow-up, whichever was earliest. All episodes from a patient were eligible for inclusion if the previous NSAID-prescription ended at least 6 months before the start of the next episode. The density of NSAID use was calculated by the number of NSAID prescription days divided by episode length. Eligible gastroprotective agents (GPAs) were proton pump inhibitors (PPIs), double-dosed histamine$_2$ receptor antagonists (H_2RAs), and misoprostol.

For the present study, nonselective NSAID users were excluded if they did not use a GPA concomitantly, or if they were non-adherent to the concomitantly used GPA (i.e. coverage of less than 80% of the nsNSAID days). In total, 68.1% of NSAID plus GPA users were highly adherent.[294] The exposure assessment and GPA adherence calculation are schematically depicted in Figure 1. The GPA adherence calculation has been described previously.[322] NSAID episodes during which patients switched between classes of NSAIDs (from nsNSAID to COX-2 inhibitor or vice versa) were excluded. Episodes during which COX-2 inhibitors were used concurrently with a GPA were also excluded. Overall, in 83.4% of COX-2 inhibitor episodes no GPA was used concomitantly.[102] This resulted in a cohort including only nsNSAID plus GPA (≥80 % adherence) and COX-2 inhibitor (alone) users.

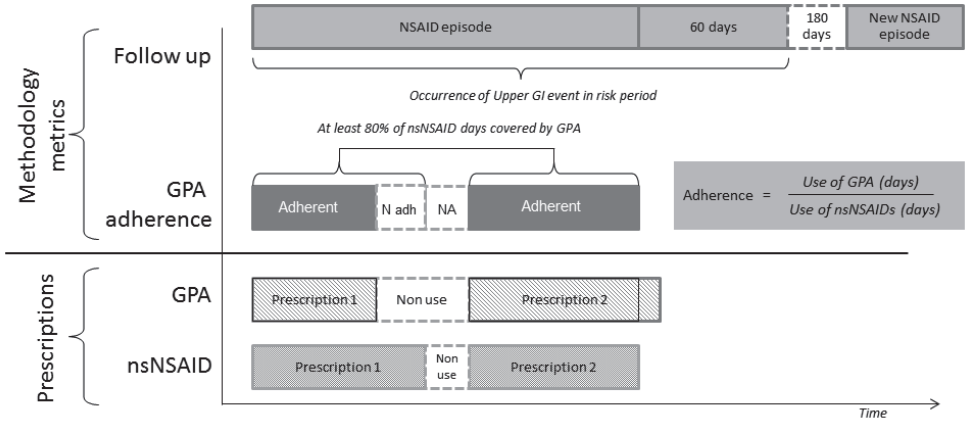


Figure 1. Schematic illustration of NSAID exposure and GPA adherence calculation.

GPA, gastroprotective agents; GI, gastrointestinal; nsNSAID, nonselective non-steroidal anti-inflammatory drugs, N adh, non adherent; NA, not applicable, time period not included in adherence calculation.

Cases and controls selection

Outcomes of interest were a composite of upper GI events (including symptomatic ulceration, upper GI bleeding, perforation or obstruction) and upper GI bleeding alone. Identification of the outcomes has been described in more detail elsewhere. [294] The date of outcome (i.e. index date) was determined as date of start of symptoms leading to the diagnosis of the upper GI event, or if this date was unknown, date of diagnosis. Events occurring within 60 days after the end of an NSAID episode were attributed to the previous NSAID use.[325]

A nested case-control study was conducted. To each case experiencing an upper GI event during or within 60 days after the end of an NSAID episode, we matched all control persons from the cohort of the corresponding database. Controls had not experienced any upper GI event at the index date of the corresponding case and were at the index date alive, using an NSAID within 60 days prior, had equal number of upper GI risk factors (see below) as the case and had similar age (±3 years) and same gender.

Covariates

We considered as risk factors for upper GI events those that are commonly reported in literature: (i) age ≥ 65 years; (ii) a history of upper GI events (bleeding/ulceration); (iii) concurrent use of anticoagulants; (iv) concomitant use of antiplatelets (including aspirin ≤ 325 mg/day); and (v) concomitant use of glucocorticoids (equipotent dose of ≥5 mg prednisone).

Presence of risk factors was determined by electronic searches in all available data prior to or noted at the index date. Additional potential confounding factors were assessed: dyspepsia in the year before the NSAID episode, (history of) smoking, presence of heart failure or diabetes mellitus, and concomitant use of drugs associated with increased risk of bleeding (selective serotonin reuptake inhibitors (SSRI), spironolactone or calcium antagonists) at the index date.

Statistical analyses

Baseline characteristics of cases and controls were described by database and compared using univariate conditional logistic regression analyses.

To estimate the risk for upper GI events and upper GI bleeding among nsNSAID + GPA users(≥80% adherence) in comparison to COX-2 inhibitor users, matched and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated using conditional logistic regression analyses for each database separately and as pooled analysis. The odds ratio can be interpreted as an estimate of the relative risk, as person-time is inherently accounted for in the analysis and the underlying source population is representative of the general population.[326] The pooling of data across databases was performed by two methods: 1) on patient-level (respecting matched cases and controls from the original database); and 2) on study-level by estimating the risk of upper GI events for nsNSAID + GPA(≥80% adherence) use versus COX-2 inhibitor use per database and pooling the three obtained risk estimates using a meta-analytic approach, resulting in an overall risk estimate (inverse variance model) using a random-effects model. The latter method is only appropriate when there is no heterogeneity.

Identification of confounders was performed by entering each potential confounder into the model one by one and were kept in the final model if the risk estimate for the drug exposure changed by more than 10%. As the duration COX-2 inhibitor use might differ from use of nsNSAIDs+GPA (≥80% adherence), we adjusted also for duration of the episodes and density of NSAID use.

Subsequent analyses evaluated the risk of upper GI events and upper GI bleeding stratified by the presence of individual risk factors: age ≥65 years, history of upper GI event, and use of concomitant medications (antiplatelets, anticoagulants and glucocorticoids). For glucocorticoids, we considered an equipotent dose of prednisone 5 to 10 mg/day as low-dosage; > 10 to 20 mg/day as moderate dosage and >20 mg/day as high-dosage. Multiplicative interaction was tested to identify effect modification by all of the individual upper GI risk factors.

All analyses were performed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Ill). Statistical significance was defined as a two-sided p-value<0.05.

RESULTS

Patient characteristics

We identified 384,469 new NSAID users in the United Kingdom (UK), 307 of who experienced an upper GI event (194 with upper GI bleeding). In the Netherlands 17 cases with an upper GI event (14 with upper GI bleeding) were identified from 55,004 new users of NSAIDs and in Italy 74 cases with an upper GI event (17 with upper GI bleeding) were identified from 177,747 new NSAID users. Overall, 57,568 event-free controls were matched to these 398 upper GI event cases. Median number of controls was 120 per case (interquartile range: 43-201).

Baseline characteristics of the cases and matched controls are shown in Table 1. In the UK, the most commonly prescribed nsNSAID was ibuprofen (56%), while celecoxib and rofecoxib were the most commonly prescribed COX-2 inhibitors (48% and 40%, respectively). In NL, the most commonly prescribed COX-2 inhibitor and nsNSAID were rofecoxib (58%) and diclofenac (52%), respectively. Diclofenac and nimesulide accounted for the greater part of nsNSAIDs in Italy (22% and 25%, respectively), whereas celecoxib (51%) and rofecoxib (41%) were the most frequently prescribed COX-2 inhibitors. Proton pump inhibitors comprised the majority of co-prescribed GPAs in nsNSAID users across countries (UK: 99.6%, NL: 97.0%, IT: 95.8%).

In the UK, upper GI event cases reported more often a history of upper GI event (OR: 1.50; 95% CI: 1.04-2.16) and used concomitant anticoagulant therapy (OR: 1.85; 95% CI: 1.06-3.25) and SSRIs more frequently (OR: 1.92; 95% CI: 1.33-2.77). In the Netherlands and Italy, upper GI event cases were significantly more likely to receive concomitant antiplatelet therapy in comparison to controls (OR_{NL}: 6.91; 95% CI: 1.07-44.57, and OR_{IT}: 3.12; 95% CI: 1.36-7.17). Upper GI bleeding cases in UK were more likely to receive concomitant anticoagulants (OR: 2.56; 95% CI: 1.38-4.75), whereas no significant differences in anticoagulant use were observed between upper GI bleeding cases and controls in the Netherlands and Italy. From all upper GI event cases in the UK, the Netherlands and Italy, respectively 11.7%, 11.8% and 32.4% had no documented upper GI risk factor. The majority of cases were identified as having one or two documented upper GI risk factors.

Across all three countries, most NSAID episodes were of short duration (i.e. less than 1 month), ranging from 53% in the UK to 85% in IT. The proportion of patients treated for 1-6 months ranged from 14% in IT to 29% in UK, while 0.9% to 19% of patients in the three countries were treated for more than 6 months. The median duration of COX-2 inhibitor episodes was 30 days (interquartile range: 20-91 days) and median duration of nsNSAID +GPA (≥80% adherence) episodes was 28 days (interquartile range: 14-79 days).

Table 1. Baseline characteristics of cases with symptomatic upper GI events (upper GI bleeding and symptomatic ulcer) and matched controls by database.

	United Kingdom			The Netherlands			Italy		
	Cases N=307 n(%)	Controls N=48,860 n(%)	P-value	Cases N=17 n(%)	Controls N=374 n(%)	P-value	Cases N=74 n(%)	Controls N=8,334 n(%)	P-value
Age in yrs (mean±sd)*	74.0 (10.9)	71.2 (9.5)	NA	75.0 (9.6)	73.9 (9.7)	NA	69.9 (10.4)	68.5 (9.4)	NA
Age category:*			NA			NA			NA
50 – 64	60 (19.5)	12,222 (25.0)		2 (11.8)	63 (16.8)		26 (35,1)	3,385 (40.6)	
65 – 74	101 (32.9)	18,422 (37.7)		6 (35.3)	119 (31.8)		22 (29,7)	2,534 (30.4)	
≥ 75	146 (47.6)	18,216 (37.3)		9 (52.9)	192 (51.3)		26 (35,1)	2,415 (29.0)	
Gender (n(%) male)*	132 (43.0)	13,544 (27.7)	NA	5 (29.4)	71 (19.0)	NA	20 (27.0)	1,668 (20.0)	NA
Upper GI risk factors:									
Age ≥ 65 yrs	247 (80.5)	36,638 (75.0)	0.243	15 (88.2)	311 (83.2)	-	48 (64.9)	4,949 (59.4)	0.670
Prior upper GI event	**57 (18.6)**	**2,634 (5.4)**	**0.028**	1 (5.9)	4 (1.1)	0.694	2 (2.7)	101 (1.2)	0.282
Use of antiplatelets	106 (34.5)	11,647 (23.8)	0.123	**10 (58.8)**	**86 (23.0)**	**0.042**	**12 (16.2)**	**329 (3.9)**	**0.007**
Use of anticoagulants	**14 (4.6)**	**676 (1.4)**	**0.032**	1 (5.9)	14 (3.7)	0.912	0 (0)	36 (0.4)	-
Use of glucocorticoids	18 (5.9)	1,298 (2.7)	0.289	0 (0)	11 (2.9)	-	3 (4.1)	98 (1.2)	0.143
Number of upper GI risk factors:*			NA			NA			NA
0	36 (11.7)	10,578 (21.6)		2 (11.8)	61 (16.3)		24 (32.4)	3,300 (39.6)	
1	131 (42.7)	24,332 (49.8)		4 (23.5)	205 (54.8)		35 (47.3)	4,567 (54.8)	
2	112 (36.5)	13,310 (27.2)		10 (58.8)	103 (27.5)		15 (20.3)	455 (5.5)	
3	25 (8.1)	619 (1.3)		1 (5.9)	5 (1.3)		0 (0)	12 (0.1)	
4	3 (1.0)	21 (0)							
Other comorbidities:									
Dyspepsia	14 (4.6)	1,613 (3.3)	0.222	1 (5.9)	16 (4.3)	0.555	2 (2.7)	296 (3.6)	0.770
Smoking	252 (82.1)	39,153 (80.1)	0.272	4 (23.5)	54 (14.4)	0.599	3 (4.1)	278 (3.3)	0.714
Heart Failure	31 (10.1)	2,101 (4.3)	0.158	0 (0)	34 (9.1)	-	1 (1.4)	138 (1.7)	0.487
Diabetes mellitus	63 (20.5)	6,542 (13.4)	0.062	2 (11.8)	62 (16.6)	0.525	13 (17.6)	878 (10.5)	0.151

Table 1. Baseline characteristics of cases with symptomatic upper GI events (upper GI bleeding and symptomatic ulcer) and matched controls by database (*continued).*

	United Kingdom			The Netherlands			Italy		
	Cases N=307 n(%)	**Controls N=48,860 n(%)**	**P-value**	**Cases N=17 n(%)**	**Controls N=374 n(%)**	**P-value**	**Cases N=74 n(%)**	**Controls N=8,334 n(%)**	**P-value**
Concomitant use of:									
SSRIs	**34 (11.1)**	**3,071 (6.3)**	**<0.001**	0 (0)	14 (3.7)	-	1 (1.4)	29 (0.3)	0.341
Spironolactone	5 (1.6)	391 (0.8)	0.423	0 (0)	6 (1.6)	-	(0)	(0)	-
Calcium channel blockers	68 (22.1)	7,619 (15.6)	0.097	0 (0)	45 (12.0)	-	(0)	(0)	0.646
Duration of episode#:									
< 1 month	151 (49.2)	25,888 (53.0)	0.150	**6 (35.3)**	**254 (67.9)**	**0.046**	66 (89.2)	7,111 (85.3)	0.329
1-6 months	**106 (34.5)**	**13,921 (28.5)**	**0.036**	**8 (47.1)**	**95 (25.4)**	**0.025**	7 (9.5)	1,151 (13.8)	0.440
6-12 months	24 (7.8)	4,095 (8.4)	0.859	1 (5.9)	14 (3.7)	0.306	0 (0)	48 (0.6)	-
> 12 months	26 (8.5)	4,956 (10.1)	0.842	**2 (11.8)**	**11 (2.9)**	**0.025**	1 (1.4)	24 (0.3)	0.098

** Matching variables: age, gender and number of individual upper GI risk factors.*

SSRIs, selective serotonin reuptake inhibitors.

NA, Not applicable; matching criteria.

 # The duration of an NSAID episode was calculated by dividing the prescribed quantity by daily dose regimen (United Kingdom/Netherlands) or the indication-specific defined daily dose (Italy). The end of an NSAID episode was defined as the end of the duration of the last NSAID prescription within that episode or the end of follow-up, whichever was earliest.

Risk of upper GI events and upper GI bleeding

To compare the risk of upper GI events between use of COX-2 inhibitors alone versus highly adherent nsNSAID+GPA use, a nested case-control study was conducted. From the adjusted model, no statistically significant decreased or increased risk was observed for nsNSAID + GPA users (≥80% adherence) as compared to COX-2 inhibitor users (Table 2). This holds true for the three countries separately and as pooled estimates on patient level (Table 2). Regarding upper GI bleeding specifically, similar results were observed. For both outcomes, a trend towards a more protective effect for nsNSAID+GPA (≥80% adherence) as compared to COX-2 inhibitors was observed in the Netherlands and Italy, but the adjusted model did not show a significant benefit (Table 2).

Meta-analysis of studies conducted at individual database-level using a random effects model (no significant heterogeneity between databases was shown, I-squared values of 0%) did not report different results from pooling on patient-level (Supplementary Figure 1). Using this meta-analytic approach, adjusted ORs for upper GI events and upper GI bleeding following nsNSAID+GPA (≥80% adherence) compared to COX-2 inhibitor use were 1.00 (95% CI: 0.73-1.33) and 1.11 (95% CI: 0.76-1.63), respectively.

Subgroup analyses

Stratification according to the predefined individual upper GI risk factors was performed to identify a possible preference for either strategy in specific risk groups (Table 3). Since most cases of upper GI events occurred in subjects aged 75 years and older, we performed additional analyses taking a different cut-off age of 75 years, which did not demonstrate different estimates from the cut-off of 65 years (data not shown). In non-antiplatelet users a non-significant increased risk both for upper GI events and upper GI bleeding was observed for nsNSAID+GPA (≥80% adherence), whereas the opposite was found for antiplatelet users. This interaction term was significant.

When we compared COX-2 inhibitor use with highly adherent nsNSAID+GPA use in glucocorticoid users, the use of nsNSAID+GPA increased the risk for upper GI events considerably (OR: 7.03; 95% CI 1.35-36.45)(P=0.020). When adjusting for the dosage of glucocorticoids, the estimated risk increased even more (OR: 9.01; 95% CI: 1.61-50.50)(P=0.012). Higher dosage of glucocorticoids affected the risk of upper GI events more as a dose-response relationship was observed (data not shown). Regarding multiplicative interaction, the interaction term for use of glucocorticoids was not significant.

The withdrawal of rofecoxib from the market in 2004 influenced in general the prescription pattern of NSAIDs. After 2004 only celecoxib, etoricoxib, valdecoxib and parecoxib were available in Europe. Therefore, stratification according to time period was performed. A decrease in percentage of cases and controls using a COX-2 inhibitor was noticed after rofecoxib was not available on the market anymore. However, this did not impact on the risk of an upper GI event for nsNSAIDs+GPA versus COX-2 inhibitors (Table 3).

Table 2. The risk of symptomatic upper GI events and upper GI bleeding in users of nsNSAID+GPA (≥80% adherence) as compared to COX-2 inhibitor users.

		Symptomatic upper GI events (upper GI bleeding and symptomatic ulcer)						Upper GI bleeding					
		Cases N (%)	Controls N (%)	OR matched (95%CI)	P-value	ORadj† (95%CI)	P-value	Cases N (%)	Controls N (%)	OR matched (95%CI)	P-value	ORadj† (95%CI)	P-value
United Kingdom	COX-2 inhibitor	128 (41.7)	24,722 (50.6)	1.00		1.00		86 (44.3)	14,835 (51.1)	1.00		1.00	
	nsNSAID+GPA#	179 (58.3)	24,138 (49.4)	1.02 (0.77-1.36)	0.883	1.05 (0.77-1.45)	0.742	108 (55.7)	14,222 (48.9)	0.90 (0.63-1.29)	0.568	1.20 (0.80-1.80)	0.375
The Netherlands*	COX-2 inhibitor	13 (76.5)	243 (65.0)	1.00		1.00		10 (71.4)	172 (60.4)	1.00		1.00	
	nsNSAID+GPA#	4 (23.5)	131 (35.0)	0.44 (0.13-1.48)	0.183	0.54 (0.16-1.84)	0.323	4 (28.6)	113 (39.6)	0.53 (0.15-1.88)	0.326	0.63 (0.18-2.24)	0.478
Italy	COX-2 inhibitor	44 (59.5)	6,201 (74.4)	1.00		1.00		6 (35.3)	1,124 (64.6)	1.00		1.00	
	nsNSAID+GPA#	30 (40.5)	2,133 (25.6)	1.22 (0.69-2.17)	0.500	0.79 (0.27-2.35)	0.673	11 (64.7)	616 (35.4)	2.85 (0.92-8.80)	0.069	0.59 (0.05-6.55)	0.669
Pooled on patient level	COX-2 inhibitor	185 (46.5)	31,166 (54.1)	1.00		1.00		102 (45.3)	16,131 (51.9)	1.00		1.00	
	nsNSAID+GPA#	213 (53.5)	26,402 (45.9)	1.01 (0.79-1.30)	0.918	1.02 (0.77-1.37)	0.880	123 (54.7)	14,951 (48.1)	0.96 (0.69-1.33)	0.800	1.14 (0.78-1.65)	0.503

Cases and controls are matched on age, gender and number of individual upper GI risk factors. ** For NL: adjusted model also includes use of antiplatelets. † Adjusted for dose of NSAID, length of NSAID episode and density of NSAID use within episode. Only subjects included with known dosage of NSAID (UK 80.2%; NL 100%; IT 35.3%). # nsNSAID+GPA (≥80% adherence).*

DISCUSSION

In this case-control study we demonstrate that the risk of an upper GI event or upper GI bleeding is not different between users of nonselective (ns)NSAIDs in combination with adherent use of a gastroprotective agent (GPA) and COX-2 inhibitor users.

Lowering the risk of NSAID-related upper GI events can be achieved by concomitant use of GPAs. In particular increasing adherence to GPAs is important in reducing the risk nsNSAID-related upper GI events.[294, 321, 322] As another preventive strategy, COX-2- selective inhibitors were developed to improve the gastrointestinal safety of NSAID therapy, especially in high-risk patients such as elderly (aged ≥65 years) patients, those with a history of upper GI events or concomitantly using anticoagulants, antiplatelets or corticosteroids. After the introduction of COX-2 inhibitors, it was shown that they indeed were associated with less gastrointestinal toxicity as compared to the traditional nonselective NSAIDs alone. [10, 11, 318, 327] Several studies on this topic have been published in recent years.[328] Though the implementation of preventive strategies has increased in recent years, there is still room for considerable improvement with regard to use of preventive strategies during NSAID therapy.[321, 329] In order to investigate which preventive strategy is superior with regard to upper GI safety, head-to-head comparisons between COX-2 inhibitors and NSAIDs combined with GPAs have been performed in randomized studies. These studies showed no preference of one strategy over the other.[76-78, 82, 317]

However, most clinical studies do not allow generalization of their results to daily clinical practice in Western countries, as many studies included selected categories of patients (i.e. high-risk patients with endoscopically documented upper GI bleed/ulcer- or with specific disease, in particular rheumatoid arthritis), and were performed in non-Caucasian persons, and in persons at very high risk of an upper GI event.

Our results are in keeping with another observational study by Targownik *et al.* showing no superiority of nsNSAID combined with PPI use to COX-2 inhibitors in the prevention of NSAID-related upper GI events.[101] Although the efficacy of both preventive strategies overall seems equivalent for the upper gastrointestinal tract in the CONDOR study, the COX-2 inhibitor-treated patients appeared to have a reduced risk of lower GI events as compared to nsNSAID plus PPI use. [82, 330] However, results from other studies evaluating lower GI tract events as an outcome were conflicting. [84, 86, 331, 332] A post hoc analysis of a prospective study showed a lower rate of serious lower GI events for rofecoxib compared to naproxen,[30] whereas this was not confirmed in a cross-sectional capsule enteroscopy study showing comparable small-bowel damage between long-term NSAID and COX-2 inhibitor users.[34] Mechanistically, whether the impact of NSAIDs on lower GI events reflect a reduction in risk by COX-2 inhibitor-use or an increase in risk by PPI-use due to altered intestinal bacteria and increased susceptibility to small intestinal bacterial overgrowth is still under debate.[333]

Table 3. Risk factors for symptomatic upper GI events (upper GI bleeding and symptomatic ulcer) and upper GI bleeding; stratified analyses on data pooled on patient level.

		Symptomatic upper GI events (upper GI bleeding and symptomatic ulcer)				Upper GI bleeding			
Individual upper GI risk factors:		**Cases n (%)**	**OR matched* (95% CI)**	**P-value**	**P-value Interaction terms**	**Cases n (%)**	**OR matched* (95% CI)**	**P-value**	**P-value Interaction terms**
Age < 65 yrs	COX-2 inhibitor	34 (38.6)	1.00			11 (31.4)	1.00		
	nsNSAID+GPA#	54 (61.4)	1.01 (0.79-1.30)	0.918	0.055	24 (68.6)	1.61 (0.67-3.87)	0.291	0.466
Age ≥ 65 yrs	COX-2 inhibitor	151 (48.7)	1.00			91 (47.9)	1.00		
	nsNSAID+GPA#	159 (51.3)	0.88 (0.67-1.17)	0.394		99 (52.1)	0.88 (0.62-1.26)	0.488	
No prior upper GI event	COX-2 inhibitor	171 (50.6)	1.00			93 (50.0)	1.00		
	nsNSAID+GPA#	167 (49.4)	0.98 (0.75-1.28)	0.877	0.152	93 (50.0)	0.86 (0.60-1.23)	0.397	0.417
Prior upper GI event	COX-2 inhibitor	14 (23.3)	1.00			9 (23.1)	1.00		
	nsNSAID+GPA#	46 (76.7)	1.73 (0.81-3.70)	0.159		30 (76.9)	1.90 (0.74-4.86)	0.182	
No use of antiplatelets	COX-2 inhibitor	120 (44.4)	1.00			59 (41.0)	1.00		
	nsNSAID+GPA#	150 (55.6)	1.23 (0.91-1.66)	0.181	**<0.001**	85 (59.0)	1.24 (0.83-1.87)	0.298	**0.008**
Use of antiplatelets	COX-2 inhibitor	65 (50.8)	1.00			43 (53.1)	1.00		
	nsNSAID+GPA#	63 (49.2)	0.69 (0.44-1.08)	0.108		38 (46.9)	0.62 (0.34-1.06)	0.079	
No use of anticoagulants	COX-2 inhibitor	182 (47.5)	1.00			99 (46.7)	1.00		
	nsNSAID+GPA#	201 (52.5)	0.99 (0.76-1.27)	0.904		113 (53.3)	0.91 (0.65-1.28)	0.603	
Use of anticoagulants	COX-2 inhibitor	3 (20.0)	-			3 (23.1)	-		
	nsNSAID+GPA#	12 (80.0)				10 (76.9)			
No use of glucocorticoids	COX-2 inhibitor	180 (47.7)	1.00			99 (46.5)	1.00		
	nsNSAID+GPA#	197 (52.3)	0.96 (0.74-1.24)	0.740	0.280	114 (53.5)	0.91 (0.65-1.27)	0.571	0.724
Use of glucocorticoids	COX-2 inhibitor	5 (23.8)	1.00			3 (25.0)	1.00		
	nsNSAID+GPA#	16 (76.2)	**7.03 (1.35-36.45)**	**0.020**		9 (75.0)	4.15 (0.72-24.01)	0.112	
Use of glucocorticoids##	nsNSAID+GPA#	16 (76.2)	**9.01 (1.61-50.50)**	**0.012**		9 (75.0)	4.81 (0.79-29.20)	0.088	
Before rofecoxib withdrawal†	COX-2 inhibitor	162 (62.5)	1.00			91 (64.1)	1.00		
	nsNSAID+GPA#	97 (37.5)	1.05 (0.79-1.40)	0.729	0.702	51 (35.9)	0.92 (0.62-1.34)	0.649	0.781
After rofecoxib withdrawal‡	COX-2 inhibitor	23 (16.5)	1.00			11 (13.3)	1.00		
	nsNSAID+GPA#	116 (83.5)	0.91 (0.57-1.47)	0.702		72 (86.7)	1.10 (0.56-2.15)	0.781	

** Matched on age, gender, database and number of individual upper GI risk factors. # nsNSAID+GPA (≥80% adherence). ## Adjusted for equipotent dosage of prednisone (low dosage: 5 to 10 mg/day; moderate dosage: 10 to 20 mg/day; high-dosage: >20 mg/day). †Rofecoxib withdrawal in September 2004, analysis until 2005. ‡ Analysis from 2005 and subsequent years.*

Another area of potential benefit of COX-2 inhibitors over nsNSAID plus GPA use might be in selected high-risk groups. In this study, we found that in glucocorticoid users, adherent use of an nsNSAID plus GPA was associated with a nine times higher upper GI event risk compared to COX-2 inhibitors. This finding is supported by the dose-response relationship we observed where a higher dosage of glucocorticoids affected the risk of upper GI events more than a lower dosage. The interaction term was not significant, but this is due to limited power since the estimates differed largely. To our knowledge, no previous study studied the comparison of COX-2 inhibitor and nsNSAID plus GPA use in glucocorticoid users separately. Although data on glucocorticoids as an independent risk factor for upper GI events are scarce, prior studies have shown a two-fold increased risk of upper GI bleeding during glucocorticoid use alone. [118, 211, 311, 334] When glucocorticoids are used in combination with NSAIDs, the risk of upper GI bleeding is estimated higher as compared to NSAID use alone or glucocorticoid use alone.[118, 211, 311, 334] Up to now, the reason for the interaction between both drugs has not been elucidated. One might speculate that glucocorticoids and NSAIDs act synergistically; experimental studies have shown that glucocorticoids inhibit the healing of gastric mucosal damage [335, 336] as well as NSAIDs do, although the mechanism of inhibition differs. Alternatively, gastric bacterial overgrowth due to acid-suppression such as what occurs by PPI use [337, 338] might aggravate gastric mucosal damage by increased exposure time of gastric flora to the mucosal surface or by delayed gastric emptying caused by PPIs. [339] The combination of nsNSAIDs and PPIs therefore may have led to the observed increased risk in concurrent glucocorticoid users. As use of steroids is a risk factor that according to guidelines often will initiate GPA in NSAID-treated patients, this aspect is important to investigate in future studies.

Although not significant, we found a tendency towards an increased upper GI event risk in patients with a history of an upper GI event among nsNSAID plus adherent GPA users as compared to COX-2 inhibitor users. In this particular high-risk patient group, one might consider the addition of a GPA to a COX-2 inhibitor. This combination has been shown to reduce the risk of NSAID-related upper GI events to a higher degree than COX-2 inhibitors alone or nsNSAIDs plus PPIs. [101]

In line with previous studies, concomitant use of low-dose aspirin seems to eliminate the upper GI risk benefit of COX-2 inhibitors. [10, 73, 327, 340] Though not significant, we observed an increased upper GI risk among nsNSAID plus adherent GPA compared to COX-2 inhibitor users who did not concomitantly use aspirin, whereas the opposite was true for concomitant aspirin users. The interaction term was significant, pointing to an increase in risk of upper GI events for COX-2 inhibitors when aspirin is used concurrently. In patients concomitantly using antiplatelets (including low-dose aspirin), GPAs should be recommended not only to nsNSAIDs users, but perhaps also to COX-2 inhibitor users.[99, 101, 102]

The strength of the current study is the scale and setting: primary health care data from three European countries were combined reflecting real-life prescription patterns. Due to the setting it was possible to study both low-risk as well as high-risk patients. Previous evidence from clinical trials focused generally on high risk patients only. [76-78]

The following limitations should be acknowledged. By performing observational studies, certain biases can be introduced of which confounding by indication is the most important one to discuss. The general practitioner's awareness of the upper GI risk profile of the patient might have influenced the prescription of preventive strategy and thereby possibly introducing confounding by indication. After the introduction of COX-2 inhibitors, high-risk patients were more likely to receive a COX-2 inhibitor instead of co-prescription of a GPA to NSAIDs. [341] Nevertheless, the preference for preventive strategies changed after warnings for an increased cardiovascular risk related to COX-2 inhibitors were released by regulatory agencies.[342] Although the risk of upper GI complications with rofecoxib used to be higher than with celecoxib,[343] in a stratified analysis the estimate of nsNSAIDs plus GPAs compared to COX-2 inhibitors without rofecoxib after 2004 (i.e. celecoxib, etoricoxib, valdecoxib and lumiracoxib only) did not differ from the estimate including rofecoxib (before withdrawal). It is therefore unlikely that data on the use of rofecoxib prior to its withdrawal would have skewed the GI safety data in favor of the nsNSAID. We feel that it is therefore unlikely that the channeling away from COX-2 inhibitors for patients with cardiovascular disease would have led to important confounding.

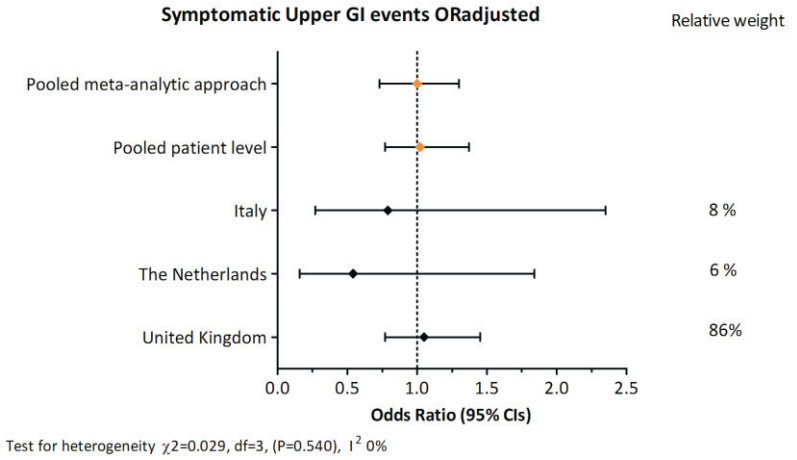
We tried to address confounding-by-indication by matching on the number of upper GI risk factors and by restricting the comparator group to nsNSAID users who were highly adherent to GPA (defined as at least 80% of nsNSAID days covered by a GPA prescription). Although crude incidence rates appeared to be equal between different levels of GPA adherence,[294] from previous studies, we know that patients adherent to the prescribed GPA are at the highest risk of nsNSAID-related upper GI events.[294, 322] Residual confounding due to exclusion of users with a lower GPA adherence level is therefore unlikely. In addition, we selected patient groups with a similar upper GI risk profile, by matching on number of upper GI risk factors, as well as gender and age. Comparison between COX-2 inhibitor and nsNSAID plus highly adherent GPA users showed no differences in number of upper GI risk factors. Confounding was also dealt with by adjusting for several co-morbid conditions. The indication of glucocorticoid use could only be identified in the Netherlands, of which 64% was for rheumatoid disorders. Nevertheless, residual confounding cannot be ruled out in observational studies.

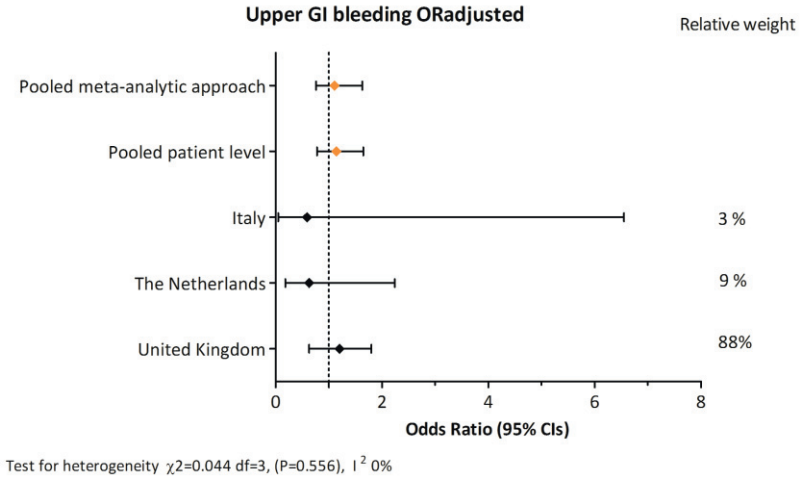
In addition, over-the-counter use of nsNSAIDs and GPA is not recorded in the databases and could have led to a potential underestimation of its use. We used drug prescription data rather than precise information on the actual use. Furthermore, the method of GPA adherence calculation used in the present study determined adherence based on days of GPA and of nsNSAID use, rather than daily coverage. However, we selected a group of highly adherent nsNSAID plus GPA users based on a cut off of 80% of GPA adherence.

In conclusion, there is no difference in the risk of upper GI events between the use of COX-2 inhibitors and use of nsNSAIDs plus adherent GPA in daily clinical practice. Neither strategy was superior in the prevention of a first or a recurrent upper GI event or upper GI bleeding. A significant increase in the risk of upper GI events for COX-2 inhibitors was observed when aspirin is used concurrently, whereas during concomitant glucocorticoid use nsNSAID

plus GPA users are at increased risk of an upper GI event compared to COX-2 inhibitor users. Future studies on this topic are needed, as use of steroids is a risk factor that, according to guidelines, often will initiate GPA therapy in NSAID-treated patients.

SUPPLEMENTARY MATERIAL





Supplementary Figure 1. Forest plots of the adjusted analysis for Upper GI events and Upper GI bleeding.

CHAPTER 4.3

Risk of Upper Gastrointestinal Bleeding from Different Drug Combinations

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Video abstract available at: https://www.youtube.com/watch?v=fxoVu-l_HDE

ABSTRACT

BACKGROUND

Concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) and low-dose aspirin increases the risk of upper gastrointestinal (GI) bleeding. Guidelines suggest avoiding certain drug combinations, yet little is known about the magnitude of their interactions.

AIM

We estimated the risk of upper GI bleeding during concomitant use of nonselective (ns)NSAIDs, cyclooxygenase -2 selective inhibitors (COX-2 inhibitors), and low-dose aspirin with other drugs.

METHODS

We performed a case series analysis of data from 114,835 patients with upper GI bleeding (930,888 person-years of follow-up) identified from 7 population-based health care databases (approximately 20 million subjects). Each patient served as his or her own control. Drug exposure was determined based on prescriptions of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin, alone and in combination with other drugs that affect the risk of upper GI bleeding. We measured relative risk (incidence rate ratio [IRR] during drug exposure vs nonexposure) and excess risk due to concomitant drug exposure (relative excess risk due to interaction [RERI]).

RESULTS

Monotherapy with nsNSAIDs increased the risk of diagnosis of upper GI bleeding (IRR, 4.3) to a greater extent than monotherapy with COX-2 inhibitors (IRR, 2.9) or low-dose aspirin (IRR, 3.1). Combination therapy generally increased the risk of upper GI bleeding; concomitant nsNSAID and corticosteroid therapies increased the IRR to the greatest extent (12.8) and also produced the greatest excess risk (RERI, 5.5). Concomitant use of nsNSAIDs and aldosterone antagonists produced an IRR for upper GI bleeding of 11.0 (RERI, 4.5). Excess risk from concomitant use of nsNSAIDs with selective serotonin reuptake inhibitors (SSRIs) was 1.6, whereas that from use of COX-2 inhibitors with SSRIs was 1.9 and that for use of low-dose aspirin with SSRIs was 0.5. Excess risk of concomitant use of nsNSAIDs with anticoagulants was 2.4, of COX-2 inhibitors with anticoagulants was 0.1, and of low-dose aspirin with anticoagulants was 1.9.

CONCLUSION

Based on a case series analysis, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs significantly increases the risk of upper GI bleeding. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk for upper GI bleeding.

INTRODUCTION

Upper gastrointestinal (GI) bleeding has a major impact on patients' quality of life and public health care costs.[344] Although great improvements in prevention and treatment of upper GI bleeding have been achieved in recent decades, upper GI bleeding-related morbidity and mortality remain substantial.[70] Most previous studies have focused on risks associated with use of non-steroidal anti-inflammatory drugs (NSAIDs), which is one of the most common causes of upper GI bleeding. Clinical guidelines therefore recommend preventive strategies for at-risk patients treated with NSAIDs, including coprescription of proton pump inhibitors. Another preventive strategy is use of cyclo-oxygenase-2 selective inhibitors (COX-2 inhibitors), developed as a safer alternative to nonselective (ns)NSAIDs, especially among high-risk patients.[11]

Use of low-dose aspirin is considered the standard of care for cardiovascular prevention. However, low-dose aspirin is also known to increase the risk of upper GI bleeding.[73] The relative risk of upper GI bleeding associated with current use of low-dose aspirin compared with no use ranges from 1.6 to 4.0.[73, 334, 345] Thus, coprescription of gastroprotective agents (GPAs) is also recommended for at-risk patients treated with low-dose aspirin as a key strategy to minimize upper gastrointestinal events.[112] Adherence to preventive strategies in patients treated with low-dose aspirin is especially important given that an estimated 20% of these patients will also use NSAIDs and approximately 35% of the elderly population regularly uses low-dose aspirin.[112]

Clinical guidelines suggest avoiding use of certain drugs in combination with nsNSAIDs as well as COX-2 inhibitors; these drugs include corticosteroids, anticoagulants, selective serotonin reuptake inhibitors (SSRIs), and antiplatelets.[99] However, the concurrent use of NSAIDs with these other drugs has not been widely studied, and it remains unknown if, and to what extent, combinations of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with specific other drug groups exert synergistic effects on the risk of upper GI bleeding.

Understanding drug synergism is important in developing strategies to minimize the risk of upper GI bleeding, particularly in elderly patients who are at high risk for upper GI bleeding and are likely to use multiple drugs.[120, 122] Therefore, we aimed to estimate the magnitude of interaction between nsNSAIDs, COX-2 inhibitors, or low-dose aspirin and specific drug groups reported to affect the risk of diagnosed upper GI bleeding.

METHODS

Data sources

Data were obtained from a network of 7 electronic health record (EHR) databases from 3 countries. The EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge) has successfully established a

platform that integrates data from various repositories of European EHRs for evaluation of drug safety.[346]

We analyzed data from 3 primary care databases (Integrated Primary Care Information [IPCI, The Netherlands]; Health Search/CSD Longitudinal Patient Database [HSD, Italy]; and Pedianet [Italy]) and 4 administrative/claims databases (Aarhus University Hospital Database [Aarhus, Denmark], PHARMO Institute [PHARMO, The Netherlands], and the regional databases of Lombardy [UNIMIB, Italy] and Tuscany [ARS, Italy]). The characteristics and study periods of the databases are shown in Table 1. All of these databases have been extensively used in epidemiological studies.[346-349]

Subjects can enter and may also leave the database at any time for several reasons (eg, death, moving out of the region, leave of practice). The primary care databases capture all prescriptions from general practitioners and some from secondary care (eg, repeat prescriptions). The study protocol was approved by the review board for all databases.

Study Design

The study population included all people registered in the database network with at least 1 year of valid and continuous data. A self-controlled case series (SCCS) analysis was performed on all identified cases of upper GI bleeding. The SCCS is a case-only study (ie, control subjects are not included) in which the relative incidence of upper GI bleeding is estimated for exposed and nonexposed time in each case. [350, 351] Each case serves as its own control. The SCCS method assumes that all cases in the analysis should (1) have exposed and unexposed person-time, (2) experience an upper GI bleeding, and (3) contribute follow-up time before and after the upper GI bleeding. The primary advantage of the SCCS is that it automatically adjusts for confounding factors that are fixed within subjects (ie, genetic factors, sex, chronic disease, or other comorbidity).

Case definition

From the study population, we identified all subjects who experienced an upper GI bleeding during follow-up by using pertinent disease codes from the different coding systems in each database.[346] Upper GI bleeding was assessed using hospital discharge codes (in claims databases) or general practitioner diagnosis/recordings (in primary care databases). We included all codes indicating gastroduodenal ulcers and hemorrhages, melena and hematemesis. Codes for variceal bleeding specifically were not included. We only included codes corresponding to an acute upper GI bleeding, because for the SCCS the outcome should be an acute event with a clear disease onset. Supplementary Table 1 shows the corresponding codes for each coding system. A free-text search of clinical narratives was performed in IPCI and HSD.

Table 1. Database Characteristics and Number of Cases of Upper GI bleeding per database.

Database (Country)	Nr of Upper GI Bleeding cases	Total person time of follow-up (person-years)	Type of database	Disease coding system	Drug coding system	Study Period	Relative contribution of Upper GI Bleeding cases to dataset pooled on patient-level (%)	PPV of codes used to identify Upper GI Bleeding in database*
Aarhus (Denmark)	11,923	75,963	Administrative /claims	ICD-10	ATC	1999-2008	10.4	77% (95% CI: 69-83)
ARS (Italy)	11,519	49,417	Administrative /claims	ICD-9-CM	ATC	2002-2008	10.0	72% (95% CI: 65-78)
UNIMIB (Italy)	69,384	680,254	Administrative /claims	ICD-9-CM	ATC	2003-2006	60.4	72% (95% CI: 65-78) †
HSD (Italy)	5,963	37,038	Primary care	ICD-9-CM + free text	ATC	2003-2009	5.2	78% (95% CI: 72-83)
Pedianet (Italy)	88	375	Primary care	ICD-9-CM	ATC	2003-2007	0.08	
IPCI (Netherlands)	9,951	37,294	Primary care	ICPC + free text	ATC	1996-2011	8.7	21% (95% CI: 18-26)
PHARMO (Netherlands)	6,007	50,547	Hybrid (Administrative with linkage to primary care)	ICD-9-CM	ATC	1998-2007	5.2	

** Positive Predictive Values were calculated in a validation study[352] demonstrating the PPV values did not affect the magnitude of risk estimates from drug-associated upper GI Bleeding. †UNIMIB database is similar in setting and clinical characteristics of ARS and PPV of ARS may be extrapolated to UNIMIB.*

A validation study was conducted in 4 of the databases used in the current study[352] and showed a high concordance for International Classification of Diseases (ICD)-9 (positive predictive value [PPV] of 78% and 72%) and ICD-10 codes (PPV of 77%) that was not seen with the International Classification for Primary Care coding system (PPV of 21% for codes and free text only).

Exposure definition

We focused on concomitant use of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin with other drugs reported to be associated with an increase or decrease in risk of upper GI bleeding. The drug groups of interest were as follows: (1) nsNSAIDs,[73] (2) COX-2 inhibitors,[353] (3) low-dose aspirin,[73, 349] (4) high-dose aspirin,[354] (5) corticosteroids,[72, 118, 211, 311, 334, 355] (6) SSRIs,[356] (citalopram, fluoxetine and paroxetine were assessed individually) (7) GPAs,[356, 357] (8) aldosterone antagonists,[348, 358] (9) calcium channel blockers,[359, 360] (10) anticoagulants,[73, 119] (11) antiplatelets,[73, 119] and (12) nitrates.[73, 357] Drugs of interest were categorized according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system.[242] Supplementary Table 2 shows the corresponding ATC codes. We created mutually exclusive exposure categories: no use of any drug of interest (reference group), use of only one drug of interest, or concurrent use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with one other drug of interest (Supplementary Figure 1). All other combinations of drugs of interest and combinations of >2 drugs were combined in a separate category. Fixed drug combinations were included in the corresponding drug combination group. Duration of exposure was calculated by dividing the total number of prescribed/dispensed pills by the number of pills per day or defined daily dosages. We assumed that all dispensed drugs were consumed. All exposed and unexposed person-time was therefore included in the analysis. Drug dose and frequency were not taken into account because such information is not consistently recorded in all databases.

Main statistical analyses

To estimate the relative incidence of upper GI bleeding, incidence rate ratios (IRRs) with 95% confidence intervals (CIs) were obtained using conditional Poisson regression by comparing the incidence rate of upper GI bleeding during periods of drug exposure with the incidence rate during all other observed time periods. Age-adjusted IRRs were calculated within each database and by pooling all data together (IRRp). To account for heterogeneity between the databases, pooling of data was also performed by a random effects meta-analytic model on the database-specific risk estimates resulting in an overall IRR. To estimate the magnitude of drug interaction (excess risk), the following measures were calculated: the relative excess risk due to interaction (RERI), the proportion attributable to interaction (AP), and the synergy index (S).[361]

Interaction on an additive scale meant that the observed effect of the drug combination was larger than the sum of the effects of the drugs separately but less than multiplicative. If the IRR of the combination was more than the sum of the 2 drugs separately, interaction (at least on an additive scale) was present. Corresponding 95% CIs were also calculated for the RERI using the Hosmer–Lemeshow delta method.[362] The estimated measure of the RERI, AP, or S itself does not provide any information on risk and cannot be interpreted in isolation. However, based on the relative risk, it can be concluded that an excess risk is present when the RERI is larger than 0 and the CIs around it do not cross 0. Additionally, it may be concluded that there is more excess risk with a RERI of 1 than with a RERI of 2 (see Supplementary Table 3 for more details).

Population attributable risk (PAR) was calculated to estimate the proportion of upper GI bleeding in the general population that is attributable to concomitant use of drugs using the following formula: PAR= (p* [IRR-1])]/(p*[IRR-1]+1).[347] For this calculation drug utilization data from the participating databases (data not shown) were used to derive the prevalence of exposure (p) to which the IRR pertained.

Sensitivity analyses

Because increasing age confers additional risk of upper GI bleeding, analyses by stratifying on age (with a cut off of 60 and 70 years) and sex were conducted to investigate effect modification by age or sex. To explore the possibility of confounding by contraindication we performed a sensitivity analysis by truncating the drug exposure at time of event. A pooled analysis excluding the IPCI database was performed due to the low PPV in IPCI.

RESULTS

Risk of Upper GI bleeding with Drug Monotherapy

In total 114,835 patients with upper GI bleeding (cases) with corresponding follow-up of 930,888 person-years were included in the analysis (Table 1). For all drugs of interest, monotherapy showed a significant increased relative risk compared with no use of any of the drugs of interest. Monotherapy with nsNSAIDs was associated with an IRRp of 4.3 (95%CI, 4.1-4.4), which is higher than monotherapy with either COX-2 inhibitors (IRRp, 2.9; 95%CI, 2.7-3.2) or low-dose aspirin (IRRp, 3.1; 95%CI, 2.9-3.2) (Table 2). The risk of diagnosed upper GI bleeding for all other drugs ranged between 1.6 for calcium channel blockers to 4.1 for corticosteroids (Table 2). IRRs were also estimated for 3 individual SSRIs and yielded an IRRp of 2.0 (95%CI, 1.6-2.5) for fluoxetine, 2.3 (95% CI, 2.1-2.5) for citalopram and 1.9 (95%CI 1.7-2.2) for paroxetine, all similar to the IRRp for the overall SSRI class 2.1 (95% CI, 1.9-2.2).

Table 2. Relative Risk of Diagnosed Upper GI Bleeding During Exposure to Specific Drug Groups (With Corresponding 95% CIs) in Monotherapy and in Combination With Other Drugs.

Drug groups	Monotherapy		Combinations with:					
			nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
	N†	IRR (95%CI)	N†	IRR (95%CI)	N†	IRR (95%CI)	N†	IRR (95%CI)
No drug*	69,664	1.00 (reference)		NA		NA		NA
nsNSAIDs	3,327	4.27 (4.11-4.44)		NA		NA	416	6.77 (6.09-7.53)
COX-2 inhibitors	635	2.90 (2.67-3.15)		NA		NA	131	7.49 (6.22-9.02)
Low-dose aspirin	4,733	3.05 (2.94-3.17)	416	6.77 (6.09-7.53)	131	7.49 (6.22-9.02)		NA
Corticosteroids	1,378	4.07 (3.83-4.32)	244	12.82 (11.17-14.72)	40	5.95 (4.25-8.33)	190	8.37 (7.14-9.81)
SSRIs	1,793	2.06 (1.94-2.18)	210	6.95 (5.97-8.08)	65	5.82 (4.45-7.62)	401	4.60 (4.09-5.17)
Gastroprotective agents	5,279	1.61 (1.56-1.66)	678	3.90 (3.59-4.24)	95	2.37 (1.92-2.93)	607	2.54 (2.32-2.78)
Aldosterone antagonists	1,211	3.27 (3.06-3.50)	76	11.00 (8.63-14.03)	10	4.02 (2.07-7.81)	131	5.01 (4.13-6.08)
Calcium channel blockers	3,546	1.57 (1.51-1.63)	363	4.45 (3.98-4.98)	77	3.11 (2.46-3.93)	1,123	3.07 (2.86-3.29)
Anticoagulants	1,760	3.01 (2.85-3.19)	143	8.69 (7.30-10.35)	21	5.01 (3.21-7.82)	168	6.94 (5.86-8.22)
Antiplatelets (excluding low-dose aspirin)	994	1.74 (1.61-1.87)	87	6.50 (5.19-8.15)	9	1.73 (0.87-3.44)	246	5.49 (4.71-6.41)
Nitrates	2,572	2.55 (2.43-2.68)	172	5.82 (4.97-6.82)	49	5.09 (3.79-6.82)	859	3.79 (3.51-4.10)

** Refers to no use of the predefined drugs of interest.*

† Number of upper GI bleeding events during exposure to specific drug group (total number do not sum up to 114,835 due to upper GI bleeding diagnoses in 'other drug category').

Abbreviations: Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Oral corticosteroids (corticosteroids); Selective serotonin reuptake inhibitors (SSRIs); Not applicable (NA).

Supplementary Table 4 shows the total duration of exposure to each drug and drug combination and Supplementary Table 5 shows the distribution of events across age groups and sex.

Risk of Upper GI bleeding with Drug Combinations

Generally, concomitant nsNSAID use with other drugs showed a higher risk for diagnosed upper GI bleeding compared with a combination with low-dose aspirin or COX-2 inhibitors (Table 2). To estimate the risk of diagnosed upper GI bleeding for drug combinations with nsNSAIDs, COX-2 inhibitors or low-dose aspirin, estimates of the separate drugs of interest were pooled. Combinations of any of the drugs of interest with nsNSAIDs yielded the highest IRR (6.9; 95%CI, 5.3-9.1), followed by combinations with low-dose aspirin (4.6; 95%CI, 3.6-6.0) and with COX-2 inhibitors (4.2; 95%CI, 3.0-5.9).

Looking at separate drug classes, the highest risk of diagnosed upper GI bleeding was observed for the combination of nsNSAIDs and corticosteroids (IRRp, 12.8; 95%CI, 11.2-14.7), which was higher than the risk with use of low-dose aspirin and corticosteroids (IRRp, 8.4; 95%CI, 7.1-9.8) or COX-2 inhibitors and corticosteroids (IRRp, 6.0; 95%CI, 4.3-8.3). Use of aldosterone antagonists with nsNSAIDs resulted in an IRRp of 11.0 (95%CI, 8.6-14.0), which was also higher than the combined use of aldosterone antagonists and low-dose aspirin (IRRp, 5.0; 95%CI, 4.1-6.1) or that with COX-2 inhibitors (IRRp, 4.0; 95%CI, 2.1-7.8).

The combination of anticoagulants with nsNSAIDs showed an IRRp of 8.7 (95%CI, 7.3-10.4), which was higher than the combination of anticoagulants with low-dose aspirin (IRRp, 6.9; 95%CI, 5.9-8.2) or that with COX-2 inhibitors (IRRp, 5.0; 95%CI, 3.2-7.8). Combinations with SSRIs were associated with a 5-, 6- and 7-fold increased risk for low-dose aspirin, COX-2 inhibitors and nsNSAIDs, respectively. When using a meta-analytic approach by applying a random-effects model, substantial heterogeneity across databases was observed for some drug combinations but generally resulted in minor attenuations of the effects (Supplementary Table 6).

Excess Risk

Excess risk due to concomitant drug use, measured by additive interaction of nsNSAIDs/COX-2 inhibitors/low-dose aspirin use with other drugs, is shown in Figure 1 and Supplementary Table 3. The highest excess risk was observed for the combination of nsNSAIDs and corticosteroids (RERI, 5.5; 95%CI, 3.7-7.3). Corticosteroids had significant interaction with low-dose aspirin as well, but not with COX-2 inhibitors. Aldosterone antagonists showed significant interaction with nsNSAIDs (RERI, 4.5; 95%CI, 1.8-7.1) but not with low-dose aspirin or COX-2 inhibitors. Anticoagulants showed significant interaction with nsNSAIDs and with low-dose aspirin but not with COX-2 inhibitors. Combinations of nsNSAIDs, COX-2 inhibitors or low-dose aspirin with GPAs or nitrates did not show excess NSAID-associated upper GI bleeding risk.

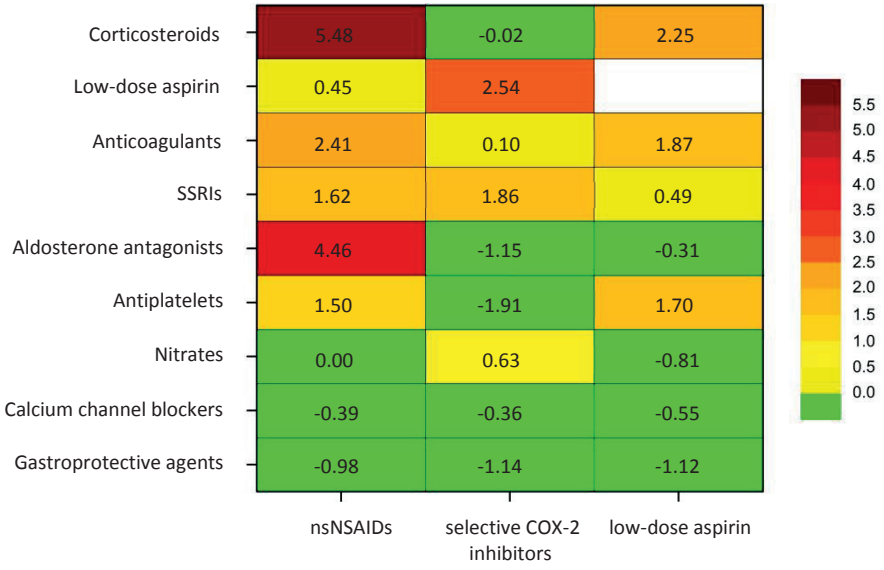


Figure 1. Heat map of interaction of nonselective NSAIDs, COX-2 inhibitors and low-dose aspirin in combination with other drugs.

Color intensity of the heat map is based on the Relative Excess Risk due to Interaction (RERI). Green represents no interaction, from yellow towards red represents presence and increasing strength of interaction. Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Not applicable (NA).

Population Attributable Risk

Based on an estimated 0.04% prevalence of nsNSAID use, the proportion of cases of upper GI bleeding in the general population attributable to nsNSAID monotherapy was 11.8 %. In other words, out of 100 people experiencing upper GI bleeding while exposed to nsNSAID monotherapy, 11.8% of these cases were attributable to nsNSAID monotherapy. The corresponding proportion attributable to corticosteroid monotherapy was 10.4% (estimated prevalence of corticosteroid use 0.04%), while the PAR for concurrent NSAID and corticosteroid use was 6.4%. The PAR for other drugs is shown in Supplementary Table 7.

Sensitivity analyses

Age stratification showed that subjects who were 60 years of age or older had higher IRRs of diagnosed upper GI bleeding than younger subjects (younger than 60 years) except for the combination of nsNSAIDs and anticoagulants and of COX-2 inhibitors with corticosteroids. No significant difference in risk between males and females subjects was observed.

Sensitivity analyses with truncation of follow-up at the time of upper GI bleeding (to avoid confounding by contraindication) showed that the exposure pattern of the drugs (and in particular the nsNSAIDs) did not change after upper GI bleeding (Supplementary Figure 2).

When adjusting for acute myocardial infarction and anaphylactic shock, the results were similar (Supplementary Figure 3). When excluding IPCI from the main analysis, the results were also similar (Supplementary Figure 4).

DISCUSSION

We determined the magnitude of increased risk of diagnosed upper GI bleeding when nsNSAIDs, COX-2 inhibitors, and low-dose aspirin were combined with specific drug classes that may be independently associated with diagnosed upper GI bleeding. Although it may seem reasonable to assume synergistic effects with concurrent use of drugs that independently increase risk, these effects have rarely been investigated. To study the risk of diagnosed upper GI bleeding during use of specific drug combinations, it is essential to have a large number of data and an efficient study design. For this study, we used data from a huge network of European electronic health care databases, representing more than 20 million subjects. In addition, the SCCS is a suitable and efficient method to address the question of excess risk of upper GI bleeding with drug combinations while at the same time controlling for time-fixed confounding factors as well as confounding by indication. We observed that, overall, the risk of upper GI bleeding during concomitant use of drugs was significantly higher compared with what would have been expected based on the sum of the risk of the individual drugs. The magnitude of statistical additive interaction, which may be seen as a surrogate measure for biological synergism, was highest for the combination of nsNSAIDs with corticosteroids and the combination of nsNSAIDs with aldosterone antagonists. In line with previous studies, we observed that the risk of nsNSAID monotherapy was higher than that of monotherapy with low-dose aspirin or COX-2 inhibitors.[72, 73] The risk of upper GI bleeding was always higher for drug combinations with nsNSAIDs than that for low-dose aspirin or COX-2 inhibitors.

Given that nsNSAIDs, COX-2 inhibitors, and low-dose aspirin are commonly consumed by elderly, with a self-reported prevalence of 35%,[112] the observed risks in the current study emphasize the substantial risk of use of nsNSAIDs, COX-2 inhibitors, and low-dose aspirin in the general population. This is especially true considering that elderly are inherently at higher risk due to physiological ageing mechanisms.[121, 122]

Corticosteroids

Interestingly, we observed that the risk of diagnosed upper GI bleeding with use of corticosteroid monotherapy was of the same magnitude as that with nsNSAID monotherapy. Previous studies have shown inconsistent results with respect to risk of upper GI bleeding with corticosteroids.[118, 211, 355] Because nsNSAIDs are known to pose greater risk for inducing upper gastrointestinal ulcers compared with COX-2 inhibitors, interaction between corticosteroids and nsNSAIDs, but not with COX-2 inhibitors, was expected.[117] The suggested pathophysiological mechanism behind this increased risk for corticosteroids is inhibition of

ulcer healing.[120] Previous studies estimated the magnitude of this risk to range from 9-fold to 12-fold,[72, 117, 118, 311, 355] although drug interaction between corticosteroids and nsNSAIDs was not consistently observed.[355] Aside from the small numbers of concomitant users of nsNSAIDs and corticosteroids in previous studies,[72, 118, 211, 311] there were also differences in outcome definitions and reference categories used (varying from no drug use in the past 7 days[355] to 180 days[72]). According to guidelines, corticosteroids should be considered an independent risk factor for upper GI bleeding and gastroprotective measures should be prescribed to patients treated with corticosteroids.[99] To translate the observed risks to the general population, we estimated the population attributable risk (PAR) due to drug use. The PAR was 6.4% for concurrent use of nsNSAIDs and corticosteroids, 11.8% for nsNSAID monotherapy, and 10.4% for corticosteroid monotherapy. This implies that the proportion of upper GI bleeding in the general population attributable to the previously mentioned therapies was high, given the assumption that the association between drug use and occurrence of upper GI bleeding is causal. Although this can be reduced by correct use of gastroprotection, future studies should investigate the risk of a combination of corticosteroids and nsNSAIDs with gastroprotective agents compared with a combination of corticosteroids and COX-2 inhibitors.

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) showed statistically significant interaction with nsNSAIDs and COX-2 inhibitors but not with low-dose aspirin. From a biological point of view, this interaction seems plausible because SSRIs decrease the serotonin level, resulting in impaired thrombocyte aggregation and an increased risk of bleeding in general, including upper GI bleeding. Based on this mechanism, NSAIDs, and low-dose aspirin to lesser extent,[363, 364] are suspected to produce synergism with SSRIs. Although previous studies report an increased risk between 2.6-fold and 16-fold for upper GI bleeding with use of SSRIs and NSAIDs when compared with drug monotherapy,[363-365] others could not show interaction.[356, 365] However, these were not performed primarily on NSAID users,[364] did not control for important confounders[363, 364] and did not create mutually exclusive drug exposure groups.[363]

Aldosterone antagonists

The risk of aldosterone antagonists concurrently used with nsNSAIDs was higher than when used with low-dose aspirin or COX-2 inhibitors. Earlier, case reports indicated a possible association between aldosterone antagonists and upper GI bleeding or upper GI ulcers.[324] More recently, case-control studies confirmed this association.[348, 358] The potential mechanism may be related to impaired healing of gastric and duodenal erosions due to inhibition of fibrous tissue formation.[348]

Anticoagulants and antiplatelets

Use of anticoagulants is an acknowledged risk factor for upper GI bleeding, with previous studies showing risks from 5.3-fold to 6.5-fold for concomitant use of anticoagulants with low-dose aspirin,[119, 353] 4.6-fold with COX-2 inhibitors,[353] and up to 19-fold with nsNSAIDs.[73] In the current study anticoagulants showed a higher risk when combined with low-dose aspirin than with nsNSAIDs or COX-2 inhibitors. The difference between these findings and previous studies may rely on less stringent control for confounders in previous studies than in the current study; furthermore, with the SCCS all within-person confounders that are fixed over time are immediately dealt with. In line with others, concomitant use of low-dose aspirin eliminates the presumed benefit of COX-2 inhibitors over nsNSAIDs on the risk of upper GI adverse events.[10, 73, 327, 340]

Gastroprotective agents

The increased risk of diagnosed upper GI bleeding observed with the concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with GPAs seems counterintuitive; however, no interaction was observed for any of these drug combinations. The increased risk is thus more likely explained by the phenomenon of “channeling”, in which high-risk patients receive concurrent prescriptions for GPAs whereas low-risk patients do not. Another explanation is protopathic bias, because GPAs might be given as treatment for first symptoms of upper GI bleeding.[366]

Age-Related COX Enzyme selectivity

As expected, the risk of diagnosed upper GI bleeding with use of the drugs of interest (monotherapy), except antiplatelets, was lower for subjects younger than 60 years of age than for subjects older than 60 years of age. Surprisingly, the difference in risk between younger and older subjects was larger for drug combinations with COX-2 inhibitors than for combinations with nsNSAIDs. Application of a cutoff level of 70 years of age did not yield different results. However, using an age cutoff of 70 years showed excess risk for the combination of COX-2 inhibitors and corticosteroids, whereas this was not present with an age cutoff of 60 years. In elderly subjects, prostaglandin-levels decreased due to decreased conversion of arachidonic acid to prostaglandin, resulting in an increased risk of upper GI bleeding. This partially accounts for the recommendation to use gastroprotective measures in elderly patients.[99] We hypothesize that COX enzyme selectivity with aging might explain the difference in drug interaction between nsNSAIDs and COX-2 inhibitors. In animal studies, older rats expressed different COX enzyme mRNA than younger rats and an impaired response of prostaglandin synthesis to irritants with older age was shown.[120] In humans, higher basal acid output in the stomach among elderly patients[121] results in lower mucosal prostaglandin concentrations in the stomach and duodenum.[367] However, these observations were related

to the COX-1 enzyme and do not explain our findings. As the SCCS, by definition, controls for confounders fixed within-person and the baseline risk, this also does not explain the difference between younger and older subjects for COX-2 inhibitor combinations in the current study. Future studies are needed to elucidate these findings.

Strengths and limitations

A major strength of the current study is that while previous studies reported data from single centers[73] or single databases, [118-120, 211, 311, 348, 353, 356, 363-365] we performed a multi-database study to increase the power for studying the risk of upper GI bleeding due to drug synergism of relatively uncommon drug combinations. Additionally, we specifically looked at drug combinations of low-dose aspirin, nsNSAIDs and COX-2 inhibitors separately.[349]

However, we acknowledge the following limitations. A key assumption of the SCCS is that the exposure distribution within the observation period and the observation period itself must be independent of the time of the event. This assumption could have been violated, because the standard of care considers use of an nsNSAID without gastroprotection as relatively contraindicated after occurrence of upper GI bleeding. However, sensitivity analyses involving truncation of follow-up at the time of the event showed that drug exposure of nsNSAIDs did not change after the event (ie, results obtained were similar to those from the original analysis), meaning that confounding by contraindication was unlikely to explain the findings (Supplementary Figure 2). The health condition of a subject may vary over time at all phases of follow-up. Nevertheless, many chronic conditions, such as type 2 diabetes mellitus, hypertension, and peripheral vascular disease, are relatively stable diseases and vary little over time. We have no reason to believe that this will influence the estimates. The sensitivity analysis adjusting for acute myocardial infarction and anaphylactic shock did not yield different estimates as compared with the main analysis (Supplementary Figure 3). In addition, the age of a subject increases during follow-up, and given that older subjects are at higher risk than when at a younger age, we also adjusted for age in the analysis. Residual confounding due to an underlying clinical condition that led to a drug prescription, although unlikely, cannot be ruled out.

Misclassification of exposure time of NSAIDs could have occurred, because NSAIDs are often used intermittently rather than continuously, although this is probably true more for over-the-counter use of NSAIDs. Over-the-counter use of NSAIDs is not captured in EHR databases and could have led to a potential underestimation of use. However, the proportion of NSAIDs used over-the-counter is limited given that prescribed NSAIDs are reimbursed whereas over-the-counter drugs are not. Although information on drug use differed between dispensing and prescribing data, patterns of use of NSAID classes varied among different countries but were similar among different databases in the same country.[346] In addition, we defined nonexposure as no use of any of the drugs of interest instead of no use of any drug. We mitigated misclassification of nonexposure by restricting the analysis to drugs that have been reported to significantly increase or decrease the risk of upper GI bleeding. We used a

rather broad definition of upper GI bleeding, including all gastroduodenal ulcers and hemorrhages, which may have led to less severe cases of upper GI bleeding in the primary care databases compared with administrative databases. A validation study was performed in 4 databases. For this purpose, a sample of upper GI bleeding cases was manually validated by medical chart review to characterize and document any outcome misclassification related to drug- associated upper GI bleeding. This showed that misclassification was uncommon and did not affect the magnitude of risk estimates.[352] Second, when excluding the data set with the lowest PPV for diagnosis of upper GI bleeding in the current study, the estimates were not different from the main analysis. In addition, incidence rates of upper GI bleeding in these databases did not differ substantially across European countries and are in accordance with literature.[346] Variceal bleeding was not included as part of the definition of upper GI bleeding. However, we cannot rule out that variceal bleeding may have been wrongly coded as a code more specific for upper GI bleeding than variceal bleeding.

Nevertheless, non-differential misclassification cannot be ruled out and may have resulted in an underestimation of the true estimates. Finally, we did not take any carry-over effect or dose of drug exposure into account, which potentially limits the generalizability concerning causality of the associations.

The SCCS assumes that observation periods should be independent of event times, which may be violated if subjects die quickly after the event. By applying an alternative method[368] in one database taking this assumption into account by weighting the post-event periods, the estimates remained within the 95% confidence limits of the original analysis.

When estimating the magnitude of interaction, the presence and direction depends on the scale that is used: either additive or multiplicative interaction. In the current study, multiplicative interaction was only observed for the combination of low-dose aspirin and antiplatelets. However, statistical interaction does not directly imply biological interaction. [361]

In conclusion, concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs is associated with a significantly increased risk of diagnosed upper GI bleeding. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists or anticoagulants were associated with an increased and excess risk of upper GI bleeding. These findings may help clinicians in tailoring therapy to minimize upper GI bleeding adverse events, and are especially valuable in the elderly who are likely to use multiple drugs concurrently.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Definition of codes of Upper GI Bleeding among different coding systems.

ICD-9 CM (ARS, HSD, Pedianet, PHARMO, UNIMIB)		ICD-10 (for Aarhus)		ICPC (for IPCI)	
531.00/ 531.01	Gastric ulcer, Acute with hemorrhage	K25.0	Gastric ulcer, Acute with hemorrhage		
531.10	Gastric ulcer, Acute with perforation	K25.1	Gastric ulcer, Acute with perforation		
531.20/531.21	Gastric ulcer, Acute with hemorrhage and perforation	K25.2	Gastric ulcer, Acute with both hemorrhage and perforation		
532.00/532.01	Duodenal ulcer, Acute with hemorrhage	K26.0	Duodenal ulcer, Acute with hemorrhage	D85	Duodenal ulcer
532.10	Duodenal ulcer, Acute with perforation	K26.1	Duodenal ulcer, Acute with perforation		
532.20	Duodenal ulcer, Acute with hemorrhage and perforation	K26.2	Duodenal ulcer, Acute with both hemorrhage and perforation		
533.00	Peptic ulcer, site unspecified, Acute with hemorrhage	K27.0	Peptic ulcer, site unspecified, Acute with hemorrhage	D86	Peptic ulcer, other
533.10	Peptic ulcer, site unspecified, Acute with perforation	K27.1	Peptic ulcer, site unspecified, Acute with perforation		
533.20	Peptic ulcer, site unspecified, Acute with hemorrhage and perforation	K27.2	Peptic ulcer, site unspecified, Acute with both hemorrhage and perforation		
534.00/534.01	Gastrojejunal ulcer, Acute with hemorrhage	K28.0	Gastrojejunal ulcer, Acute with hemorrhage		
534.10	Gastrojejunal ulcer, Acute with perforation	K28.1	Gastrojejunal ulcer, Acute with perforation		
534.20/534.21	Gastrojejunal ulcer, Acute with hemorrhage and perforation	K28.2	Gastrojejunal ulcer, Acute with both hemorrhage and perforation		
535.01	Acute gastritis, with hemorrhage	K29.0	Acute hemorrhagic gastritis		
535.11	Atrophic gastritis, with hemorrhage				
535.41	Other specified gastritis, with hemorrhage				
535.51	Unspecified gastritis and gastroduodenitis, with hemorrhage				
578.0	Hematemesis, Vomiting of blood	K92.0	Hematemesis	D15	Hematemesis
578.1	Blood in stool, Melena	K92.1	Melena	D14	Melena
578.9	Hemorrhage of gastrointestinal tract, unspecified	K92.2	Gastrointestinal hemorrhage, unspecified		

Abbreviations: International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM); International Classification of Diseases, 10th Revision (ICD-10); International Classification for Primary Care (ICPC).

Supplementary Table 2. Corresponding anatomical therapeutic chemical (ATC)-codes for drug groups of interest.[99]

Drug group	ATC-codes*
nsNSAIDs	M01AB, M01AC, M01AE, M01AG, M01AX
COX-2 inhibitors	M01AH
Low-dose aspirin	B01AC06
High-dose aspirin	N02BA01, N02BA15
Corticosteroids	H02AB
Selective serotonin reuptake inhibitors	N06AB
Gastroprotective agents	A02BC, A02BA, A02BB01
Aldosterone antagonists	C03DA01, C03DA02, C03DA03, C03DA04
Calcium channel blockers	C08CA, C08CX01, C08DA01, C08DA02, C08DB01, C08EA01, C08EA02, C08EX01, C08EX02
Anticoagulantia	B01AA, B01AB
Antiplatelets	B01AC, excluding B01AC06
Nitrates	C01DA02, C01DA04, C01DA05, C01DA07, C01DA08, C01DA09, C01DA13, C01DA14

** Including all ATC-codes belonging to this drug group.*

Supplementary Table 3. Additive interaction measures for drug combinations of nsNSAIDs, low-dose aspirin and COX-2 inhibitors with other drugs.

	RERI (95% CI)	AP	Synergy index
nsNSAIDs + LDA	0.45 (-0.27 to 1.18)	0.07	1.09
nsNSAIDs + Corticosteroids	**5.48 (3.71 to 7.26)**	**0.43**	**1.87**
nsNSAIDs + SSRIs	**1.62 (0.58 to 2.66)**	**0.23**	**1.38**
nsNSAIDs + Gastroprotective agents	-0.98 (-1.33 to -0.62)	-0.25	0.75
nsNSAIDs + Aldosterone antagonists	**4.46 (1.79 to 7.13)**	**0.41**	**1.81**
nsNSAIDs + Calcium channel blockers	-0.39 (-0.90 to 0.13)	-0.09	0.90
nsNSAIDs + Anticoagulants	**2.41 (0.89 to 3.94)**	**0.28**	**1.46**
nsNSAIDs + Antiplatelets*	**1.50 (0.03 to 2.97)**	**0.23**	**1.37**
nsNSAIDs + Nitrates	0.00 (-0.93 to 0.93)	0.00	0.10
COX-2 inhibitors + LDA	**2.54 (1.13 to 3.94)**	**0.34**	**1.64**
COX-2 inhibitors + Corticosteroids	-0.02 (-2.03 to 1.99)	-0.00	0.10
COX-2 inhibitors + SSRIs	**1.86 (0.28 to 3.44)**	**0.32**	**1.63**
COX-2 inhibitors + Gastroprotective agents	-1.14 (-1.69 to -0.59)	-0.48	0.55
COX-2 inhibitors + Aldosterone antagonists	-1.15 (-3.84 to 1.53)	-0.29	0.72
COX-2 inhibitors + Calcium channel blockers	-0.36 (-1.12 to 0.41)	-0.11	0.86
COX-2 inhibitors + Anticoagulants	0.10 (-2.15 to 2.34)	0.02	1.03
COX-2 inhibitors + Antiplatelets	-1.91 (-3.13 to -0.69)	-1.10	0.28
COX-2 inhibitors + Nitrates	0.63 (-0.87 to 2.14)	0.12	1.18
LDA + Corticosteroids	**2.25 (0.91 to 3.59)**	**0.26**	**1.44**
LDA + SSRIs	0.49 (-0.05 to 1.03)	0.10	1.16
LDA + Gastroprotective agents	-1.12 (-1.37 to -0.88)	-0.44	0.58
LDA + Aldosterone antagonists	-0.31 (-1.30 to 0.67)	-0.06	0.93
LDA + Calcium channel blockers	-0.55 (-0.79 to -0.32)	-0.18	0.79
LDA + Anticoagulants	**1.87 (0.70 to 3.05)**	**0.27**	**1.46**
LDA + Antiplatelets*	**1.70 (0.85 to 2.56)**	**0.31**	**1.61**
LDA + Nitrates	-0.81 (-1.13 to -0.50)	-0.21	0.77

*In **Bold** are drug-combinations where additive interaction is significant based on 95% CIs of RERI not crossing 0.*
*Abbreviations: Relative Excess risk due to interaction (RERI); Proportion attributable to interaction (AP); Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Low-dose aspirin (LDA); Oral steroids (steroids); Selective serotonin reuptake inhibitors (SSRIs). *Antiplatelets excluding low-dose aspirin.*
RERI = RR11 - RR10 - RR01 + 1 ; AP= RERI/RR11.
RERI or AP = 0: means no interaction. RERI or AP < 0 means negative interaction or less than additive interaction. RERI or AP > 0: means positive interaction or more than additive interaction. R01 and R10 represent relative risk of upper GI bleeding for each drug separately; RR11 represents relative risk of upper GI bleeding during combination therapy.
95% CIs of RERI is calculated based on the variance and covariance of the separate estimates and combined drug estimate.
Synergy index = (RR11 - 1) / ((RR10 - 1) + (RR01 - 1))
Synergy index = 1: means no interaction. Synergy index < 1: means negative interaction or less than additive interaction. Synergy index > 1: means positive interaction or more than additive interaction.

Supplementary Table 4. Number of upper GI bleeding events and total of exposure time (in person years) to specific drug groups (monotherapy and combinations of drugs).

	Monotherapy		Combinations with:					
			nsNSAIDs		COX-2 inhibitors		Low-dose aspirin	
Drug groups	**N†**	**Person-Years#**	**N†**	**Person-Years#**	**N†**	**Person-Years#**	**N†**	**Person-Years#**
No drug*	69,664	706,123		NA		NA		NA
nsNSAIDs	3,327	10,198		NA		NA	416	1,040
COX-2 inhibitors	635	2,825		NA		NA	131	295
Low-dose aspirin	4,733	22,219	416	1,040	131	295		NA
Corticosteroids	1,378	4,078	244	312	40	98	190	383
SSRIs	1,793	10,248	210	497	65	168	401	1,441
Gastroprotective agents	5,279	33,385	678	2,239	95	503	607	3,332
Aldosterone antagonists	1,211	4,479	76	104	10	36	131	427
Calcium channel blockers	3,546	28,260	363	1,251	77	369	1,123	5,754
Anticoagulants	1,760	7,244	143	241	21	62	168	422
Antiplatelets (excluding LDA)	994	6,718	87	204	9	72	246	820
Nitrates	2,572	15,665	172	503	49	161	859	3,959

** Refers to no use of the predefined drugs of interest.*

† Number of upper GI bleeding events during exposure to specific drug group.

 # Total of exposure time in person years to specific drug group.

Abbreviations: Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Oral steroids (steroids); Low-dose aspirin (LDA); Selective serotonin reuptake inhibitors (SSRIs); Not applicable (NA).

Supplementary Table 5. Distribution of upper GI bleeding cases per gender across age categories.

Age range (year)	Number of upper GI bleeding cases Female	Number of upper GI bleeding cases Male
Total	51,440	63,395
0-4	813	1,085
5-9	329	408
10-14	237	327
15-19	410	425
20-24	593	705
25-29	687	893
30-34	781	1,339
35-39	1,037	1,835
40-44	1,288	2,392
45-49	1,512	2,830
50-54	1,892	3,876
55-59	2,349	4,755
60-64	3,042	5,978
65-69	4,071	7,366
70-74	5,551	8,380
75-79	7,723	8,556
80-84	8,267	6,643
≥85	10,858	5,602

Supplementary Table 6. Incidence rate ratios (IRRm) of diagnosed upper GI bleeding during exposure to specific drug groups (with corresponding 95% confidence intervals) in monotherapy and in combinations by applying a meta-analysis random-effects model.

Drug groups	Monotherapy			Combinations with:								
				nsNSAIDs			COX-2 inhibitors			Low-dose aspirin		
	IRRm (95%CI)	P-value Q statistic	I^2 %	IRRm (95%CI)	P-value Q statistic	I^2 %	IRRm (95%CI)	P-value Q statistic	I^2 %	IRRm (95%CI)	P-value Q statistic	I^2 %
No drug*	1.00 (ref)	NA	NA	NA			NA			NA		
nsNSAIDs	3.11 (2.15-4.51)	0.00	98.0	NA			NA			5.05 (2.86-8.90)	<0.001	94.9
COX-2 inhibitors	2.20 (1.58-3.05)	<0.001	86.3	NA			NA			7.34 (4.74-11.36)	<0.001	70.8
Low-dose aspirin	2.34 (1.87-2.92)	0.00	96.0	5.05 (2.86-8.90)	<0.001	94.9	7.34 (4.74-11.36)	<0.001	70.8	NA		
Corticosteroids	2.37 (1.33-4.22)	0.00	98.0	7.84 (4.61-13.36)	<0.001	89.4	6.40 (4.55-9.01)	0.90	0.00	6.97 (4.92-9.88)	0.01	67.0
SSRIs	1.59 (1.20-2.12)	0.00	94.9	4.58 (2.73-7.69)	<0.001	87.2	6.30 (4.63-8.58)	0.36	8.3	3.86 (2.75-5.42)	<0.001	82.7
Gastroprotective agents	1.31 (0.97-1.77)	0.00	98.2	2.95 (1.88-4.62)	<0.001	95.9	2.02 (1.34-3.05)	0.02	62.9	1.87 (1.30-2.69)	<0.001	93.1
Aldosterone antagonists	2.10 (1.31-3.38)	0.00	95.3	9.98 (6.29-15.82)	0.07	50.2	6.59 (3.17-13.69)	0.43	0.00	3.96 (2.60-6.05)	0.01	68.5
Calcium channel blockers	1.22 (0.95-1.57)	0.00	95.3	3.35 (2.01-5.59)	<0.001	91.8	3.16 (2.11-4.73)	0.16	37.1	2.37 (1.86-3.02)	<0.001	87.5
Anticoagulants	2.24 (1.60-3.13)	0.00	95.7	6.97 (4.50-10.82)	<0.001	76.6	5.52 (3.52-8.66)	0.75	0.00	6.03 (4.48-8.12)	0.04	57.2
Antiplatelets (excluding low-dose aspirin)	1.56 (1.27-1.91)	0.00	83.0	6.30 (3.58-11.07)	<0.001	79.2	1.79 (0.90-3.55)	0.94	0.00	4.43 (2.83-6.93)	<0.001	86.7
Nitrates	1.89 (1.34-2.66)	0.00	94.9	4.94 (3.19-7.63)	0.01	65.7	5.00 (2.37-10.52)	0.04	56.7	3.14 (2.53-3.90)	<0.001	75.5

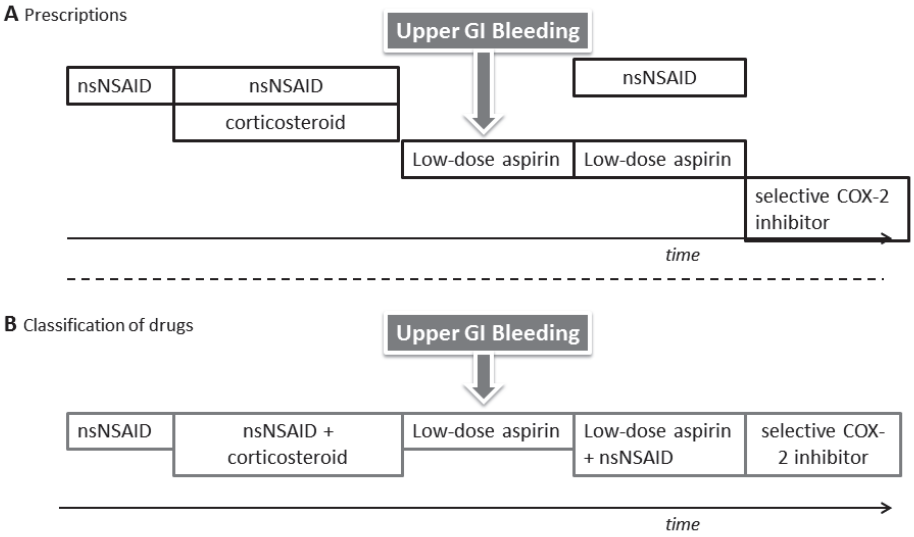
** Refers to no use of the predefined drugs of interest.*

Abbreviations: Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Oral steroids (steroids); Selective serotonin reuptake inhibitors (SSRIs); Not applicable (NA); Incidence Rate Ratio pooled on random effect meta-analytic model (IRRm).

Supplementary Table 7. Population attributable risks of upper GI bleeding for monotherapy of drugs.
The PAR is an estimate that reflects the absolute risk in the general population. The PAR is calculated using the relative risk and the exposure prevalence in the general population to which the relative risk pertains. However, the PAR does not reflect the absolute risk for a specific individual but rather the proportion of upper GI bleeding in the general population due to drug use. As example we can take the PAR of nsNSAID monotherapy: out of 100 persons experiencing upper GI bleeding while exposed to nsNSAID monotherapy 11.8% of these upper GI bleedings are attributable to nsNSAID monotherapy.

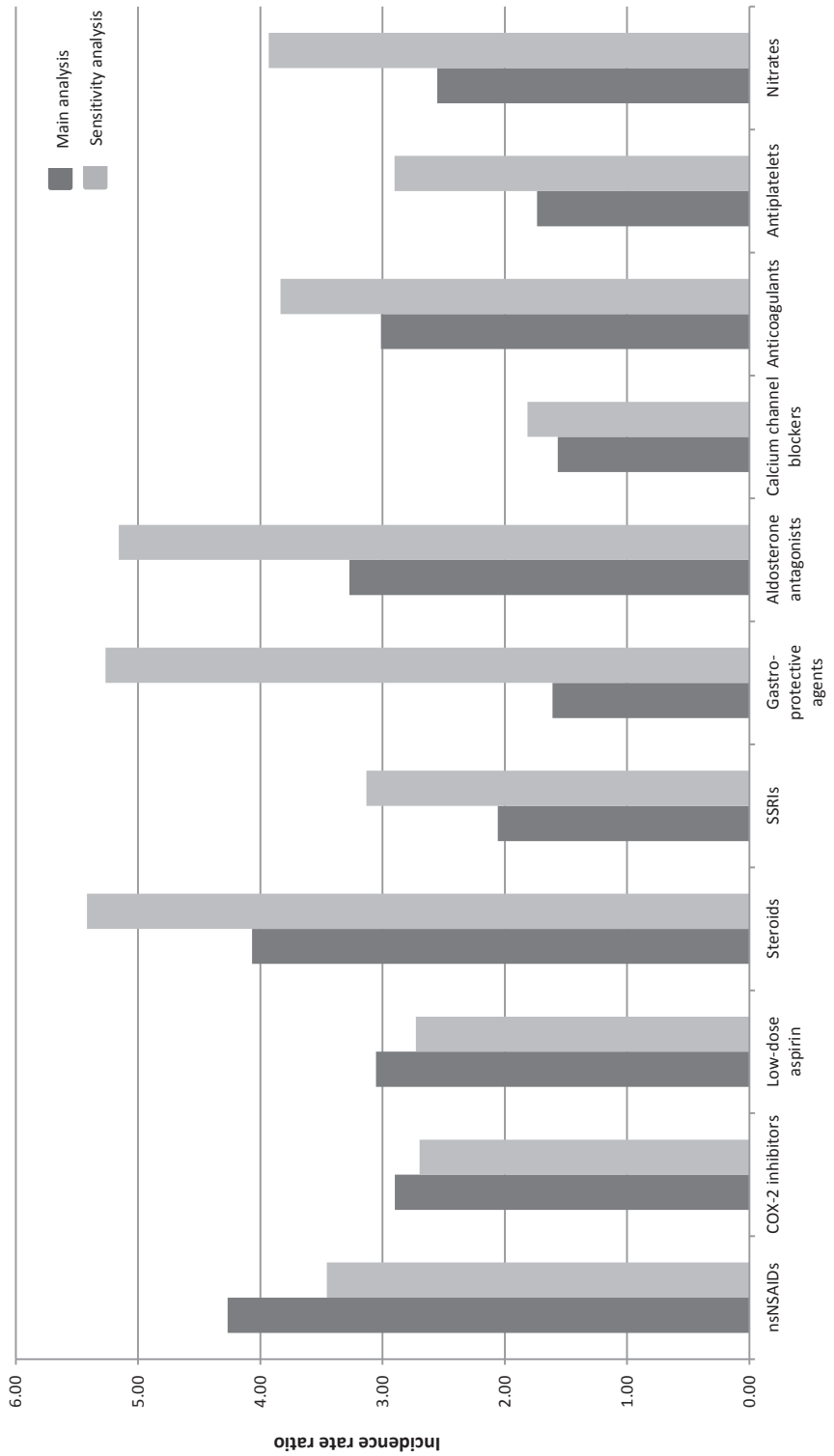
Drug groups	Monotherapy			Combinations with								
				nsNSAIDs			COX-2 inhibitors			Low-dose aspirin		
	Exposure Prevalence† (%)	IRR*	PAR (%)	Exposure Prevalence† (%)	IRR*	PAR (%)	Exposure Prevalence† (%)	IRR*	PAR (%)	Exposure Prevalence† (%)	IRR*	PAR (%)
nsNSAIDs	4.1	4.27	11.8							16.7	6.77	8.8
COX-2 inhibitors	1.7	2.90	2.0							3.5	7.49	2.2
Low-dose aspirin	6.5	3.05	11.7	16.7	6.77	8.8	3.5	7.49	2.2			
Corticosteroids	3.8	4.07	10.4	5.5	12.82	6.4	1.6	5.95	0.8	8.1	8.37	5.6
SSRIs	2.8	2.06	2.8	6.5	6.95	3.7	1.7	5.82	0.8	9.4	4.60	3.3
Gastroprotective agents	7.4	1.61	4.3	24.4	3.90	6.6	4.4	2.37	0.6	28.3	2.54	4.2
Aldosterone antagonists	1.3	3.27	2.9	1.7	11.00	1.7	0.4	4.02	0.1	5.2	5.01	2.0
Calcium channel blockers	4.0	1.57	2.2	11.8	4.45	3.9	3.0	3.11	0.6	19.5	3.07	3.9
Anticoagulants	4.2	3.01	7.8	7.3	8.69	5.3	1.3	5.01	0.5	9.8	6.94	5.5
Antiplatelets (excluding LDA)	2.4	1.74	1.8	3.5	6.50	1.9	0.7	1.73	0.1	13.6	5.49	5.8
Nitrates	3.0	2.55	4.4	6.5	5.82	3.0	1.6	5.09	0.7	20.8	3.79	5.5

† Exposure prevalence of drugs in the general population.
** Incidence Rate Ratios, used as calculated in this study (see Table 2).*
Abbreviations: Nonselective NSAIDs (nsNSAIDs); COX-2 selective inhibitors (COX-2 inhibitors); Oral steroids (steroids); Low-dose aspirin (LDA); Selective serotonin reuptake inhibitors (SSRIs); Not applicable (NA).



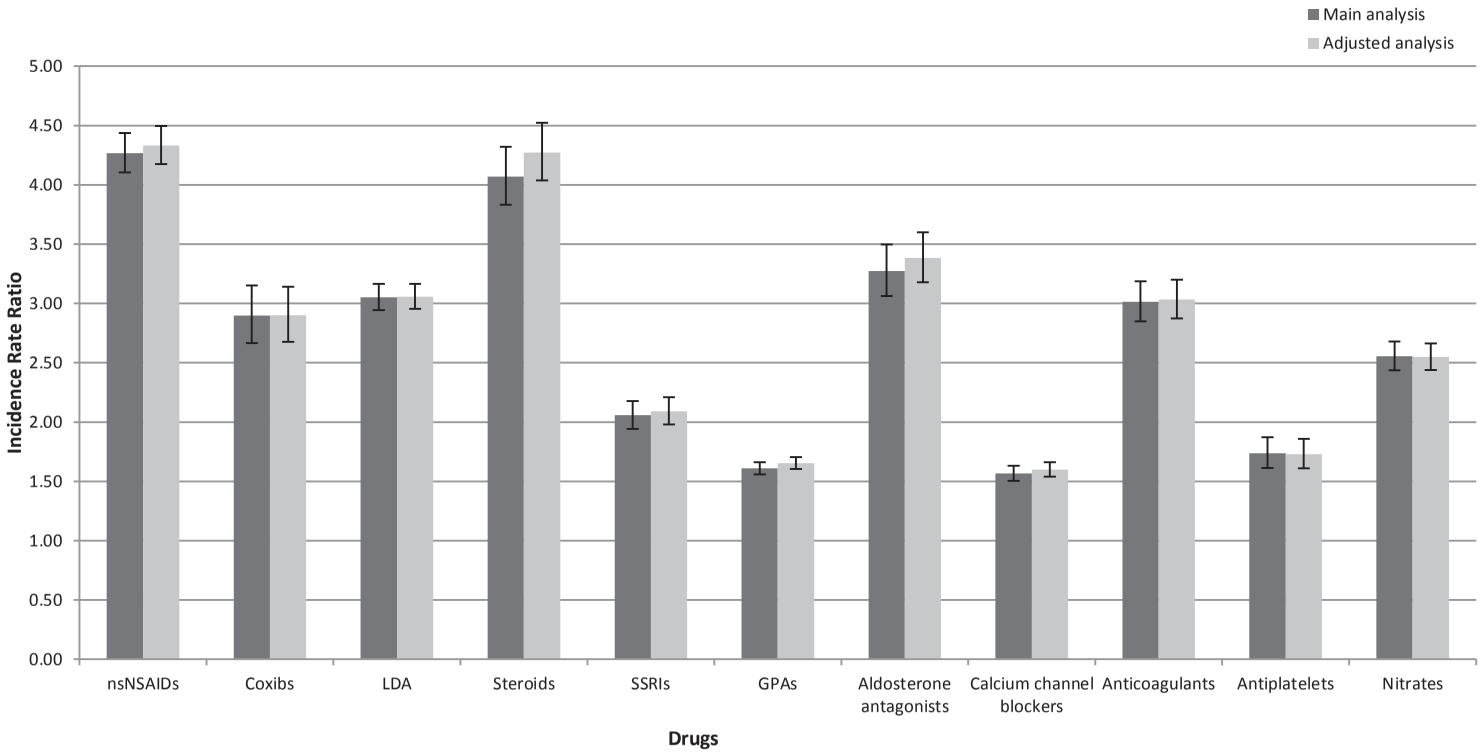
Supplementary Figure 1. Classification of drug prescriptions into the drug categories.

GI, gastrointestinal; nsNSAID, nonselective NSAID.

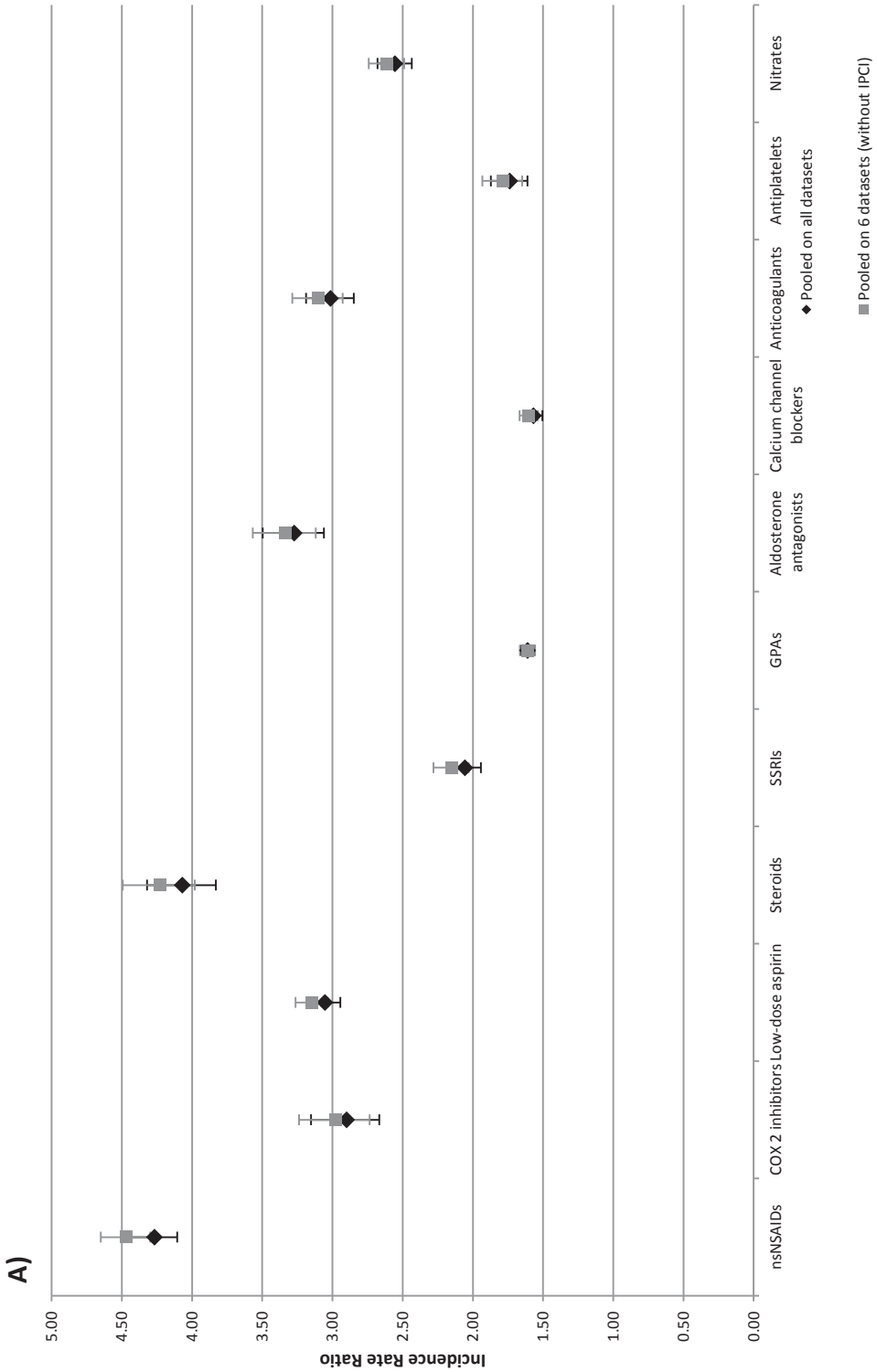

Main analysis
Sensitivity analysis
Incidence rate ratio
6.00
5.00
4.00
3.00
2.00
1.00
0.00
nsNSAIDs
COX-2 inhibitors
Low-dose aspirin
Steroids
SSRIs
Gastro-protective agents
Aldosterone antagonists
Calcium channel blockers
Anticoagulants
Antiplatelets
Nitrates
Drugs

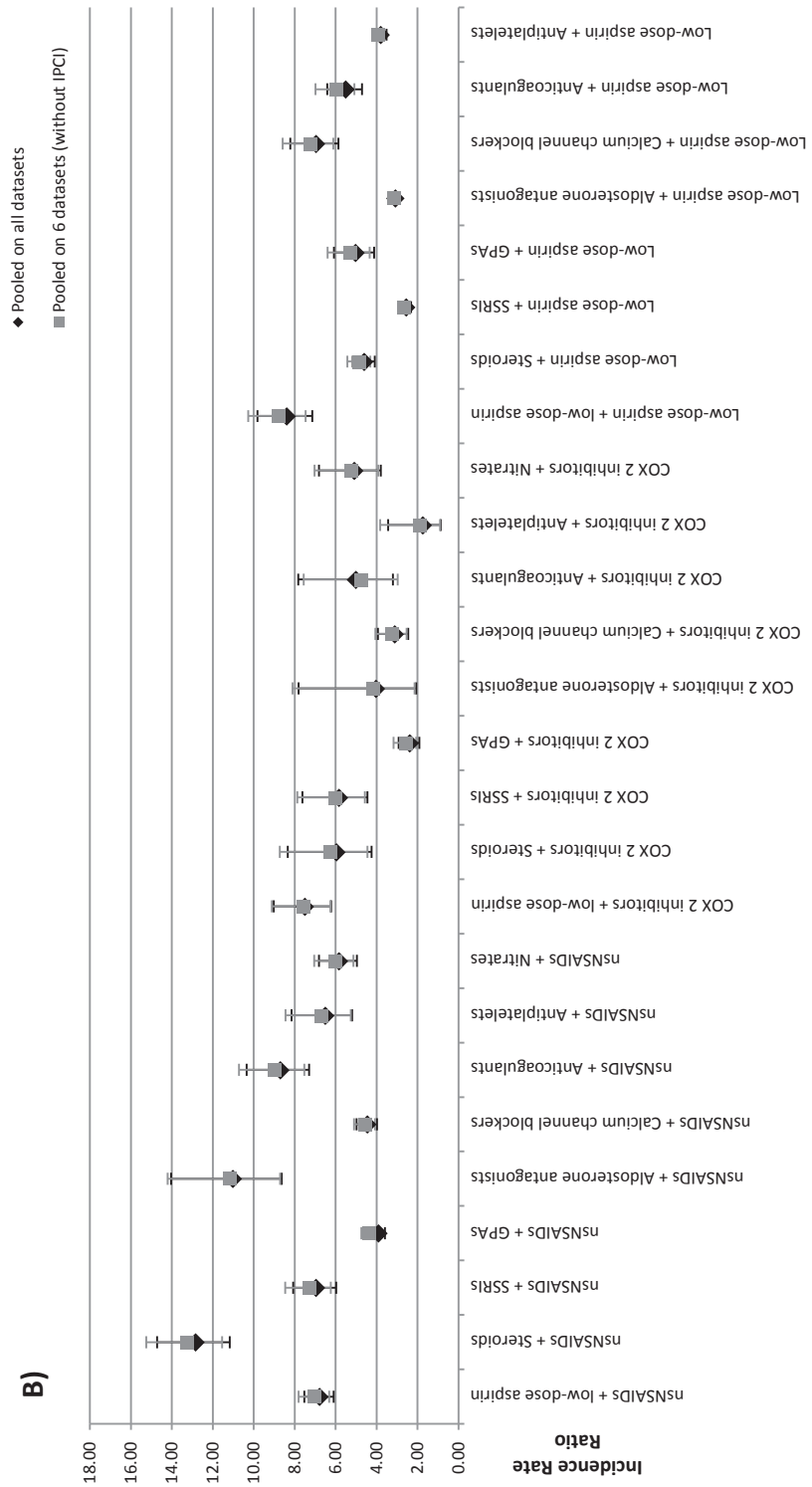
Supplementary Figure 2. Explanation of Sensitivity analysis with observation time truncated at time of event. Observed Incidence rate ratios of drug monotherapy for the main analysis in SCCS and sensitivity analysis.

Key assumption of the SCCS is that the exposure distribution within the observation period and the observation period itself must be independent of prior event times. This could have been violated for some individuals, as use of an nsNSAID without gastroprotection is relatively contra-indicated after an upper GI bleeding. By truncating the follow-up at time of the upper GI bleeding, we observed that the IRRs changed in magnitude for some drugs. We used a change of 10% of the initial estimate as arbitrarily cut-off to quantify the magnitude of change. For monotherapy of steroids, SSRIs, GPAs, aldosterone antagonists, antiplatelets and nitrates the estimates were higher and for nsNSAIDs and low-dose aspirin lower in the analysis with truncation of follow-up time at the event. Only for COX-2 inhibitor-monotherapy the estimates did not change with more than 10% of the initial estimate. These analyses implicate that the exposure of for instance nsNSAIDs did not change significantly after the event, but do show the relative contra-indication of nsNSAIDs after an upper GI bleeding, as the IRR in initial analysis was higher than in sensitivity analyses (Supplementary Figure 1). These analyses however show that confounding-by-contraindication is unlikely.



Supplementary Figure 3. Observed incidence rate ratios of drug monotherapy for main analysis and sensitivity analyses adjusted for acute myocardial infarction and anaphylactic shock.


A)
Incidence Rate Ratio
5.00
4.50
4.00
3.50
3.00
2.50
2.00
1.50
1.00
0.50
0.00
nsNSAIDs
COX 2 inhibitors
Low-dose aspirin
Steroids
SSRIs
GPAs
Aldosterone antagonists
Calcium channel blockers
Anticoagulants
Antiplatelets
Nitrates
Pooled on all datasets
Pooled on 6 datasets (without IPCI)



Supplementary Figures 4a and 4b. Observed incidence rate ratios (with 95% Confidence Intervals) of drug monotherapy for main analysis and sensitivity analysis excluding IPCI.

SECTION 5

NSAIDs and PPIs and the risk of Microscopic Colitis

CHAPTER 5.1

Incidence of Microscopic Colitis in the Netherlands in relation to the number of colonoscopies over time

Letter to article by Tong et al. Incidence, Prevalence, and Temporal Trends of Microscopic Colitis: A Systematic Review and Meta-analysis.[369]

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TO THE EDITOR:

We read with great interest the thorough review and meta-analysis by Tong *et al*.[369] about microscopic colitis (MC). Their study summarizes evidence from epidemiological studies on MC incidence and drug-associations. They report incidence rates from different countries in different time periods. They conclude that the overall incidence of MC increases with age, is higher in females than males and is comparable to the incidence of inflammatory bowel disease. Differences in study settings, geography, source population and diagnosis verification likely contributed to heterogeneity of the results. Nevertheless, MC incidences appear to have increased over time and proton pump inhibitors as well as selective serotonin reuptake inhibitors were associated with an increased risk of MC. As the authors point out, clinical awareness, more liberal use of colonoscopy, and routine random biopsy sampling in normal colonoscopies may have distorted the estimation of the 'true' incidence of the disease. These types of detection and diagnostic biases[370] are, however, difficult to account for in incidence studies. A possible solution to give insight in such detection bias is to calculate the incidence of the disease in relation to the number of diagnostic procedures. In a cohort study using data from a primary care database containing electronic medical records of 1.6 million subjects in the Netherlands, we identified 210 incident, histologically-verified, MC cases between 2003 and 2013. We calculated the rate of MC both over the number of person-years (PY) as most studies do, but also over the number of index colonoscopies, not considering follow-up colonoscopies. An increase in incidence per PY was seen that tapered off in 2011 (Figure 1). There was a substantial increase in total number of colonoscopies over this period (from 62 colonoscopies per 10,000 PY in 2003 to 283 in 2013). The rate of MC lowered when based on the number of colonoscopies from 5.6 per 1,000 colonoscopies in 2003 to 0.9 in 2013 (Figure 2).

Our findings thus suggest that the actual incidence of MC remained fairly stable during a 10-year period in the Netherlands, and that increases that may be seen on the population level are due to increasing rates of colonoscopies. These findings contrast with previous studies as summarized by Tong *et al*.[369] This contrast can explained by the fact that the majority of previous studies did not correct for increases in the number of colonoscopy procedures, and therefore ability to detect MC, over time.

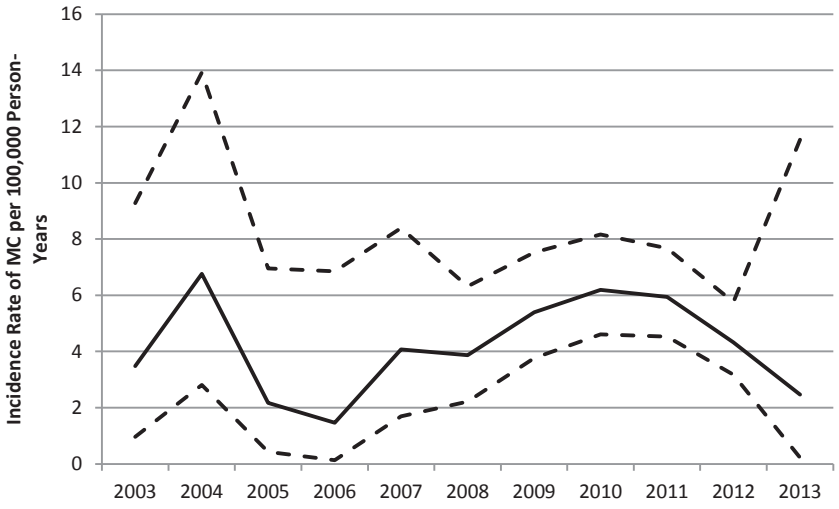

Figure 1. Incidence rate with 95% Confidence Intervals of Microscopic Colitis per 100,000 Person-Years.

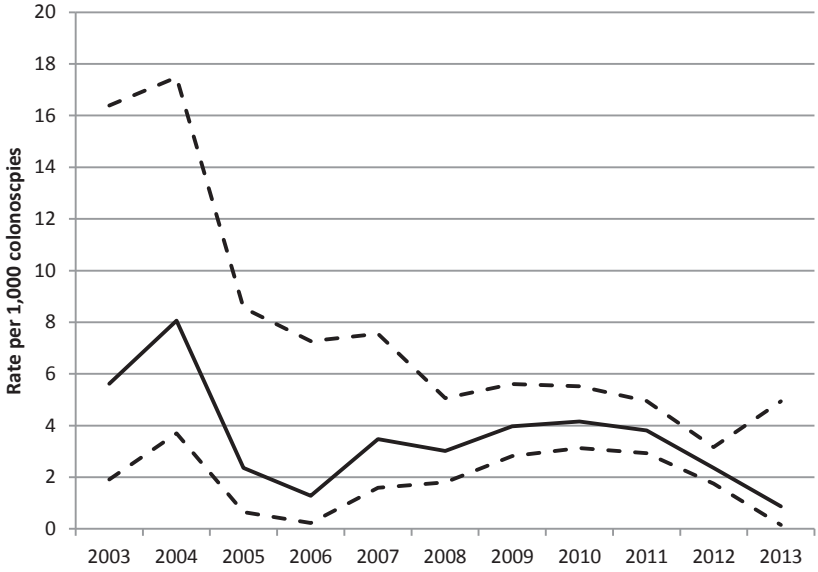

Figure 2. Rate with 95% Confidence Intervals of Microscopic Colitis per 1,000 diagnostic colonoscopies.

CHAPTER 5.2

Increased risk of Microscopic Colitis with use of Proton Pump Inhibitors and Non-Steroidal Anti-Inflammatory Drugs

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ABSTRACT

BACKGROUND

Microscopic colitis (MC) is characterized by chronic watery diarrhea. Recently several drugs were reported to increase the risk of MC. However, studies lacked a clear exposure definition, did not address duration-relationships and did not take important biases into account.

AIM

We estimated the risk of MC during drug use.

METHODS

Population-based nested case-control study using a Dutch primary care database (1999-2013). Incident microscopic colitis cases (aged ≥18 years) were matched to: 1) community-based, and 2) colonoscopy-negative controls on age, sex and primary care practice. Drug use was assessed within 1 and 2 years prior to index date. Adjusted odds ratios (OR) were calculated by conditional logistic regression.

RESULTS

From the source population of 1,458,410 subjects; 218 cases were matched to 15,045 community controls and 475 colonoscopy negative controls. Current use (≤3 months) of proton pump inhibitors (PPIs), NSAIDs, selective serotonin reuptake inhibitors, low-dose aspirin, ACE-inhibitors and beta-blockers significantly increased the risk of microscopic colitis compared to never use in community controls. Adjusted ORs ranged from 2.5 (95%CI: 1.5-4.2) for ACE-inhibitors to 7.3 (95%CI: 4.5-12.1) for PPIs in the year prior to index date. After accounting for diagnostic delay, only use of NSAIDs, PPIs, low-dose aspirin and ACE-inhibitors increased risk of MC. Compared to colonoscopy controls, only use of PPIs (ORadjusted 10.6, 1.8-64.2) and NSAIDs (ORadjusted 5.6, 1.2-27.0) increased the risk of MC.

CONCLUSION

NSAIDs and PPIs are associated with an increased risk of MC. The association of MC with use of the other drugs is probably explained by worsening of diarrhea/symptoms rather than increasing the risk of MC itself.

INTRODUCTION

Microscopic colitis (MC) is a condition characterized by chronic watery diarrhea, normal radiological and endoscopic appearance and microscopic inflammation of the colon. It is a rare disease with an incidence around 5 to 8.6 cases per 100,000 person-years. [371, 372] MC includes two distinct entities, namely lymphocytic colitis and collagenous colitis. They differ in histopathological features: collagenous colitis is characterized by a subepithelial collagen band adjacent to the basal membrane, while lymphocytic colitis is characterized by the presence of an inflammatory infiltrate in the lamina propria. The etiology of MC is largely unknown, but risk factors include autoimmune diseases such as rheumatoid arthritis and celiac disease.[373-375] MC is more prevalent in elderly, particularly among females aged 60 years and over.[372, 376] Parallel to this increase in incidence of MC is the increase in polypharmacy in elderly. Several drugs have been reported to be associated with the onset of MC. These drugs include selective serotonin reuptake inhibitors (SSRIs), [377] non-steroidal anti-inflammatory drugs (NSAIDs), [377] and proton pump inhibitors (PPIs). [378] One of the proposed mechanisms of drug-associated MC is triggering factors of colonic inflammation in a genetically predisposed individual. Both NSAIDs and PPIs have been reported to affect the bowel integrity and colonic permeability. [9, 83-88] Subsequently, luminal antigens can more easily enter the lamina propria and elicit an immune and inflammatory reaction.[83] Another mechanism by which PPIs could lead to MC is alteration of the colonic intestinal flora through acid inhibition and thereby promoting colonic microbial growth. [210, 379]

On the other hand, drugs may also be implicated in the development or worsening of diarrhea in a patient with a pre-existing, undiagnosed, MC. In other words, the drug itself may not induce MC, but rather the underlying disease or indication to receive the drug. Previous studies assessing the association between drug intake and MC have not been able to take confounding-by-indication (i.e., the indication to receive the drug) into account. Additionally, such studies were limited by small sample size, lack of clear drug exposure definitions, and lack of duration analyses. [378] The aim of this study was to assess the risk of MC during use of various drugs in a population-based nested case-control study.

METHODS

Data sources

A population-based general practice electronic healthcare record database, the Integrated Primary Care Information database (IPCI) from the Netherlands (NL) was used as data source. This database contains prospectively collected routine care data representing real-life practice.[238] In the Netherlands, all citizens are registered with a general practitioner (GP), who acts as a gatekeeper to secondary and tertiary medical care. IPCI contains >1.5 million active patients from 340 GP practices. For each individual patient all relevant medical information

from primary and secondary care is documented in the electronic record. This includes information on medical diagnoses, discharge summaries, demographics, GP notes and drug prescriptions. In IPCI the International Classification for Primary Care[240] system is used for coding of medical diagnosis and symptoms. Information on drug use is coded according to the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification . IPCI has been extensively used in pharmaco-epidemiological studies.[117, 243] In previous studies, the characteristics and incidence/prevalence of diseases such as upper gastrointestinal bleeding, Barrett's esophagus were shown to be consistent with other literature.[346, 380, 381] The study protocol was approved by the IPCI Scientific and Ethical Advisory Board.

Study Design and Population

A nested case-control study was conducted. The source population consisted of all subjects aged ≥ 18 years who were registered with one of the general practitioners and contributed data between January 1st 1999 and March 31st 2012 and had at least 1 year of valid data in the database. This one year run-in period was used to distinguish between incident and prevalent cases of MC.

Cases and control selection

MC cases were identified via key word search within the free-text narratives in the electronic medical records and were included when: 1) a record of MC diagnosis; and 2) additional evidence consisting of histology report confirming MC diagnosis were present. Only incident MC cases (i.e. newly diagnosed cases) were considered for the study. The index date (date to which we make reference for exposure assessment) was defined as the first date of recorded symptoms leading to the diagnosis of MC. Subjects with a diagnosis of colorectal cancer were excluded. Due to the availability of the medical history of each patient, we could review on which date symptoms related to microscopic diagnosis started.

Two control groups were considered for the analysis; 1) community-based controls (i.e., from the source population); and 2) colonoscopy controls (i.e., those who had undergone a colonoscopy without signs or histology of MC). We matched by incidence density sampling on age (+/- 1 year), GP practice and sex. For the colonoscopy controls the date of colonoscopy was within 6 months of the date of the corresponding case in order to rule out any effect that could be time-related. We matched on GP practice, in order to take any referral bias or prescribing preference from GPs into account.

Drug Exposure

Drugs of interest were those that previously have been reported to be associated with (either increased or decreased) risk of MC: 1) NSAIDs (including high-dose aspirin; >325 mg of aspirin per day) [377], 2) PPIs [378, 382], 3) statins [377], 4) SSRIs [377], 5) low-dose aspirin (up to 325 mg/day) [382],

6) angiotensin converting enzyme (ACE)-inhibitors [377, 378] and 7) beta-blockers.[382] Analyses with respect to individual types of NSAIDs and PPIs were conducted including assessment of heterogeneity between individual estimates.

We considered several risk periods of drug exposure because of the possibility of delay between disease onset to first time that symptoms are recorded. The different risk periods were as follows: within 1 year prior to the index date (A) and within 2 years prior to the index date (B) while excluding the last year before index date. In risk period B the first year prior to index date was not considered for exposure assessment in order to account for a potential lag-time in recorded symptoms (i.e. assuming there could be a difference of one year between actual start of the disease and first date of recorded symptoms). It would actually be the same as risk period A but moving back the index date to 1 year prior to the recorded symptom onset. For risk period B, at least 2 year of valid data should be available. Subsequently we divided exposure time into the following mutually exclusive groups: current use (≤3 months), past use (3-12 months prior to index date) and never use (no drug in 12 months prior to index date). In Figure 1 the considered exposure groups for the different risk periods are depicted.

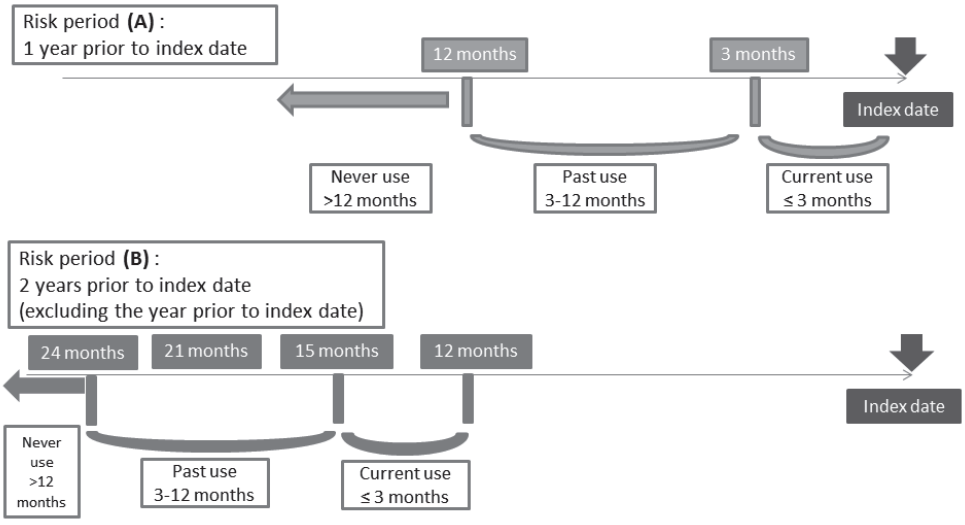


Figure 1. Risk periods used for exposure assessment.

Covariates

We considered as risk factors for MC those that have been reported previously in the literature: celiac disease [373, 375, 382]; inflammatory bowel disease [375]; rheumatoid arthritis [374]; hypothyroid disease [375]; polyarthritis [375, 382]; and diabetes mellitus type 2.[374] As a quality check

we analyzed the incidence of the covariables in the source population of the database and found that the incidence rates were similar to rates reported in the literature. For instance, we found an overall incidence of polymyalgia rheumatica of 54.3 per 100,000 person-years, which is in line with the reported incidence rates in Denmark (41.3 and 68.3/100,000 person years) and Sweden (50.0/100,000 person years). [383]

Statistical analysis

Incidence rates of MC were calculated by dividing the number of incident (i.e., newly-diagnosed) MC cases by the number of person-years at risk. The incidence rates (IR) of MC were also calculated in relation to the number of colonoscopies performed, in order to account for detection bias. Baseline characteristics of cases and controls were described and compared using univariable conditional logistic regression. To estimate the risk for MC for use of the drugs of interest, matched and adjusted odds ratios (OR) with 95% confidence intervals (CIs) were calculated using conditional logistic regression. Identification of confounders was performed by entering each potential confounder into the model one by one. Confounders were kept into the model if the risk estimate for the drug exposure changed more than 10%.[384] Duration analyses in the different risk periods were conducted according to the above specified categories. Dose effects were analysed by the cumulative amount of prescribed drug during the exposure period and expressed as the total amount of recommended defined daily dose (DDD) . Categories of DDDs were divided in 0 DDD; 1-7 DDDs; 8-15 DDDs and >15 DDDs for NSAIDs and in 0 DDD; 1-29 DDDs; 30-90 DDDs and >90 DDDs for PPIs, statins, SSRIs, ACE-inhibitors and beta-blockers.

Sensitivity analysis

As sensitivity analysis we excluded the unspecified types of MC, in order to rule out any misclassification of MC cases. Secondly, we performed subgroup analyses by type of MC (collagenous or lymphocytic colitis). Effect modification by sex and age group (≤ 45 years; >45 years) was explored by multiplicative interaction.

RESULTS

Study population

In the source population of 1,458,410 subjects we identified 218 incident MC cases (lymphocytic colitis 70, collagenous colitis 92, and unspecified 56). This yielded an IR of 5.1/100,000 PYs for MC overall; 2.1/100,000 PYS for collagenous colitis; 1.6/100,000 PYS for lymphocytic colitis and 1.3/100,000 PYs for unspecified MC. The incidence rate of MC was 3.3 per 1,000 colonoscopies. The 218 incident MC cases (who had at least 1 year of risk period assessment) were matched to 15,045 community controls. The median number of controls

was 54 per case (interquartile range: 32-93). When including only cases with at least 2 years of valid data before index date, 138 cases were retained who were matched to 9,160 community controls. For 148 cases we could match at least one colonoscopy control from the same GP practice (n=475) for a 1 year risk period assessment, and 95 cases to 296 colonoscopy controls for a 2 year risk period assessment. Characteristics of the cases on date of diagnosis and matched controls on index date are shown in Table 1. Among cases occurrence of celiac disease, inflammatory bowel disease or rheumatoid arthritis was more frequent than among controls.

Characteristics of drug exposure

Characteristics of drug exposure in the different risk periods are described for cases and community and colonoscopy controls in Table 2. Most frequently used drugs were NSAIDs and proton pump inhibitors (PPIs) in the 1 and 2 year risk periods, both among cases and community controls, with the exception of beta-blockers, which were more often used than NSAIDs by cases in the 1 year risk period. Similar exposure prevalences of the drugs were seen for colonoscopy controls as with community controls (Table 2).

Risk of microscopic colitis compared to community controls

To determine the risk of MC in association with use of drugs, a nested case-control study was conducted. When looking at the 1 year risk period (within 1 year prior to index date), current use (within 3 months of index date) of NSAIDs, PPIs, statins, SSRIs, low-dose aspirin, ACE-inhibitors and beta-blockers all significantly increased the risk of MC compared to never use. When adjusting for important confounders, current use of NSAIDs, PPIs, SSRIs, low-dose aspirin, ACE-inhibitors and beta-blockers remained associated with an increased risk of MC, ranging between 2.5 for ACE-inhibitors and 7.3 for PPIs (Table 3A, Supplementary Figure 1A and B). When taking diagnostic delay into account (by taking out the year directly prior to index date and looking in the year 1 to 2 years prior to index date), all drugs substantially increased the risk of MC in the matched analysis (Table 3A). However, adjustment for confounders resulted in elevated risks only for current use of NSAIDs, PPIs, low-dose aspirin and ACE-inhibitors (Table 3A, Supplementary Figure 1A and B), ranging between 2.3- and 8.3-fold for ACE-inhibitors and NSAIDs, respectively. Diclofenac was the most commonly used NSAID followed by ibuprofen. Omeprazole was the most frequently used PPI. Results regarding individual types of NSAIDs and PPIs are shown in Supplementary Figures 3 and Figures 4. No heterogeneity was seen between individual NSAIDs and PPIs. Analyses of dose effects are shown in Supplementary Table 1A**.**

Table 1. Characteristics of cases and controls on index date.

	COMMUNITY CONTROLS			
	1 year risk period*		2 year risk period#	
	Case	Control	Case	Control
Characteristics	N (%)	N (%)	N (%)	N (%)
Total	218 (100)	15,045 (100)	138 (100)	9,160 (100)
Median no. of controls (IQR)	53.5 (32-93)		53 (33-85)	
Type microscopic colitis				
Collagenous colitis	92 (42.2)		59 (42.8)	
Lymphocytic colitis	70 (32.1)		42 (30.4)	
Not specified	56 (25.7)		37 (26.8)	
Sex				
male	58 (26.6)	3,898 (25.9)	39 (28.3)	2,525 (27.6)
female	160 (73.4)	11,147 (74.1)	99 (71.7)	6,635 (72.4)
Mean age at index date (SD)	45.1 (2.1)	45.2 (2.0)	45.3 (2.1)	45.2 (2.1)
Median age at index date (IQR)	45.6 (44.4-46.6)	45.7 (44.4-46.7)	45.7 (44.6-46.7)	45.7 (44.5-46.7)
Age group (years)				
<40	12 (5.5)	715 (4.8)	9 (6.5)	606 (6.6)
40-45	68 (31.2)	4,788 (31.8)	37 (26.8)	2,666 (29.1)
>45	138 (63.3)	9,542 (63.4)	92 (66.7)	5,888 (64.3)
Celiac Disease yes	13 (6)	46 (0.3)	9 (6.5)	35 (0.4)
Inflammatory Bowel Disease yes	38 (17.4)	60 (0.4)	28 (20.3)	50 (0.5)
Hypothyroid Disease yes	13 (6)	388 (2.6)	1 (0.7)	2 (0)
Polyarthritis yes	**2 (0.9)**	**21 (0.1)**	**1 (0.7)**	**24 (0.3)**
Rheumatoid Arthritis yes	**5 (2.3)**	**148 (1.0)**	9 (6.5)	129 (1.4)
Diabetes Mellitus T2 yes	**7 (3.2)**	**601 (4.0)**	**5 (3.6)**	**491 (5.4)**
Index year				
1999	1 (0.5)	11 (0.1)	0 (0)	0 (0)
2000	0 (0)	0 (0)	0 (0)	0 (0)
2001	0 (0)	0 (0)	0 (0)	0 (0)
2002	1 (0.5)	49 (0.3)	1 (0.7)	49 (0.5)
2003	3 (1.4)	168 (1.1)	2 (1.4)	139 (1.5)
2004	6 (2.8)	457 (3)	5 (3.6)	388 (4.2)
2005	2 (0.9)	75 (0.5)	2 (1.4)	75 (0.8)
2006	1 (0.5)	27 (0.2)	0 (0)	0 (0)
2007	5 (2.3)	212 (1.4)	1 (0.7)	54 (0.6)
2008	14 (6.4)	1,247 (8.3)	4 (2.9)	485 (5.3)
2009	32 (14.7)	2,163 (14.4)	21 (15.2)	1,359 (14.8)
2010	47 (21.6)	2,835 (18.8)	31 (22.5)	1,716 (18.7)
2011	55 (25.2)	3,995 (26.6)	37 (26.8)	2,502 (27.3)
2012	50 (22.9)	3,762 (25.0)	33 (23.9)	2,349 (25.6)
2013	1 (0.5)	44 (0.3)	1 (0.7)	44 (0.5)

** 1 year risk period (A): assessment of characteristics for the cases and controls that are included in the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A). # 2 year risk period (B): assessment of characteristics for the cases and controls that are included in the analysis with 2 year valid data available. See Figure 1, risk period (B).*
IQR, interquartile range; SD, standard deviation. Matching factors: age, GP practice, sex, date of diagnosis (for cases). Values in bold represent non-significant different proportions between matched cases and controls.

Table 1. Characteristics of cases and controls on index date (*continued*).

	COLONOSCOPY CONTROLS			
	1 year risk period*		2 year risk period#	
	Case	Control	Case	Control
Characteristics	N (%)	N (%)	N (%)	N (%)
Total	148 (100)	475 (100)	95 (100)	296 (100)
Median no. of controls (IQR)	2 (1-4)		2 (1-4)	
Type microscopic colitis				
Collagenous colitis	61 (41.2)		29 (30.5)	
Lymphocytic colitis	48 (32.4)		31 (32.6)	
Not specified	39 (26.4)		25 (26.3)	
Sex				
male	32 (21.6)	100 (21.1)	24 (25.3)	81 (27.4)
female	116 (78.4)	375 (78.9)	71 (74.7)	215 (72.6)
Mean age at index date (SD)	45.3 (2.0)	45.7 (1.7)	45.4 (1.9)	45.6 (1.8)
Median age at index date (IQR)	45.7 (44.6-46.6)	46.1 (45.0-46.8)	45.7 (44.6-46.6)	46.2 (45.0-46.7)
Age group (years)				
<40	5 (3.4)	12 (2.5)	4 (4.2)	11 (3.7)
40-45	47 (31.8)	126 (26.5)	29 (30.5)	79 (26.7)
>45	96 (64.9)	337 (70.9)	62 (65.3)	206 (69.6)
Celiac Disease yes	9 (6.1)	17 (3.6)	6 (6.3)	6 (2)
Inflammatory Bowel Disease yes	23 (15.5)	13 (2.7)	16 (16.8)	10 (3.4)
Hypothyroid Disease yes	**12 (8.1)**	**31 (6.5)**	1 (1.1)	0 (0)
Polyarthritis yes	2 (1.4)	0 (0)	**1 (1.1)**	**1 (0.3)**
Rheumatoid Arthritis yes	**3 (2)**	**8 (1.7)**	**5 (5.3)**	**6 (2.0)**
Diabetes Mellitus T2 yes	**6 (4.1)**	**20 (4.2)**	**5 (5.3)**	**15 (5.1)**
Index year				
1999	1 (0.7)	1 (0.2)	0 (0)	0 (0)
2000	0 (0)	0 (0)	0 (0)	0 (0)
2001	0 (0)	0 (0)	0 (0)	0 (0)
2002	1 (0.7)	1 (0.2)	1 (1.1)	1 (0.3)
2003	0 (0)	0 (0)	0 (0)	0 (0)
2004	3 (2)	10 (2.1)	3 (3.2)	10 (3.4)
2005	1 (0.7)	1 (0.2)	1 (1.1)	1 (0.3)
2006	0 (0)	0 (0)	0 (0)	0 (0)
2007	2 (1.4)	5 (1.1)	1 (1.1)	4 (1.4)
2008	8 (5.4)	17 (3.6)	3 (3.2)	8 (2.7)
2009	22 (14.9)	54 (11.4)	15 (15.8)	31 (10.5)
2010	36 (24.3)	102 (21.5)	21 (22.1)	68 (23.0)
2011	39 (26.4)	137 (28.8)	27 (28.4)	90 (30.4)
2012	34 (23.0)	144 (30.3)	22 (23.2)	80 (27.0)
2013	1 (0.7)	3 (0.6)	1 (1.1)	3 (1)

** 1 year risk period (A): assessment of characteristics for the cases and controls that are included in the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A). # 2 year risk period (B): assessment of characteristics for the cases and controls that are included in the analysis with 2 year valid data available. See Figure 1, risk period (B). IQR, interquartile range; SD, standard deviation. Matching factors: age, GP practice, sex, date of diagnosis (for cases). Values in bold represent non-significant different proportions between matched cases and controls.*

Table 2. Exposure characteristics of cases and controls.

	COMMUNITY CONTROLS			
	Within 1 year before index date #		Within 2 years before index date including 1 year lag-time‡	
	Case N (%)	Control N (%)	Case N (%)	Control N (%)
Total Number	**218 (100)**	**15,045 (100)**	**138 (100)**	**9,160 (100)**
Use of NSAIDs:				
Never use (>12 mo)	175 (80)	14,597 (97)	103 (75)	8,889 (97)
Past use (3-12 mo)	16 (7.3)	237 (1.6)	11 (8)	169 (1.8)
Current use (<3 mo)	27 (12)	211 (1.4)	24 (17)	102 (1.1)
Use of PPIs:				
Never use (>12 mo)	126 (58)	14,538 (97)	93 (67)	8,880 (97)
Past use (3-12 mo)	26 (12)	139 (0.9)	9 (6.5)	93 (1.0)
Current use (<3 mo)	66 (30)	368 (2.4)	36 (26)	187 (2.0)
Use of Statins:				
Never use (>12 mo)	176 (81)	14,683 (98)	108 (78)	8,952 (98)
Past use (3-12 mo)	3 (1.4)	31 (0.2)	8 (5.8)	40 (0.4)
Current use (<3 mo)	39 (18)	331 (2.2)	22 (16)	168 (1.8)
Use of SSRIs:				
Never use (>12 mo)	195 (89)	14,940 (99)	127 (92)	9,100 (99)
Past use (3-12 mo)	3 (1.4)	15 (0.1)	3 (2.2)	13 (0.1)
Current use (<3 mo)	20 (9.2)	90 (0.6)	8 (5.8)	47 (0.5)
Use of Low-dose Aspirin:				
Never use (>12 mo)	183 (84)	14,936 (99)	118 (86)	9,101 (99)
Past use (3-12 mo)	3 (1.4)	7 (0.05)	0 (0)	10 (0.1)
Current use (<3 mo)	32 (15)	102 (0.7)	20 (14)	49 (0.5)
Use of ACE-inhibitors:				
Never use (>12 mo)	187 (86)	14,821 (99)	118 (86)	9,030 (99)
Past use (3-12 mo)	1 (0.5)	18 (0.1)	6 (4.3)	23 (0.3)
Current use (<3 mo)	30 (14)	206 (1.4)	14 (10)	107 (1.2)
Use of Beta-blockers:				
Never use (>12 mo)	169 (78)	14,672 (98)	108 (78)	8,933 (98)
Past use (3-12 mo)	2 (0.9)	25 (0.2)	3 (2.2)	47 (0.5)
Current use (<3 mo)	47 (22)	348 (2.3)	27 (20)	180 (2)

** For 2 year exposure period: current use (< 3 months), recent use (3-12 months), past use (12-24 months), never use (> 24 months).*

 # 1 year risk period (A): assessment of exposure characteristics for the cases and controls that are included in the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A).

***‡** 2 year risk period (B) : assessment of exposure characteristics for the cases and controls that are included in the analysis with 2 year valid data available, but excluding the 1 year prior to index date, thus including a 1 year lag-time. See Figure 1, risk period (B).*

Table 2. Exposure characteristics of cases and controls (*continued*).

	COLONOSCOPY CONTROLS			
	Within 1 year before index date#		Within 2 years before index date excluding the 1 year prior to index date‡	
	Case N (%)	Control N (%)	Case N (%)	Control N (%)
Total Number	**148 (100)**	**475 (100)**	**95 (100)**	**296 (100)**
Use of NSAIDs:				
Never use (>12 mo)	121 (82)	455 (96)	69 (73)	282 (95)
Past use (3-12 mo)	11 (7.4)	6 (1.3)	11 (12)	10 (3.4)
Current use (<3 mo)	16 (11)	14 (2.9)	15 (16)	4 (1.4)
Use of PPIs:				
Never use (>12 mo)	83 (56)	441 (93)	62 (65)	289 (98)
Past use (3-12 mo)	23 (16)	4 (0.8)	7 (7.4)	4 (1.4)
Current use (<3 mo)	42 (28)	30 (6.3)	26 (27)	3 (1)
Use of Statins:				
Never use (>12 mo)	120 (81)	455 (96)	75 (79)	284 (96)
Past use (3-12 mo)	3 (2.0)	2 (0.4)	5 (5.3)	3 (1.0)
Current use (<3 mo)	25 (17)	18 (3.8)	15 (16)	9 (3)
Use of SSRIs:				
Never use (>12 mo)	131 (89)	475 (100)	87 (92)	296 (100)
Past use (3-12 mo)	2 (1.4)	0 (0)	3 (3.2)	0 (0)
Current use (<3 mo)	15 (10)	0 (0)	5 (5.3)	0 (0)
Use of Low-dose Aspirin:				
Never use (>12 mo)	125 (84)	472 (99)	83 (87)	295 (99.7)
Past use (3-12 mo)	3 (2)	0 (0)	0 (0)	0 (0)
Current use (<3 mo)	20 (14)	3 (0.6)	12 (13)	1 (0.3)
Use of ACE-inhibitors:				
Never use (>12 mo)	126 (85)	457 (96)	80 (84)	286 (97)
Past use (3-12 mo)	1 (0.7)	0 (0)	5 (5.3)	2 (0.7)
Current use (<3 mo)	21 (14)	18 (3.8)	10 (11)	8 (2.7)
Use of Beta-blockers:				
Never use (>12 mo)	117 (79)	467 (98)	74 (78)	291 (98)
Past use (3-12 mo)	0 (0)	0 (0)	1 (1.1)	2 (0.7)
Current use (<3 mo)	31 (21)	8 (1.7)	20 (21)	3 (1)

** For 2 year exposure period: current use (< 3 months), recent use (3-12 months), past use (12-24 months), never use (> 24 months).*

 # 1 year risk period (A): assessment of exposure characteristics for the cases and controls that are included in the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A).

***‡** 2 year risk period (B) : assessment of exposure characteristics for the cases and controls that are included in the analysis with 2 year valid data available, but excluding the 1 year prior to index date, thus including a 1 year lag-time. See Figure 1, risk period (B).*

Higher cumulative doses of NSAIDs (>15 DDDs), SSRIs (30-90 DDDS; and >90 DDDs) and moderate to medium cumulative doses of beta-blockers (1-29 DDDs; 30-90 DDDs) were associated with an increased risk of MC in the 1 year risk period. In the 2 year risk period when only looking at the first year, all cumulative doses of NSAIDs were associated with an increased risk of MC, with the highest estimate for the highest cumulative dose (> 90 DDDs: ORa 10.8; 95% CI: 5.0-23.4). In this risk period all doses of ACE-inhibitors, between 30-90 DDDs of statins, the highest cumulative dose (>90 DDDs) of SSRIs and between 1-29 DDDs of beta-blockers were associated with MC. For PPIs all dose categories were associated with increase in risk of MC, although no dose-response effect with increasing risk estimates over higher dose categories was seen.

Risk of microscopic colitis compared to colonoscopy controls

By using a control group consisting of subjects who underwent a colonoscopy that was negative for MC or colorectal cancer, the potential impact of confounding-by-indication and diagnostic bias were taken into account. Looking at the 1 year risk period, adjusted odds ratios were only significantly increased for current use of PPIs (ORa 4.4; 95%CI: 1.6-12.1), low-dose aspirin (ORa 17.6; 95%CI: 1.9-165.9), and beta-blockers (ORa 5.8; 95%CI: 1.6-21.1) (Table 3B, Supplementary Figure 2A and B). No controls were exposed to SSRIs and thus no ORs for SSRI use could be calculated. When taking diagnostic delay (by looking at the period 1 to 2 years prior to index date and not in the 1 year prior to index date) into account, only current use of PPIs (ORa 10.6; 95%CI: 1.8-64.2) and NSAIDs (ORa 5.6; 95%CI: 1.2-27.0) remained to significantly increase the risk of MC. Results regarding individual types of NSAIDs and PPIs are shown in Supplementary Figures 3 and Figures 4. Heterogeneity for PPIs was seen for risk period B (p=0.022), but not for risk period A (p=0.0622). Analyses of dose effects for PPIs indicate that a higher cumulative dose was associated with a significant increased risk of MC in the 1 year risk period and was borderline significant for the 2 year risk period (Supplementary Table 1B). For NSAIDs, only the highest cumulative dose (>15 DDDs) was associated with MC in the 2 year risk period (ORa 5.7; 95%CI: 1.3-25.4).

Sensitivity analysis

When excluding the MC cases with unspecified type of MC, results were similar to the initial analyses (data not shown). Also, when stratifying the analyses by type of MC, results did not change substantially (data not shown). Odds ratios were higher for collagenous colitis than lymphocytic colitis during current use of PPIs. No significant effect modification by sex or age was observed on a multiplicative scale (data not shown).

Table 3A: Risk of Microscopic colitis, cases compared to community controls.

	Within 1 year before index date †				Within 2 years before index date excl the 1 year prior to index date ‡			
	ORmatched (95% CI)	P-value	ORadj# (95% CI)	P-value	ORmatched (95% CI)	P-value	ORadj# (95% CI)	P-value
Use of NSAIDs:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	6.1 (3.5-10.5)	<0.001	1.3 (0.6-2.7)	0.502	6.6 (3.3-12.9)	<0.001	2.3 (1.0-5.4)	0.056
Current use (<3 mo)	10.9 (7.0-17.1)	<0.001	2.7 (1.5-4.9)	0.001	24.3 (14.4-41.0)	<0.001	8.3 (4.1-17.0)	<0.001
Use of PPIs:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	28.2 (17.3-45.9)	<0.001	14.8 (8.1-27.3)	<0.001	11.2 (5.2-24)	<0.001	1.8 (0.6-5.2)	0.283
Current use (<3 mo)	23.4 (16.4-33.3)	<0.001	7.3 (4.5-12.1)	<0.001	21.3 (13.5-33.8)	<0.001	5.7 (3.0-10.8)	<0.001
Use of Statins:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	6.7 (2.0-22.6)	0.002	0.4 (0.1-2.5)	0.336	18.1 (7.85-42.2)	<0.001	3.4 (1.0-12.0)	0.053
Current use (<3 mo)	9.7 (6.5-14.5)	<0.001	1.2 (0.7-2.2)	0.497	11.5 (6.8-19.7)	<0.001	1.3 (0.6-3.0)	0.485
Use of SSRIs:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	15.1 (4.0-56.1)	<0.001	4.3 (0.8-24.3)	0.103	22.6 (6.0-85.8)	<0.001	15.9 (3.4-75.2)	<0.001
Current use (<3 mo)	17.4 (10.3-29.6)	<0.001	5.4 (2.8-10.4)	<0.001	12.77 (5.6-28.9)	<0.001	2.5 (0.9-7.3)	0.082
Use of Low-dose Aspirin:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	43.1 (10.1-184.4)	<0.001	5.4 (0.7-44.7)	0.118	NA		NA	
Current use (<3 mo)	23.0 (14.2-37.2)	<0.001	3.5 (1.8-6.8)	<0.001	31.4 (16.541-59.7)	<0.001	5.8 (2.2-15.0)	<0.001
Use of ACE-inhibitors:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	3.6 (0.5-28.0)	0.217	2.3 (0.5-12.1)	0.315	22.0 (8.2-58.8)	<0.001	8.6 (2.3-32.8)	0.002
Current use (<3 mo)	11.1 (7.2-17.1)	<0.001	2.5 (1.5-4.2)	0.001	11.0 (5.9-20.4)	<0.001	2.3 (1.0-5.4)	0.046
Use of Beta-blockers:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	5.6 (1.3-24.5)	0.022	0.13 (0.01-1.8)	0.128	6.1 (1.8-20.6)	0.004	0.3 (0.1-1.6)	0.167
Current use (<3 mo)	11.2 (7.7-16.3)	<0.001	2.7 (1.5-4.9)	0.001	13.1 (7.9-21.6)	<0.001	2.0 (1.0-4.1)	0.055

Table 3B. Risk of Microscopic colitis, cases compared to colonoscopy controls.

	Within 1 year before index date †				Within 2 years before index date excl the 1 year prior to index date ‡			
	ORmatched (95% CI)	P-value	ORadj# (95% CI)	P-value	ORmatched (95% CI)	P-value	ORadj# (95% CI)	P-value
Use of NSAIDs:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	6.7 (2.1-20.7)	0.001	12.4 (1.7-93.1)	0.014	4.0 (1.4-11.2)	0.009	1.7 (0.3-9.2)	0.552
Current use (<3 mo)	3.4 (1.4-7.9)	0.005	0.8 (0.2-2.7)	0.718	12.0 (3.7-38.6)	<0.001	5.6 (1.2-27.0)	0.031
Use of PPIs:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	19.7 (6.3-61.5)	<0.001	16.8 (4.2-66.7)	<0.001	4.. (1.1-16.6)	0.036	0.6 (0.1-6.7)	0.645
Current use (<3 mo)	9.8 (4.7-20.3)	<0.001	4.4 (1.6-12.1)	0.005	41.1 (9.5-178.9)	<0.001	10.6 (1.8-64.2)	0.010
Use of Statins:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	NA		NA		10.6 (2.2-51.1)	0.003	3.2 (0.1-124.2)	0.530
Current use (<3 mo)	10.7 (4.3-26.4)	<0.001	1.1 (0.3-4.3)	0.934	12.6 (3.7-42.5)	<0.001	1.1 (0.1-8.5)	0.924
Use of Low-dose Aspirin:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	NA		NA		NA		NA	
Current use (<3 mo)	30.7 (6.8-137.6)	<0.001	17.6 (1.9-165.9)	<0.001	46.7 (5.8-375.3)	<0.001	NA	
Use of ACE-inhibitors:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	NA		NA		10.3 (1.7-61.8)	0.011	NA	
Current use (<3 mo)	6.7 (2.9-15.19)	<0.001	2.2 (0.6-7.7)	0.236	12.9 (3.3-50.8)	<0.001	2.4 (0.2-36.7)	0.518
Use of Beta-blockers:								
Never use (>12 mo)	1 (ref)		1 (ref)		1 (ref)		1 (ref)	
Past use (3-12 mo)	NA		NA		4.2 (0.3-58.7)	0.283	1.7 (0.1-52.7)	0.774
Current use (<3 mo)	16.5 (6.2-43.8)	<0.001	5.8 (1.6-21.1)	0.008	53.1 (6.9-405.7)	<0.001	7.8 (0.7-82.8)	0.087

 # Adjusted for concomitant use of NSAIDs, PPIs, statins, SSRIs, low-dose aspirin, ACE-inhibitors, beta-blockers; celiac disease; inflammatory bowel disease; hypothyroid disease; polyarthritis; rheumatoid arthritis and type 2 diabetes mellitus. † 1 year risk period (A): Odds ratios from the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A). ‡ 2 year risk period (B) : Odds ratios from the analysis with 2 year valid data available, but excluding the 1 year prior to index date, thus including a 1 year lag-time. See Figure 1, risk period (B). Mo, months; SSRIs, selective serotonin reuptake inhibitors.

DISCUSSION

In this population-based nested case-control study use of NSAIDs, proton pump inhibitors, selective serotonin reuptake inhibitors, low-dose aspirin, ACE-inhibitors or beta-blockers were associated with an increased risk of MC. However, when taking confounding-by-indication, diagnostic delay and diagnostic bias into account (by comparing with subjects who have had a colonoscopy negative for colorectal cancer and MC), only PPIs and NSAIDs significantly increased the risk of MC. This finding was supported by dose analyses showing increasing estimates with higher cumulative doses used.

Different studies were done prior to this study with contradicting results. Regarding NSAIDs, an unmatched case control study compared the frequency of use of several drugs in patients with chronic watery diarrhea, but not MC, to that in patients attending an outpatient surgery unit.[377] This study suggested that NSAIDs, SSRIs and statins were significantly associated with chronic watery diarrhea.[377] Our results are well in line with this, as we showed that only PPIs, NSAIDs and low-dose aspirin increased the risk of MC when compared to colonoscopy controls. The apparent increased MC risk with use of ACE-inhibitors, beta-blockers, SSRIs and statins in that study is probably an artifact.[377] In the current study, these drugs did not increase the risk of MC when compared to community controls. They increase the likelihood of undergoing a colonoscopy by, for instance, inducing abdominal symptoms, increasing stool frequency or worsening diarrhea. In addition, NSAIDs are indicated for treatment of arthralgias, which often accompany MC. Thus, subjects with arthralgia may be more likely to undergo colonoscopy and be diagnosed with MC. Our results are in line with a recent Danish case-control study.[385] This study is however limited by the fact they classified having only 1 filled prescription in the year prior to MC diagnosis as being exposed to the drug, which may predispose to misclassification of exposure. No distinction was made between current users and past users, while filling more than only 1 prescription would provide a more robust investigation of the exposure.[385] Although the association between NSAIDs and MC may be explained by the underlying co-morbid disease, current use of NSAIDs in our population remained associated with an increased risk of MC even when we adjusted for concomitant exposure, polyarthritis and rheumatoid arthritis. Thus, it is unlikely that the indication of NSAID could explain the association between NSAIDs and MC as observed in the current study. This observation is supported by previous reports.[377, 378, 386] Also, in our study NSAIDs still increased the risk of MC up to 6-fold when taking diagnostic delay and diagnostic bias into consideration. Furthermore, the association was supported by the dose analysis providing increasing risk estimates with higher cumulative doses of NSAIDs used. To examine whether the risk of MC was different for individual types of NSAIDs we conducted analyses for individual NSAIDs. Diclofenac was the most commonly used NSAID and accounted for 52% to 67% of NSAIDs used by cases. Because fewer exposed cases could be matched to colonoscopy-negative controls, the study had insufficient power to estimate a risk estimate for each individual NSAID. The results on individual NSAIDs should thus be interpreted with caution. Physiologically the association can be explained by loosening the colonic paracellular

permeability,[85] inducing lower gastrointestinal (GI) bleeding[9, 86] and affecting the bowel integrity.[84] Subsequently, luminal antigens can more easily enter the lamina propria and elicit an immune and inflammatory reaction. Therefore we suggest that NSAIDs should be avoided in patients at risk of developing MC. To the best of our knowledge, no clinical decision models are available to weigh the benefits and risks of NSAIDs including MC as adverse event. A balanced decision should be based on clinical knowledge and the preference of the patient.

Proton Pump Inhibitors

The recent Danish study also noted the association between PPIs and MC, regardless of having had colonic biopsies.[385] Again, though they applied a second control group, the exposure definition was rather broad with only 1 filled prescription required to being classified as exposed to the drug.[385] Also, they relied on the MC diagnosis date[385] rather than the start of symptoms of MC as we could verify in the medical records. A previous case-control study from the Netherlands showed that use of PPIs was associated with an increased risk of MC.[378] However, this study may have suffered from selection bias, as cases were retrieved from a secondary and tertiary hospital, while controls were selected from the general population.[378] Another case-control study on 26 cases found contrasting results with no increased risk of MC with PPI use. This study may be limited by its sample size and by lack of adjustment for NSAIDs, which are often concomitantly used with PPIs.[387] As is shown in our study, substantial confounding-by-indication is present as the risk of MC for current use of PPIs in the 1 year risk period decreased from 7.3-fold to 4.4-fold when using colonoscopy controls instead of community controls. Similar to NSAIDs, we investigated the risk of MC for different individual PPIs. Omeprazole was the predominant PPI used and accounted for 59% to 67% of PPIs used by cases. There have been several case-series published on PPI-induced MC[388, 389] but the underlying pathophysiological mechanism remains poorly understood. Experimental studies have shown the influence of PPIs on intestinal permeability, inducing smooth muscle relaxation and inhibiting contractile activity.[83, 87, 88] The effect on the contractile activity system may also affect the actinomyosin cytoskeleton, resulting in conformational changes in the cytoskeleton of epithelial cells and subsequent alterations in the function of tight junctions.[83, 87, 88] PPIs also affect the colonic intestinal flora, thereby increasing the risk of bacterial intestinal infections. Evidence on this topic until now, however, is scarce.[210, 379]

Beta-blockers and ACE-inhibitors

Our observation that beta-blockers and ACE-inhibitors were associated with MC compared to community controls, but not compared to colonoscopy controls could be explained by two reasons. First, the association between beta-blockers and ACE-inhibitors is true, but could not be confirmed in the comparison with the colonoscopy controls due to smaller sample size. Second, the association is false and likely due to confounding-by-indication, for instance subjects on drugs may be more closely monitored. There is some evidence on a

pathophysiological mechanism by which beta-blockers augment small intestinal transit by increasing the propulsive force associated with small intestinal contractions.[390, 391] To which extent these effects result in increased bowel frequency and stool consistency has not been studied.

Selective serotonin reuptake inhibitors

We demonstrated that SSRIs increased the risk of MC when compared to community controls, but not when compared to colonoscopy controls. This could be explained by confounding-by-indication, in particular since diarrhea is a known side effect of SSRI use.[392]

Strengths and limitations

Strengths of the current study include the population-based setting based of the electronic medical records, which allowed to identify all potential MC cases while matching to community controls and colonoscopy-negative controls. By doing so, we mitigated against selection bias as the cases and controls were derived from the same source population. In this context, the odds ratio may be interpreted directly as the relative risk.[393, 394] Second, by applying different risk periods, from 1 year up to 2 years prior to the index date, we corrected for any diagnostic delay of MC, which may take up to several months. This is demonstrated by the fact that exposure closer to index date (<3 months) yielded higher risks of MC than exposure longer before (>12 months). This could be due to an actual risk increase, but is more likely affected by lag-time bias. We also chose the date of first symptoms leading to the MC diagnosis as index date in order to avoid any misclassification of the exposure in the risk periods.

We acknowledge the following limitations. First, MC is a specialist confirmed diagnosis, meaning that in a GP database underreporting of MC could have occurred. We assumed that all relevant medical information on a microscopic diagnosis is recorded by the GP. However, this may not hold true entirely and we may have missed some MC cases. Nevertheless, we extensively reviewed the medical records of all MC cases included in the current study to ensure that the MC cases included in the study had histological confirmation of the diagnosis. Misclassification of MC is therefore unlikely, but if present it will be non-differential and will have resulted in more conservative, but unbiased estimates. Additionally, by excluding the unspecified MC cases we performed sensitivity analyses which yielded similar results as the initial analyses. When stratifying by type of MC, we found similar results as for the main analysis. However, caution should be taken when interpreting the findings on the risk of collagenous and lymphocytic colitis separately by use of drugs, as the subgroup analyses were based on small numbers. We included two control groups, which both have their limitations. The colonoscopy group had a clinical indication to undergo this procedure, which you can see as a test-negative control group, however this is similarly so for the cases. Confounding for 'indication' is actually reduced in such a control group. Colonoscopies were

performed for the complete range of clinical indications, including colorectal cancer screening. However, results from analyses are consistent across the control groups, which strengthen the results and provide consistent evidence that NSAIDs and PPIs are associated with MC. Also, in the more recent years clinicians became more aware of MC. The majority of cases was diagnosed after 2006. This has an effect on the sample size, but was unlikely to provide spurious or biased associations since cases and controls were matched on calendar time. Second, information on other potential confounders such as smoking status and alcohol use is likely to be underreported in the database and was therefore not considered in the analysis. This may have resulted in residual confounding. Thirdly, the date of onset of disease could have been misclassified. Although we tried to mitigate against misspecification of the risk window by using the date of onset of symptoms as index date, we cannot account for patients delay between actual start of symptoms and recording of symptoms by the GP. Yet, in order to account for diagnostic delay, we applied two different risk periods in the current study. Fourth, we only observed that NSAIDs and PPIs were associated with MC. However, due to the smaller sample size, particularly in the risk period of 2 years while excluding the last year prior to index date, we cannot rule out that due to power issues we did not observe an association for the other drugs.

In conclusion, non-steroidal anti-inflammatory drugs and proton pump inhibitors significantly increased the risk of MC, even after taking diagnostic bias and diagnostic delay into account. Use of selective serotonin reuptake inhibitors, low-dose aspirin, beta-blockers and ACE-inhibitors were associated with increased risk of MC when compared to community controls, but not compared to colonoscopy negative controls. We suggest that the association between SSRIs, low-dose aspirin, beta-blockers, ACE-inhibitors and MC in community controls could be due to worsening of diarrhea or symptoms in patients with underlying colonic disease requiring colonoscopy rather than increasing the risk of MC itself.

SUPPLEMENTARY MATERIAL

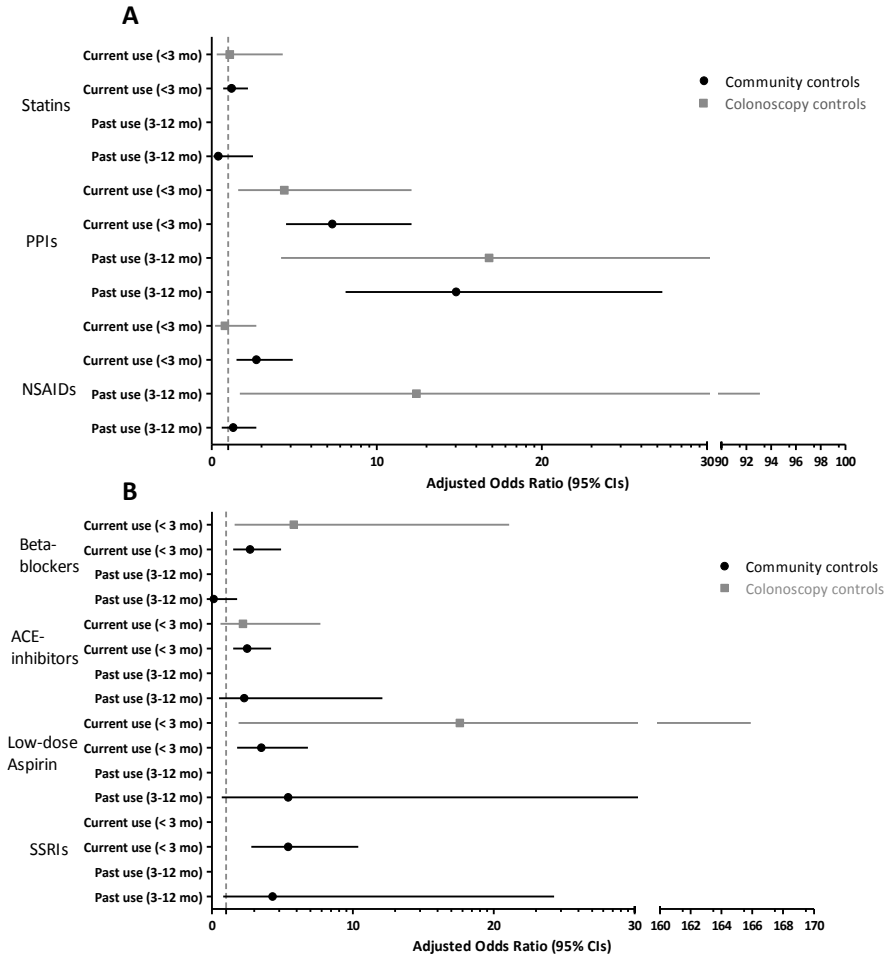
Supplementary Table 1A. Risk of microscopic colitis in relation with dose of drugs used, cases compared to community controls.

		COMMUNITY CONTROLS							
		1 year risk period†				2 year risk period‡			
		Case N (%)	Control N (%)	ORadj (95% CI)	P-value	Case N (%)	Control N (%)	ORadj (95% CI)	P-value
	DDDs*	**218 (100)**	**15,045 (100)**			**138 (100)**	**9,160 (100)**		
NSAIDS	0	176 (81)	14,599 (97.0)	1 (ref)		102 (74)	8,877 (96.9)	1 (ref)	
	1-7	8 (3.7)	160 (1.1)	0.9 (0.4-2.2)	0.851	11 (8.0)	110 (1.2)	3.7 (1.5-9.0)	0.004
	8-15	10 (4.6)	124 (0.8)	0.8 (0.3-2.0)	0.674	7 (5.1)	80 (0.9)	3.7 (1.3-10.2)	0.013
	>15	24 (11)	162 (1.1)	3.1 (1.7-5.8)	<0.001	18 (13)	93 (1.0)	10.8 (5.0-23.4)	<0.001
PPIs	0	126 (58)	14,538 (96.6)	1 (ref)		86 (62)	8,853 (96.6)	1 (ref)	
	1-29	17 (7.8)	129 (0.9)	8.7 (4.2-18.1)	<0.001	12 (8.7)	68 (0.7)	4.0 (1.4-11.4)	0.010
	30-90	23 (11)	126 (0.8)	13.9 (7.2-26.9)	<0.001	13 (9.4)	67 (0.7)	12.3 (5.5-27.4)	<0.001
	>90	52 (24)	252 (1.7)	13.9 (8.2-23.6)	<0.001	27 (20)	172 (1.9)	5.9 (3.1-11.5)	<0.001
Statins	0	176 (81)	14,683 (97.6)	1 (ref)		105 (76)	8,925 (97.4)	1 (ref)	
	1-29	4 (1.8)	34 (0.2)	1.5 (0.4-6.8)	0.567	0 (0)	18 (0.2)	-	0.981
	30-90	6 (2.8)	35 (0.2)	2.4 (0.8-7.0)	0.104	8 (5.8)	28 (0.3)	4.0 (1.3-12.1)	0.014
	>90	32 (15)	293 (1.9)	1.0 (0.6-1.9)	0.899	25 (18)	189 (2.1)	1.7 (0.8-3.6)	0.148
SSRIs	0	195 (89)	14,940 (99.3)	1 (ref)		126 (91.3)	9,093 (99.3)	1 (ref)	
	1-29	1 (0.5)	11 (0.1)	4.6 (0.5-41.4)	0.173	1 (0.7)	7 (0.1)	7.0 (0.7-71.2)	0.101
	30-90	6 (2.8)	18 (0.1)	5.1 (1.4-18.0)	0.012	1 (0.7)	12 (0.1)	2.2 (0.3-18.9)	0.487
	>90	16 (7.3)	76 (0.5)	4.0 (2.0-8.0)	<0.001	10 (7.2)	48 (0.5)	5.3 (2.2-12.6)	<0.001
ACE-inhibitors	0	187 (86)	14,821 (98.5)	1 (ref)		114 (83)	9,012 (98.4)	1 (ref)	
	1-29	4 (1.8)	47 (0.3)	1.7 (0.5-6.0)	0.378	8 (5.8)	69 (0.8)	3.2 (1.3-8.1)	0.012
	30-90	7 (3.2)	31 (0.2)	3.9 (0.9-16.0)	0.060	3 (2.2)	16 (0.2)	6.1 (1.5-24.3)	0.010
	>90	20 (9.2)	146 (1.0)	1.7 (0.9-3.5)	0.121	13 (9.4)	63 (0.7)	2.7 (1.1-6.7)	0.038
Beta-blockers	0	169 (78)	14,671 (98)	1 (ref)		104 (75)	8,908 (97.2)	1 (ref)	
	1-29	13 (6)	57 (0.4)	8.3 (3.6-19.0)	<0.001	9 (6.5)	45 (0.5)	6.8 (2.6-18.1)	<0.001
	30-90	10 (4.6)	94 (0.6)	2.7 (1.2-6.2)	0.017	7 (5.1)	51 (0.6)	2.3 (0.8-6.9)	0.123
	>90	26 (12)	223 (1.5)	1.6 (0.8-3.0)	0.168	18 (13)	156 (1.7)	1.9 (0.9-4.2)	0.099

Supplementary Table 1B. Risk of microscopic colitis in relation with dose of drugs used, cases compared to colonoscopy controls.

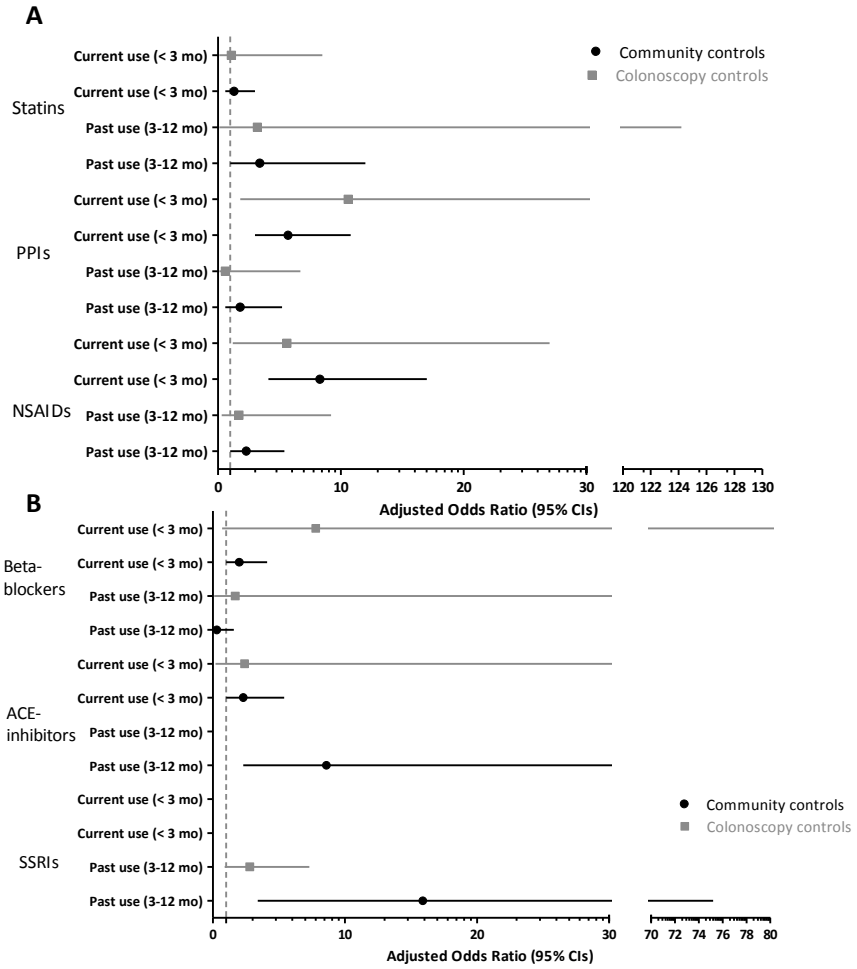
		COLONOSCOPY CONTROLS							
		1 year risk period†				2 year risk period‡			
		Case N (%)	Control N (%)	ORadj (95% CI)	P-value	Case N (%)	Control N (%)	ORadj (95% CI)	P-value
	DDDs*	**148 (100)**	**475 (100)**			**95 (100)**	**296 (100)**		
NSAIDS	0	121 (82)	455 (95.8)	1 (ref)		68 (72)	282 (95.3)	1 (ref)	
	1-7	5 (3.4)	7 (1.5)	1.9 (0.4-9.6)	0.464	8 (8.4)	6 (2.0)	2.7 (0.5-13.4)	0.229
	8-15	6 (4.1)	8 (1.7)	0.6 (0.1-3.8)	0.578	6 (6.3)	2 (0.7)	-	0.989
	>15	16 (11)	5 (1.1)	3.6 (0.7-19.2)	0.131	13 (14)	6 (2.0)	5.7 (1.3-25.4)	0.024
PPIs	0	83 (56)	441 (92.8)	1 (ref)		57 (60)	285 (96.3)	1 (ref)	
	1-29	12 (8.1)	5 (1.1)	1.9 (0.4-9.3)	0.454	11 (12)	5 (1.7)	6.9 (1.1-42.9)	0.040
	30-90	20 (14)	11 (2.3)	10.9 (3.0-40.1)	<0.001	8 (8.4)	1 (0.3)	-	0.991
	>90	33 (22)	18 (3.8)	11.7 (3.4-41.1)	<0.001	19 (20)	5 (1.7)	4.3 (1.0-17.7)	0.045
Statins	0	120 (81)	455 (95.8)	1 (ref)		74 (78)	284 (95.9)	1 (ref)	
	1-29	4 (2.7)	0 (0)	-	0.985	0 (0)	0 (0)	-	
	30-90	3 (2)	4 (0.8)	2.1 (0.2-20.6)	0.511	3 (3.2)	0 (0)	-	
	>90	21 (14)	16 (3.4)	0.5 (0.1-2.7)	0.396	18 (19)	12 (4.1)	1.4 (0.26-6.95)	0.722
ACE-inhibitors	0	126 (85)	457 (96.2)	1 (ref)		78 (82)	286 (96.6)	1 (ref)	
	1-29	4 (2.7)	14 (2.9)	-		4 (4.2)	1 (0.3)	-	
	30-90	7 (4.7)	0 (0)	-		2 (2.1)	0 (0)	-	
	>90	11 (7.4)	4 (0.8)	15.6 (1.8-132.7)	0.012	11 (12)	9 (3)	1.6 (0.2-12.9)	0.640
Beta-blockers	0	117 (79)	467 (98.3)	1 (ref)		72 (76)	290 (98.0)	1 (ref)	
	1-29	7 (4.7)	2 (0.4)	5.9 (0.7-51.9)	0.111	5 (5.3)	2 (0.7)	8.5 (0.9-84.1)	0.068
	30-90	7 (4.7)	3 (0.6)	5.9 (0.4-87.7)	0.198	5 (5.3)	3 (1)	0.5 (0.03-6.9)	0.565
	>90	17 (11)	3 (0.6)	1.8 (0.3-11.4)	0.531	13 (14)	1 (0.3)	4.3 (0.4-49.1)	0.243

**DDDs, defined daily doses. The DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. # Adjusted for concomitant use of NSAIDs, PPIs, statins, SSRIs, low-dose aspirin, ACE-inhibitors and beta-blockers. † 1 year risk period (A): Odds ratios from the analysis with a 1 year risk period assessment available. See Figure 1, risk period (A). ‡ 2 year risk period (B): Odds ratios from the analysis with 2 year valid data available, but excluding the 1 year prior to index date, thus including a 1 year lag-time. See Figure 1, risk period (B).*



Supplementary Figure 1A and 1B. Risk of microscopic colitis compared to community and colonoscopy controls in risk period 1 year prior to index date (risk period A).

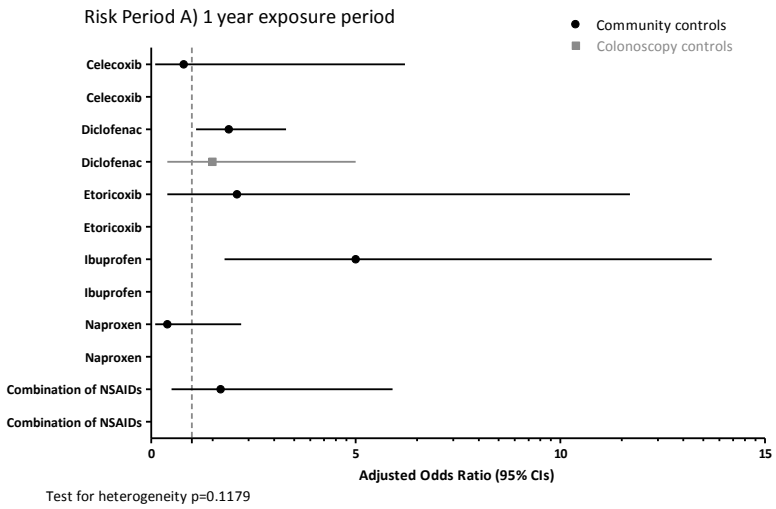
 # Adjusted for concomitant use of NSAIDs, PPIs, statins, SSRIs, low-dose aspirin, ACE-inhibitors, beta-blockers; celiac disease; inflammatory bowel disease; hypothyroid disease; polyarthritis; rheumatoid arthritis and type 2 diabetes mellitus.
Risk period (A): Odds ratios from the analysis 1 year prior to index date. See Figure 1, risk period (A).
Mo, months; SSRIs, selective serotonin reuptake inhibitors.



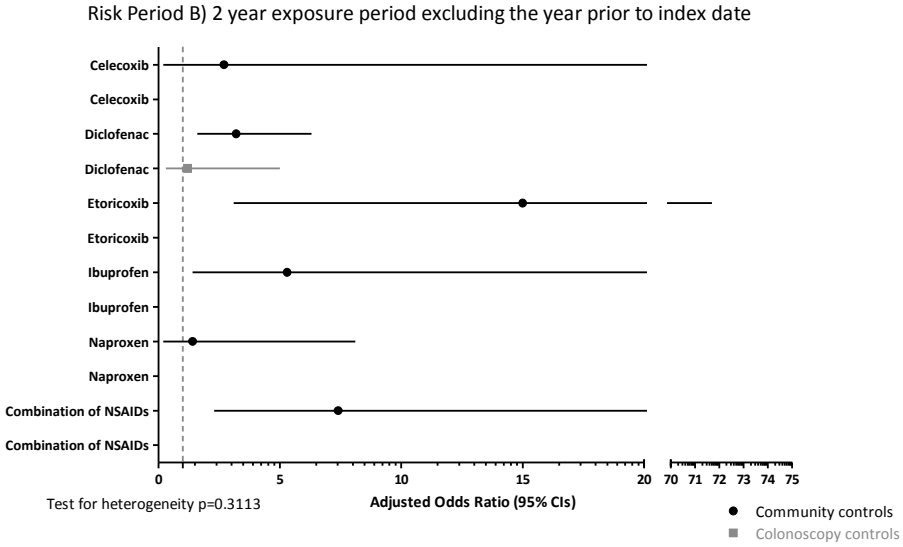
Supplementary Figure 2A and 2B. Risk of microscopic colitis compared to community and colonoscopy controls in risk period within 2 years before index date, while excluding the 1 year prior to index date (risk period B).

 # Adjusted for concomitant use of NSAIDs, PPIs, statins, SSRIs, low-dose aspirin, ACE-inhibitors, beta-blockers; celiac disease; inflammatory bowel disease; hypothyroid disease; polyarthritis; rheumatoid arthritis and type 2 diabetes mellitus.
Risk period (B): Odds ratios from the analysis within 2 years before index date while excluding the year prior to index date. See Figure 1, risk period (B).
Mo, months; SSRIs, selective serotonin reuptake inhibitors.

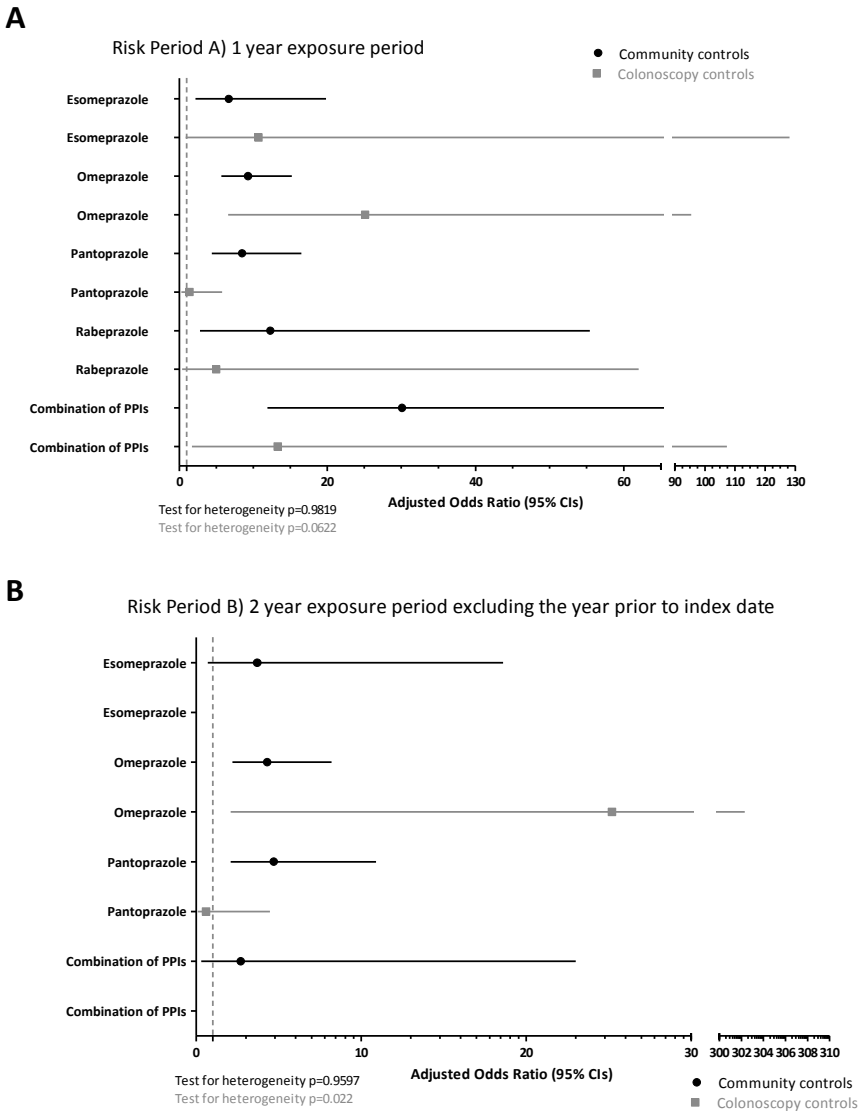
A



B



Supplementary Figure 3A and 3B. Risk of Microscopic colitis for individual types of NSAIDs, cases compared to community and colonoscopy controls.



Supplementary Figure 4A and 4B. Risk of Microscopic colitis for individual types of PPIs, cases compared to community and colonoscopy controls**.**

CHAPTER 5.3

Risk of Colorectal Neoplasia in patients with Microscopic Colitis

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ABSTRACT

BACKGROUND

Microscopic colitis (MC) is a disease characterized by chronic watery diarrhea. Affected tissue has a normal endoscopic appearance but microscopic inflammation. It is unknown whether this increases the risk for colorectal neoplasia.

AIM

We assessed the incidence of non-adenomatous polyps, adenomas and colorectal cancer (CRC) in patients with MC.

METHODS

Cohort study using nationwide population-based databases in Denmark and the Netherlands. We identified all adults (aged ≥18 years) newly diagnosed with MC and followed them until first occurrence of a polyp, adenoma, or CRC, or death during the study period (1991-2014). Standardized incidence ratios (SIRs) were used to compare the incidence of these occurrences in MC patients and in the general population. Absolute risks of the outcomes after MC diagnosis were calculated using Kaplan-Meier analysis.

RESULTS

We identified 13,061 incident MC cases in Denmark and 7,770 cases in the Netherlands. In the Danish cohort, 1,976 (15.1%) patients developed a non-adenomatous polyp, 1,039 (8.0%) developed an adenoma, and 111 (0.8%) were diagnosed with CRC. In the Dutch cohort 1,005 (12.9%) patients developed a polyp, 687 (8.8%) developed an adenoma, and 91 (1.2%) were diagnosed with CRC. The SIR for CRC was 0.90 (95% CI: 0.74-1.09) in Denmark and 0.83 (95% CI: 0.75-0.89) in the Netherlands. Within the first year after MC diagnosis, the SIR was 2.23 (95% CI: 1.68-2.91) in Denmark and 2.74 (95% CI: 1.89-4.43) in the Netherlands, and then decreased in both countries. The absolute 10-year risk of CRC was 1.3%-1.4%.

CONCLUSION

The risk of developing CRC 10 years after incident MC diagnosis is small. The high rate of non-adenomatous polyps and adenomas in the first year following MC diagnosis is probably due to heightened diagnostic efforts, with associated removal of polyps and treatment leading to a lower rate of CRC in subsequent years.

INTRODUCTION

Microscopic colitis (MC) is disease characterized by chronic watery diarrhea. Affected colonic mucosa has a normal endoscopic appearance but microscopic inflammation.[371, 372, 395] MC includes two distinct entities: lymphocytic colitis (LC) and collagenous colitis (CC). The causes of the disease are largely unknown. Risk factors include autoimmune diseases.[373-375] Use of certain drugs such as non-steroidal anti-inflammatory drugs (NSAIDs) and proton pump inhibitors (PPIs) also has been associated with MC risk.[396]

MC is recognized as a form of chronic inflammatory bowel disease (IBD), which includes Crohn's disease (CD) and ulcerative colitis (UC). IBD has been associated with increased risk of colorectal cancer (CRC) due to chronic inflammation.[397] However, it remains unknown whether the risk of gastrointestinal (GI) cancer, and more specifically CRC, is similarly elevated in MC patients. Currently there are no guidelines for routine colonoscopy surveillance in MC patients. If they are at significantly increased risk of CRC, appropriate surveillance strategies should be considered, as recommended for other forms of IBD.[398, 399]

To date, no prospective study has investigated cancer risk after a new diagnosis of MC. One US case-control study reported a decreased risk of CRC and colorectal adenomas among 647 MC cases compared to age and gender-matched patients without MC that underwent colonoscopy for colorectal screening or surveillance.[400] However, these results should be interpreted with caution, as CRC was diagnosed before or concurrently with MC. The study could not discern whether the MC patients were at higher risk due to chronic colonic inflammation.[400] Two other retrospective studies detected no increased CRC risk after a CC diagnosis.[401, 402] A Canadian cohort study including 164 incident MC cases reported only on CRC occurrence before an MC diagnosis.[403]

This study assessed the risk of non-adenomatous polyps, adenomas, and CRC in patients diagnosed with MC, using data from large populations, with long follow-up.

METHODS

We conducted a nationwide historical cohort study in Denmark and the Netherlands to compare the observed number of non-adenomatous polyps, adenomas and CRC diagnosed in MC patients with the number expected in the general population.

Data sources

In Denmark, the Danish Civil Registration System (DCRS) assigns a personal identifier to each Danish resident at birth or upon immigration, and also monitors mortality and emigration. The civil registration number can be used to link numerous Danish administrative and health registries on an individual level.[404] Since its establishment in January 1977, the Danish National Patient Registry (DNPR) has maintained records on all discharges from non-psychiatric

hospitals.[405 406] In 1995, hospital outpatient clinic visits were added to its database, accounting for essentially all specialist gastroenterology and cancer care in Denmark. DNPR data elements include patients' civil registration number, dates of hospital admission and discharge, surgical procedures, and up to 20 discharge diagnoses for each hospitalization. All inpatient stays and outpatient hospital visits are assigned diagnoses coded according to the International Classification of Diseases, Eighth Revision (ICD-8) until the end of 1993 and Tenth Revision (ICD-10) thereafter.[323] We obtained information on CRC diagnoses from the DNPR. The Danish Pathology Registry (DPR), established in 1990, provided results of pathological examinations of MC, non-adenomatous polyps and adenomas. Since 1997 all pathology departments in Denmark have been required to submit their pathology reports to the DPR. Diagnoses are coded according to a Danish version of the Systematized Nomenclature of Medicine (SNOMED).[257] Previous studies of gastrointestinal diseases have documented the accuracy of these data sources.[407]

In the Netherlands all histopathology and cytopathology reports are collected in the PALGA database, which encompasses all 55 pathology laboratories in the country.[408] Since 1991, PALGA has had nationwide coverage and currently includes >42 million reports from nearly 10 million patients. Each report contains encrypted patient information, a portion of the original pathology report, and diagnostic codes similar to the SNOMED codes issued by the College of American Pathologists.[409] A limitation is that the number and location of biopsies and the indication for performing an endoscopic procedure are not uniformly recorded. However, each pathology report can be traced to an individual patient with a unique identifier, allowing follow-up of subsequent histology.[410] In the current study, information on cases of MC, non-adenomatous polyps, adenomas, CRC, and celiac disease was extracted from the PALGA database.

Study population

In both countries, we identified a cohort of adults (aged ≥18 years) with an incident diagnosis of microscopic colitis recorded during the study period (January 1, 1990 - December 31, 2014). MC patients were excluded from the cohort if they had been diagnosed with CRC or another gastrointestinal cancer before their MC diagnosis. A previous Danish study has documented the validity of SNOMED codes for identifying MC.[411] In the Netherlands MC diagnoses were verified through review of pathology reports, as previously described.[412] MC was classified as lymphocytic, collagenous, or 'unspecified' when no further information on subtype was available.

For each patient in the MC cohorts, follow-up started on the date of first MC diagnosis and ended upon the diagnosis of non-adenomatous polyps, adenomas, or CRC, death, emigration, or end of the study period, whichever came first. Since only pathology reports were available in PALGA, the date of death was not known for each subject. In order to censor person-time and to avoid overestimating the denominator, we assumed a life expectancy similar to that of the general Dutch population.

Outcomes

Three outcomes were evaluated in the study: non-adenomatous polyps, adenomas, and CRC. We considered non-adenomatous polyps and adenomas as separate outcomes because of their different malignant potential. In case of multiple lesions, only the most advanced lesion was recorded.

Statistical Analysis

We described the characteristics of the MC cohorts in the two countries. To compare the risk of non-adenomatous polyps, adenomas, and cancer in the MC cohorts with that in the general population, we calculated standardized incidence ratios (SIRs) by dividing the observed number of cases by the expected number of cases.[413] In Denmark the number of expected cases was based on calculated reference incidence rates from a nationwide database. In The Netherlands, it was derived from Globocan.[414] Confidence intervals (95% CI) were computed based on the assumption that the observed number of cases followed a Poisson distribution. Numerators and denominators were stratified by sex, time from first recorded MC diagnosis (≤1 or > 1 year), age at MC diagnosis, and calendar year of MC diagnosis. We used Kaplan-Meier analysis to calculate the absolute (cumulative) risk of non-adenomatous polyps, adenomas, and CRC occurring within 10 years following diagnosis of MC. Kaplan-Meier analysis was stratified by sex, type of MC and age.

As only a subset of the general population undergoes colonoscopy, comparison of the study cohorts with the general population may be biased. We therefore performed sensitivity analyses in which we classified MC patients on their histology reports on the date of MC diagnosis. This means that we classified MC patients at time of MC diagnosis as (1) being free of non-adenomatous polyps or adenomas, (2) having a non-adenomatous polyp, and (3) having an adenoma. We then calculated the progression to and incidence rates (IRs) of outcomes in these three groups during follow-up and compared them with rates in populations undergoing colorectal screening (Supplementary Table 2).[415-421]

All statistical analyses were performed using SAS version 9.2. The study protocol was approved by the Danish Protection Agency (2011-41-5913) and by the PALGA Review Board.

RESULTS

We identified 13,275 subjects with incident MC in Denmark. After exclusion of patients with CRC (n=193, 1.5%) or other GI cancers (n=21, 0.2%) before or at the time of MC diagnosis, 13,061 subjects with incident MC remained and were followed for a median duration of 3.6 years (Table 1). The majority of subjects was female (71%) and median age at MC diagnosis was 66.3 years (interquartile range (IQR): 56.4-75.5 years). In the Netherlands, we identified 10,826 potential MC cases, of whom 7,896 were classified as incident MC cases and the remaining 2,930 patients did not have microscopic colitis. We excluded 126 patients with a

history of cancer before cohort entry (n=104, 1.3%; of these, CRC: n=22; 0.3%; other GI cancer), resulting in 7,770 incident MC patients who were followed for a median duration of 7.2 years. The median age was 61 years (IQR: 49-71) and the majority (73%) was female.

Among patients with incident MC in Denmark, we observed 937 patients with non-adenomatous polyps, of whom 154 were diagnosed at time of MC diagnosis; 1,039 with adenomas, of whom 24 at time of MC diagnosis; and 111 with CRC (Table 2). In the Netherlands, we observed 318 patients with non-adenomatous polyps, of whom 196 at time of MC diagnosis; 687 with adenomas of whom 388 at time of MC diagnosis; and 91 with CRC.

Table 2. Number of incident outcomes in microscopic colitis patients in Denmark and the Netherlands.

		Denmark N (%)	**the Netherlands N (%)**
MC all	Total MC	13,061 (100)	7,770 (100)
	Non-adenomatous polyps	937 (7.2)	318 (4.1)
	Adenomas	1,039 (8.0)	687 (8.8)
	Colorectal cancer	111 (0.8)	91 (1.2)
Collagenous	Total Collagenous	7,257 (100)	4,320 (100)
	Non-adenomatous polyps	449 (6.2)	167 (3.9)
	Adenomas	512 (7.1)	329 (7.6)
	Colorectal cancer	70 (1.0)	51 (1.2)
Lymphocytic	Total Lymphocytic	5,335 (100)	2,629 (100)
	Non-adenomatous polyps	455 (8.5)	130 (4.9)
	Adenomas	494 (9.3)	283 (10.8)
	Colorectal cancer	39 (0.7)	28 (1.1)
Unspecified	Total Unspecified	469 (100)	821 (100)
	Non-adenomatous polyps	33 (7.0)	21 (2.6)
	Adenomas	33 (7.0)	75 (9.1)
	Colorectal cancer	3 (0.6)	12 (1.5)

MC, microscopic colitis

In Denmark, rates of non-adenomatous polyps and adenomas in the general population were available as reference, allowing estimation of standardized incidence ratios (SIRs) for these outcomes. SIRs for non-adenomatous polyps and adenomas were significantly increased (Supplementary Table 1).

Table 1. Demographic characteristics of subjects with microscopic colitis (MC) by type in Denmark and The Netherlands.

	Denmark				The Netherlands			
	MC all N (%)	Collagenous N (%)	Lymphocytic N (%)	Unspecified N (%)	MC all N (%)	Collagenous N (%)	Lymphocytic N (%)	Unspecified N (%)
Total	13,061 (100)	7,257 (100)	5,335 (100)	469 (100)	7,770 (100)	4,320 (100)	2,629 (100)	821 (100)
Sex								
Female	9,259 (70.9)	5,472 (75.4)	3,454 (64.7)	333 (71)	5,656 (72.8)	3,264 (75.6)	1,854 (70.5)	538 (65.5)
Male	3,802 (29.1)	1,785 (24.6)	1,881 (35.3)	136 (29)	2,114 (27.2)	1,056 (24.4)	775 (29.5)	283 (34.5)
Age								
Median (IQR)	66.3 (56.4-75.5)	67.4 (58.1-76.6)	64.5 (53.7-74.0	67.2 (58.8-75.5)	61 (49-71)	60.5 (50-71)	61 (50-71)	60 (47-72)
Mean (SD)	64.9 (14.6)	66.4 (13.8)	62.7 (15.5)	66.5 (13.1)	59.4 (15.4)	59.7 (15)	59.6 (15.5)	58.0 (17.1)
Celiac Disease								
No	12,887 (98.7)	7,184 (99)	5,243 (98.3)	460 (98.1)	7,514 (96.7)	4,223 (97.8)	2,490 (94.7)	801 (97.6)
Yes	174 (1.3)	73 (1.0)	92 (1.7)	9 (1.9)	256 (3.3)	97 (2.2)	139 (5.3)	20 (2.4)
Year of MC Diagnosis								
1990					18 (0.2)	16 (0.4)	1 (0)	1 (0.1)
1991					88 (1.1)	80 (1.9)	5 (0.2)	3 (0.4)
1992					86 (1.1)	83 (1.9)	2 (0.1)	1 (0.1)
1993					79 (1.0)	72 (1.7)	4 (0.2)	3 (0.4)
1994					84 (1.1)	78 (1.8)	3 (0.1)	3 (0.4)
1995	68 (0.5)	54 (0.7)	13 (0.2)	1 (0.2)	105 (1.4)	92 (2.1)	6 (0.2)	7 (0.9)
1996	118 (0.9)	77 (1.1)	32 (0.6)	9 (1.9)	120 (1.5)	99 (2.3)	14 (0.5)	7 (0.9)
1997	136 (1.0)	84 (1.2)	46 (0.9)	6 (1.3)	213 (2.7)	161 (3.7)	29 (1.1)	23 (2.8)
1998	166 (1.3)	101 (1.4)	56 (1.0)	9 (1.9)	180 (2.3)	125 (2.9)	36 (1.4)	19 (2.3)
1999	222 (1.7)	132 (1.8)	74 (1.4)	16 (3.4)	217 (2.8)	135 (3.1)	51 (1.9)	31 (3.8)
2000	252 (1.9)	144 (2.0)	98 (1.8)	10 (2.1)	250 (3.2)	165 (3.8)	57 (2.2)	28 (3.4)
2001	305 (2.3)	195 (2.7)	96 (1.8)	14 (3.0)	259 (3.3)	140 (3.2)	70 (2.7)	49 (6)
2002	483 (3.7)	288 (4.0)	176 (3.3)	19 (4.1)	320 (4.1)	167 (3.9)	91 (3.5)	62 (7.6)
2003	615 (4.7)	376 (5.2)	223 (4.2)	16 (3.4)	340 (4.4)	173 (4.0)	116 (4.4)	51 (6.2)
2004	676 (5.2)	408 (5.6)	242 (4.5)	26 (5.5)	382 (4.9)	203 (4.7)	129 (4.9)	50 (6.1)
2005	845 (6.5)	451 (6.2)	365 (6.8)	29 (6.2)	462 (5.9)	254 (5.9)	140 (5.3)	68 (8.3)
2006	946 (7.2)	510 (7.0)	407 (7.6)	29 (6.2)	420 (5.4)	231 (5.3)	150 (5.7)	39 (4.8)
2007	1,125 (8.6)	544 (7.5)	537 (10.1)	44 (9.4)	504 (6.5)	258 (6.0)	185 (7.0)	61 (7.4)

Table 1. Demographic characteristics of subjects with microscopic colitis (MC) by type in Denmark and The Netherlands (*continued*).

	Denmark				The Netherlands			
	MC all	**Collagenous**	**Lymphocytic**	**Unspecified**	**MC all**	**Collagenous**	**Lymphocytic**	**Unspecified**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
2008	1,057 (8.1)	581 (8.0)	439 (8.2)	37 (7.9)	473 (6.1)	250 (5.8)	185 (7).0	38 (4.6)
2009	1,430 (10.9)	779 (10.7)	593 (11.1)	58 (12.4)	545 (7.0)	281 (6.5)	203 (7.7)	61 (7.4)
2010	1,465 (11.2)	855 (11.8)	546 (10.2)	64 (13.6)	550 (7.1)	275 (6.4)	229 (8.7)	46 (5.6)
2011	1,580 (12.1)	874 (12.0)	668 (12.5)	38 (8.1)	621 (8)	305 (7.1)	257 (9.8)	59 (7.2)
2012	1,572 (12)	804 (11.1)	724 (13.6)	44 (9.4)	703 (9)	320 (7.4)	337 (12.8)	46 (5.6)
2013					747 (9.6)	353 (8.2)	329 (12.5)	65 (7.9)
2014					4 (0.1)	4 (0.1)	0 (0)	0 (0)
Age at MC Diagnosis								
18-19	26 (0.2)	6 (0.1)	20 (0.4)	0 (0)	29 (0.4)	10 (0.2)	13 (0.5)	6 (0.7)
20-24	118 (0.9)	31 (0.4)	87 (1.6)	0 (0)	129 (1.7)	53 (1.2)	51 (1.9)	25 (3)
25-29	156 (1.2)	55 (0.8)	99 (1.9)	2 (0.4)	133 (1.7)	62 (1.4)	51 (1.9)	20 (2.4)
30-34	222 (1.7)	95 (1.3)	121 (2.3)	6 (1.3)	280 (3.6)	142 (3.3)	93 (3.5)	45 (5.5)
35-39	323 (2.5)	128 (1.8)	184 (3.4)	11 (2.3)	317 (4.1)	174 (4)	102 (3.9)	41 (5)
40-44	484 (3.7)	229 (3.2)	245 (4.6)	10 (2.1)	436 (5.6)	248 (5.7)	140 (5.3)	48 (5.8)
45-49	630 (4.8)	337 (4.6)	275 (5.2)	18 (3.8)	628 (8.1)	385 (8.9)	188 (7.2)	55 (6.7)
50-54	977 (7.5)	512 (7.1)	435 (8.2)	30 (6.4)	811 (10.4)	482 (11.2)	249 (9.5)	80 (9.7)
55-59	1,358 (10.4)	735 (10.1)	557 (10.4)	66 (14.1)	881 (11.3)	504 (11.7)	290 (11)	87 (10.6)
60-64	1,777 (13.6)	993 (13.7)	718 (13.5)	66 (14.1)	973 (12.5)	537 (12.4)	349 (13.3)	87 (10.6)
65-69	1,854 (14.2)	1,058 (14.6)	720 (13.5)	76 (16.2)	951 (12.2)	516 (11.9)	340 (12.9)	95 (11.6)
70-74	1,715 (13.1)	973 (13.4)	683 (12.8)	59 (12.6)	816 (10.5)	441 (10.2)	295 (11.2)	80 (9.7)
75+	3,421 (26.2)	2,105 (29.0)	1191 (22.3)	125 (26.7)	1386 (17.8)	766 (9.9)	468 (6)	152 (2)
Follow-up Time								
<= 7 years	10,224 (78.3)	5,583 (76.9)	4287 (80.4)	354 (75.5)	3,780 (48.6)	1,874 (43.4)	1,571 (59.8)	335 (40.8)
> 7 years	2,837 (21.7)	1,674 (23.1)	1048 (19.6)	115 (24.5)	3,990 (51.4)	2,446 (56.6)	1,058 (40.2)	486 (59.2)

MC, microscopic colitis; SD, standard deviation.

The incidence rate (IR) of CRC among patients with incident MC was 190.1 per 100,000 person-years in Denmark and 145.0 per 100,000 person-years in the Netherlands (Table 3). Comparison of the observed number of CRC cases with the country-specific incidence rate of CRC in the general population yielded SIRs of 0.90 (95% CI: 0.74-1.09) in Denmark and 0.83 (95% CI: 0.75-0.89) in the Netherlands. The IR of CRC was particularly high during the first year after MC diagnosis, resulting in increased SIRs in both Denmark and the Netherlands. Following the first year, the incidence of CRC was lower and the SIR was decreased. The SIR was higher when MC was diagnosed at a younger age. No consistent pattern was observed over calendar time.

Table 3. Risk of colorectal cancer among MC patients in Denmark and the Netherlands compared to the Danish and Dutch general populations.

	Denmark				
	Observed N	**Expected N**	**Crude IR***	**SIR**	**95% CI**
Total	111	122.9	190.1	0.90	(0.74-1.09)
Sex					
Male	42	41.8	262.3	1.00	(0.72-1.36)
Female	69	81.1	162.8	0.85	(0.66-1.08)
Follow-up time					
<= 1 year	55	24.6	460.2	2.23	(1.68-2.91)
>1 year	56	98.3	120.6	0.57	(0.43-0.74)
Age at MC Dx					
18-39	1	0.4	20.7	2.61	(0.07-14.52)
40-59	21	16.4	110.7	1.28	(0.79-1.95)
60-74	46	61.2	195.4	0.75	(0.55-1.00)
75+	43	44.9	388.6	0.96	(0.69-1.29)
Age at CRC Dx					
18-39	1	0.1	31.1	8.51	(0.22-47.38)
40-59	13	7.6	89.0	1.70	(0.91-2.91)
60-74	46	51.5	186.5	0.89	(0.65-1.19)
75+	51	63.7	320.7	0.80	(0.60-1.05)
Year of CRC Dx					
1990-1999#	9	2.1	665.3	4.21	(1.93-7.99)
2000-2009	55	61.4	179.9	0.90	(0.68-1.17)
2010-2014	47	59.5	177.6	0.79	(0.58-1.05)
Type of MC					
Collagenous	70	72.6	210.5	0.96	(0.75-1.22)
Lymphocytic	38	45.3	166.5	0.84	(0.59-1.15)

IR, incidence rate; PYs, person-years; SIR, standardized incidence ratio; 95%CI, 95% Confidence Intervals; Dx, diagnosis.
 # in Denmark the period was 1995-1999. Crude IR per 100,000 Person-Years.*

Table 3. Risk of colorectal cancer among MC patients in Denmark and the Netherlands compared to the Danish and Dutch general populations (*continued*).

	The Netherlands				
	Observed N	**Expected N**	**Crude IR***	**SIR**	**95% CI**
Total	91	109.9	145.0	0.83	(0.75-0.89)
Sex					
Male	27	35.9	157.3	0.75	(0.59-0.86)
Female	64	66.3	140.3	0.96	(0.89-0.99)
Follow-up time					
<= 1 year	35	12.8	499.0	2.74	(1.89-4.43)
>1 year	56	90.9	116.0	0.62	(0.51-0.71)
Age at MC Dx					
18-39	1	0.4	17.8	2.40	(1.08-25.92)
40-59	24	9.7	117.6	2.47	(1.66-4.24)
60-74	46	49.8	205.7	0.92	(0.82-0.97)
75+	20	58.1	139.1	0.34	(0.24-0.47)
Age at CRC Dx					
18-39	1	0.4	17.8	2.40	(1.08-25.92)
40-59	19	9.7	93.1	1.95	(1.40-3.28)
60-74	34	49.8	152.0	0.68	(0.54-0.80)
75+	37	58.1	257.4	0.64	(0.51-0.75)
Year of CRC Dx					
1990-1999#	29	30.6	168.8	0.95	(0.81-0.99)
2000-2009	45	58.7	146.6	0.77	(0.64-0.86)
2010-2014	17	13.7	258.4	1.24	(1.08-1.76)
Type of MC					
Collagenous	51	68.6	131.6	0.74	(0.63-0.83)
Lymphocytic	28	30.2	163.9	0.93	(0.78-0.98)

IR, incidence rate; PYs, person-years; SIR, standardized incidence ratio; 95%CI, 95% Confidence Intervals; Dx, diagnosis.
 # in Denmark the period was 1995-1999. Crude IR per 100,000 Person-Years.*

The cumulative risk of CRC 1 year after MC diagnosis was 0.4% (95% CI: 0.3%-0.6%) in Denmark and 0.5% (95% CI: 0.3%-0.6%) in the Netherlands (Table 4) and was higher in patients diagnosed with MC after age 60 years compared to patients diagnosed before age 60 years (*p* log-rank <0.0001 in both Denmark and the Netherlands). Absolute risks did not differ by sex, type of MC, or history of celiac disease.

Table 4. Cumulative risks of colorectal neoplasia in Microscopic Colitis patients Denmark and the Netherlands.

		Denmark MC all		the Netherlands MC all	
		Cumulative risk (%)	95% CI	Cumulative risk (%)	95% CI
Non-adenomatous polyps	1 year	5.4	5.0-5.8	2.8	2.5-3.2
	5 years	7.2	6.8-7.7	3.5	3.1-4.0
	10 years	8.9	8.3-9.6	4.4	3.9-4.9
Adenomas	1 year	6.4	6.0-6.8	5.5	5.0-6.0
	5 years	8.0	7.5-8.5	7.1	6.6-7.7
	10 years	9.6	8.9-10.2	9.5	8.8-10.2
Colorectal Cancer	1 year	0.5	0.4-0.6	0.5	0.3-0.6
	5 years	0.8	0.7-1.0	0.9	0.7-1.1
	10 years	1.4	1.1-1.7	1.4	1.1-1.8

95% CI, 95% confidence interval

In the Kaplan-Meier analyses for non-adenomatous polyps, the cumulative risk differed by type of MC (log-rank p=0.0009), with higher risk for lymphocytic colitis than for collagenous or unspecified colitis. The risk did not differ by sex or age. For adenomas, the cumulative risk was 6.4% in Denmark and 5.5% in the Netherlands during the first year after MC diagnosis. Five years after diagnosis, it was 8.0% in Denmark and 7.1% in the Netherlands. These risks differed by sex, type of MC, and age (all log-rank p<0.0001), with higher risks for males, presence of lymphocytic colitis, and age 60 years or older.

In sensitivity analyses we classified the MC groups based on their index histology at cohort entry [presence/absence of non-adenomatous polyp(s) and adenoma(s)]. In Denmark 12,883 subjects and in the Netherlands 7,186 subjects had no polyps or adenomas at baseline. Among these subjects, 1,005 (7.8%) in Denmark and 292 (4.1%) in the Netherlands developed an adenoma, and 107 (0.8%) in Denmark and 88 (1.2%) in the Netherlands developed CRC after median follow-up of 3.6 and 2.2 years, respectively. This yielded an incidence rate of CRC of 1.9 (95%CI: 1.5-2.2) per 1,000 person-years in Denmark and 1.5 (95%CI: 1.2-1.8) per 1,000 person-years in the Netherlands. In Denmark, 154 MC subjects had a non-adenomatous polyp and 24 MC subjects had an adenoma at baseline. Three (2%) of the subjects with a non-adenomatous polyp and 1 (4.2%) with an adenoma developed CRC during follow-up. In the Netherlands, among subjects with a non-adenomatous polyp or adenoma at baseline 2 (1.4%) and 1 (0.3%) were diagnosed with CRCs after median follow-up of 2.9 and 0.2 years, respectively (Table 5). Our sensitivity analysis showed that incidence of CRC was higher in MC subjects with a non-adenomatous polyp or adenoma at baseline compared to MC subjects without these baseline findings.

DISCUSSION

This population-based nationwide study in Denmark and the Netherlands found a high incidence of non-adenomatous polyps and adenomas during the first year after diagnosis of MC, both in in terms of cumulative risk and compared with the general population. CRC risk was approximately 0.4% in the first year after MC diagnosis, with a much higher incidence than in the general population. However, CRC incidence was lower among MC patients than among the general population starting one year after MC diagnosis. This suggests that a MC diagnosis may lead to better follow-up and treatment for non-adenomatous polyps and adenomas during the year after diagnosis, subsequently resulting in a lower rate of CRC.

This is the first study to assess the risk of CRC after a MC diagnosis. Because previous studies focused on CRC detection before or at the same time as a MC diagnosis,[400-403, 422] they were unable to establish a potential causal effect of MC-associated inflammation on colorectal carcinogenesis. A recent case-control study concluded that chronic inflammatory conditions of the colon, including MC, were associated with a decreased prevalence of non-adenomatous polyps and adenomas.[342] While these findings seem contradictory to our results, the study addressed a different question. It compared the prevalence of non-adenomatous polyps and adenomas detected during colonoscopy among patients concurrently diagnosed with MC and among patients not concurrently diagnosed with MC.[409] In contrast, we examined the occurrence of non-adenomatous polyps, adenomas, and CRC in patients with MC *after* MC diagnosis. In the current study, the frequency of non-adenomatous polyps and adenomas detected at time of the colonoscopy that led to a MC diagnosis in The Netherlands was 7.5%, while the proportion of MC subjects diagnosed with a non-adenomatous polyp or adenoma in the case-control study was comparable at 8.5%.[342] We found that patients diagnosed with MC are more likely to be diagnosed subsequently with non-adenomatous polyps and adenomas than persons in the general population. This finding may be explained in part by enhanced diagnostic surveillance and an associated increased chance for diagnosis, a phenomenon also seen with other diseases.[407, 423, 424] Our study subjects underwent a colonoscopy for MC complaints, and by having a colonoscopy they were more likely to be diagnosed with non-adenomatous polyps, adenomas, or CRC than persons without MC symptoms particularly in the event of follow-up colonoscopies.[425]

In our sensitivity analysis we did not observe more adenomas or CRC in the MC cohort than in other screening populations (Supplementary Table 2). In accordance with studies assessing outcomes at first colonoscopy screening [415, 416, 419, 426] and at surveillance colonoscopy following a previous colorectal adenoma,[420, 421] we found that 1.3% of MC subjects in the Netherlands and 1.5% of subjects in Denmark had a concurrent diagnosis of CRC at baseline; we subsequently excluded these patients to identify incident CRC cases. In our study population the incidence rate of CRC in Denmark and in the Netherlands was in line with the incidence rate reported in other studies, ranging between 0.6 to 1.5 per 1,000 person-years.[415, 421, 426, 427] We found that patients who developed CRC during follow-up were generally older at time of their MC diagnosis than patients who did not develop CRC.

Table 5. Presence of non-adenomatous polyps, adenomas, and colorectal cancers at cohort entry by subsequent diagnosis of these outcomes in the Danish and Dutch cohorts.

	Denmark						
	No polyps and no adenomas at baseline			Non-adenomatous polyp at baseline			Adenoma at baseline
Development of:	Total N=12,883	Males N=3,729	Females N=9,154	Total N=154	Males N=58	Females N=96	Total N=24
Non-adenomatous polyp							
Number of subjects (%)	860 (6.68)	563 (15.1)	297 (3.24)	NA	NA	NA	NA
Time to polyp, median (IQR)	3.3 (1.4-6.2)	3.1 (1.2-5.8)	3.4 (1.5-6.4)				
Age at MC diagnosis, median (IQR)*	64.6 (57.0-72.2)	65.0 (57.2-71.9)	64.4 (56.8-72.3)				
Incidence per 1,000 person-years	15.82	38.39	7.48				
Adenoma							
Number of subjects (%)	1,005 (7.8)	434 (11.64)	571 (6.24)	24 (15.58)	13 (22.41)	11 (11.46)	
Time to adenoma, median (IQR)	3.3 (1.3-6.2)	2.9 (1.0-5.8)	3.5 (1.5-6.4)	4.3 (1.3-6.3)	4.6 (2.0-6.8)	3.9 (0.5-6.0)	
Age at MC diagnosis, median (IQR)*	68.5 (60.8-75.6)	68.4 (60.2-74.9)	68.5 (61.1-76.2)	65.4 (61.1-72.8)	68.4 (60.2-74.9)	68.5 (61.1-76.2)	
Incidence per 1,000 person-years	18.54	30.31	14.32	34.99	53.74	24.77	
CRC							
Number of subjects (%)	107 (0.83)	40 (1.07)	67 (0.73)	3 (1.95)	1 (1.72)	2 (2.08)	1 (4.17)
Time to CRC, median (IQR)	3.6 (1.6-6.4)	3.3 (1.5-6.1)	3.7 (1.7-6.6)	4.7 (2.5-7.2)	4.5 (2.1-7.1)	4.8 (2.5-7.4)	2.9 (2.0-6.2)
Age at MC diagnosis, median (IQR)*	70.9 (60.8-81.4)	68.8 (57.2-80.7)	72.0 (65.7-81.4)	70.0 (61.7-73.5)	73.5	65.8 (61.7-70.0)	61.4
Incidence per 1,000 person-years	1.86	2.55	1.60	3.94	3.53	4.18	9.95

Table 5. Presence of non-adenomatous polyps, adenomas, and colorectal cancers at cohort entry by subsequent diagnosis of these outcomes in the Danish and Dutch cohorts (*continued*).

	The Netherlands						
	No polyps and no adenomas at baseline			Non-adenomatous polyp at baseline			Adenoma at baseline
	Total	Males	Females	Total	Males	Females	Total
Development of:	**N=7,186**	**N=1,918**	**N=5,268**	**N=196**	**N=57**	**N=139**	**N=388**
Non-adenomatous polyp							
Number of subjects (%)	111 (1.54)	26 (1.36)	85 (1.61)	NA	NA	NA	NA
Time to polyp, median (IQR)	4.0 (1.8-7.2)	4.6 (2.9-8.0)	3.8 (1.6-6.7)				
Age at MC diagnosis, median (IQR)*	58 (49-66)	56.5 (52-65)	58 (49-67)				
Incidence per 1,000 person-years	1.87	1.62	1.97				
Adenoma							
Number of subjects (%)	292 (4.06)	102 (5.32)	190 (3.61)	7 (3.57)	2 (3.51)	5 (3.6)	NA
Time to adenoma, median (IQR)	5.2 (2.4-9.1)	5.2 (1.9-9.0)	5.2 (2.4-9.4)	2.8 (0.4-6.4)	4.6 (2.8-6.4)	2.8 (0.4-4.8)	
Age at MC diagnosis, median (IQR)*	60 (52-68)	61.5 (50-68)	60 (52-68)	62 (49-66)	54.5 (47-62)	65 (59-66)	
Incidence per 1,000 person-years	4.98	6.50	4.43	6.58	6.65	6.55	
CRC							
Number of subjects (%)	88 (1.22)	27 (1.41)	61 (1.16)	2 (1.02)	0 (0)	2 (1.44)	1 (0.26)
Time to CRC, median (IQR)	2.2 (0.1-6.2)	1.6 (0.1-7.6)	2.4 (0.3-5.6)	2.9 (1.8-4.1)		2.9 (1.8-4.1)	0.19
Age at MC diagnosis, median (IQR)*	67 (59-73.5)	66 (58-73)	68 (59-74)	70 (65-75)		70 (65-75)	59
Incidence per 1,000 person-years	1.48	1.63	1.41	1.85		2.58	0.42

** Age for those that develop the outcome; NA, not applicable.*

As well, the time to CRC for patients with MC was relatively short after cohort entry (median 3.6 years in Denmark and 2.2 years in the Netherlands). This suggests that a neoplastic lesion could have been missed or incompletely removed at initial scopy that resulted in the MC diagnosis. This may be evidence that other factors, such as age, diagnostic bias, and clinical awareness contributed to the peak in CRC incidence during the first year following MC diagnosis.

Importantly, we observed that MC patients were more likely to be diagnosed with non-adenomatous polyps and adenomas more than a year following a MC diagnosis. This supports the hypothesis that inflammation associated with MC produces structural cell changes leading to precancerous lesions. The length of time between progression of neoplastic polyps to CRC and the relatively short follow-up period in our study (median of 3.6 and 7.2 years in the Danish and Dutch cohorts, respectively) limited our ability to identify any association with increased CRC risk in the long-term. Our findings are in accordance with reports in the literature showing a higher risk of CRC among males and older persons.[428] This provides reassurance about the validity of our data and results.

Notably, we observed a decreased risk of CRC more than 1 year after MC diagnosis. This could be explained by several factors. Now, and especially in the early years, a substantial group of MC patients are treated with 5-aminosalicylic acid (5-ASA) compounds, sometimes for many years. Though still controversial, it has been suggested that 5-ASA may affect tumour growth and survival and thus may protect against development of CRC.[429, 430] Another explanation could be that colonoscopies conducted for symptoms of MC lead to the detection of CRC precursor lesions, subsequent surveillance colonoscopies in time and thus prevents subsequent CRC development.[275]

Apart from the increased and prolonged duration of colonic inflammation in MC patients, observed associations may be explained by shared or common risk factors for MC, non-adenomatous polyps, adenomas, and CRC. Prior studies have suggested that some lymphoproliferative diseases and malignancies are more frequent in patients with celiac disease, including malignant lymphoma and intestinal cancers.[241, 431, 432] As about 10% of MC patients have celiac disease and 33% of celiac disease patients have histological characteristics consistent with MC,[373] there may be a differential risk of non-adenomatous polyps, adenomas, and CRC in MC patients with versus without celiac disease. We did not observe a significantly different CRC risk in the presence/absence of celiac disease, though our analysis may have been limited by the small number of patients in these strata.

Strengths of the study are its large scale and use of nationwide population-based data sources to identify microscopic colitis patients, mitigating selection bias. Through follow-up of patients using population-based registries, we were able to calculate the risk of non-adenomatous polyps, adenomas, and CRC after MC diagnosis.

Our study has several limitations. First, using the general population as the reference population could lead to Berkson's bias. We tried to mitigate such bias by also comparing the proportion and rates of the outcomes in our study population with those in screening populations that underwent colonoscopy. Second, diagnoses of MC and colorectal outcomes

could have been subject to misclassification. However, the pathology codes used to identify the cancers are registered prospectively for pathologically confirmed diseases assuming that patients underwent colonoscopy with biopsies at that moment. The positive predictive value for CRC in the DNRP and DCR has been found to be 88.9%.[433] In the Dutch database we reviewed the pathology reports of all patients in order to verify the diagnoses of MC and outcomes. A third concern is that left censoring of MC diagnosis could have occurred, resulting in the classification of patients as incident cases when they were actually prevalent cases. This could lead to overestimation of cancer risk. However, since cancer is rare and takes decades to progress to overt disease, overestimation is unlikely. Fourth, we lacked information on CRC stage. This may have confounded our results, as detection bias could have led to earlier diagnosis and earlier CRC stage in MC patients compared to the reference populations.

In conclusion, patients newly diagnosed with microscopic colitis were not at increased risk of CRC one or more years after their diagnosis, compared to the general population in Denmark and the Netherlands. The high observed incidence of non-adenomatous polyps, adenomas, and CRC, particularly in the first year following MC diagnosis, was probably due to surveillance bias, with better screening and treatment for precursor lesions leading to a lower rate of CRC.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Standardized incidence ratio of non-adenomatous polyps and adenomas among microscopic colitis patients in Denmark compared to the Danish general population.

	Colorectal Polyps				Colorectal Adenomas			
	Observed	**Expected**	**SIR**	**95%CI**	**Observed**	**Expected**	**SIR**	**95%CI**
Total	939	156.2	6.01	5.63-6.41	1040	209.2	4.97	4.67-5.28
Sex								
Male	330	49.2	6.71	6.00-7.47	455	72.8	6.25	5.69-6.85
Female	609	107.0	5.69	5.25-6.16	585	136.4	4.29	3.95-4.65
Time in follow-up								
<= 1 year	698	31.7	22.05	20.45-23.75	833	41.2	20.22	18.87-21.64
>1 year	241	124.6	1.93	1.70-2.20	207	168.0	1.23	1.07-1.41
Age at MC diagnosis								
18-39	25	2.6	23.37	15.12-34.49	14	0.6	21.68	11.84-36.38
40-59	255	41.8	10.01	8.82-11.32	199	24.7	8.05	6.97-9.25
60-74	466	80.8	5.71	5.20-6.25	521	105.5	4.94	4.53-5.38
75+	193	31.0	4.02	3.47-4.62	306	78.4	3.90	3.48-4.37
Type of MC*								
Collagenous	449	91.1	4.93	4.48-5.41	512	122.1	4.19	3.84-4.57
Lymphocytic	457	58.8	7.78	7.08-8.52	495	78.7	6.29	5.75-6.87
Year of CRC Diagnosis								
1995-1999	34	1.9	17.59	12.18-24.58	27	1.9	14.35	9.45-20.87
2000-2009	522	79.7	6.55	6.00-7.14	555	100.4	5.53	5.08-6.01
2010-2012	383	74.6	5.14	4.63-5.68	458	107.0	4.28	3.90-4.69

** Numbers do not add up to Total Number of events as MC types were classified into Collagenous, Lymphocytic and Unspecified.*
Abbreviations: SIR, standardized incidence ratio; 95%CI, 95% Confidence Intervals.

Supplementary Table 2. Proportions of patients with polyps or adenomas at baseline and progression to colorectal neoplasia in screening populations described in the literature.

Study	Population	Non-advanced adenoma			Advanced neoplasia (composite of advanced adenoma+CRC)			Advanced adenoma*			CRC		
		Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)
No adenoma/polyp at baseline													
Brenner 2015[415]	55 years older men and women in GE		22.3%	14.9%					9%	5.2%			
Brenner 2014[416]	55 years older men and women in GE N=4,322,085								6.7-10.6 %	3.6-7.0%	0.6-2.7%	0.3-1.7%	
Stegeman[419]	50-75 year old men and women in NL N=1,236				110 (8.9)			103 (8.3)			7 (0.6)		
Stoop[418]	50-75 year old men and women in NL N=1,276				111 (9)			104 (8.2)			7 (0.5)		
Current Study Denmark	All MC subjects N=12,883				1,112 (8.6)						107 (0.8)	40 (1.1)	67 (0.7)
Current Study - NL	55 year old MC subjects N=4,554				280 (6.1)						72 (1.6)	22 (1.8)	50 (1.5)
Current Study NL	All MC subjects N=7,186				380 (5.3)						88 (1.2)	27 (1.4)	61 (1.2)
Previous colorectal polyp													
Elena-Martinez[417]	Pooled analysis screening cohorts N=9,167				1082 (11.8)			1024 (11.2)			58 (0.6)		
Current Study Denmark	All MC subjects N=154				27 (17.5)						3 (2)	1 (1.7)	2 (2.1)
Current Study - NL	55 year old MC subjects N=141				7 (5)						2 (1.4)	0	2 (2)
Current Study NL	All MC subjects N=196				9 (4.6)						2 (1)	0	2 (1.4)

Supplementary Table 2. Proportions of patients with polyps or adenomas at baseline and progression to colorectal neoplasia in screening populations described in the literature (*continued*).

Study	Population	Non-advanced adenoma			Advanced neoplasia (composite of advanced adenoma+CRC)			Advanced adenoma*			CRC		
		Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)	Total N (%)	M N (%)	F N (%)
Previous colorectal adenoma													
Loeve[421]	Model on national polyp study in NL N=1,418 PALGA in NL										1.5 per 1,000 PYs		
Van Heijningen[420]	All surveillance colonoscopies N=2,990 PALGA in NL	954 (32)			203 (7)			165 (5.5)			38 (1.3)		
Current Study Denmark	At first surveillance colonoscopy N=2,990 All MC subjects N=24	655 (21.9)			171 (5.7)						1 (4.2)		
Current Study - NL	55 year old MC subjects N=312										1 (0.3)		
Current Study NL	All MC subjects N=388										1 (0.3)		

M, males; F, females; NL, the Netherlands.
** Definition of advanced adenoma differs per study, in general advanced adenomas are defined as at least 1 adenoma ≥ 1 cm or at least 1 adenoma with villous components or high-grade dysplasia*

SECTION 6

NSAIDs and the risk of Cardiovascular Events

CHAPTER 6.1

Risk of Acute Myocardial Infarction during use of individual NSAIDs: a nested case-control study in the SOS project

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ABSTRACT

BACKGROUND

Use of selective COX-2 non-steroidal anti-inflammatory drugs (NSAIDs) has been associated with an increase in the risk of acute myocardial infarction (AMI), but the magnitude of risk is unknown for individual nonselective NSAIDs.

METHODS

A case-control study was performed nested in a cohort of new NSAID users ≥18 years (1999-2011) matching cases to a maximum of 100 controls on database, sex, age, and AMI diagnosis date. Data were retrieved from six healthcare databases using the same protocol and data transformations: IPCI, PHARMO (Netherlands); SISR, OSSIFF (Italy); GePaRD (Germany) and THIN (United Kingdom). Adjusted odds ratios (ORs) were estimated per database comparing current use of NSAIDs to past use. Pooling was done by a random effects model (ORmeta) and unweighted pooling (ORpooled).

RESULTS

In a cohort of 8.5 million new NSAID users 79,553 AMI cases were identified. The risk was significantly elevated for current use of ketorolac (ORmeta 2.06; 95%CI: 1.83-2.32, ORpooled 1.80; 95%CI: 1.49-2.18) followed in descending order by indometacin, etoricoxib, rofecoxib, diclofenac, fixed combination of diclofenac with misoprostol, piroxicam, ibuprofen, naproxen, celecoxib, meloxicam, nimesulide and ketoprofen (ORmeta 1.12; 95%CI: 1.03-1.22, ORpooled 1.00; 95%CI: 0.86-1.16). For other NSAIDs there was no significantly increased risk, amongst those dexketoprofen (ORpooled 1.01; 95%CI: 0.50-2.04), sulindac (ORpooled 1.01; 95%CI: 0.48-2.15) proglumetacin (ORpooled 1.00; 95%CI: 0.41-2.47) and tiaprofenic acid (ORpooled 1.01; 95%CI: 0.49-2.10) had upper 95% limits that exceeded 2. Higher doses showed higher risk estimates than lower doses.

CONCLUSION

The risk of AMI differed between 28 individual NSAIDs. The risk was highest for ketorolac, but was increased also for several other selective COX-2 and nonselective NSAIDs and was higher when using higher daily doses. The increased risk of AMI should not be considered an effect of some selective COX-2 inhibitors only.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used to reduce inflammation and provide pain relief. They act via reversible, competitive inhibition of cyclo-oxygenase (COX) enzymes. As inhibition of the COX-1 enzyme decreases the production of prostaglandins, gastrointestinal adverse events including ulcerations and bleeding occur often during NSAID use. This led to development of selective COX-2 inhibitors, which were marketed as coxibs. However, after successful market introduction of selective COX-2 inhibitors [10, 75] concerns were raised about their cardiovascular (CV) safety resulting in the voluntary withdrawal of rofecoxib in 2004.[11] Reviews by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) concluded that coxibs increase the risk of CV events.[93] It was recommended in 2005 to avoid the use of selective COX-2 inhibitors in patients with ischemic heart disease, stroke or peripheral arterial disease.[89, 94, 95] At that point in time little information was available about the CV risk of NSAIDs, but further studies showed signals of increased arterial thrombosis risk for the nonselective (ns) NSAIDs, particularly when used in high doses and for long-term.[96, 97] Based on the uncertainty, EMA requested a review of the CV safety of nsNSAIDs as well. The Safety of Non-Steroidal Anti-inflammatory Drugs (SOS) project was developed as a research and development project funded by the Directorate General of Research and Innovation of the European Commission under the Seventh Framework Programme to support EMA in their regulatory decision making.[434] This SOS study aimed to assess and summarize the risk of AMI associated with the use of individual NSAIDs in Europe.

METHODS

Study design and data sources

A nested case-control study was conducted within a cohort of new NSAID users during the study period.

Data for this study was obtained from six different longitudinal population-based health care databases from four European countries [GePaRD from Germany (GE), OSSIFF and SISR from Italy (IT), IPCI and PHARMO from the Netherlands (NL) and THIN from the United Kingdom (UK)] covering a source population of around 32 million subjects. All databases have been used for pharmacoepidemiological research (Supplementary Table 1)[237, 238, 435, 436] and are described more detailed elsewhere.[437]

In short, the German Pharmacoepidemiological Research Database (GePaRD) is a database comprising data from five statutory health insurances throughout Germany that is created and maintained by BIPS. It currently covers around 14 million insurants and represents approximately 20% of the German population.[436] The Health Improvement Network (THIN) database is a general practice database in the UK and currently captures medical records of 11.1 million patients.[237, 266] The Integrated Primary Care Information (IPCI) database is also a

general practice database but from the Netherlands and currently covers over 1.5 million people,[238] PHARMO database is a medical record linkage system of 2.2 million community-dwelling inhabitants in the Netherlands.[435] OSSIFF (Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia) is a database capturing national health service data and clinical registries from several local health agencies in Lombardy) for a population of about 2.9 million people. The second Italian database SISR (Sistema Informativo Sanitario Regionale) obtains national health service data from the Lombardy region, with about nine million inhabitants (approximately 16% of the national population). OSSIFF was included in addition to the Lombardy SISR as it allows for validation of outcomes, overlapping patients were excluded from the Lombardy SISR.

All general practice and claims databases contain information on demographics of the population, diagnoses (in- and/or outpatient), and drug prescriptions/dispensings. The diagnoses captured by the databases are coded with four different disease coding systems including the International Classification of Diseases (ICD) 9th or 10th revision,[323] International Classification for Primary Care (ICPC),[240] or READ.[438] Mapping of concepts and codes was performed using the Unified Medical Language System (UMLS), a biomedical terminology integration system handling more than 150 medical dictionaries, according to a previously described workflow.[439, 440] All drugs were mapped to the World Health Organization's (WHO) classification of Anatomical Therapeutic Chemical (ATC).[242] A distributed approach was used for collaboration: all database custodians extracted data locally; original data were transformed into a simple common data model (Jerboa© input files); mapping of codes for outcome and covariates was verified using an extensive harmonization strategy; and a common standardized script (Jerboa©, Java based)[346] was supplied to create the aggregated tables that were subsequently encrypted and shared on a central data warehouse for further analysis and pooling. Details have been described previously. [346, 437]

Study cohort

In each database, we identified a cohort of patients aged ≥18 years who received at least one new NSAID prescription (Supplementary Table 2) during the database-specific study period within the general study period which started 1 January 1999 and ended December 31st 2011 (Supplementary Table 1). Before inclusion in the cohort subjects were deemed to have at least one year of continuous data enrollment in the database.

The date of first NSAID prescription/dispensation during the study period was defined as cohort entry date. Patients were excluded if they received any NSAID prescription in the year before in order to construct a new user cohort and avoid prevalent user bias.[168] Patients needed to have at least one year of continuous database history, to allow uniform assessment of potential confounding factors and exclusion criteria. All subjects with a cancer diagnosis (except non-melanoma skin cancer) during the one year preceding cohort entry were excluded from the cohort. All NSAID cohort members were followed from the date of cohort

entry until the date of acute myocardial infarction diagnosis, cancer, death, last data supply, transferring out of the database, or end of the study period, whichever was earliest.

Cases and controls

The outcome was a first hospitalization with a discharge diagnosis code of acute myocardial infarction (AMI) (GePaRD, PHARMO, OSSIFF, and SISR) or a first diagnosis of an AMI (THIN and IPCI) during follow-up (Supplementary Table 3 for ICD-9, ICD-10, READ and ICPC codes included). The date of recorded diagnosis or admission date of AMI was used as index date. Controls were members of the incident NSAID cohort who did not develop AMI during follow-up until the cases' index date. Within each database, up to 100 controls were matched to each case by risk set sampling on age (± 1 year), sex and cohort entry (± 28 days). Controls were assigned the same index date as the case.

NSAID-exposure

Exposure to individual NSAIDs was obtained from either prescriptions (THIN and IPCI) or from outpatient drug dispensings claims (GePaRD, PHARMO, OSSIFF, and SISR). Duration of a single NSAID dispensing/prescription was obtained by dividing the total units by the daily number of units prescribed (THIN, IPCI, and PHARMO: prescribed duration), for other databases standard durations were used based on the country specific defined daily dose (DDD) values.[242]

Classification of the recency of exposure to individual NSAIDs was based on the interval between index date and the end of the most recent NSAID use before the index date. If the exposure period 1) overlapped or ended within 14 days before index date NSAID use was classified as 'current' use; 2) ended between 15 and 183 days before the index date as 'recent' use and; 3) ended 184 days or more before the index date as 'past' use. Exposure periods were considered mutually exclusive. Duration of current use was then classified into very short (1-6 days), short (7-29), medium (30-89) and long (≥ 90). If multiple NSAIDs were used in the current period, NSAID use was distributed to current use of all NSAIDs. Current use of an NSAID always overruled past use of other NSAIDs if patients switched between NSAIDs. Past use of any NSAID was considered as common reference group in order to compare across NSAIDs.

In IPCI, THIN and PHARMO the daily dose of NSAID was estimated from the prescribing regimen and strength. Dose of current exposure to each individual NSAID was classified using the ratio of prescribed daily dose (PDD) compared to DDD in order to allow for aggregation and comparison across NSAIDs. For categorical analysis dose categories were defined as low dose (<0.8 PDD/DDD), normal dose (0.8-1.2 PDD/DDD) and high dose (≥1.3 PDD/DDD) (see Supplementary Table 4 for DDD value for each individual NSAID evaluated).

Covariates

Covariates were classified into based on recorded diagnoses or conditions (history of ischemic heart disease (excluding AMI); history of stroke; heart failure; diabetes mellitus type 2; hyperlipidemia; smoking) or their proxies based on used of medications for these diseases or conditions (use of ACE inhibitors, antithrombotic agents, low-dose aspirin, beta blockers, calcium channel blockers, diuretics, glucocorticoids, nitrates, oral contraceptives, platelet aggregation inhibitors, lipid lowering drugs and postmenopausal hormone therapy). They were measured during the 12 months prior to cohort entry (for all co-variates that could be intermediates between treatment and AMI, or in 30 or 90 days before index date (if not potential intermediates). In case there was no or missing information on the variable in the specific time window, the variable was considered as absence of the condition.

Statistical analyses

Baseline characteristics of cases and controls are described by database. To estimate the risk for AMI among current use of an individual NSAID in comparison to past use of any NSAID, matched odds ratios (ORmatched) and matched adjusted odds ratios (ORadj) with 95% Confidence Intervals (CIs) were calculated using conditional logistic regression analyses for each database separately if five or more exposed cases per database were available. Pooled NSAID-specific ORs (ORmeta) were calculated both using the inverse variance weighting method (fixed effect pooled estimates) and DerSimonian and Laird method to account for heterogeneity across databases (random effect pooled estimates).[441] The degree of statistical heterogeneity across databases was measured by I^2.[442] Confidence limits of random effects estimates were calculated accounting for the uncertainty of tau, e.g. the value representing the variation in the true effect estimates across the databases.[443]

Additionally, pooling of data across databases was performed by combining the matched case control sets without weighting and using a conditional logistic regression adjusted for covariates. This approach has most power and provides one overall risk measure (ORpooled) for all NSAIDs with at least five exposed cases across DBs.

A stepwise approach was used for confounder selection in both approaches: 1) a-priori selected confounders were always included; 2) univariate analyses for each potential confounder with a prevalence of 5% in controls, which were added to the model if Wald *p*-value was <0.05; 3) backward selection of potential confounders (*p*-value>0.05).

Categorical duration analyses were performed within current users of each individual NSAID, using short duration (7-29 days) as reference group. Dose analyses were done by categories comparing dose levels to past use of any NSAID and by continuous analyses through restricted cubic splines (3 knots) and through fractional polynomial regression (maximum of 2 terms) which provides greater flexibility to dose-response curves.[444] Since potency of NSAIDs is based on normal therapeutic doses, the relationship between COX-2 potency and the relative risk of AMI was plotted using normal daily doses (PDD/DDD between 0.8 and 1.2) and

therefore could only be done in the databases that provided prescribed daily dose regimens. In line with the study by Garcia-Rodriguez,[97] naproxen was removed from this plot, since it was used at very high doses. Correlation was estimated using the R^2.

Subsequent analyses evaluated the risk of AMI stratified by sex, age (≤60 or >60 years), prior ischemic heart disease, and use of aspirin or lipid lowering drugs. Current use of any NSAID was also analyzed by stratifying factors to increase the power to detect effect modification. Multiplicative interaction was tested to identify effect modification by stratifying factors.

For each database, the population attributable risk (PAR) was calculated to estimate the proportion of AMI in the target population that may be attributable to use of each NSAIDs using the following formula: PAR = (p*[OR-1])/(p*[OR-1]+1).[347] where OR is the adjusted odds ratio from the nested case-control analysis and p is the exposure prevalence.[445] For this calculation, we estimated p by the percentage of exposed cases.

All analyses were performed using SAS (Cary, NC version 9.2).

RESULTS

The study cohort comprised 8,535,952 new NSAID users (Supplementary Figure 1), of whom 101,227 patients developed an AMI after cohort entry. Of these, 79,553 (78.6%) cases could be matched to at least one control using the five matching criteria. Baseline characteristics of cases and matched controls are shown in Table 1. Cases had more often risk factors for AMI such as a prior history of ischemic heart disease, other cardiovascular diseases or use of cardiovascular drugs.

The distribution of NSAID exposure in cases and controls is reported in Table 2. Whereas in the UK, NL and Germany similar NSAIDS were often used, Italy uses quite a different range of NSAIDs, for 11 individual NSAIDs data were not available from other countries but Italy (Supplementary Table 5).

Meta-analytic estimates of the adjusted ORs across databases could be calculated for 21 NSAIDs. The adjusted OR for current use ranged between 0.93 for oxaprozin to 2.06 for ketorolac (Figure 1, Table 2), but the width of the confidence intervals vary. Ten NSAIDs were associated with a significantly increased risk, for none of the 11 NSAIDs with non-significant associations in meta-analytic pooling the upper 95% limit was above 2. For most NSAIDs (except for celecoxib, diclofenac, ibuprofen and naproxen) no heterogeneity was seen according to the estimated I^2 across databases (Table 2).

In order to estimate the risk of AMI associated with infrequently used NSAIDs we also combined all matched case-control pairs across datasets without weighting (Figure 1, Table 2), this yielded estimates for 28 individual NSAIDs. For most NSAIDs, which had both estimates, the meta-analytic and pooled estimate were quite similar. The results of this combined analysis showed that the risk of AMI is significantly elevated for 12 NSAIDs. Compared to past use of any NSAID the odds ratio was highest for ketorolac, followed by indometacin, etoricoxib and rofecoxib (Figure 1), though the 95% confidence limits overlap between these NSAIDs.

Table 1. Characteristics of AMI cases and matched controls by database.

	United Kingdom		The Netherlands			
	THIN		IPCI		PHARMO	
	Cases	Controls	Cases	Controls	Cases	Controls
Total Number	**13,511**	**1,232,506**	**1,070**	**38,688**	**9,974**	**896,907**
	%	**%**	**%**	**%**	**%**	**%**
Mean age (SD)*	64.3 (13.3)	63.1 (12.5)	63.3 (13.6)	58.7 (11.3)	61.0 (13.7)	59.3 (12.9)
Sex*						
Male	62.7	62.8	63.4	63.7	65.4	65.4
Female	37.3	37.2	36.6	36.3	34.6	34.6
A-priori confounders						
Diseases**						
Diabetes mellitus type 2	9.1	4.9	7.7	3.8	10.4	5.8
Heart Failure	1.5	0.5	3.4	1.5	0.7	0.4
Hyperlipidemia	18.5	12.3	12.6	8.9	17	11.7
Ischemic Heart Disease	5.1	2.3	4.6	2.2	1.8	0.9
Smoking	11.2	7.2	17.5	18.6	NA	NA
Stroke	0.5	0.3	2.4	1.8	0.1	0.1
Use of Drugs***						
ACE inh/AT II Antagonists	19.2	13.4	11.5	6.8	14.6	10.4
Low-dose Aspirin	33.4	20.4	15.7	5.6	28	16.7
Beta Blockers	19.5	13.6	14.7	7.4	20.4	13.7
Calcium Channel Blockers	18.8	12.1	10.3	3.5	12.6	7.4
Diuretics	24.7	18.4	10.0	5.4	14.2	10.2
Glucocorticoids	7.1	4.1	3.9	1.6	6.4	3.7
Lipid lowering agents	32.9	22.5	14.2	8.8	24.3	18.0
Nitrates	20.3	5.5	6.1	1.0	15.6	4.4
Oral Contraceptives#	0.4	0.6	1.3	1.2	1.2	0.8
Hypertensive Drugs	1.2	0.9	2.5	2.7	4.2	3.5
Antiplatelets	6.8	2.4	2.9	0.7	4.9	2.3
Hormone Therapy#	6.5	6.7	2.8	1.9	5.8	8.0
Potential Confounders						
Diseases**						
Alcohol Abuse	8.5	8.3	7.0	7.3	0.2	0.1
AF and AFl	0.6	0.4	4.8	1.2	0.4	0.3
Chronic Liver Disease	0.1	0.1	2.1	1.6	0.1	0.1
Kidney Failure	0.2	0.1	1.1	0.4	0.04	0.01
Obesity	8.6	6.8	1.6	1.3	0.3	0.2
Osteoarthritis	12.7	10.6	2.6	3.1	1.2	1.1
Other CV Disease	1.9	1.2	6.8	3.7	1.2	1.1
PAD	0.02	0.01	1.3	0.8	0.3	0.1
RA and Infl Polyarthritis	8.7	6.7	11.1	9.4	1.2	0.9
Use of Drugs***						
Anticoagulants	3.0	2.4	2.5	1.3	6.1	4.6
Cardiac Glycosides			1.0	0.3	1.9	1.4
CYP2C9 Inducer drugs†	0.01	0.02			0.01	0.01
CYP2C9 Inhibitor drugs‡	1.1	0.6	0.9	0.2	8.7	6.7

** Age and sex are matching criteria. # Percentage only in females. † Includes Carbamazepine, Norethisterone (and estrogen combination) and Prednisone. ‡ Includes Cimetidine, Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Ticlopidine, Indometacin, Probenecid, Oxcarbazepine, Felbamate, Topiramate, Fluoxetine, Fluvoxamine, Modafinil and Ketoconazole. ** Assessed at 12 months prior to cohort entry. *** Assessed at 30 or 90 days before indexdate. AF and AFl, atrial fibrillation and flutter; RA and Infl Polyarthritis, rheumatoid arthritis and inflammatory polyarthritis; PAD, peripheral arterial disease.*

Table 1. Characteristics of AMI cases and matched controls by database (*continued*).

	Germany		Italy			
	GePaRD		SISR		OSSIFF	
	Cases	Controls	Cases	Controls	Cases	Controls
Total Number	**9,930**	**957,016**	**25,719**	**2,523,118**	**19,349**	**1,840,368**
	%	**%**	**%**	**%**	**%**	**%**
Mean age (SD)*	62.4 (12.4)	62.0 (11.8)	69.8 (12.2)	69.5 (12.1)	67.7 (12.2)	67.0 (11.8)
Sex*						
Male	77.5	78.1	54.7	54.6	56.5	56.3
Female	22.5	21.9	45.3	45.4	43.5	43.7
A-priori confounders						
Diseases**						
Diabetes mellitus type 2	16.2	8.5	21.3	10.4	15.1	6.8
Heart Failure	12.5	7.2	5.9	3.1	4.3	2.1
Hyperlipidemia	26.1	17.7	22.7	16	14.6	9.4
Ischemic Heart Disease	29.0	15.9	5.5	1.9	4.6	1.6
Smoking	NA	NA	NA	NA	NA	NA
Stroke	6.9	4.0	1.0	0.5	1.1	0.6
Use of Drugs***						
ACE Inh/AT II Antagonists	30.2	22.2	33.8	26.1	25.2	18.4
Low-dose Aspirin	11.5	5.4	29.1	19.2	24.1	15.2
Beta Blockers	33.6	23.7	20.1	13.0	14.2	8.7
Calcium Channel Blockers	18.0	12.3	32.4	21.9	26.9	17.2
Diuretics	17.8	11.7	22.9	16.7	15.5	10.7
Glucocorticoids	5.9	4.1	5.7	3.7	5.0	3.3
Lipid lowering agents	24.3	17.1	21.2	14.5	19.3	12.6
Nitrates	10.6	3.0	21.4	7.8	20.7	7.0
Oral Contraceptives#	0.1	0.0	0.2	0.2	2.6	1.8
Hypertensive Drugs	21.0	16.6	22.5	20.4	16.7	14.8
Antiplatelets	5.6	1.9	9.8	4.7	7.6	3.5
Hormone Therapy#	10.1	13.6	1.3	1.7	1.9	1.9
Potential Confounders						
Diseases**						
Alcohol Abuse	2.1	1.4	0.1	0.1	0.2	0.2
AF and AFl	5.7	4.6	1.6	1.1	1.3	0.9
Chronic Liver Disease	11.3	10.6	0.7	0.5	0.5	0.5
Kidney Failure	6.9	3.5	0.2	0.1	0.1	0.04
Obesity	14.5	10.8	0.6	0.3	0.2	0.1
Osteoarthritis	22.1	21.8	1.3	1.2	1.3	1.1
Other CV Disease	20.0	16.2	6.3	4.8	4.8	3.5
PAD	8.9	4.9	1.6	0.5	1.4	0.5
RA and Infl Polyarthritis	7.2	5.9	0.6	0.3	0.7	0.5
Use of Drugs***						
Anticoagulants	5.9	5.1	7.0	5.2	7.0	5.1
Cardiac Glycosides	4.0	2.4	5.2	3.9	4.6	3.3
CYP2C9 Inducer drugs†	0.02	0.01				
CYP2C9 Inhibitor drugs‡	1.1	0.8	2.5	1.7	0.7	0.4

** Age and sex are matching criteria. # Percentage only in females. † Includes Carbamazepine, Norethisterone (and estrogen combination) and Prednisone. ‡ Includes Cimetidine, Omeprazole, Pantoprazole, Lansoprazole, Rabeprazole, Ticlopidine, Indometacin, Probenecid, Oxcarbazepine, Felbamate, Topiramate, Fluoxetine, Fluvoxamine, Modafinil and Ketoconazole. ** Assessed at 12 months prior to cohort entry. *** Assessed at 30 or 90 days before indexdate. AF and AFl, atrial fibrillation and flutter; RA and Infl Polyarthritis, rheumatoid arthritis and inflammatory polyarthritis; PAD, peripheral arterial disease.*

Table 2. Association between current use of individual NSAIDs and AMI by meta-analysis (random and fixed effects) and by unweighted (matched set) pooled dataset.

			Meta-analysis approach (random effects)			Fixed effects	Pooled dataset
	Cases N	Controls N	Number of DBs	ORmeta (95% CI)	I^2 * (%)	ORfixed (95% CI)	ORpooled (95% CI)
Past Use	55,657	5,307,077	6	1 (ref)		1 (ref)	1 (ref)
Recent Use#	23,896	2,181,526	6	1.08 (1.04-1.11)	65	1.08 (1.06-1.09)	1.08 (1.06-1.11)
Current use of:							
Aceclofenac	214	20,370	4	1.04 (0.90-1.19)	0	1.04 (0.9-1.19)	1.08 (0.85-1.36)
Acemetacin	14	1,178	1				1.00 (0.58-1.71)
Celecoxib	886	76,132	5	1.15 (1.00-1.32)	67	1.12 (1.05-1.20)	1.15 (1.05-1.25)
Dexibuprofen	41	2,651	2	1.15 (0.79-1.68)	0	1.15 (0.79-1.68)	1.06 (0.61-1.82)
Dexketoprofen	9	723	1				1.01 (0.50-2.04)
Diclofenac	3,064	230,213	6	1.31 (1.23-1.40)	60	1.32 (1.27-1.37)	1.28 (1.22-1.34)
Diclofenac comb	399	27,923	6	1.27 (1.12-1.43)	19	1.27 (1.15-1.40)	1.30 (1.17-1.45)
Etodolac	37	2,761	1	1.17 (0.85-1.63)			1.07 (0.76-1.50)
Etoricoxib	497	37,478	6	1.28 (1.16-1.42)	12	1.27 (1.16-1.39)	1.39 (1.24-1.57)
Flurbiprofen	27	1,972	2	1.05 (0.66-1.67)	0	1.05 (0.66-1.67)	1.00 (0.56-1.78)
Ibuprofen	1,564	119,219	6	1.24 (1.13-1.37)	61	1.25 (1.19-1.32)	1.25 (1.18-1.33)
Indometacin	196	11,789	5	1.47 (1.27-1.70)	0	1.47 (1.27-1.70)	1.51 (1.28-1.80)
Ketoprofen	559	47,969	3	1.12 (1.03-1.22)	0	1.12 (1.03-1.22)	1.00 (0.86-1.16)
Ketorolac	272	11,732	2	2.06 (1.83-2.32)	0	2.06 (1.83-2.32)	1.80 (1.49-2.18)
Lornoxicam	40	3,095	2	1.08 (0.77-1.52)	0	1.08 (0.77-1.51)	1.08 (0.62-1.87)
Mefenamic acid	12	981	1				1.02 (0.55-1.90)
Meloxicam	492	38,806	6	1.18 (1.08-1.29)	0	1.18 (1.08-1.29)	1.13 (1.02-1.27)
Nabumetone	46	3,795	4	1.03 (0.76-1.40)	0	1.03 (0.76-1.40)	1.03 (0.72-1.47)
Naproxen	486	38,659	6	1.19 (1.04-1.37)	47	1.18 (1.08-1.29)	1.22 (1.10-1.35)
Nimesulide	1,652	133,462	2	1.16 (1.10-1.22)	0	1.16 (1.10-1.22)	1.12 (1.03-1.22)
Oxaprozin	22	2,709	2	0.93 (0.63-1.38)	0	0.93 (0.63-1.38)	0.97 (0.52-1.79)
Piroxicam	636	51,898	5	1.17 (1.03-1.33)	34	1.20 (1.10-1.30)	1.27 (1.13-1.42)
Proglumetacin	11	930	1				1.00 (0.41-2.47)
Rofecoxib	690	51,674	4	1.26 (1.17-1.37)	0	1.26 (1.17-1.36)	1.30 (1.19-1.43)
Sulindac	11	494	1				1.01 (0.48-2.15)
Tenoxicam	32	3,104	2	1.02 (0.72-1.46)	0	1.02 (0.71-1.46)	0.99 (0.56-1.74)
Tiaprofenic acid	8	710					1.01 (0.49-2.10)
Valdecoxib	25	2,159	3	1.00 (0.66-1.52)	0	1.00 (0.66-1.52)	1.07 (0.58-1.99)

** A high level of heterogeneity is present with an I^2 value above 75%.*

For 16 NSAIDs the association with AMI was not significantly elevated, but there might be a risk present. However only for four of these 95%CI limits were wide with an upper limit above 2, due to small numbers. When plotting the relative risk of AMI associated to current use of normal dose as 0.8 to 1.2 defined daily doses of the most frequently used NSAIDs (obtained from databases where we could investigate daily dose relationships) with the potency of inhibition of COX-2 there appears to be a small correlation (*R2*=0.45) (Supplementary Figure 2).

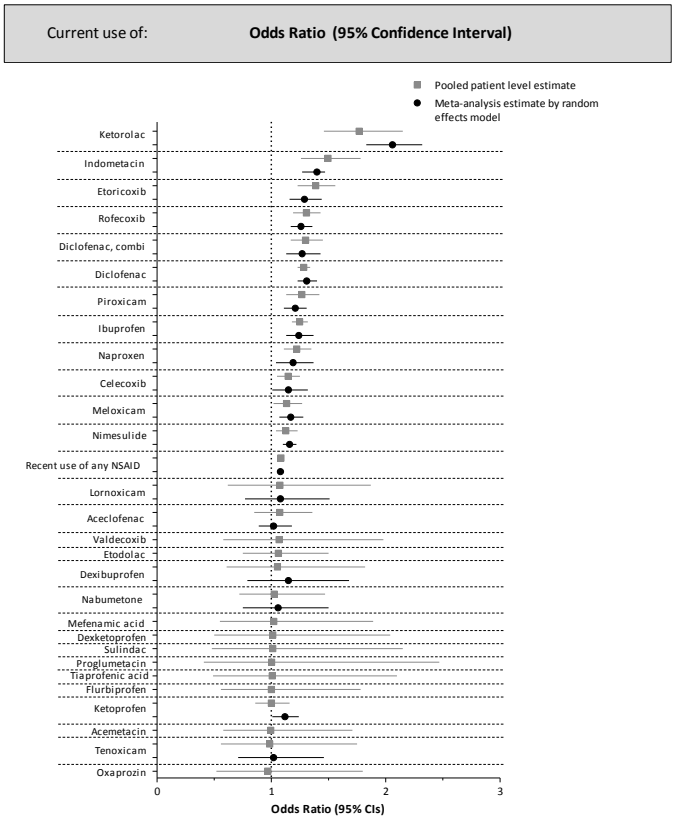


Figure 1. Adjusted risk estimates of AMI for current use of individual NSAIDs versus past use of any NSAID in the pooled dataset ranked on magnitude of risk in the analyses 1) meta-analytic pooling by random effects model and 2) on individual datasets.

In the THIN, IPCI and PHARMO databases NSAID dose and duration analyses could be conducted as prescription regimens were available. Categorical dose response analyses versus past use of any NSAID in this subset showed that higher doses of celecoxib, the fixed combination of diclofenac and misoprostol, etoricoxib and naproxen increased the risk of AMI (Figure 2). Continuous dose-response curves with cubic splines showed a significant dose response for diclofenac only (Supplementary Figure 3). For duration, no clear patterns were seen (Supplementary Figure 4). The risk of AMI seemed highest with shortest duration for diclofenac, which was also seen for ibuprofen and rofecoxib although confidence limits between categories overlapped.

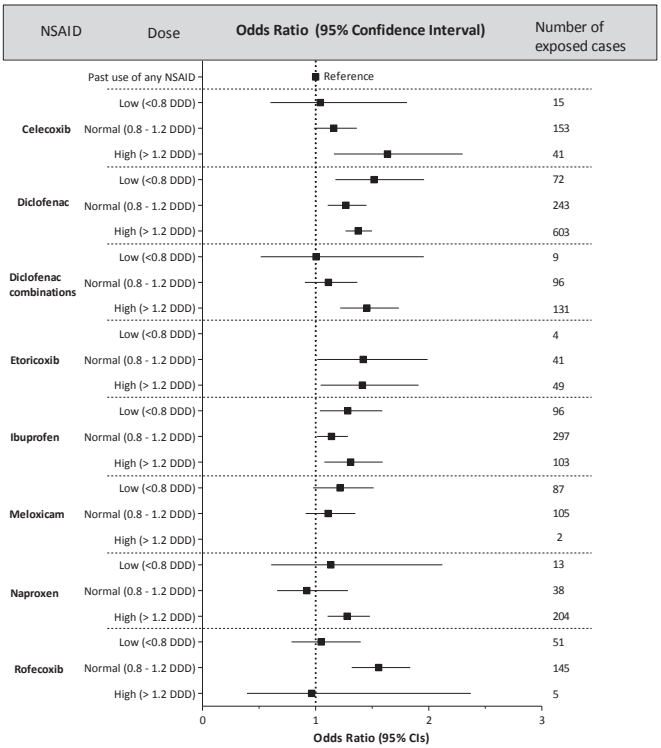


Figure 2. Adjusted risk estimates for AMI in current users for dose of use of individual NSAIDs in three databases pooled (THIN, IPCI, PHARMO) using past use of any NSAID as common reference group**.**

DDD, defined daily dose. Number of exposed cases do not add up to all current users of that particular NSAID in all three databases pooled as dose information could have been missing.

Stratification by AMI risk factors did not reveal clear consistent patterns for potential effect modifiers across individual NSAIDs (Supplementary Table 6). Current use of any NSAID (grouping all individual NSAIDs together) showed significant effect modification for concurrent use of aspirin, lipid lowering drugs and by age, pointing to higher risk in non-users of aspirin and lipid lowering drugs and younger age.

The population attributable risk (PAR) percentages varied between 0% and 2% for different NSAIDs and were slightly higher when the upper limit of the confidence interval was considered (Supplementary Table 7). In most of the databases the PAR was highest for diclofenac and ibuprofen, except in Italy where ibuprofen use is low and the PAR was highest for nimesulide and diclofenac.

DISCUSSION

In this multinational case-control study nested in a new user NSAID cohort of more than 8.5 million persons, we assessed the association with acute myocardial infarction for 28 individual NSAIDs. The study is unique in its kind. It capitalizes on the heterogeneity of prescribing patterns across countries, which allowed for analyses on more drugs than otherwise would be possible in a single database, while using a common data model, protocol, definitions, data transformation and analysis, which is a clear improvement from meta-analyses of heterogeneous observational studies, which has been practice for many years.

Principal findings

The highest point estimate for the risk of AMI was observed for current use of ketorolac in Italian databases. Various other widely used nonselective NSAIDs, such as indometacin, diclofenac, piroxicam, ibuprofen, naproxen, meloxicam and nimesulide; and selective COX-2 inhibitors, as etoricoxib, rofecoxib and celecoxib, were associated with a small increase in risk of AMI. The percentage of AMI cases that can be avoided by taking away the exposure (PAR) was between 0% and 2% and highest for the most frequently used NSAIDS across all databases: ibuprofen and diclofenac in UK, NL and Germany and nimesulide and diclofenac in Italy.

Following the withdrawal of rofecoxib and subsequent referral procedures for nonselective NSAIDs, many single studies have been conducted using different protocols and definitions.[96, 97, 446-448] Meta-analyses of these observational studies identified large variability between studies and several methodological issues (e.g. including prevalent users, immortal time and recall bias) plus gaps in knowledge about dose effects, and effect estimates on individual NSAIDs, particularly for less commonly studied NSAID.[434, 449] With this SOS study we tried to address most of these gaps and limitations.

Comparison with other studies

Our risk estimates are slightly lower (except for naproxen and etoricoxib) than the estimates from meta-analyses of clinical trials[293] for the six NSAIDs (celecoxib, diclofenac, etoricoxib, ibuprofen, naproxen, rofecoxib) that have been studied in RCT meta-analyses (Table 3). Explanation might be that some of the large efficacy trials were done for comparison of gastro-intestinal effects and used higher dosages than what is used in the majority of everyday practice.[450] For the nine NSAIDs for which we have evidence from meta-analyses of published observational studies the SOS estimates were within the width of the confidence intervals (except for naproxen and etodolac). This consistency for the nine NSAIDs where we had external benchmarks gives us reassurance to the interpretation of results of the nineteen additional NSAIDs that were studied.[293, 434]

Table 3. Risk estimates of AMI for individual NSAIDs from current SOS study, meta-analysis from observational studies[434] and randomized clinical trials,[293] using major vascular events as outcome.

	SOS study (pooled dataset) Adjusted ORpooled (95% CI)	Meta-analysis published observational studies Relative Risk (random effects)	Composite Endpoint from meta-analysis of randomized clinical trials# Adjusted Rate Ratio
Reference group	Past Use of any NSAID	No / remote NSAID use	Placebo
Current use of:			
Aceclofenac	1.08 (0.85-1.36)		
Acemetacin	1.00 (0.58-1.71)		
Celecoxib	1.15 (1.05-1.25)	1.23 (1.00-1.52)*	1.36 (0.91–2.02)
Dexibuprofen	1.06 (0.61-1.82)		
Dexketoprofen	1.01 (0.50-2.04)		
Diclofenac	1.28 (1.22-1.34)	1.41 (1.08-1.86)*	1.41 (1.12-1.78)
Diclofenac, comb	1.30 (1.17-1.45)		
Etodolac	1.07 (0.76-1.50)	1.55 (1.16-2.06)	
Etoricoxib	1.39 (1.24-1.57)	1.97 (1.35-2.89)	0.83 (0.18–3.77)
Flurbiprofen	1.00 (0.56-1.78)		
Ibuprofen	1.25 (1.18-1.33)	1.20 (0.97-1.48)*	1.44 (0.89–2.33)
Indometacin	1.51 (1.28-1.80)	1.40 (1.21-1.62)	
Ketoprofen	1.00 (0.86-1.16)		
Ketorolac	1.80 (1.49-2.18)		
Lornoxicam	1.08 (0.62-1.87)		
Mefenamic acid	1.02 (0.55-1.90)		
Meloxicam	1.13 (1.02-1.27)	1.25 (1.04-1.49)	
Nabumetone	1.03 (0.72-1.47)		
Naproxen	1.22 (1.10-1.35)	0.85 (0.73-1.00)*	0.93 (0.69–1.27)
Nimesulide	1.12 (1.03-1.22)		
Oxaprozin	0.97 (0.52-1.79)		
Piroxicam	1.27 (1.13-1.42)		
Proglumetacin	1.00 (0.41-2.47)		
Rofecoxib	1.30 (1.19-1.43)	1.43 (1.21-1.66)*	1.38 (0.99–1.94)
Sulindac	1.01 (0.48-2.15)		
Tenoxicam	0.99 (0.56-1.74)		
Tiaprofenic acid	1.01 (0.49-2.10)		
Valdecoxib	1.07 (0.58-1.99)		

** in new users exposed to NSAIDs.*

 # The outcome major vascular events included non-fatal MI, coronary death, MI or CHD death, non-fatal stroke, stroke death, any stroke and other vascular death). Daily dose studied in Clinical Trials: Diclofenac (150 mg); Ibuprofen (2400 mg); Naproxen (1000 mg); Celecoxib (100-800 mg, typical doses contributing the majority of information on major vascular events 400 mg); Rofecoxib (12.5-125 mg; typical dose 25 mg); Lumiracoxib (100-800 mg; typical dose 200 mg); Etoricoxib (5-120 mg; typical dose 60/90 mg); Valdecoxib (1-80 mg; typical dose 20 mg).

What are the key findings for individual nsNSAIDs in this study? The first is that diclofenac (median dose 150 mg, 1.5 DDD), a very frequently used NSAID in Europe, is associated with an increased risk of AMI of a similar magnitude as rofecoxib (median dose 25 mg, 1 DDD). Some recent meta-analyses have shown this as well.[293, 434] With support of SOS data, regulatory action was therefore taken by EMA in 2013 to restrict the use of diclofenac.[451] The second key finding is that there was one nonselective NSAID that was even more strongly associated with AMI than diclofenac: ketorolac, a finding supporting the negative overall safety profile of ketorolac in Italy, which among other NSAIDs also has showed the highest risk of acute liver failure needing transplantation.[452] The third finding is that we observed a 22% increase in risk of AMI with naproxen use, which is in contrast with some previous studies[96, 293, 434, 446, 453, 454] but in line with others.[96, 453, 455-457] In previous observational studies, naproxen increased the risk of AMI between 14% [456] and 19% [457] as compared to remote NSAID use, a similar comparator group we have chosen. Although trials provide higher level evidence for the specific study population, our finding on naproxen is in fact in line with the ones observed in clinical trials. In the TARGET trial, which was specifically designed to assess the gastrointestinal and cardiovascular safety of lumiracoxib, naproxen and ibuprofen, it appeared that there were no significant differences between the three drugs and the incidence of AMI, regardless of low-dose aspirin use.[458] Our findings may as well be explained by different prescribing patterns in Germany since the increased risk was largely driven by the estimate from the German database which did not provide information on prescribed dose. In the dose response analyses that included UK and Dutch databases only, the OR was only significantly increased for the highest dose of naproxen as compared to past use of any NSAID and the median dose for naproxen was 2 times the daily recommended dose (1000 mg). However, in the Dutch PHARMO databases the risk for naproxen was increased, whereas in the other Dutch database (IPCI) and the Italian and UK databases, the confidence levels of the estimate of naproxen included 1 and thus did not provide a significant increased risk. In the stratified analyses presence of ischemic heart disease yielded an higher risk for naproxen (ORadj 1.95) than in subjects without prior ischemic heart disease (ORadj 1.18) whereas for celecoxib, etoricoxib and rofecoxib the opposite effects were seen, suggesting that selective prescribing may have occurred. Other potential explanations could be potential protopathic bias, which was reported before.[459]

The key findings related to selective COX-2 inhibitors are that the risk of AMI for etoricoxib compared to past use of any NSAID was higher than for diclofenac compared to past use of any NSAID and almost equal to that for rofecoxib, though the confidence limits of these risks were overlapping. An increased risk for etoricoxib was also found in the meta-analysis of observational studies.[434] Although etoricoxib has not been studied extensively in placebo-controlled trials, effects of etoricoxib, rofecoxib and celecoxib seemed similar in trials comparing COX-2 selective inhibitors to diclofenac.[293] However, in the MEDAL trial the rate of thrombotic cardiovascular events (including a range of endpoints) was similar in the diclofenac and the etoricoxib treated group (hazard ratio 0.95; 95%CI: 0.81-1.11).[460] This is very similar to our results if we would compare to observed association of diclofenac indirectly with the odds

ratio of etoricoxib. Our results regarding celecoxib are consistent with the meta-analysis of observational studies and show only a small (15%) increase in risk.[434]

Dose response analyses showed that AMI risk varied by dose, which means that the overall estimates are largely driven by the dose that will be used in a country or given setting. Lower doses in general, but not for all drugs, have a lower risk in the databases we could use to study this. When comparing the potency of individual NSAIDs in the degree of COX-2 inhibition by normal therapeutic doses, our results show a small correlation in line with a previous study but we could only look at 6 different NSAIDs whereas Garcia Rodriguez studied.[97] This supports the previously suggested hypothesis that the extent of inhibition of COX-2–dependent prostacyclin may represent an independent determinant of the increased risk of AMI among NSAIDs with nonfunctional suppression of platelet COX-1, a property shared by most NSAIDs.[461, 462]

Upon stratification for concurrent use of aspirin, lipid lowering drugs, presence of ischemic heart disease, sex, and age several significant interactions were observed, however some were incidental findings for single NSAIDs. E.g. the risk for AMI associated with diclofenac was higher in females than males. The risk was significantly higher in younger persons (<60 years) than older for naproxen, but when current use of all NSAIDs was aggregated, this effect modification was significant for the class. The risk of AMI was higher in non-users of aspirin than in users of aspirin during current use of any NSAID, however not all the databases had adequate information on low dose aspirin. The NSAID associated AMI risk was higher in non-users of lipid lowering drugs than in users, in particular for diclofenac.[434] We did not observe a consistent pattern for the interaction between current use of any NSAID and risk of AMI by presence of co-morbid ischemic heart disease, although for most NSAIDs the risk of AMI was higher in patients with a history of ischemic heart disease. These findings are consistent with previous findings that show that the relative risk of AMI in current users of NSAIDs is higher in low-CV risk subjects, than in high-risk subjects, although the absolute risk may be higher in high-CV risk patients due to higher background rates. [96, 453 293]

Strengths and limitations of study

We acknowledge the following limitations. Since NSAID use was assessed through computerized prescriptions/dispensing, we could not capture over-the-counter NSAID use, this may lead to non-differential misclassification. Channeling of COX-2 inhibitors to high GI-risk patients in the initial marketing phase and the cardiovascular contra-indications after 2004 may have led to time-varying confounding by indication. However, firstly, we matched on calendar time both for the index date as well as cohort entry. Secondly past use of any NSAID was used as comparator (so past users had an indication to receive an NSAID), third we matched on database. In addition we adjusted for a large range of known risk factors for AMI. The matched and adjusted estimates were very similar, indicating that most of the potential confounding variables were time, sex and age-related and taken care of by the matching. Some residual confounding may remain due to inability to measure these confounders

accurately (e.g. smoking), however because of the matching on database this is not likely to differ for cases and controls. However, any residual confounding should be really strong to explain the observed associations.[442, 463] Our primary aim was to compare the risk of AMI across individual NSAIDs, taking the different doses across NSAIDs into account and therefore used 'past' use of any NSAID as common reference group. Though past users may differ from current users, using a different reference group, such as a single NSAID as comparator, is less appropriate as that particular NSAID may be used in different doses than the compared drugs and prescribing differences across countries could result in biased and less stable estimates. On the other hand, the use of a common reference group across all countries and DBs does allow interpretation of risks across different NSAIDs. Finally, although we applied a random effects model thereby providing conservative estimates, we observed heterogeneity for some NSAIDs when pooling results across databases. Multiple factors can explain the differences in risk estimates for the same individual NSAID across databases, such as regional susceptibility to AMI, also in relation to local eating behavior or lifestyle; differential drug utilization and differences in health care systems. We used a stepwise approach for inclusion of confounders in the model in order to derive a model with robust estimates. Although a model with inclusion of all confounders may have been an option, given that some conditions were very rare and not including these in the model will only lead to confounding when associations are large. Furthermore most confounders were forced into the model based on a priori knowledge.

Conclusion and policy implications

In conclusion, this study provides risk estimates for the association between the use of 28 different NSAIDs and the risk of AMI. This allows for evaluating the variability of AMI risk across these NSAIDs in real life practice circumstances. The risk of AMI seems to correlate with COX-2 inhibition potency. The extent of the inhibition of COX-2–dependent prostacyclin among NSAIDs with nonfunctional suppression of platelet COX-1 is a property shared by most NSAIDs. Because the relative risks for AMI are only slightly elevated for most of the individual NSAIDs, the population attributable risks percentages are highest for the products with the highest prevalence of use across all the studied populations, which are diclofenac and ibuprofen in Germany, the Netherlands and the United Kingdom and nimesulide and diclofenac in Italy.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Characteristics of participating databases.

Database	GePaRD	IPCI	PHARMO	SISR	OSSIFF	THIN
Country	Germany	Netherlands	Netherlands	Italy	Italy	United Kingdom
Type of Database	Claims database	General practice database	Record linkage system	National Health Services registry (claims)	National Health Services registry (claims)	General practice database
Study period	2005 - 2009	1999 – 2011	1999 – 2008	2000 – 2009	2002 – 2009	1999 – 2008
Coding system for diagnoses	ICD-10-GM	ICPC and free text	ICD-9-CM	ICD-9-CM	ICD-9-CM	READ
Outpatient hospital diagnoses	Available	Available, as free text or codes	Available	Available	Available	Available
Hospital discharge diagnoses	Available	Available, as free text or codes	Available	Available	Available	Available
Diagnostic procedures	Available	Not available	Available	Available	Available	Available
Laboratory tests	Available ordering of the test	Available	Available, for a subset	Available	Available	Available
Coding system for drugs	ATC	ATC	ATC	ATC	ATC	BNF/ Multilex
Date of prescription/dispensing	Available	Available	Available	Available	Available	Available
Dosing regimen	Not available	Available	Available	Not available	Not available	Available
Drug quantity	Available	Available	Available	Available	Available	Available

ICD-10-GM: International Classification of Diseases, 10th Revision German Modified; ICD-9-CM: International Classification of Diseases, 9th Revision Clinically Modified; ICPC: International Classification for Primary Care; ATC: Anatomical Therapeutic Chemical classification; BNF: British National Formulary.

Supplementary Table 2. NSAIDs included in the SOS project with prevalence of use per 100,000 person-years.

	ATC	Substance	GePaRD	IPCI	PHARMO	SISR	OSSIFF	THIN
M01AA		**Butylpyrazolidines**						
	M01AA01	Phenylbutazone	39.9	2.8	3.0			0.04
	M01AA02	Mofebutazone	1.5					
	M01AA03	Oxyphenbutazone						
	M01AA05	Clofezone						
	M01AA06	Kebuzone						
M01AB		**Acetic acid derivatives and related substances**						
	M01AB01	Indometacin	218.5	97.2	154.2	134.6	215.0	138.3
	M01AB02	Sulindac		9.1	23.4	1.0	1.3	3.5
	M01AB03	Tolmetin		0.2	1.3			
	M01AB04	Zomepirac						
	M01AB05	Diclofenac	8,092.4	5,482.9	4,373.6	1,666.9	2,342.2	3,379.8
	M01AB06	Alclofenac						
	M01AB07	Bumadizone						
	M01AB08	Etodolac						87.0
	M01AB09	Lonazolac	4.9					
	M01AB10	Fentiazac				0.3	0.6	
	M01AB11	Acemetacin	177.9			0.1	0.5	5.4
	M01AB12	Difenpiramide						
	M01AB13	Oxametacin						
	M01AB14	Proglumetacin	26.4			5.8	11.0	
	M01AB15	Ketorolac				430.9	887.7	0.6
	M01AB16	Aceclofenac	77.7	17.5	43.1	411.9	411.9	12.2
	M01AB17	Bufexamac						
	M01AB51	Indometacin, combinations					8.9	
	M01AB55	Diclofenac, combinations	194.5	1,085.1	1,094.7	72.3	126.9	359.6
M01AC		**Oxicams**						
	M01AC01	Piroxicam	300.9	142.8	201.9	853.2	1535.2	78.0
	M01AC02	Tenoxicam		0.5	1.1	54.3	82.6	3.3
	M01AC04	Droxicam						
	M01AC05	Lornoxicam	28.3			76.7	84.8	0.004
	M01AC06	Meloxicam	215.3	411.4	570.3	272.2	450.6	285.9
M01AE		**Propionic acid derivatives**						
	M01AE01	Ibuprofen	8,478.5	1,889.1	3,692.5	555.3	575.1	2,957.7
	M01AE02	Naproxen	192.4	1,649.9	2,384.1	184.8	298.5	692.3
	M01AE03	Ketoprofen	42.1	23.9	45.5	1,193.1	1,519.7	23.9
	M01AE04	Fenoprofen						0.9
	M01AE05	Fenbufen						4.4
	M01AE06	Benoxaprofen						
	M01AE07	Suprofen						
	M01AE08	Pirprofen						
	M01AE09	Flurbiprofen	0.042	3.2	7.9	33.9	62.8	22.8
	M01AE10	Indoprofen						
	M01AE11	Tiaprofenic acid	12.9	58.1	34.7	2.2	7.1	7.1
	M01AE12	Oxaprozin	0.7			62.7	91.5	
	M01AE13	Ibuproxam						
	M01AE14	Dexibuprofen	93.5	7.6	29.6	71.1	74.4	4.9
	M01AE15	Flunoxaprofen						
	M01AE16	Alminoprofen						
	M01AE17	Dexketoprofen	269.8	0.9	2.7	0.019	0.028	14.2
	M01AE18	Naproxcinod						
	M01AE51	Ibuprofen, combinations					0.009	10.2

Supplementary Table 2. NSAIDs included in the SOS project with prevalence of use per 100,000 person-years (*continued*).

	ATC	Substance	GePaRD	IPCI	PHARMO	SISR	OSSIFF	THIN
	M01AE52	Naproxen and esomeprazole		0.1				
	M01AE53	Ketoprofen, combinations				0.005	0.009	
M01AG		**Fenamates**						
	M01AG01	Mefenamic acid	0.003			1.2	1.0	397.0
	M01AG02	Tolfenamic acid		1.2	1.1			7.0
	M01AG03	Flufenamic acid						
	M01AG04	Meclofenamic acid				0.005		
M01AH		**Selective COX-2 inhibitors**						
	M01AH01	Celecoxib	241.6	217.8	303.1	501.2	897.4	386.4
	M01AH02	Rofecoxib	0.3	186.0	576.5	311.3	738.3	301.1
	M01AH03	Valdecoxib	83.5	2.8	11.7	27.1	30.1	17.8
	M01AH04	Parecoxib	7.1					0.039
	M01AH05	Etoricoxib	412.9	406.1	284.5	382.6	434.8	155.6
	M01AH06	Lumiracoxib	14.6					3.2
M01AX		**Other anti-inflammatory and antirheumatic agents, non-steroids**						
	M01AX01	Nabumetone	7.1	51.4	148.7	22.8	42.8	31.0
	M01AX02	Niflumic acid				0.01	5.4	
	M01AX04	Azapropazone		10.5	15.8			7.6
	M01AX07	Benzydamine						
	M01AX13	Proquazone						
	M01AX17	Nimesulide				1,540.3	2,042.7	
	M01AX18	Feprazone						
	M01AX22	Morniflumate				0.1	2.5	
	M01AX23	Tenidap						
	M01AX68	Feprazone, combinations						

Supplementary Table 3. List of diagnostic codes (plus related label) for acute myocardial infarction case identification in electronic medical records stratified by coding system.

ICD 9 (for PHARMO, OSSIFF, SISR)		ICD 10 (for GePaRD)		ICPC (for IPCI)		READ (for THIN)	
410/ 410.9/ 410.90	Acute myocardial infarction	I21	Acute myocardial infarction	K75	Acute myocardial infarction	G30..00	Acute myocardial infarction
410.7	Acute subendocardial myocardial infarction	I21.4	Acute subendocardial myocardial infarction				
410/ 410.01/ 410.02	Acute myocardial infarction of anterolateral wall	I21.0	Acute transmural myocardial infarction of anterior wall			G300.00	Acute anterolateral infarction
410.08	Acute infarction of papillary muscle					G30y100	Acute papillary muscle infarction
410.01	Acute anteroseptal myocardial infarction					G301100	Acute anteroseptal infarction
410.04	Acute myocardial infarction of inferior wall	I21.1	Acute transmural myocardial infarction of inferior wall				
410.08	Acute myocardial infarction of atrium					G30y000	Acute atrial infarction
						G30yz00	Other acute myocardial infarction NOS
						G301000	Acute anteroapical infarction
410.08	Acute myocardial infarction of septum					G30y200	Acute septal infarction
410.03/ 410.3/ 410.31/ 410.32	Acute myocardial infarction of inferoposterior wall					G303.00	Acute inferoposterior infarction
410.02/ 410.2/ 410.21/ 410.22	Acute myocardial infarction of inferolateral wall					G302.00	Acute inferolateral infarction
410.01	Acute myocardial infarction of anterior wall (disorder)					G380.00	Postoperative transmural myocardial infarction anterior wall

Supplementary Table 3. List of diagnostic codes (plus related label) for acute myocardial infarction case identification in electronic medical records stratified by coding system (*continued*).

ICD 9 (for PHARMO, OSSIFF, SISR)		ICD 10 (for GePaRD)		ICPC (for IPCI)	READ (for THIN)	
410.01/ 410.1/ 410.11/ 410.12	Acute myocardial infarction, of other anterior wall					
410.04/ 410.4/ 410.41/ 410.42	Acute myocardial infarction, of other inferior wall				G308.00	Inferior myocardial infarction NOS
					G381.00	Postoperative transmural myocardial infarction inferior wall
410.05/ 410.5/ 410.51/ 410.52	Acute myocardial infarction, of other lateral wall				G305.00	Lateral myocardial infarction NOS
410.07/ 410.71/ 410.72	Acute myocardial infarction, subendocardial infarction				G307.00	Acute subendocardial infarction
410.08/ 410.8/ 410.81/ 410.82	Acute myocardial infarction, of other specified sites				G30z.00	Acute Myocardial infarction NOS
410.06/ 410.6/ 410.61/ 410.62	True posterior myocardial infarction				G306.00	True posterior myocardial infarction
					G304.00	Posterior myocardial infarction NOS
		I21.2/ I21.3 / I21.9	Acute transmural myocardial infarction of other sites/ Acute transmural myocardial infarction of unspecified site / Acute Myocardial infarction, unspecified		Gyu34	Acute transmural myocardial infarction of unspecified site
410.91	Acute myocardial infarction, unspecified site, initial episode of care					
410.92	Acute myocardial infarction, unspecified site, subsequent episode of care					
410	ST elevation (STEMI) and non-ST elevation (NSTEMI) myocardial infarction				G309.00	Acute Q-wave infarct
					G307000	Acute non-Q-wave infarction

Supplementary Table 4. Doses considered in the current study in the three databases that captured prescribed doses (THIN, IPCI, PHARMO).

Current use of:	DDD value	PDD/DDD*			
		Cases		Controls	
		Median (Q1-Q3)	Mean (SD)	Median (Q1-Q3)	Mean (SD)
Diclofenac	100 mg	1.5 (1.0-1.5)	1.3 (0.4)	1.5 (1.0-1.5)	1.3 (0.5)
Fixed Combination of Diclofenac with misoprostol	100 mg	1.5 (1.0-1.5)	1.3 (0.3)	1.2 (1.0-1.5)	1.2 (0.3)
Ibuprofen	1200 mg	1.0 (1.0-1.0)	1.0 (0.4)	1.0 (1.0-1.0)	1.0 (0.3)
Naproxen	500 mg	2.0 (1.5-2.0)	1.7 (0.5)	2.0 (1.5-2.0)	1.7 (0.6)
Meloxicam	15 mg	1.0 (0.5-1.0)	0.8 (0.3)	1.0 (0.5-1.0)	0.8 (0.3)
Celecoxib	200 mg	1.0 (1.0-1.0)	1.1 (0.5)	1.0 (1.0-1.0)	1.1 (0.4)
Rofecoxib	25 mg	1.0 (0.5-1.0)	0.9 (0.3)	1.0 (0.5-1.0)	0.9 (0.3)
Etoricoxib	60 mg	1.5 (1.0-1.5)	1.3 (0.5)	1.5 (1.0-1.5)	1.3 (0.5)

PDD, prescribed daily dose; DDD, defined daily dose.

** PDD/DDD: the ratio of the prescribed daily dose with the defined daily dose as defined by the WHO.*

Supplementary Table 5. Association between current use of individual NSAID and risk of AMI compared with past use of any NSAID by database.

	GePaRD				IPCI			
	Cases N = 9,930	Controls N = 957,016	ORmatched (95% CI)	ORadj (95% CI)	Cases N = 1,070	Controls N = 38,688	ORmatched (95% CI)	ORadj (95% CI)
Past Use of any NSAID	5,339 (53.8)	542,672 (56.7)	1 (ref)	1 (ref)	597 (55.8)	19,025 (49.2)	1 (ref)	1 (ref)
Recent Use of any NSAID	3,138 (31.60)	301,266 (31.48)	1.02 (0.97-1.07)	1.04 (0.98-1.09)	341 (31.87)	14,962 (38.67)	1.01 (0.85-1.2)	1.02 (0.85-1.22)
Current Use of:								
Aceclofenac	6 (0.06)	336 (0.04)	1.64 (0.73-3.68)	1.16 (0.46-2.94)	0 (0)	1 (0.00)		
Acemetacin	11 (0.11)	1,028 (0.11)	1.03 (0.57-1.87)	0.95 (0.52-1.72)				
Celecoxib	13 (0.13)	1,446 (0.15)	0.86 (0.50-1.49)	0.79 (0.46-1.37)	3 (0.28)	94 (0.24)		
Dexibuprofen	2 (0.02)	279 (0.03)			0 (0)	3 (0.01)		
Dexketoprofen	8 (0.08)	604 (0.06)	1.32 (0.65-2.65)	1.12 (0.54-2.33)				
Diclofenac	771 (7.76)	64,062 (6.69)	**1.19 (1.10-1.29)**	**1.22 (1.13-1.33)**	58 (5.42)	2,454 (6.34)	1.07 (0.80-1.44)	1.08 (0.79-1.47)
Diclofenac, combinations	19 (0.19)	1,068 (0.11)	**1.63 (1.03-2.57)**	**1.68 (1.06-2.65)**	13 (1.21)	554 (1.43)	0.80 (0.45-1.43)	0.75 (0.41-1.36)
Etodolac								
Etoricoxib	47 (0.47)	3,401 (0.36)	1.31 (0.98-1.75)	1.29 (0.96-1.72)	5 (0.47)	250 (0.65)	0.88 (0.36-2.18)	0.94 (0.38-2.33)
Flurbiprofen					0 (0)	2 (0.01)		
Ibuprofen	504 (5.08)	35,593 (3.72)	**1.39 (1.26-1.53)**	**1.36 (1.23-1.50)**	18 (1.68)	556 (1.44)	1.28 (0.78-2.10)	1.23 (0.74-2.06)
Indometacin	24 (0.24)	1,277 (0.13)	**1.79 (1.19-2.70)**	**1.71 (1.13-2.56)**	1 (0.09)	30 (0.08)		
Ketoprofen	0 (0)	238 (0.02)			1 (0.09)	7 (0.02)		
Ketorolac								
Lornoxicam	1 (0.01)	98 (0.01)						
Mefenamic acid								
Meloxicam	19 (0.19)	1,459 (0.15)	1.24 (0.79-1.96)	1.22 (0.78-1.93)	8 (0.75)	206 (0.53)	1.33 (0.63-2.78)	1.40 (0.65-3.02)
Nabumetone	1 (0.01)	66 (0.01)			1 (0.09)	13 (0.03)		
Naproxen	21 (0.21)	1,009 (0.11)	**1.97 (1.28-3.05)**	**1.87 (1.20-2.89)**	16 (1.50)	463 (1.20)	1.29 (0.76-2.20)	1.27 (0.74-2.17)
Nimesulide								
Oxaprozin								
Piroxicam	14 (0.14)	1,639 (0.17)	0.82 (0.48-1.38)	0.84 (0.50-1.43)	4 (0.37)	25 (0.06)		
Proglumetacin	1 (0.01)	137 (0.01)						
Rofecoxib					4 (0.37)	43 (0.11)		
Sulindac					0 (0)	6 (0.02)		
Tenoxicam								
Tiaprofenic acid	0 (0)	68 (0.01)			2 (0.19)	22 (0.06)		
Valdecoxib	0 (0)	79 (0.01)						

ORmatched, matching criteria age, sex, indexdate (± 1 year), cohort entry (± 28 days) and database. ORadj, ORadjusted for backward selected confounders (for each database these may differ); 95% CI, 95 % Confidence Intervals. Values in bold represent statistically significant estimates.

Supplementary Table 5. Association between current use of individual NSAID and risk of AMI compared with past use of any NSAID by database (*continued*).

	PHARMO				THIN			
	Cases N = 9,974	Controls N = 896,907	ORmatched (95% CI)	ORadj (95% CI)	Cases N = 13,511	Controls N = 1,232,506	ORmatched (95% CI)	ORadj (95% CI)
Past Use of any NSAID	6,444 (64.6)	618,802 (69.0)	1 (ref)	1 (ref)	8377 (62.0)	799,331 (64.9)	1 (ref)	1 (ref)
Recent Use of any NSAID	2316 (23.22)	200,396 (22.34)	**1.09 (1.03-1.15)**	**1.11 (1.05-1.17)**	3034 (22.46)	62,979 (21.34)	**1.11 (1.06-1.17)**	**1.14 (1.10-1.19)**
Current Use of:								
Aceclofenac	5 (0.05)	272 (0.03)	1.68 (0.69-4.06)	1.52 (0.57-4.03)	4 (0.03)	350 (0.03)		
Acemetacin					2 (0.01)	127 (0.01)		
Celecoxib	54 (0.54)	2,553 (0.28)	**1.71 (1.30-2.25)**	**1.73 (1.32-2.27)**	183 (1.35)	14,771 (1.20)	1.1 (0.95-1.28)	1.11 (0.95-1.28)
Dexibuprofen	4 (0.04)	95 (0.01)			0 (0)	46 (0.00)		
Dexketoprofen	0 (0)	14 (0.00)			1 (0.01)	105 (0.01)		
Diclofenac	420 (4.21)	26,381 (2.94)	**1.41 (1.27-1.56)**	**1.44 (1.30-1.59)**	649 (4.80)	54,019 (4.38)	**1.15 (1.06-1.25)**	**1.24 (1.14-1.34)**
Diclofenac, combinations	122 (1.22)	7,748 (0.86)	**1.29 (1.08-1.55)**	**1.36 (1.13-1.63)**	147 (1.09)	11,210 (0.91)	**1.19 (1.01-1.40)**	**1.22 (1.04-1.44)**
Etodolac					37 (0.27)	2,761 (0.22)	1.22 (0.88-1.69)	1.17 (0.85-1.63)
Etoricoxib	48 (0.48)	2,413 (0.27)	**1.65 (1.24-2.20)**	**1.67 (1.25-2.23)**	53 (0.39)	3,635 (0.29)	1.31 (1.00-1.72)	1.28 (0.97-1.68)
Flurbiprofen	2 (0.02)	92 (0.01)			4 (0.03)	260 (0.02)		
Ibuprofen	207 (2.08)	14,065 (1.57)	**1.33 (1.16-1.54)**	**1.43 (1.24-1.65)**	472 (3.49)	40,291 (3.27)	1.05 (0.96-1.16)	**1.15 (1.04-1.26)**
Indometacin	23 (0.23)	1,293 (0.14)	**1.60 (1.06-2.43)**	**1.61 (1.06-2.44)**	47 (0.35)	3,363 (0.27)	1.31 (0.98-1.74)	**1.36 (1.02-1.82)**
Ketoprofen	1 (0.01)	437 (0.05)			6 (0.04)	701 (0.06)	0.80 (0.36-1.78)	0.94 (0.45-1.98)
Ketorolac					0 (0)	5 (0.00)		
Lornoxicam								
Mefenamic acid					12 (0.09)	910 (0.07)	1.26 (0.71-2.23)	1.18 (0.66-2.09)
Meloxicam	82 (0.82)	5,396 (0.60)	**1.27 (1.02-1.58)**	1.25 (1.00-1.55)	128 (0.95)	10,205 (0.83)	1.12 (0.94-1.34)	1.10 (0.92-1.31)
Nabumetone	10 (0.10)	903 (0.10)	0.99 (0.53-1.86)	1.03 (0.55-1.92)	8 (0.06)	839 (0.07)	0.94 (0.48-1.83)	0.94 (0.48-1.83)
Naproxen	144 (1.44)	9,838 (1.10)	**1.31 (1.10-1.55)**	**1.34 (1.13-1.59)**	156 (1.15)	13,389 (1.09)	1.09 (0.93-1.28)	1.12 (0.96-1.32)
Nimesulide								
Oxaprozin								
Piroxicam	9 (0.09)	1,199 (0.13)	0.67 (0.35-1.30)	0.65 (0.33-1.29)	21 (0.16)	1,654 (0.13)	1.19 (0.77-1.82)	1.16 (0.75-1.78)
Proglumetacin								
Rofecoxib	83 (0.83)	4,974 (0.55)	**1.46 (1.17-1.83)**	**1.46 (1.17-1.83)**	164 (1.21)	11,225 (0.91)	**1.32 (1.12-1.54)**	**1.28 (1.09-1.5)**
Sulindac	7 (0.07)	300 (0.03)	1.87 (0.88-3.96)	1.41 (0.65-3.09)	0 (0)	94 (0.01)		
Tenoxicam	0 (0)	11 (0.00)			1 (0.01)	110 (0.01)		
Tiaprofenic acid	1 (0.01)	231 (0.03)			3 (0.02)	182 (0.01)		
Valdecoxib	0 (0)	39 (0.00)			6 (0.04)	287 (0.02)	1.87 (0.83-4.21)	1.13 (0.39-3.29)

ORmatched, matching criteria age, sex, indexdate (± 1 year), cohort entry (± 28 days) and database. ORadj, ORadjusted for backward selected confounders (for each database these may differ); 95% CI, 95 % Confidence Intervals. Values in bold represent statistically significant estimates.

Supplementary Table 5. Association between current use of individual NSAID and risk of AMI compared with past use of any NSAID by database (*continued*).

	SISR				OSSIFF			
	Cases N = 25,719	Controls N = 2,523,118	ORmatched (95% CI)	ORadj (95% CI)	Cases N = 19,349	Controls N = 1,840,368	ORmatched (95% CI)	ORadj (95% CI)
Past Use of any NSAID	12,265 (47.7)	1,311,705 (52.0)	1 (ref)	1 (ref)	10,732 (55.5)	1,093,813 (59.4)	1 (ref)	1 (ref)
Recent Use of any NSAID	9,128 (35.49)	63,409 (34.22)	**1.08 (1.05-1.11)**	**1.05 (1.02-1.08)**	**5,939 (30.69)**	38,476 (29.26)	**1.10 (1.06-1.14)**	**1.07 (1.03-1.10)**
Current Use of:								
Aceclofenac	141 (0.55)	14,200 (0.56)	0.97 (0.82-1.15)	1.01 (0.85-1.19)	58 (0.30)	5,211 (0.28)	1.05 (0.81-1.36)	1.06 (0.81-1.37)
Acemetacin	1 (0.00)	4 (0.00)			0 (0)	19 (0.00)		
Celecoxib	366 (1.42)	34,595 (1.37)	1.05 (0.94-1.16)	1.08 (0.97-1.20)	267 (1.38)	22,673 (1.23)	1.13 (1.00-1.28)	1.11 (0.98-1.26)
Dexibuprofen	24 (0.09)	1,539 (0.06)	**1.54 (1.03-2.30)**	1.17 (0.75-1.84)	11 (0.06)	689 (0.04)	1.52 (0.84-2.75)	1.12 (0.57-2.22)
Dexketoprofen								
Diclofenac	720 (2.80)	52,244 (2.07)	**1.38 (1.28-1.49)**	**1.39 (1.29-1.50)**	446 (2.31)	31,053 (1.69)	**1.39 (1.26-1.53)**	**1.36 (1.24-1.50)**
Diclofenac, combinations	64 (0.25)	4,398 (0.17)	**1.44 (1.12-1.84)**	**1.35 (1.05-1.74)**	34 (0.18)	2,945 (0.16)	1.10 (0.79-1.55)	1.09 (0.77-1.53)
Etodolac								
Etoricoxib	229 (0.89)	19,631 (0.78)	**1.15 (1.01-1.31)**	**1.17 (1.02-1.33)**	115 (0.59)	8,148 (0.44)	**1.33 (1.10-1.60)**	**1.34 (1.11-1.61)**
Flurbiprofen	15 (0.06)	834 (0.03)	**1.78 (1.06-2.96)**	1.14 (0.62-2.11)	6 (0.03)	784 (0.04)	0.73 (0.33-1.63)	0.93 (0.45-1.91)
Ibuprofen	272 (1.06)	20,588 (0.82)	**1.30 (1.15-1.47)**	**1.23 (1.09-1.39)**	91 (0.47)	8,126 (0.44)	1.04 (0.85-1.29)	1.02 (0.83-1.25)
Indometacin	58 (0.23)	3,722 (0.15)	**1.54 (1.18-1.99)**	**1.33 (1.02-1.75)**	43 (0.22)	2,104 (0.11)	**1.94 (1.43-2.63)**	**1.59 (1.16-2.20)**
Ketoprofen	376 (1.46)	30,916 (1.23)	**1.20 (1.09-1.34)**	**1.16 (1.05-1.29)**	175 (0.90)	15,670 (0.85)	1.07 (0.92-1.24)	1.04 (0.89-1.21)
Ketorolac	148 (0.58)	6,567 (0.26)	**2.24 (1.90-2.64)**	**2.00 (1.70-2.35)**	124 (0.64)	5,160 (0.28)	**2.31 (1.93-2.77)**	**2.14 (1.79-2.55)**
Lornoxicam	22 (0.09)	2,036 (0.08)	1.05 (0.69-1.61)	1.01 (0.66-1.55)	17 (0.09)	961 (0.05)	**1.67 (1.02-2.68)**	1.21 (0.70-2.08)
Mefenamic acid	0 (0)	60 (0.00)			0 (0)	11 (0.00)		
Meloxicam	171 (0.66)	13,501 (0.54)	**1.25 (1.07-1.45)**	**1.28 (1.10-1.49)**	84 (0.43)	8,039 (0.44)	0.99 (0.80-1.23)	1.01 (0.82-1.26)
Nabumetone	14 (0.05)	1,209 (0.05)	1.15 (0.68-1.94)	1.03 (0.60-1.79)	12 (0.06)	765 (0.04)	1.52 (0.86-2.69)	1.13 (0.59-2.16)
Naproxen	87 (0.34)	8,332 (0.33)	1.03 (0.83-1.27)	1.01 (0.81-1.24)	62 (0.32)	5,628 (0.31)	1.06 (0.83-1.37)	1.07 (0.83-1.38)
Nimesulide	1,069 (4.16)	85,349 (3.38)	**1.26 (1.18-1.34)**	**1.18 (1.11-1.26)**	583 (3.01)	48,113 (2.61)	**1.18 (1.08-1.28)**	**1.12 (1.04-1.23)**
Oxaprozin	14 (0.05)	1,740 (0.07)	0.80 (0.47-1.35)	0.93 (0.57-1.54)	8 (0.04)	969 (0.05)	0.80 (0.40-1.60)	0.92 (0.49-1.73)
Piroxicam	324 (1.26)	27,361 (1.08)	**1.17 (1.05-1.31)**	**1.17 (1.04-1.31)**	264 (1.36)	20,020 (1.09)	**1.27 (1.12-1.44)**	**1.28 (1.13-1.45)**
Proglumetacin	6 (0.02)	489 (0.02)	1.19 (0.53-2.67)	1.03 (0.42-2.49)	4 (0.02)	304 (0.02)		
Rofecoxib	180 (0.70)	16,002 (0.63)	1.13 (0.97-1.31)	1.16 (1.00-1.35)	259 (1.34)	19,430 (1.06)	**1.31 (1.15-1.48)**	**1.27 (1.12-1.44)**
Sulindac	3 (0.01)	69 (0.00)			1 (0.01)	25 (0.00)		
Tenoxicam	21 (0.08)	1,877 (0.07)	1.10 (0.71-1.69)	1.05 (0.67-1.63)	10 (0.05)	1,106 (0.06)	0.86 (0.46-1.61)	0.97 (0.53-1.78)
Tiaprofenic acid	1 (0.00)	124 (0.00)			1 (0.01)	83 (0.00)		
Valdecoxib	10 (0.04)	1,299 (0.05)	0.75 (0.40-1.41)	0.91 (0.53-1.59)	9 (0.05)	455 (0.02)	1.86 (0.96-3.61)	1.14 (0.51-2.55)

ORmatched, matching criteria age, sex, indexdate (± 1 year), cohort entry (± 28 days) and database. ORadj, ORadjusted for backward selected confounders (for each database these may differ); 95% CI, 95 % Confidence Intervals.Values in bold represent statistically significant estimates.

Supplementary Table 6. Effect modification by important (proxy) risk factors for AMI on the matched pooled dataset.

NSAID	Sex					Age				
	Females		Males			<= 60 Years		> 60 Years		
Current use of:	Cases N	ORadj (95% CI)	Cases N	ORadj (95% CI)	P-value interaction	Cases N	ORadj (95% CI)	Cases N	ORadj (95% CI)	P-value interaction
Aceclofenac	123	1.01 (0.73-1.41)	91	1.22 (0.87-1.69)	0.447	**38**	**2.26 (1.41-3.60)**	**176**	**0.99 (0.76-1.29)**	**0.016**
Acemetacin	3	0.92 (0.35-2.46)	11	1.08 (0.57-2.04)	0.238	5	1.24 (0.48-3.21)	9	0.96 (0.50-1.82)	0.306
Celecoxib	529	1.13 (1.00-1.27)	357	1.17 (1.03-1.34)	0.833	112	1.36 (1.08-1.71)	774	1.12 (1.02-1.23)	0.124
Dexibuprofen	20	0.95 (0.43-2.12)	21	1.28 (0.63-2.62)	0.083	4	0.93 (0.25-3.41)	37	1.13 (0.63-2.03)	0.375
Dexketoprofen	0	NA	9	1.14 (0.53-2.47)	-	3	0.99 (0.32-3.14)	6	1.03 (0.42-2.50)	0.844
Diclofenac	**1,201**	**1.38 (1.28-1.49)**	**1,863**	**1.25 (1.18-1.32)**	**0.008**	879	1.39 (1.28-1.50)	2,185	1.25 (1.19-1.32)	0.069
Diclofenac combinations	186	1.27 (1.08-1.50)	213	1.28 (1.11-1.48)	0.745	79	1.34 (1.06-1.69)	320	1.22 (1.08-1.38)	0.549
Etodolac	17	1.10 (0.66-1.83)	20	1.09 (0.69-1.72)	0.823	9	1.24 (0.63-2.44)	28	1.07 (0.73-1.58)	0.644
Etoricoxib	261	1.24 (1.03-1.48)	236	1.46 (1.23-1.72)	0.133	74	1.41 (1.09-1.84)	423	1.31 (1.14-1.50)	0.524
Flurbiprofen	14	1.05 (0.49-2.27)	13	0.94 (0.39-2.22)	0.362	3	1.06 (0.24-4.75)	24	1.00 (0.53-1.85)	0.825
Ibuprofen	660	1.30 (1.19-1.43)	904	1.24 (1.15-1.34)	0.369	403	1.31 (1.17-1.46)	1,161	1.22 (1.14-1.31)	0.277
Indometacin	66	1.48 (1.06-2.08)	130	1.56 (1.28-1.90)	0.471	36	1.19 (0.82-1.72)	160	1.74 (1.44-2.10)	0.076
Ketoprofen	291	1.01 (0.82-1.24)	268	1.00 (0.81-1.23)	0.800	78	0.72 (0.46-1.12)	481	1.04 (0.89-1.22)	0.143
Ketorolac	138	1.94 (1.49-2.52)	134	2.16 (1.69-2.77)	0.924	33	1.55 (0.93-2.58)	239	2.19 (1.81-2.66)	0.153
Lornoxicam	24	1.07 (0.51-2.20)	16	1.19 (0.53-2.68)	0.488	4	0.93 (0.17-5.16)	36	1.17 (0.67-2.07)	0.388
Mefenamic acid	8	1.05 (0.49-2.25)	4	1.01 (0.36-2.83)	0.815	6	1.12 (0.48-2.58)	6	1.02 (0.43-2.44)	0.996
Meloxicam	267	1.08 (0.92-1.26)	225	1.17 (1.00-1.36)	0.498	69	1.09 (0.83-1.42)	423	1.11 (0.98-1.25)	0.930
Nabumetone	29	1.10 (0.68-1.79)	17	0.96 (0.56-1.65)	0.419	3	0.57 (0.18-1.83)	43	1.15 (0.79-1.67)	0.063
Naproxen	190	1.19 (1.01-1.40)	296	1.24 (1.09-1.40)	0.689	**165**	**1.44 (1.22-1.70)**	**321**	**1.09 (0.96-1.24)**	**0.013**
Nimesulide	837	1.10 (0.98-1.24)	815	1.17 (1.04-1.32)	0.772	226	1.32 (1.05-1.65)	1,426	1.11 (1.01-1.21)	0.273
Oxaprozin	12	0.96 (0.40-2.30)	10	0.95 (0.39-2.30)	0.980	2	0.95 (0.16-5.52)	20	0.95 (0.48-1.86)	0.951
Piroxicam	342	1.31 (1.12-1.54)	294	1.18 (1.00-1.39)	0.396	86	1.19 (0.90-1.57)	550	1.22 (1.08-1.39)	0.730
Proglumetacin	7	0.99 (0.27-3.63)	4	1.03 (0.29-3.65)	0.699	1	1.03 (0.12-8.81)	10	1.00 (0.37-2.71)	0.849
Rofecoxib	378	1.24 (1.09-1.40)	312	1.40 (1.23-1.60)	0.256	80	1.34 (1.04-1.72)	610	1.30 (1.18-1.43)	0.790
Sulindac	6	1.04 (0.38-2.78)	5	0.99 (0.32-3.07)	0.589	2	1.02 (0.13-8.15)	9	1.03 (0.46-2.29)	0.991
Tenoxicam	17	0.95 (0.43-2.08)	15	1.03 (0.44-2.37)	0.494	3	0.91 (0.17-4.76)	29	0.99 (0.53-1.82)	0.651
Tiaprofenic acid	5	1.06 (0.36-3.15)	3	0.95 (0.35-2.57)	0.260	1	0.88 (0.18-4.18)	7	1.04 (0.45-2.38)	0.418
Valdecoxib	15	1.13 (0.50-2.51)	10	1.08 (0.43-2.76)	0.728	3	1.12 (0.22-5.70)	22	1.13 (0.59-2.16)	0.846
Recent use of any NSAID	10,378	1.07 (1.03-1.11)	13,518	1.09 (1.06-1.12)	0.609	**5,663**	**1.17 (1.12-1.21)**	**18,233**	**1.05 (1.03-1.08)**	**<0.001**
Current use of any NSAID		1.25 (1.2-1.31)		1.27 (1.22-1.31)	0.894		**1.35 (1.28-1.43)**		**1.23 (1.19-1.26)**	**0.001**

ORadj, ORadjusted for backward selected confounders. Bold numbers indicate significant interaction-terms.

Supplementary Table 6. Effect modification by important (proxy) risk factors for AMI on the matched pooled dataset (*continued*).

NSAID	Co morbid ischemic heart disease					Current use of low-dose aspirin				
	Yes		No			Yes		No		
Current use of:	Cases N	ORadj (95% CI)	Cases N	ORadj (95% CI)	P-value interaction	Cases N	ORadj (95% CI)	Cases N	ORadj (95% CI)	P-value interaction
Aceclofenac	9	1.39 (0.34-5.79)	205	1.12 (0.88-1.43)	0.727	65	1.14 (0.72-1.80)	149	1.08 (0.81-1.42)	0.591
Acemetacin	3	0.79 (0.27-2.30)	11	1.04 (0.53-2.02)	0.405	4	NA	10	0.97 (0.53-1.78)	-
Celecoxib	57	0.89 (0.57-1.38)	829	1.16 (1.06-1.28)	0.305	227	1.00 (0.84-1.19)	659	1.20 (1.08-1.33)	0.070
Dexibuprofen	1	NA	40	1.15 (0.65-2.00)	-	13	1.13 (0.38-3.40)	28	1.07 (0.57-2.01)	0.821
Dexketoprofen	4	NA	5	1.01 (0.40-2.57)	-	3	1.13 (0.19-6.65)	6	1.00 (0.45-2.22)	0.368
Diclofenac	360	1.13 (0.98-1.30)	2,704	1.32 (1.26-1.38)	0.952	759	1.19 (1.08-1.31)	2,305	1.32 (1.25-1.39)	0.708
Diclofenac combinations	24	1.11 (0.62-2.02)	375	1.26 (1.13-1.41)	0.560	125	1.19 (0.97-1.46)	274	1.27 (1.12-1.45)	0.918
Etodolac	0	NA	37	1.16 (0.82-1.63)	-	14	1.19 (0.67-2.12)	23	1.08 (0.70-1.66)	0.847
Etoricoxib	**24**	**0.57 (0.31-1.05)**	**473**	**1.39 (1.23-1.58)**	**0.013**	133	1.35 (1.05-1.74)	364	1.34 (1.17-1.55)	0.792
Flurbiprofen	0	NA	27	1.02 (0.57-1.82)	-	10	1.02 (0.36-2.94)	17	1.00 (0.50-2.02)	0.813
Ibuprofen	**256**	**1.32 (1.13-1.55)**	**1,308**	**1.23 (1.16-1.31)**	**0.001**	414	1.18 (1.04-1.33)	1150	1.27 (1.19-1.36)	0.602
Indometacin	25	1.97 (1.16-3.34)	171	1.53 (1.28-1.83)	0.217	53	1.64 (1.17-2.32)	143	1.59 (1.31-1.94)	0.976
Ketoprofen	42	1.35 (0.62-2.96)	517	0.99 (0.85-1.16)	0.504	175	1.01 (0.76-1.35)	384	0.98 (0.82-1.16)	0.523
Ketorolac	29	1.42 (0.52-3.91)	243	2.03 (1.68-2.45)	0.670	87	2.80 (1.97-3.98)	185	1.75 (1.40-2.19)	0.074
Lornoxicam	4	NA	36	1.17 (0.67-2.03)	-	14	0.98 (0.31-3.06)	26	1.17 (0.62-2.21)	0.261
Mefenamic acid	0	NA	12	1.07 (0.56-2.01)	-	3	NA	9	1.05 (0.50-2.23)	-
Meloxicam	36	0.87 (0.49-1.56)	456	1.11 (0.99-1.25)	0.839	141	0.94 (0.76-1.16)	351	1.20 (1.05-1.37)	0.051
Nabumetone	2	NA	44	1.07 (0.74-1.54)	-	16	1.25 (0.69-2.26)	30	0.96 (0.61-1.52)	0.119
Naproxen	30	1.95 (1.17-3.23)	456	1.18 (1.06-1.31)	0.222	146	1.21 (1.00-1.47)	340	1.18 (1.05-1.34)	0.614
Nimesulide	108	1.03 (0.58-1.82)	1,544	1.15 (1.06-1.26)	0.336	523	0.99 (0.82-1.18)	1,129	1.19 (1.08-1.31)	0.085
Oxaprozin	2	NA	20	0.96 (0.50-1.84)	-	6	0.95 (0.27-3.35)	16	0.96 (0.46-2.00)	0.770
Piroxicam	41	0.86 (0.49-1.51)	595	1.22 (1.08-1.37)	0.616	163	0.92 (0.71-1.20)	473	1.31 (1.15-1.48)	0.078
Proglumetacin	1	NA	10	1.00 (0.38-2.63)	-	1	1.02 (0.09-11.22)	10	1.00 (0.37-2.75)	0.746
Rofecoxib	53	1.20 (0.73-1.96)	637	1.32 (1.21-1.45)	0.408	198	1.20 (1.01-1.42)	492	1.37 (1.23-1.53)	0.291
Sulindac	1	NA	10	1.02 (0.49-2.16)	-	4	NA	7	1.01 (0.36-2.81)	-
Tenoxicam	4	NA	28	0.92 (0.50-1.69)	-	4	NA	28	1.02 (0.53-1.95)	-
Tiaprofenic acid	1	NA	7	1.01 (0.46-2.21)	-	2	NA	6	0.98 (0.43-2.25)	-
Valdecoxib	0	NA	25	1.15 (0.62-2.13)	-	2	NA	23	1.20 (0.61-2.36)	-
Recent use of any NSAID	2,119	1.05 (0.96-1.14)	21,177	1.09 (1.06-1.11)	0.257	6,444	1.07 (1.02-1.12)	17,452	1.09 (1.06-1.11)	0.132
Current use of any NSAID		1.14 (1.02-1.27)		1.27 (1.24-1.31)	0.337		**1.16 (1.10-1.23)**		**1.28 (1.24-1.33)**	**0.041**

ORadj, ORadjusted for backward selected confounders. Bold numbers indicate significant interaction-terms.

Supplementary Table 6. Effect modification by important (proxy) risk factors for AMI on the matched pooled dataset (*continued*).

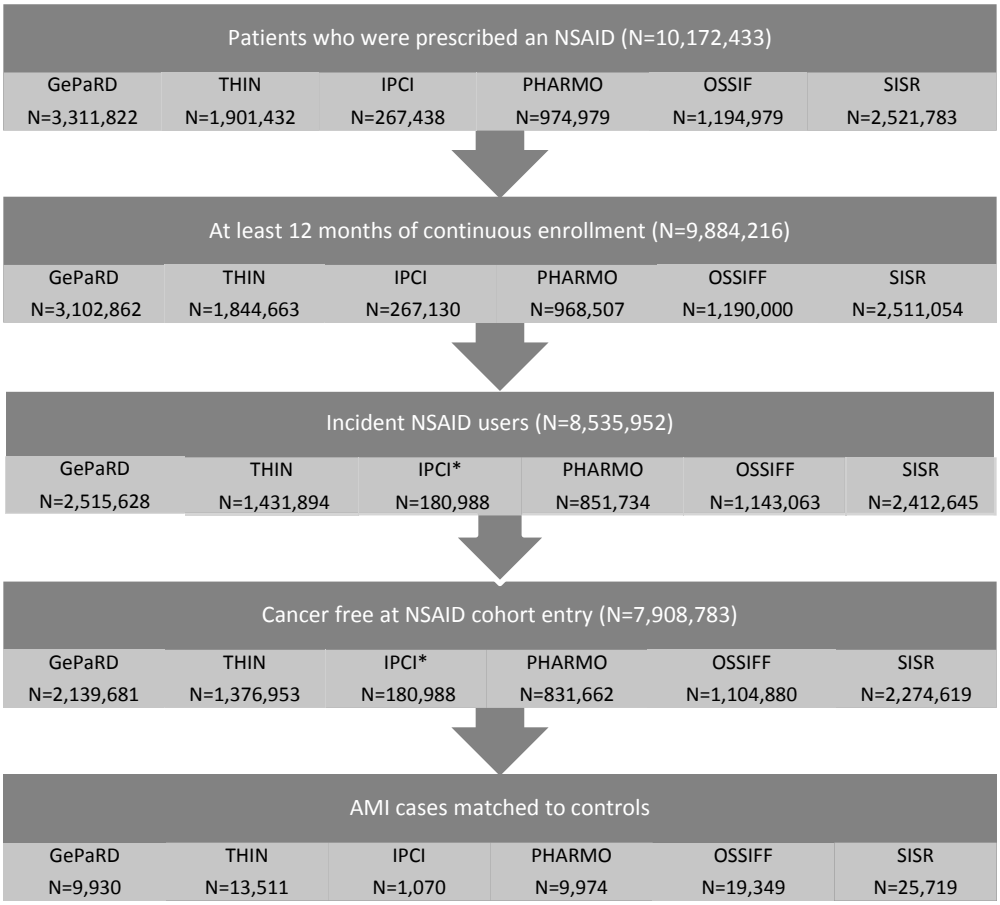
	Use of lipid lowering drugs				
NSAID	**Yes**		**No**		
Current Use of:	**Cases N**	**ORadj (95% CI)**	**Cases N**	**ORadj (95% CI)**	**P-value interaction**
Aceclofenac	38	1.31 (0.78-2.20)	176	1.07 (0.82-1.41)	0.395
Acemetacin	4	NA	10	0.99 (0.52-1.89)	-
Celecoxib	187	1.08 (0.89-1.31)	699	1.15 (1.04-1.28)	0.879
Dexibuprofen	12	1.14 (0.39-3.35)	29	1.06 (0.56-1.99)	0.721
Dexketoprofen	3	NA	6	1.01 (0.43-2.39)	-
Diclofenac	**680**	**1.10 (1.00-1.21)**	**2,384**	**1.35 (1.29-1.42)**	**0.002**
Diclofenac, combinations	99	1.19 (0.95-1.49)	300	1.30 (1.15-1.48)	0.301
Etodolac	16	1.28 (0.75-2.17)	21	1.03 (0.66-1.60)	0.654
Etoricoxib	113	1.44 (1.13-1.84)	384	1.35 (1.17-1.55)	0.886
Flurbiprofen	6	0.88 (0.23-3.36)	21	1.02 (0.53-1.96)	0.641
Ibuprofen	376	1.16 (1.02-1.31)	1,188	1.30 (1.22-1.39)	0.115
Indometacin	40	1.49 (1.04-2.15)	156	1.64 (1.36-1.99)	0.412
Ketoprofen	108	0.65 (0.44-0.97)	451	1.06 (0.90-1.24)	0.287
Ketorolac	61	2.02 (1.28-3.20)	211	1.91 (1.56-2.35)	0.117
Lornoxicam	9	1.33 (0.40-4.49)	31	1.07 (0.56-2.01)	0.369
Mefenamic acid	1	NA	11	1.08 (0.53-2.18)	-
Meloxicam	113	1.00 (0.79-1.26)	379	1.19 (1.05-1.36)	0.101
Nabumetone	7	0.79 (0.36-1.75)	39	1.10 (0.74-1.65)	0.271
Naproxen	134	1.17 (0.96-1.43)	352	1.20 (1.07-1.35)	0.846
Nimesulide	361	1.13 (0.92-1.39)	1,291	1.14 (1.03-1.25)	0.314
Oxaprozin	6	0.92 (0.20-4.23)	16	0.97 (0.48-1.95)	0.563
Prioxicam	119	1.22 (0.92-1.62)	517	1.26 (1.11-1.43)	0.933
Proglumetacin	3	NA	8	0.98 (0.36-2.68)	-
Rofecoxib	146	1.21 (0.98-1.49)	544	1.36 (1.22-1.50)	0.632
Sulindac	4	NA	7	1.02 (0.39-2.66)	-
Tenoxicam	3	NA	29	0.99 (0.53-1.83)	-
Tiaprofenic acid	1	NA	7	1.03 (0.45-2.34)	-
Valdecoxib	5	1.05 (0.28-3.94)	20	1.12 (0.55-2.26)	0.645
Recent use of any NSAID	5,380	1.04 (1.00-1.09)	18,516	1.09 (1.06-1.12)	0.471
Current use of any NSAID		**1.13 (1.07-1.20)**		**1.30 (1.26-1.34)**	**0.002**

ORa, ORadjusted for backward selected confounders. Bold numbers indicate significant interaction-terms.

Supplementary Table 7. Attributable risk and population attributable risk of AMI within each database.

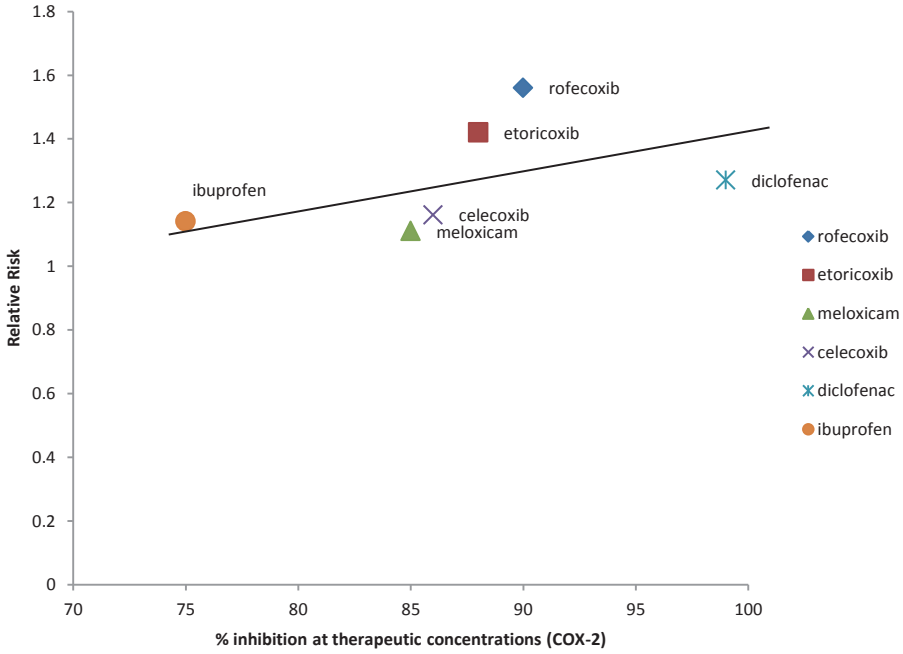
The PAR is an estimate that reflects the percentage of cases that can be avoided in the target population if the exposure is removed from the population. Two estimates are provided. One is based on the point estimate of the adjusted OR in the database and the other is based on the upper limit of the confidence interval of the adjusted OR in that database. Empty cells mean that the OR could not be estimated for that database due to lack of exposure or because the OR was below 1.

Substance PAR	GePaRD In %	GePaRD Using upper limit of ORadj	IPCI In %	IPCI Using upper limit of ORadj	PHARMO In %	PHARMO Using upper limit of ORadj	LOMBARDY In %	LOMBARDY Using upper limit of ORadj	OSSIFF In %	OSSIFF Using upper limit of ORadj	THIN In %	THIN Using upper limit of ORadj
Aceclofenac							0.01	0.10	0.02	0.11		
Acemetacin		0.08										
Celecoxib		0.05			0.39	0.68	0.11	0.28	0.15	0.36	0.15	0.38
Dexibuprofen							0.02	0.08	0.01	0.07		
Dexketoprofen	0.01	0.11	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
Diclofenac	1.68	2.50	0.43	2.48	1.82	2.42	1.08	1.38	0.82	1.14	1.14	1.61
Diclofenac combinations	0.13	0.31		0.43	0.44	0.76	0.09	0.18	0.02	0.10	0.24	0.48
Etodolac											0.05	0.17
Etoricoxib	0.14	0.34			0.32	0.59	0.15	0.29	0.20	0.36	0.11	0.26
Flurbiprofen							0.01	0.07				
Ibuprofen	1.80	2.48	0.38	1.75	0.89	1.33	0.24	0.41	0.01	0.12	0.52	0.90
Indometacin	0.17	0.37			0.14	0.33	0.08	0.17	0.13	0.26	0.13	0.29
Ketoprofen							0.23	0.42	0.04	0.19		
Ketorolac							0.58	0.78				
Lornoxicam							0.00	0.05				
Mefenamic acid											0.02	0.10
Meloxicam	0.04	0.18			0.20	0.45	0.18	0.32	0.00	0.11	0.09	0.29
Nabumetone					0.00	0.09	0.00	0.04	0.01	0.07		
Naproxen	0.18	0.40	0.40	1.72	0.49	0.84	0.00	0.08	0.02	0.12	0.14	0.37
Nimesulide							0.74	1.07				
Oxaprozin							0.00	0.03				
Piroxicam		0.06					0.21	0.39	0.38	0.61	0.03	0.12
Proglumetacin					0.00	0.00	0.00	0.03				
Rofecoxib					0.38	0.68	0.11	0.24	0.36	0.59	0.34	0.60
Sulindac					0.03	0.15					0.00	0.00
Tenoxicam							0.00	0.05	0.00	0.04		
Tiaprofenic acid	0.00	0.00					0.00	0.00				
Valdecoxib							0.00	0.02				



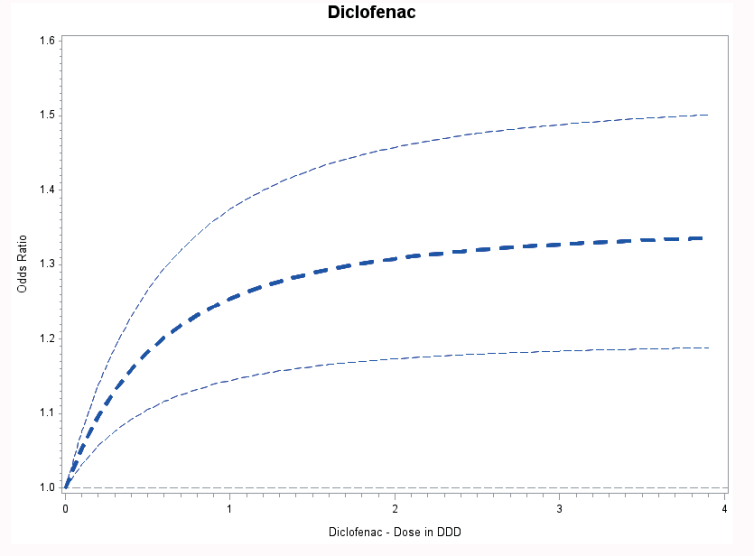
Supplementary Figure 1. Flowchart of source population and study population per database

** In IPCI cancer subjects have been excluded from the incident NSAID users cohort in order to do case validation of outcomes, therefore numbers in the flowchart at the level of 'Incident NSAID users' and 'Cancer free at NSAID cohort entry' for IPCI are similar.*



Supplementary Figure 2. Relation between degree of inhibition of whole blood COX-2 [461] and risk of AMI for individual NSAIDs in the three databases that included doses (THIN, IPCI, PHARMO).

* the OR for dose 0.8-1.2 pdd/ddd was chosen for plotting in this figure.



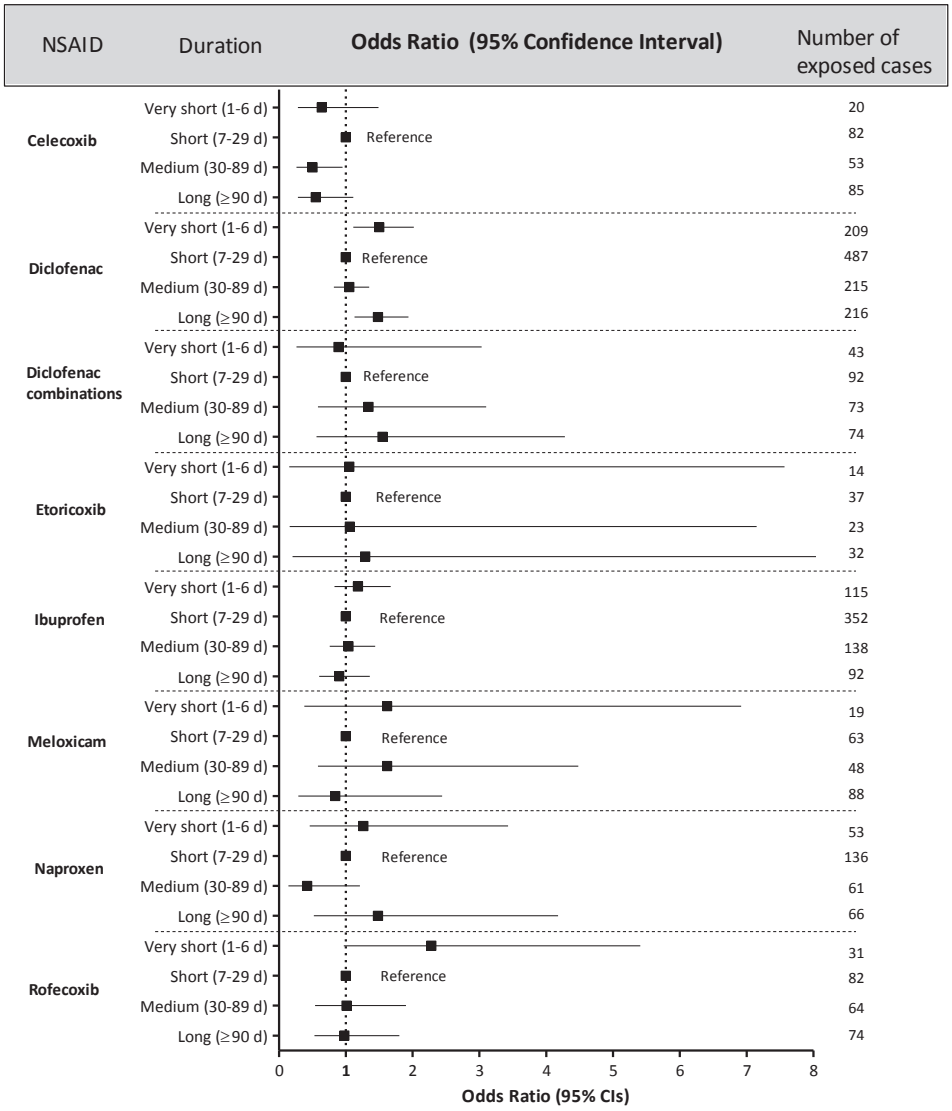
Supplementary Figure 3. Dose response estimated by fractional polynomial regression for diclofenac

Supplementary Figure 3A shows the estimated dose-response curves for current use of diclofenac.

The dose-response relationship is modeled through restricted cubic splines, implemented in a conditional logistic regression model. A cubic spline is a smoothly joined piecewise cubic polynomial curve. In particular, in cubic spline models the observed range of exposure is divided into different categories, and within each category a third-order polynomials is fitted. Cubic spline models provide great flexibility for fitting dose-response curves to data. To obtain a regular pattern even in the most extreme ranges of the dose, restricted cubic splines were considered. Restricted cubic splines have a linear trend outside the most extreme knots. In the present analysis three knots were considered corresponding to 0 DDD, 0.8 DDDs and 1.2 DDDs. This choice of knots allows to represent a dose-response relationship potentially non-linear in the dose range from 0 DDD to 1.2 DDD, and assumed to be linear for doses over 1.2 DDDs

The bold blue line represents the polynomial curve with 1st degree term with corresponding 95% confidence intervals, the bold red line represents polynomial curve with 2nd degree term with corresponding 95% confidence intervals.

Dose on the x-asis represents the dose as was estimated from the prescribing regimen and strength. The dose is calculated by dividing the prescribed dose by the recommended daily dose (DDD).



Supplementary Figure 4. Adjusted risk estimates of AMI in current users of individual NSAIDs for duration of use in three databases pooled (THIN, IPCI, PHARMO) using short duration (7-29 days) as reference group.

CHAPTER 6.2

Individualized NSAID prescribing based on gastrointestinal and cardiovascular risks: a decision model in the SOS project

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ABSTRACT

BACKGROUND

Use of non-steroidal anti-inflammatory drugs (NSAIDs) increases the risk of upper gastrointestinal (GI) complications and cardiovascular (CV) events. However, the risk may differ between individual NSAIDs and subjects. Decision models for selecting the safest NSAID to treat individual patients are not available.

AIM

To develop a decision model integrating GI and CV risks.

METHODS

The decision model integrated information from 1) case-control studies risks of individual NSAIDs on GI and CV events [acute myocardial infarction (AMI), ischemic stroke (IS), heart failure (HF)]; 2) a risk function for patient characteristics associated with GI and CV events; 3) disutility weights for each outcome. Data were retrieved from six European healthcare data sources: IPCI, PHARMO (NL); SISR, OSSIFF (Italy); GePaRD (Germany) and THIN (UK) during 1999-2011. For thirteen individual NSAID we provided an overall risk from the decision model.

RESULTS

In the case-control studies 15,046 upper GI complication; 95,163 HF; 79,553 AMI and 35,691 IS cases were identified among 8.9 million new NSAID users. The lowest risks were seen for use of celecoxib for upper GI complication (OR=1.1) and for HF (OR=1.0), for IS for ketoprofen (OR=0.9) and for AMI for tenoxicam and aceclofenac (OR=1.0). For all outcomes ketorolac yielded the highest risks. In the risk function and for each outcome, age was the most important predictor, followed by history of the outcome and sex. In the final decision model, over different scenarios, most preferable NSAIDs were aceclofenac and celecoxib, thereafter nimesulide and ibuprofen. Piroxicam and ketorolac were the least preferable NSAIDs.

CONCLUSION

We provided an integrated GI and CV safety decision model for new NSAID users, which may guide physicians in clinical decision making.

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used painkillers with antipyretic, anti-inflammatory and pain relieving properties and are considered relatively harmless drugs. However, since long time it is known that their use is restricted by the occurrence of upper gastrointestinal (GI) complications such as peptic ulcer perforations, obstructions, and bleeding.[325] In order to reduce the upper GI complication risk associated with NSAID use, selective cyclo-oxygenase (COX)-2 inhibitors were developed. By preferentially inhibiting COX-2, and to a lesser extent the house-keeper isoform COX-1, selective COX-2 inhibitors are effective pain relievers while having a lower risk of upper GI complication compared with the traditional, nonselective (ns)NSAIDs.[10, 11, 464] Yet, this preferable benefit of COX-2 inhibitors over the traditional NSAIDs was abolished by the risk increase of serious cardiovascular (CV) events following clinical trials.[11, 89, 95] This led to the recommendation from the United States (US) Food and Drug Administration (FDA) and the European Medicines Agency (EMA) to avoid selective COX-2 inhibitors in patients with ischemic heart disease, stroke or peripheral arterial disease.[89, 94, 95, 465] However, subsequent signals regarding the increased arterial thrombosis risk for use of the traditional nsNSAIDs arose,[293] particularly when they were used at high doses and for long-term therapy leading to restriction of diclofenac use in 2013.[451]

The integration of this information for clinicians is difficult as the risk of an NSAID-related adverse event may be different between individuals and dependent on underlying co-morbid conditions and indications of use. For instance, the GI and CV risk profile of subjects influence the risk of NSAID-related adverse events which in turn may influence the choice for NSAID prescription to either a nsNSAID or a selective COX-2 inhibitor. Besides, we currently know that the risk of GI and CV events differs for each individual NSAID and should not be considered class-specific (eg. nsNSAIDs and selective COX-2 inhibitors). A decision model is an intuitive tool to visualize the sequences of events that can occur following decisions, taking the negative impact of health outcomes into account. Previous decision analytic studies have reported on a difference in risk for single outcomes,[466] provided cost-effectiveness analyses,[467] reported population risk estimates rather than the risk for an individual patient, or did not differentiate between individual types of NSAIDs.[468, 469] However, in clinical practice it is more informative to know which individual NSAID yields the lowest upper GI and CV risk for an individual patient. The SOS (Safety of Non-steroidal Anti-inflammatory Drugs) project was initiated as a project funded by the European Commission to address issues on CV and UGI risks for the EMA. The aim of the current study was to provide a decision analytic model for each individual NSAID compound balancing the upper GI and CV safety for individual patients.

METHODS

Data sources

Data for this study was obtained from six different longitudinal population-based health care databases from four European countries [Germany (GE), Italy (IT), Netherlands (NL) and United Kingdom (UK)] covering a source population of around 32 million subjects. All databases have been used for pharmacoepidemiological research (see Supplementary Table 1 Chapter 6.1).[237, 238, 435, 436]

In short, the German Pharmacoepidemiological Research Database (GePaRD) is a database comprising data from five statutory health insurances throughout Germany that is created and maintained by BIPS. It currently covers around 14 million insurants and represents approximately 20% of the German population.[436] The Health Improvement Network (THIN) database is a general practice database in the UK and currently captures medical records of 11.1 million patients.[237] The Integrated Primary Care Information (IPCI) database is also a general practice database but from the Netherlands and currently covers over 1.5 million people,[238] PHARMO database is a medical record linkage system of 2.2 million community-dwelling inhabitants in the Netherlands.[435] OSSIFF (Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia) is a database capturing national health service data and clinical registries from several local health agencies in Lombardy) for a population of about 2.9 million people. The second Italian database SISR (Sistema Informativo Sanitario Regionale) obtains national health service data from the Lombardy region, with about nine million inhabitants (approximately 16% of the national population). OSSIFF was included in addition to the Lombardy SISR as it allows for validation of outcomes; overlapping patients were excluded from the Lombardy SISR.

All general practice and claims databases contain information on demographics of the population, diagnoses (in- and/or outpatient), and drug prescriptions/dispensings. The diagnoses captured by the databases are coded with four different disease coding systems including the International Classification of Diseases (ICD) 9th or 10th revision,[323] International Classification for Primary Care (ICPC),[240] or READ.[438] Mapping of concepts and codes was performed using the Unified Medical Language System (UMLS), a biomedical terminology integration system handling more than 150 medical dictionaries, according to a previously described workflow.[439, 440] All drugs were mapped to the World Health Organization's (WHO) classification of Anatomical Therapeutic Chemical (ATC).[242] A distributed approach was used for collaboration: all database custodians extracted data locally; original data were transformed into a simple common data model (Jerboa© input files); mapping of codes for outcome and covariates was verified using an extensive harmonization strategy; and a common standardized script (Jerboa©, Java-based)[346] was supplied to create the aggregated tables that were subsequently encrypted and shared on a central data warehouse for further analysis and pooling. Details have been described previously.[346, 380]

NSAID Cohort

In each database, we identified a cohort of patients aged 18 years or older who received at least one NSAID prescription (see Supplementary Table 2 Chapter 6.1) during the database-specific study period which started at the first of January 1999 or later, depending on data availability (see Supplementary Table 1 Chapter 6.1).

Cohort entry was defined as the date of first NSAID prescription/dispensing during the study period. Subjects receiving any NSAID prescription in the year prior to cohort entry were excluded in order to construct a new user cohort to avoid potential biases derived from the inclusion of prevalent users.[470] Patients were required to have at least one year of continuous database history. All subjects with a cancer diagnosis (except non-melanoma skin cancer) in the year preceding cohort entry were excluded from the cohort. All NSAID cohort members were followed from the date of cohort entry until the date of outcome (see below), exclusion criteria, death, last data supply, transferring out of the database, or end of the database-specific study period, whichever was earliest.

Definition of Outcomes and related risk factors

Events of interest included upper GI complication, acute myocardial infarction (AMI), ischemic stroke (IS) and heart failure (HF). More detailed information is given in Supplementary Table 3. The choice of risk factors was made based on literature review, consortium agreement and on importance of the risk factors and ease and availability in clinical practice. In order to keep the model as simple as possible but still including the most relevant risk factors, age, sex and a prior history of the outcome were included.

Decision model development

The decision model was developed following the process depicted in Figure 1. The model was derived from 1) risk estimates for individual NSAIDs for each of the four outcomes; 2) absolute risk of outcomes based on risk factors; and 3) impact of the event on the health of the individual, presented as disutility. The decision model integrated all these results to provide one overall absolute risk yielding the relative safety for each individual NSAID for a specific patient with certain characteristics.

1. *Risk estimates from case-control studies*

Four matched case-control studies nested within a new NSAID user cohort were conducted within each database. For each outcome (upper GI complication, AMI, IS and HF) the odds ratios and corresponding 95% confidence intervals (CI) during individual NSAID exposure were obtained by conditional logistic regression models, adjusting for selected confounders. These confounders were classified into two sets: 1) a priori confounders that were always considered

in the model; and 2) a set of confounders that underwent a backward selection. A random effects meta-analytic approach was applied to obtain an overall pooled estimate for each individual NSAID per outcome. The risk estimates for each NSAID are shown in Table 1.

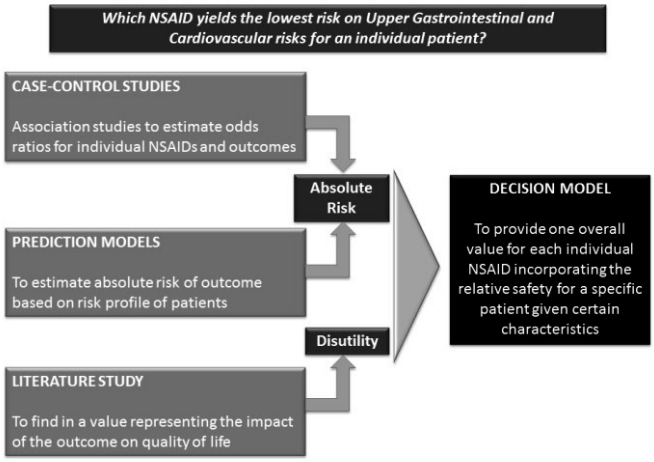


Figure 1. Work flow for development of the decision model.

Table 1. Odds Ratio estimates from random effects meta-analysis model on individual NSAIDs from the SOS case control studies (current use vs. past use of any NSAID).

	Upper gastro-intestinal complication	Heart failure	Acute myocardial infarction	Ischemic Stroke	Available in decision model
Past use of any NSAID	1 (ref)	1 (ref)	1 (ref)	1 (ref)	
Current use of:					
Aceclofenac	1.20	0.97	1.04	1.24	Yes
Celecoxib	1.16	0.96	1.15	1.02	Yes
Diclofenac	3.26	1.21	1.31	1.30	Yes
Diclofenac, combi	2.15	1.02	1.27		No
Etoricoxib	3.26	1.67	1.28	1.11	Yes
Flurbiprofen	3.69		1.05		
Ibuprofen	1.53	1.24	1.24	1.16	Yes
Indometacin	3.00	1.55	1.47	1.18	Yes
Ketoprofen	2.83	1.04	1.12	0.93	Yes
Ketorolac	6.53	1.85	2.06	1.46	Yes
Lornoxicam	4.06		1.08		No
Meloxicam	3.17	1.04	1.18	0.99	Yes
Nabumetone		1.48	1.03		No
Naproxen	2.96	1.18	1.19	1.06	Yes
Nimesulide	1.21	1.19	1.16	1.14	Yes
Oxaprozin	6.07		0.93		No
Piroxicam	4.16	1.28	1.17	1.13	Yes
Rofecoxib	2.12	1.36	1.26	1.18	Yes
Tenoxicam	2.88		1.02		No
Valdecoxib			1.00		No
Nr of studied NSAIDs	**18**	**15**	**20**	**13**	**13**

2. *Risk estimates from prediction models*

A risk function was built to investigate the effect of patient characteristics such as age, sex, medical history of an outcome, country of origin and follow-up period on the risk of each outcomes using a Poisson regression model. Age was categorized in 10 year groups (18-29; 30-39; 40-49; 50-59; 60-69; 70-79 and ≥80 years) using age group 40-49 years as reference group. We fitted models in each of the six databases and pooled the regression coefficients by a random effects model in order to account for clustering of patients within databases and to obtain an overall estimate for each characteristic. The model intercepts were adjusted per database for the pooled regression coefficients.

3. *Utilities of health states*

Utilities are cardinal values between 0 (death) and 1 (perfect health). A value representing the impact of the outcome on the quality of life (utility) was derived from literature.[471] The disutility (i.e., 1-utility) is the negative impact of the occurrence of the event on the patient's quality of life. By using disutilities, the probabilities (i.e., the risk based on risk functions) of developing an outcome can be compared between individual NSAIDs. We considered utilities of outcomes in two periods: at 4 weeks (for an acute effect) and at 1 year (for a chronic effect) (Table 2). It shows that experiencing IS provides the largest disutility both on the short term and long term. This means that NSAIDs associated with a higher risk of IS (given all other risks remain the same) will be preferred less.

Table 2. Disutilities used to assess the impact of the occurrence of the outcome on the quality of life*.

Time Horizon	Outcome			
	Upper Gastrointestinal Complication	Heart Failure	Acute Myocardial Infarction	Ischemic Stroke
Acute effect	0.54	0.29	0.63	0.65
Chronic effect	0.02	0.00	0.12	0.29

***** Derived from Latimer *et al.*[471]. Acute effect at 4 weeks, chronic effect at 1 year.

Integration of results

To arrive from the cumulative risk estimates to NSAID associated absolute risk, the risk needs to be integrated with the relative risk associated with the NSAID. The risk functions provided the absolute risk of an outcome given a certain follow-up period. In order to calculate the NSAID related absolute risk the relative risk estimates from the case-control studies should be included as well. Thus the final decision model required information from the risk function, utilities and the estimates from the case-control studies. In order to combine this information for the calculation of the absolute risks, the baseline risk in each database was adjusted for the

proportion of follow-up time that consisted of the duration of NSAID exposure. In this way, the original database specific intercepts were independent of the overall effect of NSAIDs. Finally the estimates from the case-control analyses for each individual NSAID were incorporated to the model. By applying the disutilities the final cumulative risks were obtained.

Model performance

Model performance of the prediction models was assessed through calibration and discrimination. Calibration provides information on whether the predictions agree with the actual observations. It was evaluated by the slope of the linear predictor of the regression model used to compare the observed and predicted outcomes. Ideally the calibration slope is equal to 1. The calibration slope was calculated through a Poisson regression model for the outcome and the linear predictors as only covariable.[472] The linear predictor was calculated as summing up the products of the regression coefficients of the model and the predictor values. Discrimination is the ability to distinguish between patient with and without the event. Discrimination was assessed by concordance (c) statistic. The *c*-statistic ranges from 0.5 (no discriminative ability; no better than flipping a coin) to 1.0 (model perfectly discriminates between those patients who will develop an event and who not).

Validation

The performance of prediction models in new patients is often worse than expected based on performance estimated from the development data. This optimism and overfitting was diminished by applying an internal validation technique as cross-validation. Six-fold cross validation was done by creating a model and quantifying the model performance (calibration and discrimination) six times while omitting one database each time from the development process and using as validation cohort.

Subgroup analyses

We performed subgroup analyses by considering the use of PPIs and low-dose aspirin as an effect modifier for the NSAID effect on the outcomes (for PPI on upper GI complication and for low-dose aspirin on upper GI complication and AMI).

RESULTS

Study Population

The study population included 8.9 million new NSAID users, of which the majority was female (55%-57%) in the Netherlands, Italy and the United Kingdom, except for Germany in which 49% was female (Table 3). Mean age in the cohort of incident NSAID users was between 46

and 49 years in the Netherlands, Germany and the United Kingdom, but was higher in Italy (55 to 57 years). The mean time spent in the NSAID cohort was shortest in IPCI with 2 years and longest in the Italian database OSSIFF with 4.1 years.

Upper GI complications had the lowest incidence (between 3.4-9.7) per 10,000 person-years (PYs), with a total of 23,411 events occurring after a median of 1.1 years (IPCI) up to 2 years (OSSIFF and TIN) after start of NSAID therapy (Table 3). There were 79,876 events of heart failure resulting in incidence rates between 14 and 40 events per 10,000 PYs with the highest incidence in Italy. We observed 68,757 AMI events, yielding incidence rates between 16 and 30 events per 10,000 PYs and we captured 35,691 IS with incidences ranging between 6.5 (THIN) and 18.5 (GePaRD) per 10,000 PYs.

Risk estimates from case-control studies

Over all databases, 15,046 upper GI complication; 95,163 HF; 79,553 AMI and 35,691 IS cases were included in the case-control studies. For thirteen individual NSAIDs a risk estimate was available for all four outcomes. Ketorolac had the highest risk estimate for all outcomes (Table 1). For other NSAIDs, ranking differed across the outcomes. Risk estimates were highest for the outcome upper GI complications.

Risk estimates from prediction models

The incidence rate ratios derived from the prediction models are shown in Table 4. For all outcomes increasing age, male sex, a history of the event were predictors of the outcome. A longer follow-up was inversely associated with the outcome. Cumulative risk could be calculated for each of the outcomes based on the integration of the prediction models and NSAID specific risk estimates. The cumulative risk varied by age, sex, a prior history of the event and time horizon. In Figure 2 the cumulative risks of each of the outcomes at 1 year for a male subject with and without a prior history of the event are shown.

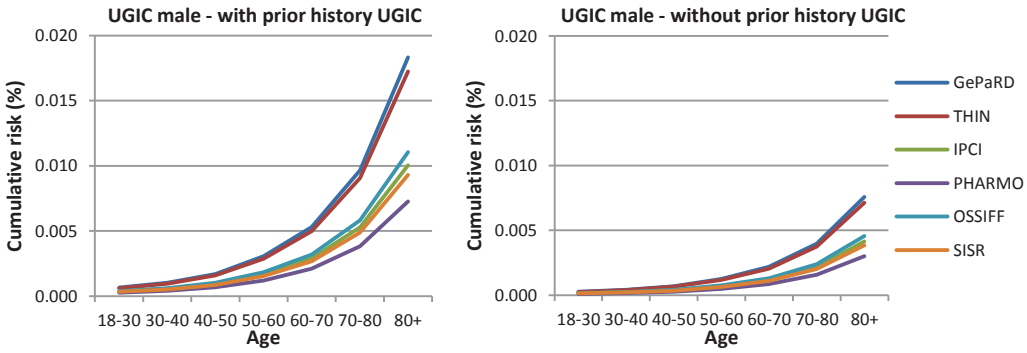


Figure 2. Cumulative 1 year risk of outcomes in male patients with and without a prior history of the outcome by age and by database.

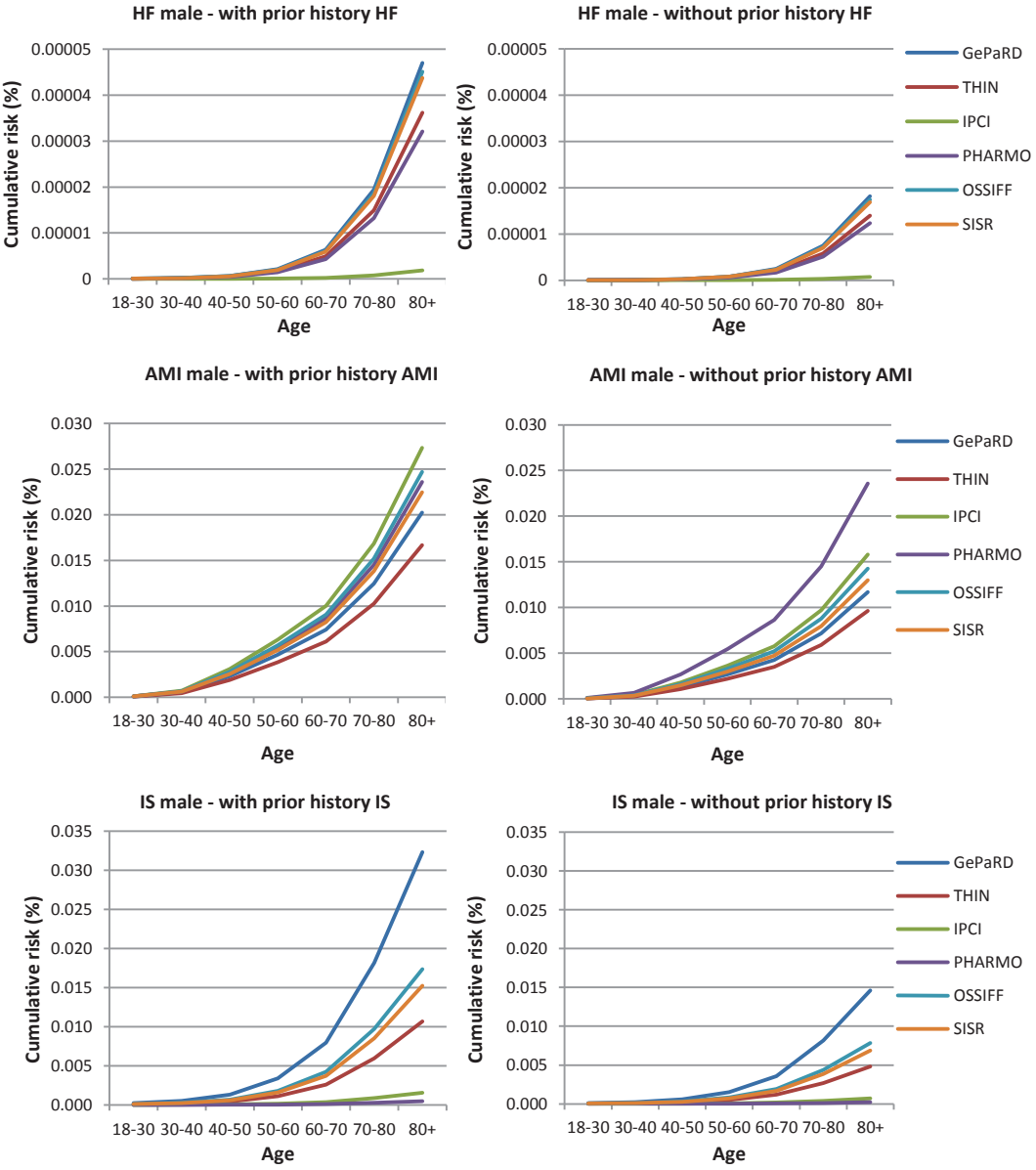


Figure 2. Cumulative 1 year risk of outcomes in male patients with and without a prior history of the outcome by age and by database.

Table 3. Demographics of study population per database.

	Netherlands		Italy		Germany	United Kingdom
	PHARMO	IPCI	OSSIFF	SISR	GePaRD	THIN
Nr of subjects	952,345	190,920	1,165,303	2,451,574	2,595,738	1,587,646
Females (%)	525,701 (55)	106,570 (56)	652,759 (56)	1,400,806 (57)	1,263,901 (49)	879,244 (55)
Age Mean (SD)	46 (17.3)	49 (16.7)	55 (17)	57 (16.6)	48 (15.8)	49 (17.4)
Age Median (IQR)	44 (33-58)	48 (37-61)	56 (42-68)	58 (42-68)	47 (37-60)	47 (35-61)
Mean follow-up (years)	3.8	2.0	4.1	3.5	2.5	3.6
Age in categories: (%)						
18-29	18.9	13.3	7.7	5.8	14.9	14.9
30-39	20.9	17.2	13.8	12.1	19.3	19.3
40-49	20.2	22.6	16.7	15.9	19.9	19.9
50-59	16.5	19.8	19.2	19.3	17.7	17.7
60-69	11.5	14.2	20.5	21.7	14.2	14.2
70-79	8.1	8.9	15.6	17.3	9.4	9.4
≥ 80	3.8	4.1	6.7	8.0	4.7	4.7
Upper GI complications						
Nr of events	1,232	223	3,713	6,257	6,498	5,488
Person Time (PYs)	3,675,376	387,149	4,876,260	8,609,191	6,715,040.50	5,774,448
Rate per 10,000 PYs	3.4	5.8	7.6	7.3	9.7	9.5
Median time until UGIC in years (IQR) †	1.8 (0.5-3.2)	1.1 (0.5-2.2)	2.0 (0.7-3.5)	1.9 (0.7-3.2)	1.4 (0.5-2.5)	2.0 (0.8-3.3)
Heart Failure						
Nr of events	5,150	NA	18,074	34,176	11,153	11,323
Person Time (PYs)	3,579,388	NA	4,734,179	8,566,871	6,544,561	5,765,051
Rate per 10,000 PYs	14.4	NA	38.2	39.9	17.0	19.6
Median time until HF in years (IQR) †	2.2 (1.0-3.6)	1.9 (1.1-3.3)	2.3 (1.1-3.6)	2.1 (1-3.4)	1.5 (0.7-2.6)	2.0 (0.9-3.3)
Acute Myocardial Infarction						
Nr of events	6,659	918	14,150	25,391	12,674	8,965
Person Time (PYs)	3,573,658	376,805	4,737,697	8,577,055	6,540,328	5,767,358
Rate per 10,000 PYs	18.6	24.3	29.9	29.6	19.4	15.5
Median time until AMI in years (IQR) †	2.2 (1.0-3.5)	1.3 (0.6-2.4)	2.4 (1.2-2.6)	2.1 (1-3.4)	1.5 (0.7-2.6)	2.0 (0.9-3.3)

Table 3. Demographics of study population per database (*continued*).

	Netherlands		Italy		Germany	United Kingdom
	PHARMO	**IPCI**	**OSSIFF**	**SISR**	**GePaRD**	**THIN**
Nr of subjects	952,345	190,920	1,165,303	2,451,574	2,595,738	1,587,646
Ischemic Stroke						
Nr of events	NA	NA	7,155	12,669	12,090	3,777
Person Time (PYs)	NA	NA	4,751,317	8,600,081	6,541,726	5,778,751
Rate per 10,000 PYs	NA	NA	15.1	14.7	18.5	6.5
Median time until IS in years (IQR) †	2.7 (1.3-3.7)	1.4 (0.6-2.1)	2.4 (1.2-3.7)	2.1 (1-3.4)	1.6 (0.7-2.6)	2.2 (1-3.5)
Comorbidities:						
Prior Upper GI complication	0	4.6	0.1	0.1	1.1	0.4
Prior Upper GI disease	0	1.8	0.3	0.2	8.6	1.8
Chronic hepatic disorders	0	1.8	0.5	0.6	6.8	0.1
Alcohol abuse	0.1	5.2	0.2	0.2	1.1	11.8
Smoking	0	15.1	0	0	0	6.7
Inflammatory polyarthritis	0.1	14.7	0.1	0.2	2.2	0.4
Osteoarthritis	0.7	3	0.6	0.7	14.4	5.7
Cancer	0.1	8.7	2	2.5	9.7	1
Use of:						
Glucocorticoids	1.1	0.8	2	2.3	2.5	0.9
Low-dose aspirin	5.6	5.4	4.4	6.5	1.8	6.4
Antiplatelets	0.5	0.7	0.7	1.2	0.6	0.6
Anticoagulants	1.4	1.7	1.7	2.1	2.4	0.4
Gastroprotective agents	9.3	19.7	5.6	8.7	8.3	9.5

(†) only among those who experimented the event; NA, not assessable; PYs, person-years; GI, gastrointestinal; HF, heart failure; AMI, acute myocardial infarction; IS, ischemic stroke; IQR, interquartile range, Nr, number.

Table 4. Multivariable rate ratios of risk factors for the outcome after pooling the estimates across databases by a random effects meta-analysis.

	Upper GI Compl IRR (95%CI)	Heart Failure IRR (95%CI)	AMI IRR (95%CI)	Ischemic Stroke IRR (95%CI)
Age (years):				
40-49	1 (ref)	1 (ref)	1 (ref)	1 (ref)
18-29	0.38 (0.3-0.5)	0.10 (0.08-0.13)	0.04 (0.03-0.05)	0.18 (0.14-0.23)
30-39	0.60 (0.5-0.7)	0.32 (0.29-0.36)	0.24 (0.23-0.26)	0.39 (0.33-0.45)
50-59	1.80 (1.6-2.0)	3.33 (2.97-3.72)	2.04 (1.94-2.15)	2.60 (2.45-2.76)
60-69	3.13 (2.6-3.8)	9.94 (9.42-10.49)	3.24 (3.09-3.41)	6.14 (5.81-6.49)
70-79	5.71 (4.2-7.8)	30.65 (28.10-33.46)	5.46 (5.04-5.91)	14.07 (12.58-15.73)
> 80	10.9 0(6.9-17)	74.13 (70.27-78.21)	8.91 (7.35-10.81)	25.25 (20.49-31.11)
Sex:				
Male	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Female	0.63 (0.5-0.8)	0.65 (0.64-0.66)	0.42 (0.39-0.44)	0.64 (0.59-0.70)
History of Outcome*:				
No	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Yes	2.43 (1.9-3.1)	2.59 (1.84-3.64)	1.74 (1.11-2.73)	2.23 (1.70-2.92)
Follow-up time:				
0-2 weeks	1 (ref)	1 (ref)	1 (ref)	1 (ref)
2-4 weeks	0.69 (0.6-0.8)	0.79 (0.69-0.90)	0.78 (0.65-0.94)	0.83 (0.73-0.93)
4 weeks-1 year	0.32 (0.2-0.5)	0.57 (0.50-0.65)	0.64 (0.56-0.72)	0.72 (0.64-0.81)
1-2 years	0.29 (0.2-0.4)	0.59 (0.53-0.66)	0.66 (0.58-0.75)	0.74 (0.68-0.82)
2-5 years	0.30 (0.2-0.4)	0.67 (0.64-0.71)	0.71 (0.63-0.81)	0.85 (0.78-0.92)
Databases:				
SISR	1 (ref)	1 (ref)	1 (ref)	1 (ref)
GePaRD	1.98 (1.9-2.1)	1.08 (1.05-1.10)	0.90 (0.88-0.92)	2.14 (2.08-2.19)
THIN	1.86 (1.8-1.9)	0.83 (0.81-0.85)	0.74 (0.72-0.76)	0.70 (0.67-0.72)
IPCI	1.08 (1.0-1.2)	0.04 (0.03-0.06)	1.22 (1.14-1.30)	0.10 (0.07-0.14)
PHARMO	0.78 (0.7-0.8)	0.73 (0.72-0.76)	1.05 (1.02-1.07)	0.03 (0.02-0.04)
OSSIFF	1.19 (1.1-1.2)	1.03 (1.01-1.05)	1.10 (1.08-1.12)	1.14 (1.11-1.18)

Cross validation

The performance of the prediction models showed a fairly good *c*-statistic for each of the outcomes in each database by means of cross validation (Supplementary Table 4). Only for upper GI complication when the model was created in SISR, OSSIFF, PHARMO, THIN and GePaRD and subsequently tested in IPCI, the predictive ability for upper GI complication was lower than in the other databases.

The calibration slopes were in general close to 1, except for upper GI complication (IPCI and THIN <1 representing optimism), AMI (IPCI) and IS (PHARMO).

Decision Model

By integration of the cumulative risks with the disutilities we could compare the different NSAIDs over a number of scenarios (Table 5). For thirteen NSAIDs we had a risk estimate for all four outcomes and these NSAIDs were included in the decision model. In general, celecoxib

was first or second preferred NSAID over all different scenarios. Thereafter, ketoprofen and aceclofenac were often first or second preferred choices, particularly when a prior history of events was present, though they also ranked up to 6th option. Naproxen was between 5th to 7th option, rofecoxib between 5th and 9th option, while diclofenac ranked from 9th option to 11th option. Ketorolac and etoricoxib ranked lowest and were least preferable NSAIDs. However based on the absolute risks, for some scenarios all NSAIDs may provide a similar absolute risk and thus more NSAIDs may be considered appropriate than the first or second highest ranked NSAID (Supplementary Table 5). For instance, in scenario 7; a male aged between 18 and 29 in the UK without any history of the outcomes, the absolute risks ranged between 0.000016% for celecoxib (safest) and 0.000038% for etoricoxib (most harmful) which is a doubling in risk, but the absolute difference is still small.

Subgroup analyses

When considering the use of PPIs as effect modifier for upper GI complications (e.g. those using an NSAID concurrently with a PPI have a lower risk of upper GI complications than those only using an NSAID) still celecoxib, ketoprofen and aceclofenac were most preferred NSAIDs and ketorolac and etoricoxib least preferred NSAIDs (data not shown). Low-dose aspirin affects the risk of cardiovascular events and upper GI complications, therefore when LDA is used concomitantly with an NSAID again ketoprofen and celecoxib were considered relatively safest. Meloxicam also was relatively safe. Ketorolac, indometacin and diclofenac were considered most harmful (data not shown).

Table 5. Decision model outcome: example of the result of the decision model; the NSAID which is considered the safest with respect to upper gastrointestinal complication, heart failure, acute myocardial infarction, and ischemic stroke is ranked highest. Effectiveness in pain relief is assumed similar between NSAIDs.

	Scenario	1	2	3	4	5
	DB	United Kingdom	United Kingdom	United Kingdom	United Kingdom	United Kingdom
	Sex	Female	Male	Female	Male	Female
	Age	50-60	50-60	60-70	60-70	18-30
	UGIC	No	No	No	No	No
	AMI	No	No	No	No	No
	HF	No	No	No	No	No
	IS	No	No	No	No	No
	Time period	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks
Safest	1	Celecoxib	Ketoprofen	Ketoprofen	Aceclofenac	Celecoxib
	2	Ketoprofen	Celecoxib	Celecoxib	Celecoxib	Aceclofenac
	3	Aceclofenac	Aceclofenac	Meloxicam	Nimesulide	Nimesulide
	4	Nimesulide	Nimesulide	Nimesulide	Ibuprofen	Ibuprofen
	5	Meloxicam	Meloxicam	Aceclofenac	Rofecoxib	Rofecoxib
	6	Naproxen	Naproxen	Naproxen	Ketoprofen	Ketoprofen
	7	Ibuprofen	Ibuprofen	Ibuprofen	Naproxen	Naproxen
	8	Rofecoxib	Piroxicam	Rofecoxib	Meloxicam	Indometacin
	9	Piroxicam	Rofecoxib	Piroxicam	Indometacin	Meloxicam
	10	Diclofenac	Diclofenac	Indometacin	Diclofenac	Diclofenac
	11	Indometacin	Indometacin	Diclofenac	Piroxicam	Etoricoxib
Most	12	Ketorolac	Etoricoxib	Ketorolac	Etoricoxib	Piroxicam
harmful	13	Etoricoxib	Ketorolac	Etoricoxib	Ketorolac	Ketorolac

Table 5. Decision model outcome: example of the result of the decision model; the NSAID which is considered the safest with respect to upper gastrointestinal complication, heart failure, acute myocardial infarction, and ischemic stroke is ranked highest. Effectiveness in pain relief is assumed similar between NSAIDs (*continued*).

	Scenario	**6**	**7**	**8**	**9**	**10**
	DB	United Kingdom	United Kingdom	United Kingdom	Italy (SISR)	Italy (SISR)
	Sex	Female	Male	Male	Female	Male
	Age	80+	18-30	80+	50-60	50-60
	UGIC	No	No	No	No	No
	AMI	No	No	No	No	No
	HF	No	No	No	No	No
	IS	No	No	No	No	No
	Time period	4 weeks	4 weeks	4 weeks	4 weeks	4 weeks
Safest	1	Ketoprofen	Celecoxib	Ketoprofen	Ketoprofen	Ketoprofen
	2	Celecoxib	Nimesulide	Celecoxib	Celecoxib	Celecoxib
	3	Meloxicam	Aceclofenac	Meloxicam	Meloxicam	Aceclofenac
	4	Nimesulide	Ibuprofen	Nimesulide	Aceclofenac	Meloxicam
	5	Naproxen	Ketoprofen	Aceclofenac	Nimesulide	Nimesulide
	6	Aceclofenac	Rofecoxib	Naproxen	Naproxen	Naproxen
	7	Ibuprofen	Meloxicam	Ibuprofen	Piroxicam	Piroxicam
	8	Rofecoxib	Naproxen	Piroxicam	Ibuprofen	Ibuprofen
	9	Piroxicam	Indometacin	Rofecoxib	Rofecoxib	Rofecoxib
	10	Indometacin	Piroxicam	Indometacin	Diclofenac	Diclofenac
	11	Diclofenac	Diclofenac	Diclofenac	Indometacin	Indometacin
Most	12	Ketorolac	Ketorolac	Ketorolac	Ketorolac	Ketorolac
harmful	13	Etoricoxib	Etoricoxib	Etoricoxib	Etoricoxib	Etoricoxib
	Scenario	**11**	**12**	**13**	**14**	**15**
	DB	United Kingdom	United Kingdom	United Kingdom	United Kingdom	NL (IPCI)
	Sex	Female	Female	Female	Female	Female
	Age	50-60	50-60	50-60	50-60	50-60
	UGIC	No	Yes	Yes	No	No
	AMI	No	Yes	Yes	No	No
	HF	No	Yes	Yes	No	No
	IS	No	Yes	Yes	No	No
	Time period	1 year	1 year	4 weeks	5 years	4 weeks
Safest	1	Ketoprofen	Celecoxib	Celecoxib	Aceclofenac	Aceclofenac
	2	Celecoxib	Ketoprofen	Ketoprofen	Celecoxib	Celecoxib
	3	Aceclofenac	Aceclofenac	Aceclofenac	Nimesulide	Nimesulide
	4	Nimesulide	Nimesulide	Nimesulide	Ibuprofen	Ibuprofen
	5	Meloxicam	Meloxicam	Meloxicam	Rofecoxib	Rofecoxib
	6	Naproxen	Naproxen	Naproxen	Ketoprofen	Ketoprofen
	7	Ibuprofen	Ibuprofen	Ibuprofen	Naproxen	Naproxen
	8	Piroxicam	Rofecoxib	Rofecoxib	Meloxicam	Meloxicam
	9	Rofecoxib	Piroxicam	Piroxicam	Indometacin	Diclofenac
	10	Diclofenac	Diclofenac	Indometacin	Diclofenac	Etoricoxib
	11	Indometacin	Indometacin	Diclofenac	Piroxicam	Piroxicam
Most	12	Ketorolac	Ketorolac	Ketorolac	Etoricoxib	Indometacin
harmful	13	Etoricoxib	Etoricoxib	Etoricoxib	Ketorolac	Ketorolac

NL, the Netherlands

DISCUSSION

In the current study we provided an integrated decision model for new NSAID users on upper gastrointestinal and cardiovascular outcomes as we took advantage of the heterogeneity of NSAID exposure across European countries and of the sample size. Individualized predictions of NSAID treatment effects did not differ largely on patient characteristics as age, sex, country or comorbid diseases. Over a range of scenarios least harmful NSAIDs included celecoxib and ketoprofen, while ketorolac and etoricoxib were preferred less.

In recent years we have learned that the cardiovascular safety of NSAIDs was not a sole feature attributed to selective COX-2 inhibitors but as well to the nonselective NSAIDs.[96, 97, 293, 434, 446-449, 473, 474] Particularly for diclofenac evidence - for observational studies derived from the SOS-project - of an increased risk of AMI has accumulated in past years.[293, 434] This resulted in the European regulatory agency EMA to restrict the use of diclofenac.[475] However, the benefit-risk balance of NSAIDs includes besides cardiovascular outcomes also the upper gastrointestinal tract. Selective COX-2 inhibitors were developed as safer NSAIDs than the traditional ones and have been proven to be less harmful in clinical trials with respect to the upper gastrointestinal tract.[10, 11] The dilemma about cardiovascular and gastrointestinal risks of different NSAIDs is however what a physician in routine clinical care needs to deal with. Individualized predictions of NSAID treatment effects therefore, provide an opportunity to determine what the implications of NSAID treatment decisions would be on an individual level. Making treatment decisions on the basis of a predicted treatment effect for individual patients may in some situations result in more net benefit on a group level than treating all patients.

There are only a few studies available integrating CV and GI risks for NSAIDs. In line with a simulation study comparing the additional number of GI and CV events that would occur for use of diclofenac, ibuprofen and naproxen compared to use of celecoxib,[476] also celecoxib appeared to have the least harmful profile. However, this study relied on a simulated population and information on relative risks of individual NSAIDs on coronary heart disease, congestive heart failure and peptic ulcer complications was retrieved from the literature.[476] Another simulation study showed that the harm-benefit ratio of selective COX-2 inhibitors on the incidence of upper GI events may be offset by an increase in AMI events, when assuming drug effects from trials or the CPRD population.[468] In contrast to both studies, we were able to estimate both the individual NSAID effects in a new user NSAID cohort and the risk factors for the outcomes in the same underlying cohort. A decision analysis comparing only rofecoxib with naproxen, as a typical participant of the VIGOR trial that resulted in the rofecoxib scandal, incorporated AMI risk and upper GI toxicity on life expectancy.[477] Apart from the result that naproxen may result in longer life expectancy in 58-year old women with rheumatoid arthritis, the generalizability of the study is limited as it included only 2 individual NSAID compounds.[477] The results of the decision model in the current study were mainly driven by the highest risk estimates that were seen for upper GI complication as outcome. Although the impact of having an AMI and IS at 4 weeks and 1 year was considered worse than an upper GI

complication, NSAIDs risks on upper GI complication ranged between 1.2 and 6.5 whereas those for AMI and IS between 0.9 and 2.1 and 1.0 and 1.3, respectively. Even when considering that PPIs and low-dose aspirin affect the risk of upper GI[243] and cardiovascular endpoints[293], results of the decision model were pretty consistent.

In this study we took the perspective of the physician and of the patient, rather than of the healthcare payer. We have not considered cost-effectiveness of treatments in the models, because since PPIs and NSAIDs have become available generically on the market, costs of adding a PPI to NSAID therapy, both nsNSAIDs and selective COX-2 inhibitors, has been shown cost-effective.[478]

The strengths of the current study include the setting and design of the study. We were able to estimate NSAID treatment effects in a new user cohort in all six databases using the same protocol and data transformations. By profiting the heterogeneity of NSAID exposure and the size of the SOS platform we were able to include thirteen different individual NSAID compounds and provide robust estimates from cross-validated prediction models.

We acknowledge the following limitations. Firstly, we assumed that all NSAID compounds were equally effective in pain relief, though this is generally observed in clinical trials [11, 318, 458] and based on a review [479] it may not be necessarily applicable to our study population. Secondly, we assumed that prognostic risk factors for the outcomes, such as male sex, were similar for the different NSAIDs. Thirdly, the risk of upper GI complication and CV outcomes on short-term and long-term was based on baseline information and did not incorporate the duration of NSAID therapy. This was considered given common clinical practice where a physician needs to decide which NSAID to prescribe based on information at that current moment. Fourthly, the disutilities chosen may not be applicable to all patients. For instance, the impact of an outcome may differ between each individual patient and the disutility at 1 year may not be the same at 5 years, though we did consider it as such in the model.

In conclusion, we assessed and compared the cardiovascular and gastrointestinal safety of individual NSAIDs and provided a decision analytic model to aid in the choice of treatment, taking into account both the cardiovascular (ischemic stroke, myocardial infarction, heart failure) and upper gastrointestinal complications risks. Over a range of scenarios celecoxib and ketoprofen were considered the relative safest of 13 individual NSAIDs studied. Our results may aid physicians in clinical decision making.

SUPPLEMENTARY MATERIAL

Supplementary Table 3. Definition of Events of Interest.

Event	Definition
Upper Gastrointestinal Complication	Upper gastrointestinal complication (UGIC) events were defined as a patient with peptic ulcer disease or gastritis complicated by bleeding, perforation or obstruction. Uncomplicated peptic ulcer disease, lower GI disease, unspecified GI bleeding, or symptoms indicating UGI bleeding, such as melena or hematemesis without a diagnosis of peptic ulcer disease, were not considered as UGI event.
Acute Myocardial Infarction	Acute myocardial infarction was defined as an infarction of myocardial tissue including transmural, subendocardial, or unspecified acute myocardial infarction.
Heart Failure	Heart failure was defined as a patient with congestive heart failure, left sided heart failure and unspecified heart failure being the main reason for hospitalization or diagnosis. Heart failure incidental to hospitalization for other causes were not considered.
Ischemic stroke	Ischemic stroke was defined as an occlusion of cerebral arteries resulting in signs and disturbances of cerebral function lasting > 24 hours. Transient cerebral ischemia (TIA) was not considered as ischemic stroke. Stroke secondary to a trauma was also not included.

Events of interest included a first encountered hospitalization of the event in hospital discharge or administrative databases (GePaRD, PHARMO, OSSIFF and SISR) or a first diagnosis of the event in primary care databases (THIN, IPCI).

Supplementary Table 4. Performance of prediction models at cross validation by outcomes.

Dataset	SISR	OSSIFF	PHARMO	IPCI	THIN	GePaRD
	Upper gastrointestinal complications					
***c*-statistic**	0.75	0.75	0.75	0.75	0.75	0.75
calibration slope (SE)	1.15 (0.016)	1.15 (0.016)	1.15 (0.016)	1.15 (0.016)	1.15 (0.016)	1.15 (0.016)
	Heart Failure					
***c*-statistic**	0.84	0.84	0.89	0.87	0.87	0.87
calibration slope (SE)	1.05 (0.006)	1.01 (0.007)	1.01 (0.007)	0.96 (0.172)	0.95 (0.009)	1.06 (0.007)
	Acute myocardial infarction					
***c*-statistic**	0.75	0.75	0.75	0.75	0.75	0.75
calibration slope (SE)	1.06 (0.009)	1.06 (0.009)	1.06 (0.009)	1.06 (0.009)	1.06 (0.009)	1.06 (0.009)
	Ischemic stroke (IS)					
***c*-statistic**	0.79	0.79	0.79	0.79	0.79	0.79
calibration slope (SE)	1.10 (0.011)	1.10 (0.011)	1.10 (0.011)	1.10 (0.011)	1.10 (0.011)	1.10 (0.011)

Supplementary Table 5. Decision model ranking with absolute risks associated with each individual NSAID per scenario.

	Scenario	1	Absolute risk (%)	2	Absolute risk (%)	3	Absolute risk (%)	4	Absolute risk (%)	5	Absolute risk (%)
	DB	United Kingdom		United Kingdom		United Kingdom		United Kingdom		United Kingdom	
	Sex	Female		Male		Female		Male		Female	
	Age	50-60		50-60		60-70		60-70		18-30	
	Prior UGIC	No		No		No		No		No	
	Prior AMI	No		No		No		No		No	
	Prior HF	No		No		No		No		No	
	Prior IS	No		No		No		No		No	
	Time period	4 weeks		4 weeks		4 weeks		4 weeks		4 weeks	
Safest	1	Celecoxib	0.000188	Ketoprofen	0.000376	Ketoprofen	0.000358	Aceclofenac	0.000366	Celecoxib	0.000010
	2	Ketoprofen	0.000189	Celecoxib	0.000376	Celecoxib	0.000360	Celecoxib	0.000369	Aceclofenac	0.000010
	3	Aceclofenac	0.000195	Aceclofenac	0.000380	Meloxicam	0.000381	Nimesulide	0.000383	Nimesulide	0.000010
	4	Nimesulide	0.000198	Nimesulide	0.000394	Nimesulide	0.000384	Ibuprofen	0.000425	Ibuprofen	0.000012
	5	Meloxicam	0.000201	Meloxicam	0.000399	Aceclofenac	0.000386	Rofecoxib	0.000480	Rofecoxib	0.000016
	6	Naproxen	0.000206	Naproxen	0.000408	Naproxen	0.000393	Ketoprofen	0.000499	Ketoprofen	0.000020
	7	Ibuprofen	0.000209	Ibuprofen	0.000416	Ibuprofen	0.000403	Naproxen	0.000530	Naproxen	0.000021
	8	Rofecoxib	0.000216	Piroxicam	0.000424	Rofecoxib	0.000415	Meloxicam	0.000542	Indometacin	0.000022
	9	Piroxicam	0.000217	Rofecoxib	0.000428	Piroxicam	0.000416	Indometacin	0.000592	Meloxicam	0.000023
	10	Diclofenac	0.000237	Diclofenac	0.000465	Indometacin	0.000454	Diclofenac	0.000592	Diclofenac	0.000024
	11	Indometacin	0.000240	Indometacin	0.000481	Diclofenac	0.000457	Piroxicam	0.000632	Etoricoxib	0.000026
Most	12	Ketorolac	0.000336	Etoricoxib	0.000668	Ketorolac	0.000626	Etoricoxib	0.000693	Piroxicam	0.000029
harmful	13	Etoricoxib	0.000368	Ketorolac	0.000674	Etoricoxib	0.000769	Ketorolac	0.001013	Ketorolac	0.000046

Supplementary Table 5. Decision model ranking with absolute risks associated with each individual NSAID per scenario *(continued)*.

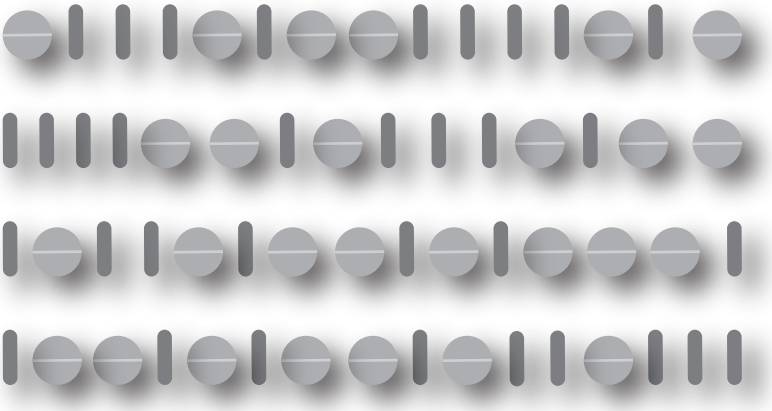
	Scenario	6	Absolute risk (%)	7	Absolute risk (%)	8	Absolute risk (%)	9	Absolute risk (%)	10	Absolute risk (%)
	DB	United Kingdom		United Kingdom		United Kingdom		SISR		SISR	
	Sex	Female		Male		Male		Female		Male	
	Age	80+		18-30		80+		50-60		50-60	
	Prior UGIC	No		No		No		No		No	
	Prior AMI	No		No		No		No		No	
	Prior HF	No		No		No		No		No	
	Prior IS	No		No		No		No		No	
	Time period	4 weeks		4 weeks		4 weeks		4 weeks		4 weeks	
Safest	1	Ketoprofen	0.001237	Celecoxib	0.000016	Ketoprofen	0.002284	Ketoprofen	0.000261	Ketoprofen	0.000523
	2	Celecoxib	0.001253	Nimesulide	0.000017	Celecoxib	0.002317	Celecoxib	0.000269	Celecoxib	0.000538
	3	Meloxicam	0.001318	Aceclofenac	0.000017	Meloxicam	0.002429	Meloxicam	0.000277	Aceclofenac	0.000546
	4	Nimesulide	0.001349	Ibuprofen	0.000018	Nimesulide	0.002470	Aceclofenac	0.000281	Meloxicam	0.000554
	5	Naproxen	0.001366	Ketoprofen	0.000018	Aceclofenac	0.002477	Nimesulide	0.000284	Nimesulide	0.000563
	6	Aceclofenac	0.001377	Rofecoxib	0.000020	Naproxen	0.002508	Naproxen	0.000286	Naproxen	0.000569
	7	Ibuprofen	0.001406	Meloxicam	0.000020	Ibuprofen	0.002585	Piroxicam	0.000296	Piroxicam	0.000583
	8	Rofecoxib	0.001451	Naproxen	0.000020	Piroxicam	0.002643	Ibuprofen	0.000298	Ibuprofen	0.000593
	9	Piroxicam	0.001456	Indometacin	0.000022	Rofecoxib	0.002662	Rofecoxib	0.000305	Rofecoxib	0.000606
	10	Indometacin	0.001565	Piroxicam	0.000023	Indometacin	0.002905	Diclofenac	0.000330	Diclofenac	0.000650
	11	Diclofenac	0.001603	Diclofenac	0.000023	Diclofenac	0.002916	Indometacin	0.000335	Indometacin	0.000674
Most	12	Ketorolac	0.002134	Ketorolac	0.000034	Ketorolac	0.003976	Ketorolac	0.000456	Ketorolac	0.000923
harmful	13	Etoricoxib	0.002889	Etoricoxib	0.000038	Etoricoxib	0.004909	Etoricoxib	0.000530	Etoricoxib	0.000960

Supplementary Table 5. Decision model ranking with absolute risks associated with each individual NSAID per scenario (*continued*).

	Scenario	11	Absolute risk (%)	12	Absolute risk (%)	13	Absolute risk (%)	14	Absolute risk (%)	15	Absolute risk (%)
	DB	United Kingdom		United Kingdom		United Kingdom		United Kingdom		Netherlands (IPCI)	
	Sex	Female		Female		Female		Female		Female	
	Age	50-60		50-60		50-60		50-60		50-60	
	Prior UGIC	No		Yes		Yes		No		No	
	Prior AMI	No		Yes		Yes		No		No	
	Prior HF	No		Yes		Yes		No		No	
	Prior IS	No		Yes		Yes		No		No	
	Time period	1 year		1 year		4 weeks		5 years		4 weeks	
Safest	1	Ketoprofen	0.000374	Celecoxib	0.000738	Celecoxib	0.000370	Aceclofenac	0.000061	Aceclofenac	0.000059
	2	Celecoxib	0.000375	Ketoprofen	0.000743	Ketoprofen	0.000375	Celecoxib	0.000061	Celecoxib	0.000063
	3	Aceclofenac	0.000390	Aceclofenac	0.000782	Aceclofenac	0.000392	Nimesulide	0.000064	Nimesulide	0.000064
	4	Nimesulide	0.000396	Nimesulide	0.000784	Nimesulide	0.000393	Ibuprofen	0.000072	Ibuprofen	0.000071
	5	Meloxicam	0.000398	Meloxicam	0.000792	Meloxicam	0.000400	Rofecoxib	0.000083	Rofecoxib	0.000077
	6	Naproxen	0.000408	Naproxen	0.000813	Naproxen	0.000411	Ketoprofen	0.000090	Ketoprofen	0.000077
	7	Ibuprofen	0.000416	Ibuprofen	0.000824	Ibuprofen	0.000414	Naproxen	0.000095	Naproxen	0.000082
	8	Piroxicam	0.000429	Rofecoxib	0.000854	Rofecoxib	0.000429	Meloxicam	0.000098	Meloxicam	0.000083
	9	Rofecoxib	0.000430	Piroxicam	0.000864	Piroxicam	0.000438	Indometacin	0.000104	Diclofenac	0.000090
	10	Diclofenac	0.000470	Diclofenac	0.000942	Indometacin	0.000475	Diclofenac	0.000106	Etoricoxib	0.000091
	11	Indometacin	0.000477	Indometacin	0.000942	Diclofenac	0.000475	Piroxicam	0.000117	Piroxicam	0.000092
Most harmful	12	Ketorolac	0.000664	Ketorolac	0.001315	Ketorolac	0.000667	Etoricoxib	0.000121	Indometacin	0.000095
	13	Etoricoxib	0.000734	Etoricoxib	0.001532	Etoricoxib	0.000770	Ketorolac	0.000187	Ketorolac	0.000154

SECTION 7

Pooling of data from multiple data sources



CHAPTER 7.1

Pooling of individual patient-level data or summary estimates from multiple nested case-control studies in the SAFEGUARD project

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ABSTRACT

BACKGROUND

Combining data from several databases is increasingly gaining popularity. There is uncertainty whether analysis of pooled individual-patient level data (one-stage) or meta-analysis of database-specific estimates (two-stage) should be preferred.

AIM

To compare one- and two-stage analyses in the context of a matched nested case-control design.

METHODS

Within the SAFEGUARD project 8 European and 1 US database collected data on incident T2DM subjects (1999-2013). Within each database a common work-up of definitions and data model was used. Cases with acute myocardial infarction (AMI) were matched to maximum 10 controls on age (±1 year), sex, database and follow-up time (±3 months). Effects of metformin and glimepiride monotherapy were estimated relative to a common reference exposure. One- and two-stage analyses were conducted including common confounders. In the one-stage model, we evaluated whether database acted as an effect modifier for confounders and exposure estimates. Heterogeneity in meta-analytic pooling was assessed by I2 values.

RESULTS

In total 25,979 AMI cases were matched to 127,570 controls. Metformin monotherapy was used by 24% of cases; glimepiride monotherapy by 6.9%. Unadjusted one-stage and two-stage analyses provided similar estimates (metformin: $OR_{one\text{-}stage}$=0.82, 95% CI: 0.78-0.86; OR_{fixed}=0.83, 95% CI: 0.79-0.88; I^2=49%; glimepiride: $OR_{one\text{-}stage}$=0.99, 95% CI: 0.93-1.05 versus OR_{random}=1.04, 95% CI: 0.90-1.20; I^2=68.1%;). Adjusting for confounders did not provide larger differences between the models. In one-stage analysis, the database does however seem to act as an effect modifier when including interactions with exposure and covariates (P<0.05).

CONCLUSION

One- and two-stage analyses yielded similar estimates including a range of confounders in the setting of the SAFEGUARD project with a common work up and common data model. In the one-stage analysis the database seemed to act as an effect modifier for confounder and exposure effects despite homogeneity in the exposure estimates according to meta-analytic pooling.

INTRODUCTION

One of the most important reasons to conduct observational studies is the allowance of addressing research questions of drug safety in the "real world" that cannot be addressed in randomized clinical trials.[133, 480] Observational studies utilizing electronic healthcare data from primary or secondary care are therefore particularly valuable when adverse events are unknown or considered rare.[133] Initially, these studies were conducted independently of each other. This resulted in studies addressing the same research question by different study designs and different definitions of outcomes, covariables and exposure. In order to derive more robust evidence from these single studies, study-specific results were combined in meta-analyses. In recent years, collaboration between data sources to collectively study the same research question has gained popularity.[243, 346, 440, 481, 482] This resulted in several multi-database studies using multiple data sources from different sites and countries with a high potential of heterogeneity between the data sources. Combining data from several sources is possible in mainly two ways: 1) one-stage analysis; which consists of performing the analysis on one large database where individual patient-level data from different databases is pooled; or 2) two-stage meta-analysis; in which the analyses are performed on each single database and the summary statistics are combined using standard meta-analysis techniques.[483] There is an ongoing debate whether one of the two techniques should be preferred over the other.[484] Despite clear practical and flexibility reasons for analyzing individual patient-level data, the main disadvantage of these analyses remains data sharing and privacy issues.[484] Another proposed method of pooling data from different study sites is pooling on propensity scores.[485] Cohort studies using this propensity score-based pooling yielded similar estimates as derived from meta-analyzing the estimates when adjusting for universal (common) or local (data site specific) confounders.[485-487] How these methods perform in the context of multi-database studies with a matched case-control design is unknown, particularly when a common data model is used. The aim of the current study is to compare one-stage and two-stage meta-analyses using data from the SAFEGUARD project.

METHODS

Data sources

Data for this study was obtained from nine longitudinal population-based health care databases participating in the SAFEGUARD project (Safety Evaluation of Adverse Reactions in Diabetes: http://www.safeguard-diabetes.org/) from five European countries [Germany (GE), Italy (IT), the Netherlands (NL), Spain (ES), the United Kingdom (UK)] and the United States (US) covering a source population of around 50 million subjects. All databases have been extensively used for pharmacoepidemiological research. Characteristics of the databases are summarized in Table 1. In short, the Clinical Practice Research Datalink (CPRD) database is a

general practice (GP) database in the UK and currently captures medical records of 13.2 million patients. BIFAP (Base de Datos para la Investigación Farmacoepidemiologica en Atención Primaria) is a Spanish GP database in which GPs from different communities in Spain are captured.[488] The Integrated Primary Care Information (IPCI) database is a GP database from the Netherlands and covers over 1 million people.[238] PHARMO database is a medical record linkage system of 2.2 million community-dwelling inhabitants in the Netherlands.[435] Three Italian databases were included: the Health Search Database/CSD Longitudinal Patient (HSD), Regional Database Puglia (CMNS), and Regional Database Lombardy (UNIMIB). HSD is a GP database which covers 1.5 million patients (aged 15 years and older). CMNS and UNIMIB are administrative databases with regional coverage of the Italian citizens. UNIMIB has full population coverage of the Lombardia region, resulting in electronic medical records from 16% of the Italian population. The German Pharmacoepidemiological Research Database (GePaRD) is a database comprising data from five statutory health insurances throughout Germany. It currently covers around 14 million insurants and represents approximately 20% of the German population.[436] The Caremark-Medicare linked database provides healthcare transaction data on US community-dwelling patients 65 years and older who receive their health insurance through Medicare. Medicare retrieves information on drug prescriptions and claims through Caremark.

All GP and administrative databases contain information on demographics of the population, diagnoses (in- and/or outpatient), and drug prescriptions/dispensings. The diagnoses captured by the databases are coded with four different disease coding systems including the International Classification of Diseases (ICD) 9th or 10th revision,[323] International Classification for Primary Care (ICPC),[240] or READ system.[438] Details on the databases regarding coding systems, study period and drug exposure are listed in Table 1.

Mapping of concept and codes was performed using the Unified Medical Language System (UMLS). The UMLS is a biomedical terminology integration system handling more than 150 medical dictionaries, according to a previously described workflow.[380, 440] All drugs were mapped to the World Health Organization's (WHO) classification of Anatomical Therapeutic Chemical (ATC).[242] A distributed approach was used for collaboration: all database custodians processed data locally; original data were transformed into a simple common data model (Jerboa ©);[346] mapping of codes for outcome and covariates was verified using an extensive harmonization strategy; and a common standardized script was used to create an aggregated data output for all databases that were subsequently encrypted and shared on a central remote research environment for further analysis and pooling. Details on such a collaborative approach have been described previously.[346, 380]

Approval by the institutional review boards was obtained.

Table 1. Characteristics of the Databases involved in the SAFEGUARD project.

Country	Germany		Italy		Spain	UK	NL		USA
Name of data source	**GePaRD**	**CMNS**	**UNIMIB**	**HSD**	**BIFAP**	**CPRD**	**IPCI**	**PHARMO**	**Medicare**
Type of data source	Administrative database	Administrative database	Administrative database	Electronic medical record	Electronic medical record	Electronic medical record	Electronic medical record	Record linkage system	Administrative database (≥65 years)
Period covered	2003-2009	2001-2010	1999-2010	2000-2010	2001-2011	199-2011	1999-2012	1998-2010	2005-2008
No. source population	> 14 million	5 million	9 million	1.4 million	3.2 million	8 million	1.1 million	4 million	>4 million
Setting	In- and outpatient care	Outpatient care	Outpatient care	Primary care	Primary care	Primary care	Primary care	Out and in patient care	In- and outpatient care
Diagnosis terminology*	ICD-10-GM	ICD-9 CM	ICD-9 CM	ICD-9 CM and free text	ICPC and free text	READ codes	ICPC and free text	ICD-9 CM	ICD-9 CM
Drugs	Dispensings	Dispensings	Dispensings	Prescriptions	Prescriptions	Prescriptions	Prescriptions	Dispensings	Dispensings
Drug coding system **	ATC	ATC	ATC	ATC	ATC	Multilex	ATC	ATC	NDC System
Laboratory values	No	No	No	Yes	Yes	Yes	Yes	Yes (subset)	No

** ICD-9= International Classification of Diseases, 9th edition; ICD-10= International Classification of Diseases, 10th edition; ICD-10-GM= International Classification of Diseases, 10th edition German Modification; ICPC= International Cassification of Primary Care; READ: It is the clinical terminology system used in General Practice in the United Kingdom.*
*** ATC= Anatomical Therapeutic Chemical Classification System; NDC System=National Drug Code System; Multilex BNF=British National Formulary.*

Study Cohorts

A cohort of patients with type 2 diabetes mellitus (T2DM) was identified using a harmonized definition of T2DM across the databases. The cohort included all patients who an incident prescription of non-insulin blood glucose lowering drug (NIBGLD). At least one year of available healthcare data prior to study entry was required in order to assess the patient's medical history and to discriminate between prevalent and incident T2DM.

Follow-up started at the date of first NIBLGD prescription recording and ended at date of study outcome (see below), death, end of study period (Table 1) or moving out of region, whichever was earliest. Gestational diabetes was not considered as inclusion criterion. Subjects with any type of malignancy (except for non-melanoma skin cancer) before cohort entry were excluded. Cancers occurring during cohort time were censored at date of cancer diagnosis.

Cases and controls

In the SAFEGUARD project several outcomes were analyzed. For this study, we used acute myocardial infarction (AMI) as outcome as this is a clearly defined outcome and has been validly used in previous studies. Codes used to identify AMI are given in Supplementary Table 1. Cases experiencing their first AMI during cohort time were matched to a maximum of 10 controls by incidence density sampling on age (±1 year), sex, database and time in the cohort (±3 months).

Exposure

Exposure to NIBGLDs was obtained from either prescriptions (BIFAP, CPRD, HSD, IPCI, PHARMO) or from outpatient drug dispensings claims (CMNS, GePaRD, MEDICARE, PHARMO and UNIMIB). Duration of a single NIBGLD dispensing/prescription was obtained by dividing the total units by the daily number of units prescribed (BIFAP, CPRD, HSD, IPCI, PHARMO), for other databases standard durations were used based on the country specific defined daily dose (DDD) values.[242]

Classification of the recency of exposure to NIBGLDs was based on the interval between index date and the end of the most recent NIBGLD use before the index date. If the exposure period 1) overlapped or ended within 30 days before index date use was classified as 'current' use; 2) ended between 31 and 62 days before the index date as 'recent' use and; 3) ended more than 63 days before the index date as 'past' use.

Exposure of interest included two medications that are likely to be commonly used, namely metformin and glimepiride as monotherapy. We considered current use of metformin with a sulfonylurea (either in fixed or loose combination) as reference category to compare our exposures of interest to. Current use of any other NIBGLD as monotherapy or combination of drugs was considered as separate category. Exposure groups were therefore mutually

exclusive. It should be noted that monotherapy of metformin and glimepiride are primarily used in the first stage of T2DM treatment, whereas the common reference group to which we compared our exposures of interest to is considered at a second stage of T2DM therapy. For the purpose of comparing the one- and two-stage analyses we assumed the stage at which the drug is considered would not affect the comparison between one-stage and two-stage analyses.

Covariate selection

For the SAGFEGUARD study, a list of covariates was defined based on scientific and clinical knowledge. Time window of covariate assessment was 1 year prior to cohort entry date or index date for comorbid diseases and 30 days prior to cohort entry or index date for use of drugs. Covariates that were assessed at 1) cohort entry included use of ACE-inhibitors, anticoagulants, anti-hypertensive drugs, angiotensin II agonists, beta-blockers, calcium antagonists, hormone replacement therapy, diuretics, lipid lowering drugs, oestrogens, systemic contraceptives, vasodilators; 2) at index date use of anti-arrythmic drugs, anticoagulants, antiplatelets, high-dose aspirin (>325 mg/day), low-dose aspirin (≤325 mg/day), hormone replacement therapy, estrogens, systemic contraceptives, vasodilators; hyperlipidemia, heart failure, obesity, smoking and hypoglycemic events; 3) or both at cohort entry and index date: atrial fibrillation, cerebrovascular diseases, chronic kidney disease, ischemic heart disease, myocardial infarction, peripheral arterial disease, renal failure, alcohol abuse, cardiomyopathy, chronic liver disease, coagulopathies, congenital heart disease, chronic obstructive pulmonary disease, drug abuse, deep vein thrombosis and pulmonary embolism, endocarditis, cardiac valve disorders, ventricular arrhythmia. In case there was no or missing information on the variable in the specific time window, the variable was considered as absence of the condition.

We considered different ways to include confounders, based on: 1) the prevalence of the confounder; 2) their association with the outcome, e.g. the difference between the crude beta and beta adjusted for the confounder; 3) the strength of confounding as defined by the Bross formula,[442] which is a function of the first two steps as described above. Covariates were selected for adjustment in the three abovementioned ways in each database separately and in the pooled data. Furthermore we selected single confounders and confounders that were present in all databases ('common confounders') and showed the strongest potential for confounding across the databases (point 3 as described above).

Statistical analyses

The study populations were described by database. Conditional logistic regression was conducted both within each database and within the pooled data (one-stage analysis). In case a confounder was not available or present in a database this database was left out of the one- and two-stage analyses.

We investigated whether database acted as effect modifier for confounder and exposure associations by adding interactions of database with confounders to allow for varying strengths of confounding effects across the databases and the one-stage analysis is 'allowed' and one overall estimate for exposure and confounders can be considered in the individual patient-level pooled dataset.

The two-stage analysis was conducted by meta-analyzing the estimates obtained in each single database and weighing each database using the inverse of the variance.[491] As a measure of heterogeneity in the estimates across the databases the I^2 was calculated.[492]

RESULTS

Out of the source population of over 52 million subjects we identified 1.8 million incident T2DM subjects. In this cohort, we could match 25,979 AMI cases to 127,570 controls (Table 2). Basic demographics and prevalence of confounders in cases and controls per database are shown in Table 3. Mean age at index date was lowest for IPCI (64.2 and 63.2 years, for cases and controls respectively) and highest for Medicare (77.9 years both). Most study subjects were male (51% to 69%). Median time in the cohort for cases varied between 0.8 year (IPCI) and 3.5 years (UNIMIB); and varied for controls between 0.7 year (IPCI) and 3.6 years (UNIMIB).

Table 2. Exposure of metformin and glimepiride per database.

	Total Number of Cases	Total Number of Controls	Metformin monotherapy		Glimepiride monotherapy	
			Cases	Controls	Cases	Controls
			N (%)	N (%)	N (%)	N (%)
GePaRD	3,511	16,153	1,174 (33.4)	6,027 (37.3)	405 (11.5)	1,451 (9.0)
CMNS	2,062	10,375	346 (16.8)	2,037 (19.6)	131 (6.4)	639 (6.2)
UNIMIB	9,794	48,154	1,508 (15.4)	7,945 (16.5)	807 (8.2)	3,586 (7.4)
HSD	748	3,678	165 (22.1)	880 (23.9)	53 (7.1)	285 (7.7)
BIFAP	802	3,848	252 (31.4)	1,360 (35.3)	22 (2.7)	96 (2.5)
CPRD	4,598	22,429	1,764 (38.4)	9,247 (41.2)	66 (1.4)	260 (1.2)
IPCI	76	303	48 (63.2)	206 (68.0)	0 (0)	0 (0)
PHARMO	1,483	7,359	510 (34.4)	2,595 (35.3)	137 (9.2)	705 (9.6)
MEDICARE	2,905	15,271	486 (16.7)	3,456 (22.6)	181 (6.2)	756 (5.0)
Pooled dataset	25,979	127,570	6,253 (24.1)	33,753 (26.5)	1,802 (6.9)	7,778 (6.1)

Prevalence of Confounders

Prevalences of confounders in cases and controls varied between databases (Table 3). In general, use of antiplatelets, low-dose aspirin beta-blockers, vasodilators and respiratory drugs close to index date and presence of cerebrovascular diseases, chronic kidney disease, ischemic heart disease, hyperlipidemia, peripheral arterial disease, renal failure and smoking were more frequent among cases than controls. Presence of obesity and chronic liver disease was more

common among controls than among cases. The prevalence of some confounders among cases and controls was different between databases, for instance use of diuretics was more common among cases in Medicare and BIFAP, whereas the opposite was seen in the other databases. Use of ACE-inhibitors was almost as frequent as in controls in all databases except for CPRD and Medicare.

Exposure

Current metformin use was common at index date, with between 15% and 63% of cases and between 16% and 68% of controls exposed. Glimepiride was less often used, by 1.4% to 11.5% of cases and 1.2% to 9.6% of controls. None of the study subjects in IPCI was exposed to glimepiride, thus IPCI was not included in the analyses on glimepiride.

Unadjusted analysis

Estimates per database and from one-stage and two-stage analyses are shown in Figure 1. For metformin heterogeneity between databases was observed (I^2=49%) with one-stage and two-stage analyses providing very similar estimates ($OR_{one\text{-}stage}$=0.82, 95% CI: 0.78-0.86; OR_{fixed}=0.83, 95% CI: 0.79-0.88). For glimepiride the level of heterogeneity was larger (I^2=68%). The estimates from one-stage and two-stage analyses were still close to each other ($OR_{one\text{-}stage}$=0.99, 95% CI: 0.93-1.05 versus OR_{random}=1.04, 95% CI: 0.90-1.20), with the estimate from the random effects model was included in the 95% confidence limit of the one-stage analysis.

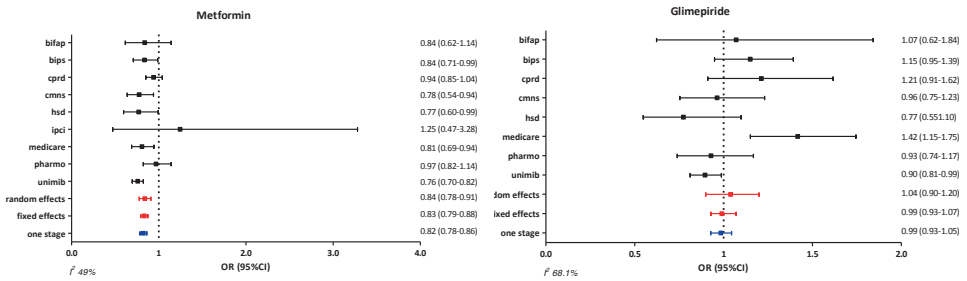


Figure 1. Unadjusted odds ratios by one- and two-stage analyses for current use of metformin as monotherapy and glimepiride as monotherapy versus current use of metformin plus a sulfonylurea.

Table 3. Prevalence of Confounders in cases and controls per database.

	GePaRD		CMNS		UNIMIB	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	3,511	16,153	2,062	10,375	9,794	48,154
Age						
Mean (SD)	67.6 (11.2)	67.4 (11.1)	67.5 (11.6)	67.5 (11.5)	69.5 (11.9)	69.3 (12)
Median (IQR)	68 (60-75)	68 (60-75)	67 (59-77)	67 (59-76)	70 (61-79)	70 (61-78)
Sex						
Female	1,079 (30.7)	4,931 (30.5)	646 (31.3)	3,236 (31.2)	3,139 (32.05)	15,514 (32.2)
Male	2,432 (69.3)	11,222 (69.5)	1,416 (68.7)	7,139 (68.8)	6,655 (67.9)	32,640 (67.8)
A priori defined confounders						
Use of:						
ACE-inhibitors*	1,056 (30.1)	4,572 (28.3)	412 (20.0)	2,018 (19.5)	2,346 (23.95)	10,750 (22.3)
Anticoagulants*	114 (3.2)	522 (3.2)	39 (1.9)	175 (1.7)	233 (2.38)	1,045 (2.17)
Anti-hypertensive drugs*	112 (3.2)	433 (2.7)	49 (2.4)	296 (2.85)	311 (3.18)	1,296 (2.7)
Angiotensin II antagonists*	431 (12.3)	1974 (12.2)	212 (10.3)	1,071 (10.2)	1,064 (10.9)	4,722 (9.8)
Beta-blockers*	1064 (30.3)	4495 (27.8)	216 (10.5)	796 (7.7)	1,498 (15.3)	5,527 (11.5)
Calcium antagonists*	260 (7.4)	1,011 (6.3)	121 (5.9)	463 (4.5)	769 (7.9)	2,853 (5.9)
Hormone replacement therapy*	64 (1.8)	338 (2.1)			53 (0.5)	329 (0.7)
Diuretics*	1,141 (32.5)	5,135 (31.8)	445 (21.6)	2,380 (22.9)	2,311 (23.6)	10,628 (22.1)
Lipid lowering drugs*	682 (19.4)	2,738 (17.0)	287 (13.9)	1,215 (11.7)	1,498 (15.3)	6,084 (12.6)
Oestrogens*	61 (1.7)	323 (2.0)	6 (0.3)	22 (0.2)	71 (0.72)	432 (0.9)
Systemic contraceptives*					13 (0.13)	64 (0.1)
Vasodilators*	263 (7.5)	665 (4.1)	174 (8.4)	443 (4.3)	958 (9.78)	2,402 (5.0)
Hyperlipidemia‡	1,999 (56.9)	8294 (51.3)	487 (23.6)	2,110 (20.3)	2,299 (23.47)	9,135 (19.0)
Anti-arrythmic drugs#	20 (0.6)	114 (0.7)	45 (2.28)	234 (2.3)	273 (2.79)	1,358 (2.8)
Anticoagulants#	197 (5.6)	791 (4.9)	72 (3.5)	336 (3.2)	373 (3.81)	1,403 (2.9)
Antiplatelets#	232 (6.6)	531 (3.3)	142 (6.9)	384 (3.7)	508 (5.19)	1,541 (3.2)
Aspirin in high dose#	30 (0.9)	106 (0.7)				
Low-dose aspirin#	452 (12.9)	1,295 (8.0)	470 (22.8)	2,126 (20.5)	2,073 (21.17)	7,727 (16.0)
Hormone replacement therapy#	51 (1.5)	315 (2.0)			20 (0.2)	139 (0.3)
Oestrogens#	50 (1.4)	297 (1.8)	7 (0.3)	22 (0.2)	30 (0.31)	186 (0.39)
Systemic contraceptives#					7 (0.1)	22 (0.05)
Vasodilators#	398 (11.3)	667 (4.1)	256 (12.4)	575 (5.5)	1558 (15.9)	3,221 (6.7)
Comorbid diseases:						
Atrial Fibrillation†	424 (12.1)	1,485 (9.2)	84 (4.1)	331 (3.2)	525 (5.4)	2,054 (4.3)
Any cerebrovascular disease†	856 (24.4)	3,244 (20.1)	199 (9.7)	615 (5.9)	1,104 (11.3)	3,510 (7.3)
Chronic Kidney disease†	853 (24.3)	3,256 (20.2)	119 (5.7)	298 (2.9)	499 (5.1)	1,317 (2.7)
Ischemic Heart Disease†	1,916 (54.6)	4,819 (29.8)	372 (18.0)	811 (7.8)	1,755 (17.9)	4,627 (9.6)
Myocardial Infarction†	1,088 (31.0)	1334 (8.3)	172 (8.3)	391 (3.8)	1,051 (10.7)	2,864 (5.9)
Peripheral Arterial Disease†	794 (22.6)	2,694 (16.7)	115 (5.6)	275 (2.7)	584 (5.96)	1,323 (2.7)
Renal Failure†	39 (1.1)	66 (0.4)	12 (0.6)	10 (0.10)	61 (0.62)	104 (0.22)
Heart Failure‡	586 (16.7)	1,856 (11.5)	98 (4.8)	358 (3.5)	530 (5.4)	1,586 (3.3)
Obesity‡	943 (26.9)	4,518 (28.0)	33 (1.6)	162 (1.6)	125 (1.3)	536 (1.1)
Smoking‡						
Cancer	240 (6.8)	1,235 (7.6)	72 (3.5)	330 (3.2)	506 (5.2)	2,382 (4.9)

Table 3. Prevalence of Confounders in cases and controls per database (*continued*).

	GePaRD		CMNS		UNIMIB	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	3,511	16,153	2,062	10,375	9,794	48,154
Potential Confounders						
Use of:						
PDE5 inhibitors*						
Respiratory drugs*	173 (4.9)	594 (3.7)	96 (4.7)	382 (3.7)	354 (3.6)	1,516 (3.1)
Cardiac glycosides#	101 (2.9)	288 (1.8)	58 (2.8)	247 (2.4)	195 (2.0)	718 (1.5)
PDE5 inhibitors#						
Respiratory drugs#	226 (6.4)	697 (4.3)	120 (5.8)	441 (4.3)	522 (5.3)	1,818 (3.8)
Glucocorticoids#	205 (5.8)	535 (3.3)	109 (5.3)	318 (3.1)	288 (2.9)	822 (1.7)
Comorbid diseases:						
Alcohol Abuse†	186 (5.3)	828 (5.1)	14 (0.7)	68 (0.7)	105 (1.1)	495 (1.0)
Cardiomyopathy†	103 (2.9)	292 (1.8)	27 (1.3)	96 (0.9)	194 (2.0)	636 (1.3)
Chronic Liver disease†	918 (26.1)	4,493 (27.8)	144 (7.0)	619 (6.0)	389 (4.0)	1942 (4.0)
Coagulopathies†	214 (6.1)	935 (5.8)	9 (0.4)	33 (0.3)	49 (0.5)	198 (0.4)
Congenital heart disease†	22 (0.6)	87 (0.5)			17 (0.2)	58 (0.1)
Chronic Obstructive Pulmonary Disease†	591 (16.8)	2162 (13.4)	226 (11.0)	771 (7.4)	565 (5.8)	2008 (4.2)
Drug abuse†	52 (1.5)	207 (1.3)			9 (0.1)	40 (0.1)
Deep Vein Thrombosis/ Pulmonary Embolism†	93 (2.6)	355 (2.2)	6 (0.3)	22 (0.2)	85 (0.9)	346 (0.7)
Endocarditis†	21 (0.6)	126 (0.8)				
Cardiac valve disorders†	512 (14.6)	1581 (9.8)	68 (3.3)	193 (1.9)	238 (2.4)	853 (1.8)
Ventricular arrythmia†	69 (2.0)	165 (1.0)	12 (0.6)	31 (0.3)	53 (0.5)	222 (0.5)
Hypoglycemic events#	21 (0.6)	67 (0.4)			9 (0.1)	18 (0.04)

** assessed in 30 days before cohort entry; # assessed 30 days before index date; † assessed at cohort entry and index date; ‡ assessed 1 year before cohort entry.*

Table 3. Prevalence of Confounders in cases and controls per database (*continued*).

	HSD		CPRD		BIFAP	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	748	3,678	4,598	22,429	802	3,848
Age						
Mean (SD)	68.5 (10.9)	68.6 (10.6)	67.5 (12.8)	67.5 (12.5)	67.8 (12.5)	67.4 (12)
Median (IQR)	69 (61-77)	69 (61-77)	68 (58-77)	69 (59-77)	68 (58-78)	68 (58-77)
Sex						
Female	247 (33.0)	1,223 (33.3)	1,708 (37.1)	8,365 (37.3)	235 (29.3)	1,094 (28.4)
Male	501 (67.0)	2,455 (66.7)	2,890 (62.9)	14,064 (62.7)	567 (70.7)	2,754 (71.6)
A priori defined confounders						
Use of:						
ACE-inhibitors*	144 (19.3)	747 (20.3)	1,175 (25.6)	5,084 (22.7)	128 (16.0)	659 (17.1)
Anticoagulants*	13 (1.7)	89 (2.4)	128 (2.8)	443 (2.0)	28 (3.5)	102 (2.7)
Anti-hypertensive drugs*	15 (2.0)	89 (2.4)	164 (3.6)	843 (3.8)	18 (2.2)	74 (1.9)
Angiotensin II antagonists*	73 (9.8)	342 (9.3)	294 (6.4)	1,302 (5.8)	75 (9.4)	339 (8.8)
Beta-blockers*	27 (3.6)	148 (4.0)	1,113 (24.2)	4,451 (19.8)	70 (8.7)	290 (7.5)
Calcium antagonists*	62 (8.3)	325 (8.8)	638 (13.9)	2,659 (11.9)	43 (5.4)	210 (5.5)
Hormone replacement therapy*			92 (2.0)	410 (1.8)		
Diuretics*	141 (18.9)	758 (20.6)	1,272 (27.7)	5,612 (25.0)	191 (23.8)	803 (20.9)
Lipid lowering drugs*	89 (11.9)	431 (11.7)	1,646 (35.8)	6,815 (30.4)	154 (19.2)	761 (19.8)
Oestrogens*			118 (2.6)	501 (2.2)		
Systemic contraceptives*						
Vasodilators*	38 (5.1)	140 (3.8)	539 (11.7)	1,045 (4.7)	28 (3.5)	99 (2.6)
Hyperlipidemia‡	140 (18.7)	639 (17.4)	1,875 (40.8)	7,677 (34.2)	217 (27.1)	1087 (28.2)
Anti-arrythmic drugs#	15 (2.0)	72 (2.0)	62 (1.3)	216 (1.0)	9 (1.1)	33 (0.9)
Anticoagulants#	47 (6.3)	140 (3.8)	246 (5.4)	860 (3.8)	47 (5.9)	178 (4.6)
Antiplatelets#	56 (7.5)	192 (5.2)	405 (8.8)	1,015 (4.5)	71 (8.9)	199 (5.2)
Aspirin in high dose#			61 (1.3)	159 (0.7)		
Low-dose aspirin#	235 (31.4)	1,023 (27.8)	2,015 (43.8)	8,532 (38.0)	218 (27.2)	809 (21.0)
Hormone replacement therapy#			56 (1.2)	284 (1.3)		
Oestrogens#			80 (1.7)	353 (1.6)		
Systemic contraceptives#						
Vasodilators#	110 (14.7)	254 (6.9)	869 (18.9)	1,347 (6.0)	83 (10.3)	153 (4.0)
Comorbid diseases:						
Atrial Fibrillation†	30 (4.0)	120 (3.3)	292 (6.4)	827 (3.7)	33 (4.1)	126 (3.3)
Any cerebrovascular disease†	81 (10.8)	306 (8.3)	321 (7.0)	1,017 (4.5)	49 (6.1)	151 (3.9)
Chronic Kidney disease†	64 (8.6)	147 (4.0)	760 (16.5)	3,019 (13.5)	27 (3.4)	87 (2.3)
Ischemic Heart Disease†	108 (14.4)	268 (7.3)	1,150 (25.0)	2,563 (11.4)	79 (9.9)	116 (3.0)
Myocardial Infarction†	5 (0.7)	81 (2.2)	180 (3.9)	603 (2.7)	7 (0.9)	74 (1.9)
Peripheral Arterial Disease†	31 (4.1)	83 (2.3)	627 (13.6)	2,131 (9.5)	35 (4.4)	85 (2.2)
Renal Failure†			56 (1.2)	192 (0.9)		
Heart Failure‡	21 (2.8)	108 (2.9)	98 (2.1)	210 (0.9)	27 (3.5)	92 (2.4)
Obesity‡	45 (6.0)	204 (5.5)	1,660 (36.1)	7,629 (34.0)	169 (21.1)	919 (23.9)
Smoking‡	36 (4.8)	96 (2.6)	259 (5.6)	1,121 (5.0)	105 (13.1)	393 (10.2)
Cancer	38 (5.1)	190 (5.2)	177 (3.8)	549 (2.4)	15 (1.9)	111 (2.9)

Table 3. Prevalence of Confounders in cases and controls per database (*continued*).

	HSD		CPRD		BIFAP	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	748	3,678	4,598	22,429	802	3,848
Potential Confounders						
Use of:						
PDE5 inhibitors*			83 (1.8)	378 (1.7)		
Respiratory drugs*	32 (4.3)	100 (2.7)	480 (10.4)	1474 (6.7)	33 (4.1)	207 (5.4)
Cardiac glycosides#	22 (2.9)	105 (2.9)	197 (4.3)	585 (2.6)	25 (3.1)	77 (2.0)
PDE5 inhibitors#			192 (4.2)	1118 (5.0)		
Respiratory drugs#	43 (5.7)	135 (3.7)	624 (13.6)	1702 (7.6)	56 (7.0)	248 (6.4)
Glucocorticoids#	23 (3.1)	89 (2.4)	480 (10.4)	1238 (5.5)	26 (3.2)	75 (1.9)
Comorbid diseases:						
Alcohol Abuse†	5 (0.7)	49 (1.3)	121 (2.6)	541 (2.4)	37 (4.6)	217 (5.6)
Cardiomyopathy†			18 (0.4)	38 (0.2)	9 (1.1)	31 (0.8)
Chronic Liver disease†	28 (3.7)	217 (5.9)	70 (1.5)	255 (1.1)		
Coagulopathies†	6 (0.8)	22 (0.6)	21 (0.5)	63 (0.3)	10 (1.2)	44 (1.14)
Congenital heart disease†			5 (0.1)	15 (0.1)		
Chronic Obstructive Pulmonary Disease†	50 (6.7)	167 (4.5)	409 (8.9)	1,056 (4.7)	38 (4.7)	148 (3.85)
Drug abuse†	41 (5.5)	182 (4.9)	18 (0.4)	25 (0.1)		
Deep Vein Thrombosis/ Pulmonary Embolism†			85 (1.8)	239 (1.1)	14 (1.7)	36 (0.9)
Endocarditis†						
Cardiac valve disorders†	19 (2.5)	59 (1.6)	118 (2.6)	320 (1.4)	19 (2.4)	44 (1.1)
Ventricular arrythmia†	9 (1.2)	12 (0.3)				
Hypoglycemic events#						

** assessed in 30 days before cohort entry; # assessed 30 days before index date; † assessed at cohort entry and index date; ‡ assessed 1 year before cohort entry.*

Table 3. Prevalence of Confounders in cases and controls per database (*continued*).

	IPCI		PHARMO		MEDICARE	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	76	303	1,483	7,359	2,905	15,271
Age						
Mean (SD)	64.2 (11.2)	63.2 (10.4)	67.7 (12)	67.6 (11.8)	77.9 (6.7)	77.9 (6.7)
Median (IQR)	65 (55.5-71.5)	65 (55-70)	69 (59-77)	69 (59-77)	78 (72-83)	77 (72-83)
Sex						
Female	28 (36.8)	117 (38.6)	507 (34.2)	2498 (33.9)	1,374 (47.3)	7,458 (48.8)
Male	48 (63.2)	186 (61.4)	976 (65.8)	4861 (66.1)	1,531 (52.7)	7,813 (51.2)
A priori defined confounders						
Use of:						
ACE-inhibitors*	10 (13.2)	38 (12.5)	225 (15.2)	1,065 (14.5)	283 (9.7)	1,212 (7.9)
Anticoagulants*		3 (1.0)	74 (5.0)	310 (4.2)	118 (4.1)	451 (3.0)
Anti-hypertensive drugs*	2 (2.6)	11 (3.6)	12 (0.8)	66 (0.9)	71 (2.4)	199 (1.3)
Angiotensin II antagonists*	9 (11.8)	34 (11.2)	158 (10.7)	661 (9.0)	245 (8.4)	896 (5.9)
Beta-blockers*	6 (7.9)	29 (9.6)	444 (29.9)	1,835 (24.9)	478 (16.5)	1682 (11.0)
Calcium antagonists*	15 (19.7)	59 (19.5)	117 (7.9)	426 (5.8)	307 (10.6)	992 (6.5)
Hormone replacement therapy*	2 (2.6)	12 (4.0)	10 (0.7)	62 (0.8)	27 (0.9)	127 (0.8)
Diuretics*	0 (0.0)	1 (0.3)	391 (26.4)	1,854 (25.2)	537 (18.5)	1,948 (12.8)
Lipid lowering drugs*	17 (22.4)	84 (27.7)	335 (22.6)	1,567 (21.3)	613 (21.1)	2,356 (15.4)
Oestrogens*	2 (2.6)	4 (1.3)	28 (1.9)	124 (1.7)	11 (0.4)	70 (0.4)
Systemic contraceptives*	2 (2.6)	2 (0.7)	17 (1.1)	62 (0.8)		
Vasodilators*	3 (3.9)	5 (1.65)	143 (9.6)	332 (4.5)	108 (3.7)	196 (1.3)
Hyperlipidemia‡	16 (21.1)	55 (18.2)	379 (25.6)	1,748 (23.8)	1272 (43.8)	4,954 (32.4)
Anti-arrythmic drugs#	0 (0.0)	1 (0.3)	14 (0.9)	79 (1.1)	60 (2.1)	265 (1.7)
Anticoagulants#	1 (1.3)	5 (1.7)	128 (8.6)	533 (7.2)	323 (11.1)	1,332 (8.7)
Antiplatelets#	0 (0.0)	2 (0.7)	334 (22.5)	1,093 (14.9)	626 (21.5)	1,729 (11.3)
Aspirin in high dose#	8 (10.5)	23 (7.6)				
Low-dose aspirin#	0 (0.0)	1 (0.3)	305 (20.6)	1,165 (15.8)		
Hormone replacement therapy#	0 (0.0)	2 (0.7)	10 (0.7)	46 (0.6)	71 (2.4)	434 (2.8)
Oestrogens#	1 (1.3)	3 (1.0)	28 (1.9)	97 (1.3)	35 (1.2)	246 (1.6)
Systemic contraceptives#	1 (1.3)	2 (0.7)	18 (1.2)	51 (0.7)		
Vasodilators#	3 (3.9)	4 (1.3)	294 (19.8)	451 (6.1)	338 (11.6)	716 (4.7)
Comorbid diseases:						
Atrial Fibrillation†	0 (0.0)	1 (0.3)	65 (4.4)	256 (3.5)	491 (16.9)	1,414 (9.3)
Any cerebrovascular disease†	0 (0.0)	2 (0.7)	77 (5.2)	212 (2.9)	535 (18.4)	1,373 (9.0)
Chronic Kidney disease†	2 (2.6)	3 (1.0)	18 (1.2)	55 (0.7)	616 (21.2)	1,454 (9.5)
Ischemic Heart Disease†	1 (1.3)	2 (0.7)	226 (15.2)	474 (6.4)	1,354 (46.6)	3,405 (22.3)
Myocardial Infarction†	2 (2.63	0 (0.0)	104 (7.0)	256 (3.5)	375 (12.9)	942 (6.2)
Peripheral Arterial Disease†	0 (0.0)	1 (0.3)	45 (3.0)	116 (1.6)	449 (15.5)	989 (6.5)
Renal Failure†	0 (0.0)	0 (0.0)	5 (0.3)	14 (0.2)	73 (2.5)	87 (0.6)
Heart Failure‡	25 (32.9)	101 (33.3)	27 (1.8)	94 (1.3)	446 (15.4)	1057 (6.9)
Obesity‡	2 (2.6)	1 (0.3)	6 (0.4)	27 (0.4)	81 (2.8)	288 (1.9)
Smoking‡	4 (5.3)	9 (3.0)			118 (4.1)	295 (1.9)
Cancer	3 (3.9)	1 (0.3)	55 (3.7)	257 (3.5)	170 (5.9)	617 (4.0)

Table 3. Prevalence of Confounders in cases and controls per database (*continued*).

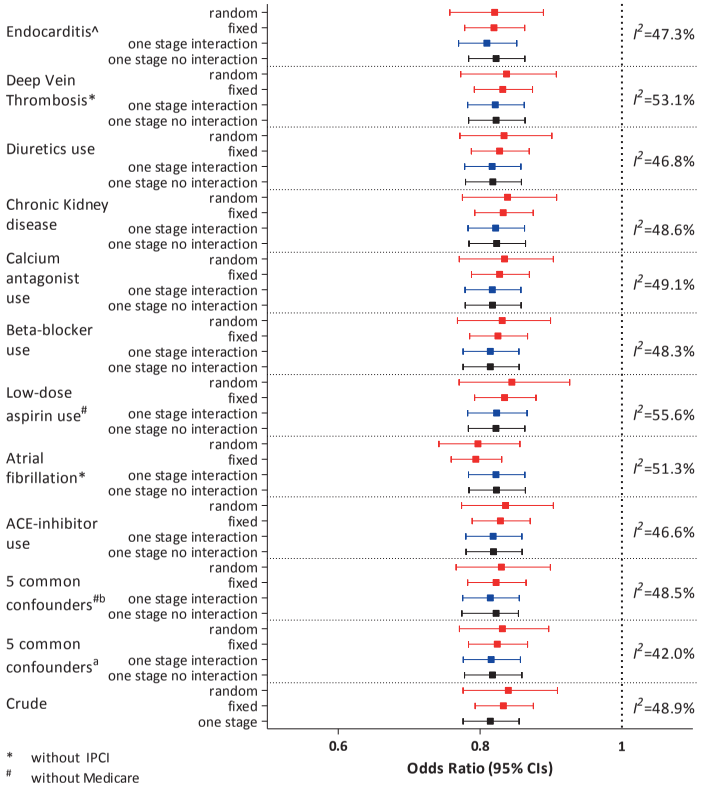
	IPCI		PHARMO		MEDICARE	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total number	76	303	1,483	7,359	2,905	15,271
Potential Confounders						
Use of:						
PDE5 inhibitors*	0 (0)	1 (0.3)			12 (0.4)	57 (0.4)
Respiratory drugs*	2 (2.6)	16 (5.3)	87 (5.9)	459 (6.2)	103 (3.5)	234 (1.5)
Cardiac glycosides#	2 (2.6)	4 (1.3)	47 (3.2)	197 (2.7)	128 (4.4)	478 (3.1)
PDE5 inhibitors#			19 (1.3)	59 (0.8)	28 (1.0)	138 (0.9)
Respiratory drugs#	2 (2.6)	18 (5.9)	122 (8.2)	548 (7.4)	258 (8.9)	761 (5.0)
Glucocorticoids#	2 (2.6)	7 (2.3)	86 (5.8)	278 (3.8)	182 (6.3)	450 (2.9)
Comorbid diseases:						
Alcohol Abuse†	1 (1.3)	1 (0.3)	11 (0.7)	42 (0.6)	31 (1.1)	68 (0.4)
Cardiomyopathy†	2 (2.6)	0 (0.0)	5 (0.3)	23 (0.3)	180 (6.2)	356 (2.3)
Chronic Liver disease†	0 (0.0)	1 (0.3)	8 (0.5)	40 (0.5)	76 (2.6)	286 (1.9)
Coagulopathies†					199 (6.9)	522 (3.4)
Congenital heart disease†					21 (0.7)	56 (0.4)
Chronic Obstructive Pulmonary Disease†			39 (2.6)	150 (2.0)	610 (21.0)	1,513 (9.9)
Drug abuse†					29 (1.0)	58 (0.4)
Deep Vein Thrombosis/ Pulmonary Embolism†					80 (2.8)	217 (1.4)
Endocarditis†	0 (0.0)	1 (0.3)			21 (0.7)	57 (0.4)
Cardiac valve disorders†	1 (1.3)	1 (0.3)	21 (1.4)	76 (1.0)	344 (11.8)	861 (5.6)
Ventricular arrythmia†			5 (0.34)	31 (0.42)	7 (0.2)	18 (0.1)
Hypoglycemic events#					53 (1.8)	58 (0.4)

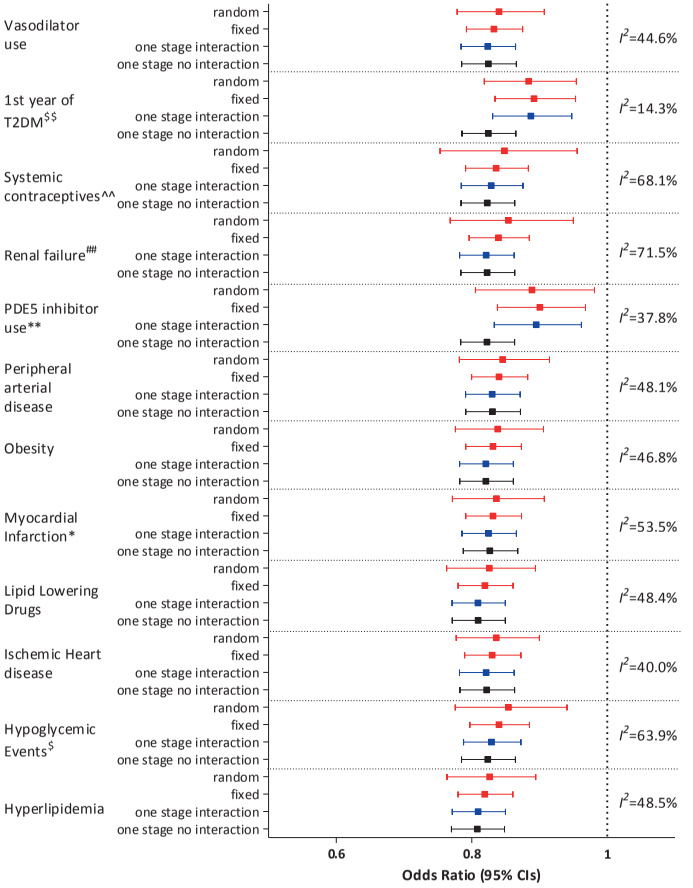
** assessed in 30 days before cohort entry; # assessed 30 days before index date; † assessed at cohort entry and index date; ‡ assessed 1 year before cohort entry.*

Adjusted analyses

Figure 2 shows the estimates for metformin obtained from one-stage and two-stage analyses when adjusting for a single confounder. Little effect on the estimate by adjusting for single variables was seen. Also adding 5 common confounders to the models did not affect the exposure estimate. The difference between the estimate from one- and two-stage analyses was small when adjusting for most confounders. However, when we adjusted for 1st year of type 2 diabetes mellitus or for use of PDE5 inhibitors and no interaction term of the covariate with database was included, the one-stage estimate was different from the two-stage estimate (T2DM: $OR_{one\text{-}stage}$=0.82, 95% CI: 0.79-0.87 versus OR_{random}=0.88, 95% CI: 0.82-0.95; PDE5 inhibitors: $OR_{one\text{-}stage}$=0.82, 95% CI: 0.78-0.86 versus OR_{random}=0.89, 95% CI: 0.81-0.98) (Figure 2 and Supplementary Table 2). When adding the interaction term, the exposure estimates were very similar for all adjusted estimates. However, based on the P-value of the interaction terms, one should consider to stratify in the one-stage analysis on database level (P interaction terms < 0.05) when adjusting for most confounders; which means database specific estimates should be considered.

Figure 2. Unadjusted and adjusted odds ratios by one- and two-stage analyses for current use of metformin as monotherapy compared to current use of metformin with a sulfonylurea.





* without IPCI
\# without Medicare
^ without IPCI, PHARMO
$ without CMNS, HSD, IPCI
** without BIFAP, BIPS, CMNS, IPCI, UNIMIB
without BIFAP, IPCI
^^ without BIFAP, BIPS, Medicare
$$ without Medicare, UNIMIB

a adjusted for hyperlipidemia, ischemic heart disease, use of lipid lowering drugs, vasodilators and beta-blockers
b adjusted for hyperlipidemia, use of lipid lowering drugs, vasodilators, low-dose aspirin and beta-blockers

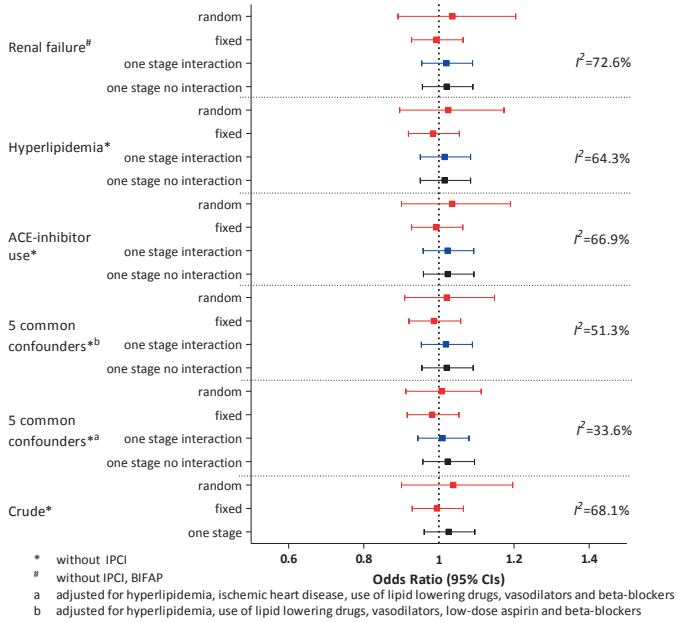


Figure 3. Unadjusted and adjusted odds ratios by one- and two-stage analyses for current use of glimepiride as monotherapy compared to current use of metformin with a sulfonylurea.

For glimepiride the one-stage and two-stage analyses yielded similar estimates, also when adjusting for a single confounder of when adjusting for multiple common confounders. However, for most adjusted estimates a higher level of heterogeneity was seen than for metformin. Adding the interaction term of confounder with database did not affect the exposure estimate, though the interaction terms were significant (Supplementary Table 3).

DISCUSSION

In this matched nested case-control study among nine databases in the SAFEGUARD project using a common data model we compared one-stage and two-stage analyses to obtain an overall meta-analytic estimate. Both analyses provided similar estimates even when including a variety of confounders and interactions of database with the covariates.

Nowadays there are many projects that are using a common data model or distributed network, such as Mini-Sentinel,[490, 493] HMO Research Network,[494] the Observational Medical Outcomes Partnership (OMOP),[489] the EU-ADR project[346] and IMI-PROTECT.[237] One of the key reasons that such distributed networks have been developed is the need to conduct large-scale epidemiologic studies while preserving data privacy and legacy issues. Within these networks it is possible that data partners contribute summary data or results while keeping

data on individual-level locally and thus accounting for security issues. In one-stage analyses information from individual study subjects is needed. A disadvantage of the one-stage analysis, also known as individual patient-level pooled data analysis, is that only variables and exposures common to all databases can be used, whereas in two-stage meta-analysis estimates can be pooled when adjustment for varying confounders between the databases was performed or when not all separate databases provide a risk estimate. On the contrary, in two-stage meta-analyses statistical heterogeneity is often obtained rapidly due to the sizes of the single databases, but this may not be always clinically relevant.[492] However, neglecting the fact that the confounder strength could vary between databases analyzing individual patient-level pooled data as one large dataset may result in biased exposure estimates. The inclusion of the data source as a possible effect modifier in one-stage analyses may encounter these effects.

Several studies from the US have used local or universal propensity score (PS) models to summarize individual-level data from a large number of covariates in such way that use of this non identifiable measure of the propensity score subsequently allows pooling of site specific data.[485-487] These cohort studies showed that estimates from analyses with adjustment for local or universal PS provided results that are similar to results from analyses using individual-patient level data.[485-487] Despite that PS-based pooling allows for consistency of adjustment for common confounders across the data sites, it does not fully use additional confounder information that may be available at certain data sites. The final obtained exposure estimates in each of the data sites should still be summarized in a summary and overall statistic.[485] A key advantage of the ability to pool individual patient-level data is to conduct more specific and flexible analyses, such as multivariable-adjusted and stratified analyses. Additionally, considering a rare exposure it may be possible to obtain enough exposed events when combining all data from partners, whereas this may not be possible when each individual data site provides a risk estimate. However, when considering that different data sources may contain heterogeneous populations and variations of the ability to capture covariates we evaluated whether individual-patient level pooling of data should be preferred over two-stage analysis that is usually considered in distributed networks.[490]

We noticed that both methods provided similar results, not only when adjusting for single variables, but also when adjusting for covariates that were common across all the databases. It has been proven that, if there is no heterogeneity of the exposure effect among databases, the individual-patient level data analysis and meta-analysis provide similar results when a maximum likelihood estimation, such as in logistic regression, is used.[495] What may be one of the main reasons that we observed very similar results between the one-stage and two-stage analyses is the common work-up in a distributed network of electronic healthcare databases. The EU-ADR project has provided a platform that allowed data partners to locally extract and transform data to a standard format before running the common software (Jerboa©).[346] By using a common model, uniform data-file structures, definitions of events and covariates are achieved. The subsequent statistical analysis on the obtained data is a fairly easy step which may be easily applied to each site-specific dataset. Besides this common data

model, a huge effort within the SAFEGUARD project was done to harmonize definitions of events and covariates to identify disease codes from different coding systems, health care systems and different natures of the databases for the same clinical concept. As we have learned in the past years, interpretation of the same research question or even same protocol applied to the same database may lead to different programming specifications and diverse conclusions.[496-499] The statistical combination of results from different databases may be more problematic and jeopardized when underlying populations, definitions and confounding aspects are more heterogeneous between the databases.[500] It is therefore highly important to consider combining data or results only from populations and databases that in principle can be considered equal or comparable. Although the US population in the current study may be of older age, it appeared that the exposure effect and confounder-outcome associations showed the same pattern as in the other databases. For instance, we included two versions of adjustment for five common confounders with one version excluding the Medicare dataset as this did not contain information on low-dose aspirin use. Nevertheless, both versions of adjustment for common confounders provided similar results.

Within the incident type 2 diabetes mellitus cohort we matched on the most important factors for outcomes in these patients. This may subsequently have resulted in removing most important confounding, although the matching itself may as well have introduced residual confounding.

Strength of the current study is the availability of data on both stages of the models while having a common work-up, data transformation and statistical analyses in a large distributed network of data partners. By doing so, we removed any influence of different interpretations and programming specifications from each data site.

Our study also suffers from limitations. First, we used a nested case-control design matching up to 10 controls to each case thus we relied on conditional logistic regression whereas generalized linear mixed models may allow more flexible analyses. Also, we used a common data model and thus our results of comparison between one- and two-stage analyses may not necessarily be applicable to studies or distributed networks not using a common data model. As we have investigated acute myocardial infarction, assuming this is a commonly investigated outcome and likely captured accurately in all of the participating databases, our results are theoretically only applicable to this outcome and two exposures. Although caution should be considered, interpretation of our results in the context of other acute, common and easily defined outcomes and other types of drugs may be applicable.

In conclusion, in this nested case-control study among nine databases in the SAFEGUARD project using a common data model estimates from one-stage and two-stage analyses were similar in unadjusted analyses and when including a variety of confounders. When sharing individual-level data is not possible, meta-analysis of estimates from different data sites obtained in a distributed network with a common data model may be considered an as good alternative to one-stage analysis.

SUPPLEMENTARY MATERIAL

Supplementary Table 1. Codes used to identify Acute Myocardial Infarction in databases participating in SAFEGUARD project.

ICD-9 codes	ICD-10 codes	ICPC codes	Read codes
CMNS, MEDICARE, PHARMO, UNIMIB	GePaRD	BIFAP, IPCI	CPRD
	Hospital main discharge diagnosis		
			323..00 - ECG: myocardial infarction
			G30..00 - Acute myocardial infarction
			G30..15 - MI - acute myocardial infarction
			G309.00 - Acute Q-wave infarct
			G30X000 - Acute ST segment elevation myocardial infarction
			G307000 - Acute non-Q wave infarction
			G307100 - Acute non-ST segment elevation myocardial infarction
			G309.00 - Acute Q-wave infarct
		K75 - Acute myocardial infarction	G30..11 - Attack – heart
410 - Acute myocardial infarction	I21 - Acute myocardial infarction		G30..14 - Heart attack
	I21.0 - acute transmural myocardial infarction of anterior wall		
410.0x - Of anterolateral wall			G300.00 - Acute anterolateral infarction
			3233 - ECG: antero-septal infarct.
			G301100 - Acute anteroseptal infarction
			G301.00 - Other specified anterior myocardial infarction
			G301000 - Acute anteroapical infarction
410.1x - Of other anterior wall			G301z00 - Anterior myocardial infarction NOS
	I21.1 - Acute transmural myocardial infarction of inferior wall		
410.2x - Of inferolateral wall			G302.00 - Acute inferolateral infarction
			3234 - ECG:posterior/inferior infarct
			G304.00 - Posterior myocardial infarction NOS
410.3x - Of inferoposterior wall			G303.00 -Acute inferoposterior infarction
410.4x - Of other inferior wall			G308.00 - Inferior myocardial infarction NOS
			3236 - ECG: lateral infarction
			G305.00 -Lateral myocardial infarction NOS
410.5x - Of other lateral wall			G30B.00 - Acute posterolateral myocardial infarction
410.6x - True posterior wall infarction			G306.00 - True posterior myocardial infarction
			3235 - ECG: subendocardial infarct
410.7x - Subendocardial infarction	I21.4 - Acute subendocardial myocardial infarction		G307.00 - Acute subendocardial infarction
			G30y000 - Acute atrial infarction
	I21.2 - Acute transmural myocardial infarction of other sites		G30y100 - Acute papillary muscle infarction
410.8x - Of other specified sites			G30y200 - Acute septal infarction
			323Z.00 - ECG: myocardial infarct NOS
			G30z.00 -Acute myocardial infarction NOS
			G30yz00 -Other acute myocardial infarction NOS
	I21.3 - Acute transmural myocardial infarction of unspecified site		G30y.00 -Other acute myocardial infarction
410.9x - Unspecified site			G30X.00 -Acute transmural myocardial infarction of unspecif site

Supplementary Table 1. Codes used to identify Acute Myocardial Infarction in databases participating in SAFEGUARD project (*continued*).

ICD-9 codes	ICD-10 codes	ICPC codes	Read codes
CMNS, MEDICARE, PHARMO, UNIMIB	GePaRD	BIFAP, IPCI	CPRD
	I21.9 - Acute myocardial infarction unspecified		889A.00 - Diab mellit insulin-glucose infus acute myocardial infarct G30..13 - Cardiac rupture following myocardial infarction (MI) G30..17 - Silent myocardial infarction G35..00 - Subsequent myocardial infarction G350.00 - Subsequent myocardial infarction of anterior wall G351.00 - Subsequent myocardial infarction of inferior wall G353.00 - Subsequent myocardial infarction of other sites G35X.00 - Subsequent myocardial infarction of unspecified site G38..00 - Postoperative myocardial infarction G380.00 - Postoperative transmural myocardial infarction anterior wall G381.00 - Postoperative transmural myocardial infarction inferior wall G384.00 - Postoperative subendocardial myocardial infarction G38z.00 - Postoperative myocardial infarction, unspecified

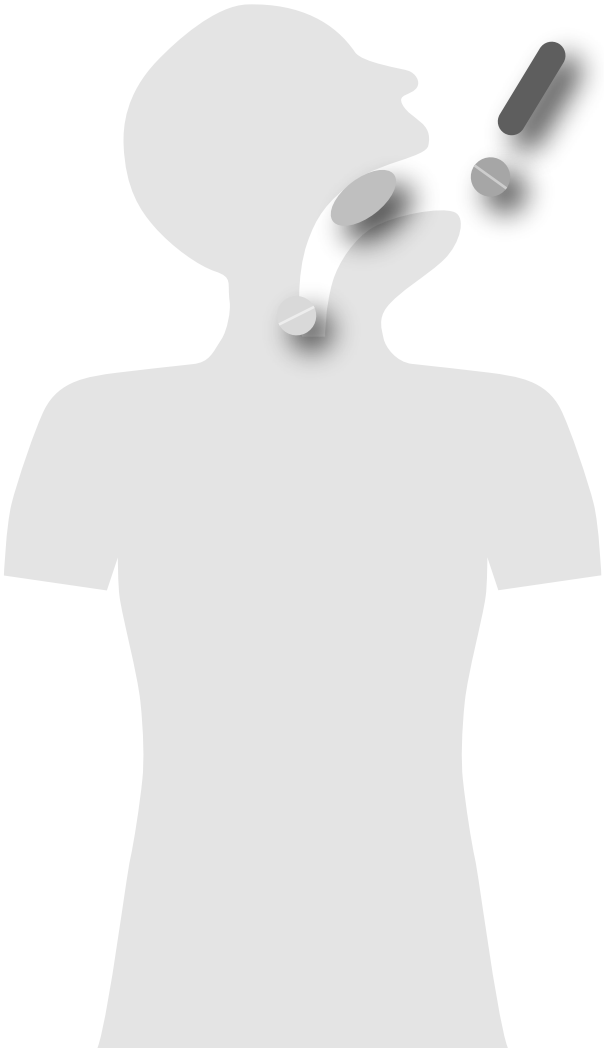
Supplementary Table 2. Odds Ratios from one-stage and two-stage analyses for current use of metformin monotherapy compared to current use of metformin with a sulfonylurea.

	One-Stage					Two-Stage				
	No interaction		Interaction		P-value	Fixed effects		Random effects		
Model	OR	95%CI	OR	95%CI	‡	OR	95%CI	OR	95%CI	I^2
Matched	0.82	0.78-0.86	NA			0.83	0.79-0.88	0.84	0.78-0.91	49
Adjusted:										
5 common confounders*	0.82	0.78-0.86	0.82	0.78-0.86		0.82	0.78-0.87	0.83	0.77-0.90	42
5 common confounders#	0.81	0.77-0.85	0.81	0.78-0.86		0.82	0.78-0.86	0.83	0.77-0.90	49
Use of:										
ACE-inhibitors	0.82	0.78-0.86	0.82	0.78-0.86	0.001	0.83	0.79-0.87	0.84	0.77-0.90	47
Low-dose aspirin	0.82	0.78-0.86	0.82	0.78-0.87	<0.0001	0.83	0.79-0.88	0.84	0.77-0.93	56
Beta-blockers	0.81	0.78-0.86	0.81	0.78-0.85	<0.0001	0.83	0.79-0.87	0.83	0.77-0.90	48
Calcium antagonists	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.83	0.79-0.87	0.83	0.77-0.90	49
Diuretics	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.83	0.79-0.87	0.83	0.77-0.90	47
Lipid lowering drugs	0.81	0.77-0.85	0.81	0.77-0.85	<0.0001	0.82	0.78-0.86	0.83	0.76-0.89	49
PDE5 inhibitors	0.82	0.78-0.86	0.90	0.83-0.96	0.341	0.90	0.84-0.97	0.89	0.81-0.98	38
Systemic contraceptives	0.82	0.78-0.86	0.83	0.78-0.88	0.657	0.84	0.79-0.88	0.85	0.75-0.96	68
Vasodilators	0.82	0.79-0.87	0.82	0.78-0.86	<0.0001	0.83	0.79-0.88	0.84	0.78-0.91	45
Diseases:										
Atrial Fibrillation	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.79	0.76-0.83	0.80	0.74-0.86	51
Chronic Kidney Disease	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.83	0.79-0.88	0.84	0.78-0.91	49
Deep Vein Thrombosis/Pulmonary embolism	0.82	0.78-0.86	0.82	0.78-0.86	0.068	0.83	0.79-0.87	0.84	0.77-0.91	53
Endocarditis	0.82	0.78-0.86	0.81	0.77-0.85	0.916	0.82	0.78-0.86	0.82	0.76-0.89	47
Hyperlipidemia	0.81	0.77-0.85	0.81	0.77-0.85	<0.0001	0.82	0.78-0.86	0.83	0.76-0.89	49
Hypoglycemic events	0.82	0.78-0.86	0.83	0.79-0.87	0.004	0.84	0.8-0.89	0.85	0.78-0.94	64
Ischemic Heart Disease	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.83	0.79-0.87	0.84	0.78-0.9	40
Myocardial Infarction	0.83	0.79-0.87	0.82	0.79-0.87	<0.0001	0.83	0.79-0.87	0.84	0.77-0.91	54
Obesity	0.82	0.78-0.86	0.82	0.78-0.86	0.008	0.83	0.79-0.87	0.84	0.78-0.91	47
PAD†	0.83	0.79-0.87	0.83	0.79-0.87	<0.0001	0.84	0.8-0.88	0.85	0.78-0.91	48
Renal Failure	0.82	0.78-0.86	0.82	0.78-0.86	<0.0001	0.84	0.8-0.89	0.85	0.77-0.95	72
1st year of T2DM	0.82	0.79-0.87	0.89	0.83-0.95	0.111	0.89	0.83-0.95	0.88	0.82-0.95	14

NA, not applicable.
**adjusted for hyperlipidemia, ischemic heart disease, use of lipid lowering drugs, vasodilators and beta-blockers.*
 # adjusted for hyperlipidemia, use of lipid lowering drugs, vasodilators, low-dose aspirin and beta-blockers.
† PAD, peripheral arterial disease. ‡ P-value interaction.

SECTION 8

Summary and General Discussion



SUMMARY

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for pain relief and anti-inflammatory purposes. They are often combined with proton pump inhibitors (PPIs), the most potent blockers of gastric acid secretion to reduce gastroduodenal complications of NSAID use. This thesis studied the use and safety of NSAIDs and PPIs. An overview of the main results of studies in this thesis is shown in Table 1. After an introduction to the topic in the first section we continue in the second section with a review of the use of PPIs in elderly. PPIs are often co-prescribed with NSAIDs in order to mitigate the risk of NSAID-related upper gastrointestinal (GI) erosions and ulcers, including complicated ulcer disease. However, the use of PPIs is associated with increased risks of adverse events, as is discussed in *Chapter 2.1*. The evidence that has been accumulated for these associations so far is, nevertheless, scarce.

In Section 3 we focus on the occurrence of two esophageal diseases [i.e., Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC)] that may be prevented or treated by use of NSAIDs or PPIs. The pathogenesis of Barrett's esophagus (BE) include prolonged gastro-esophageal reflux from the stomach into the lower esophagus. Subsequently, esophageal adenocarcinoma (EAC) could develop through stepwise progression from BE to low-grade and high-grade dysplasia until neoplasia. Current treatment regimens for patients diagnosed with BE include amongst others the use of proton pump inhibitors. We first showed that the incidence of BE increased in the Netherlands and the United Kingdom until 2003 and levelled off thereafter. In contrast, the incidence of EAC continued to increase until now. However, among BE patients incident EAC occurred in only 0.3% of BE patients (*Chapter 3.1*). The survival rate of EAC is still very poor, leaving substantial need for additional therapy or prevention of EAC. However, we could not demonstrate that NSAIDs and PPIs resulted in a decrease in risk of EAC among BE patients (*Chapter 3.2*).

Section 4 is devoted to the risk of upper gastrointestinal (GI) events associated with NSAIDs. NSAIDs inhibit cyclo-oxygenase (COX)-1 and COX-2 enzyme to a varying extent. After the introduction of selective COX-2 inhibitors on the market, these were preferentially prescribed to high-risk patients. In *Chapter 4.1* we demonstrate that use of a propensity score based on information in the electronic health care record allows to take channeling of NSAIDs to higher risk patients into account. Based on a similar propensity (or chance) to receive either nonselective (ns) NSAIDs or selective COX-2 inhibitors the use of a PPI with traditional nsNSAIDs yielded an equal risk of upper GI complications as selective COX-2 inhibitors (*Chapter 4.2*). The risk of upper GI events may be influenced by other patient characteristics and by use of other drugs. Though guidelines suggest to avoid certain drug combinations it was unclear to which extent the risk of upper GI bleeding was increased and whether there could be a difference between nsNSAIDs and selective COX-2 inhibitors. In *Chapter 4.3* we show that when multiple drugs are used concomitantly with nsNSAIDs, selective COX-2 inhibitors or low-

dose aspirin, the risk of upper GI bleeding differs and may be higher than expected on the basis of the individual risks.

In section 5 we look at the effects of NSAIDs and PPIs on the lower GI tract. First we looked at the occurrence of microscopic colitis (MC) and demonstrated that the increase in incidence of MC in the Netherlands is not explained by an increase in the total number of colonoscopies in the last decade, which is a procedure that is required to detect microscopic colitis (*Chapter 5.1*). We demonstrated that NSAIDs and PPIs were associated with an increase in the risk of MC (*Chapter 5.2*). In the last chapter of section 5 (*Chapter 5.3*) we looked at the prognosis of MC patients by using data from the national pathology registers in Denmark and the Netherlands. Patients with MC were more often diagnosed with colorectal polyps and adenomas during follow-up as compared to the general population.

In section 6 we continued with NSAIDs but now focused on their cardiovascular effects. Based on a multi-national project we were able to estimate the risk of acute myocardial infarction (AMI) for twenty-eight individual NSAID compounds. The risk of AMI was increased for thirteen different NSAIDs (*Chapter 6.1*). When combining all evidence from different studies in the multi-national project we were able to provide a decision model to assess for an individual patient which NSAID is relatively the safest choice (*Chapter 6.2*). It appeared that celecoxib and ketoprofen were most favorable NSAIDs while ketorolac and etoricoxib were most harmful NSAIDs.

Since all of the work in the previous sections is based on the use of electronic health care databases in one or more countries, the last section (section 7, *Chapter 7.1*) describes a methodological approach on how to integrate and how to combine results or data from these separate data sources. Individual patient-level data analysis appeared to provide very similar results as compared to the regular meta-analysis from data site specific results.

Table 1. Overview of main study results of studies in this thesis.

Chapter	Research Topic	Result
2.1	Use and safety of proton pump inhibitors among elderly	Use of PPIs among elderly provided inconsistent evidence with low strengths of association for drug interaction with clopidogrel, low-dose aspirin and levothyroxine; bone fractures, pneumonia and vitamin B12 absorption. Moderate strength was seen for *Clostridium difficile* infection and other enteric infections. Unknown strengths for iron absorption, hypomagnesemia and acute interstitial nephritis.
3.1	Incidence of BE and EAC among BE patients	Incidence rates of BE in the UK and NL increased until 2003, but levelled off thereafter. In contrast, the IR of EAC continued to increase until now, although among BE patients, incident EAC occurred in only 0.3% of BE patients.
3.2	Chemoprevention of EAC among patients with BE	Use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of high-grade dysplasia and EAC among patients with BE in a population based cohort.
4.1	Generating high-dimensional propensity score on unstructured information from medical records	It was possible to generate a PS model with use of unstructured free text and relevant covariates for the PS model to be identified automatically.
4.2	Selective COX-2 inhibitors or nonselective NSAIDs plus gastroprotective agents and risk of upper GI outcomes	The risk of upper GI events was similar in nsNSAID+GPA (≥80% adherence) and COX-2 inhibitors users. In patients concurrently using glucocorticoids a significant increase in the risk of upper GI events for nsNSAID+GPA users was observed and COX-2 inhibitors should be preferred.
4.3	Concomitant use of drugs with nsNSAIDs, selective COX-2 inhibitors and low-dose aspirin and risk of upper GI bleeding	Concomitant use of nsNSAIDs, COX-2 inhibitors, or low-dose aspirin with SSRIs significantly increases the risk of upper GI bleeding. Concomitant use of nsNSAIDs or low-dose aspirin, but not COX-2 inhibitors, with corticosteroids, aldosterone antagonists, or anticoagulants produces significant excess risk for upper GI bleeding.
5.1	Incidence of microscopic colitis in relation to number of colonoscopies	The incidence of MC remained fairly stable during a 10-year period in the Netherlands and increases that may be seen on the population level are due to increasing rates of colonoscopies.
5.2	Risk of microscopic colitis during use of drugs	NSAIDs and PPIs are associated with an increased risk of MC. The association of MC with use of the other drugs is probably explained by worsening of diarrhea/symptoms rather than increasing the risk of MC itself.
5.3	Risk of colorectal neoplasia in microscopic colitis	Patients newly diagnosed with microscopic colitis were not at increased risk of CRC one or more years after their diagnosis, compared to the general population in Denmark and The Netherlands. The high observed incidence of non-adenomatous polyps, adenomas, and CRC, particularly in the first year following MC diagnosis, was probably due to surveillance bias, with better screening and treatment for precursor lesions leading to a lower rate of CRC.
6.1	Risk of acute myocardial infarction during use of individual NSAIDs	The risk of AMI differed between 28 individual NSAIDs. The risk was highest for ketorolac, but was increased also for several other selective COX-2 and nonselective NSAIDs and was higher when using higher daily doses.
6.2	Individualized NSAID prescribing based on cardiovascular and GI risks	We provided an integrated decision model for new NSAID users on upper gastrointestinal and cardiovascular outcomes. Over a range of scenarios least harmful NSAIDs included celecoxib and ketoprofen, while ketorolac and etoricoxib were preferred less.
7.1	Pooling of data from multiple data sources	One- and two-stage analyses yielded similar estimates including a range of confounders in the setting of the SAFEGUARD project with a common work up and common data model.

AMI, acute myocardial infarction; BE, Barrett's esophagus; CRC, colorectal cancer; EAC, esophageal adenocarcinoma; GI, gastrointestinal; GPA, gastroprotective agent; MC, microscopic colitis; NL, the Netherlands; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PS, propensity score; SSRI, selective serotonin reuptake inhibitor; UK, United Kingdom.

DISCUSSION

USE AND EFFECTS OF PROTON PUMP INHIBITORS

Health care is a rapidly evolving and developing area. Nowadays, many novel, experimental therapies are being studied, implemented and becoming available for a wide variety of patients. The field of medicine is shifting from patient care to cure and prevention of disease. This goes hand in hand with increasing use of medical diagnostic and therapeutic utilities, including medication. In this thesis, we focus on the gastro-intestinal (GI) tract. Proton pump inhibitors are drugs that are used for gastrointestinal diseases and have been on the market for decades. The use of proton pump inhibitors have made a major change in the frequency of hospitalizations for GI events in the past decades.

As PPIs are the most potent acid-inhibiting drugs, they are often co-prescribed with NSAIDs to prevent the negative effect that NSAIDs may have on the GI tract. However, there are other indications for use of PPIs as described in this thesis The majority of PPI users are elderly people and use of these drugs in elderly has been reported to be associated with adverse events such as fractures, bacterial enteric infections and vitamin deficiencies. However based on the available literature, we could not find evidence that there would be strong associations between PPI use and outcomes including bone fractures, pneumonia, vitamin B12 and iron absorption, *Clostridium difficile* infection and other enteric infections, hypomagnesemia and acute interstitial nephritis. Also the inconsistency of evidence leaves it unclear whether drug-interaction between PPIs and clopidogrel or low-dose aspirin would be clinically relevant. The risks reported in the different studies are modest and many questions can be raised when interpreting the results. In addition the outcomes are rare resulting in low excess risks in the population even if the risk would be slightly elevated. Considering the benefits and the risks of PPIs the relevant question to ask nowadays is probably not so much whether we should treat or not with a PPI based on potential risks, but whether the elderly patient has the proper indication for continued use of the PPI. Properly balancing the indication, benefits and harms of PPI therapy on an individual level can substantially minimize avoidable risk, morbidity and reduce health care costs.

We know that PPIs are very effective drugs to reduce the risk of upper GI events, such as bleeding and perforation. Furthermore in recent years, the costs of PPIs have dropped considerably. The widespread use of PPIs for a large variety of indications and often prolonged duration led to an enormous amount of costs in health care budgets.[16] The minister of Health, Welfare and Sport decided in 2013 therefore that PPIs should no longer be reimbursed for all patients. Since this decision could have a negative effect on the prevention of GI bleedings when using NSAIDs or low-dose aspirin it was surprising that the number of upper GI bleedings was reported to decrease in 2014.[16] Not only a decrease in the budget of PPI reimbursement was achieved, but as well in care of patients with upper GI bleeding or complications. However

this was an ecological study (a study in which variables are correlated based on group level measurements). Typically ecological studies are used to describe patterns among the population, e.g. the incidence of cancer in different geographical areas in a country, but do not allow to make causal statements. This implies that the observed simultaneous occurrence of reduced reimbursement of PPIs and a decrease in incidence of upper GI bleedings can also be attributed to an ecological fallacy. It would be highly counterintuitive to assume that not reimbursing PPIs (thereby reducing the use in the population) reduces the risk of upper GI bleeding. It is likely that other factors may explain this finding, such as: those that need the PPIs the most, e.g. high risk patients actually are using the PPIs; whereas the 'inappropriate' users are not anymore. A more in to depth and detailed study on the actual intake of PPIs, the characteristics of patients using PPIs and the outcome of these patients (e.g. need of emergency department visits, hospitalization, endoscopy) should be performed before making such a strong statement on the 'effective' removal of PPI reimbursement.

NSAIDS AND PPIS IN THE CONTEXT OF BARRETT'S ESOPHAGUS AND ESOPHAGEAL ADENOCARCINOMA

Incidence of Barrett's esophagus and esophageal adenocarcinoma

Barrett's esophagus (BE) is characterized by replacement of the squamous epithelium of the esophagus by metaplastic columnar epithelium. It is considered a consequence of prolonged gastro-esophageal reflux into the lower esophagus.[219, 220] Apart from obesity and smoking, BE is an important risk factor for the development of esophageal adenocarcinoma (EAC) via a stepwise pathway of low-grade and high-grade dysplasia.[219, 220] It is estimated that the risk of EAC is increased approximately 30 to 125 fold in persons with BE.[221] Endoscopic surveillance for EAC among patients with BE is therefore recommended,[222] though there is only modest evidence that endoscopic surveillance of BE improves EAC-related outcomes.[501] Although several studies reported on incidences of BE based on selected patients in hospitals or specialty clinics,[232, 234, 235] the epidemiology of BE and EAC among the general population, and particularly of EAC among patients with BE remained until some years ago largely unknown. We showed that the incidence of BE increased in the beginning of the millennium both in the United Kingdom with 35% and in the Netherlands with 41%, but the incidence levelled off after 2003. In contrast, the incidence of EAC in a cohort of BE patients continues to increase. The one-year risk of EAC among newly diagnosed BE patients was 0.09%.The levelling off of BE incidence was also observed by others,[223] and may be explained by the following items: 1) restriction of gastroscopy referrals in dyspepsia guidelines; 2) birth cohort effect; 3) better and earlier treatment of GERD and dyspepsia. Since BE is a well acknowledged risk factor for EAC development, patterns in the incidence of BE are likely to impact the incidence of EAC as well, although any effect of this is likely to appear in the next 10 to 15 years due to the decade-long

lag time between BE and EAC development. Given the fact that many BE patients are asymptomatic, identifying the 'true' incidence of BE among the general population is challenging. A population-based screening program to diagnose and detect all subjects with BE in the population may not be cost-effective as screening for EAC is not cost effective either.[502] Although we adhere to the stepwise development of neoplasia approach from BE to EAC, it was shown that 95% of subjects undergoing EAC resection had not been diagnosed with BE before.[503] The current endoscopic surveillance regimen for patients with BE is therefore under debate.[504] This debate is also fueled by the fact that 25% of EACs are diagnosed within 1 year after initial BE diagnosis.[504] A better diagnostic approach may be to screen high-risk patients. Additional risk stratification methods such as molecular markers may be considered for this and are currently being studied.[502] In order to identify the most promising markers for appropriate and optimal risk stratification with individual patient predictions requires close collaboration across different Barrett's disease cohorts to capitalize on power and heterogeneity across populations. The benefit of screening for BE or EAC should not be limited to the effect of EAC development but also to the effect on EAC-specific and overall mortality. Recognizing a large variety of potential, yet imperfect, strategies and markers to control the overall burden of EAC, the optimal way at the moment to gain effective primary prevention of BE and EAC would be controlling for risk factors of BE such as obesity, smoking and gastro-esophageal reflux.[502]

Risk of esophageal adenocarcinoma in patients with Barrett's esophagus

Gastrointestinal cancers account for almost 25% of all cancers and approximately 4.9% of all deaths worldwide.[225] Death rates of most cancers decreased in recent years, while the marked increase in death rate for esophageal adenocarcinoma between 1970 and 2005 is now also slowly tapering off and decreasing.[505] Despite the evolving therapeutic options for esophageal cancer, the age-standardized mortality rate remains 5.1/100,000 person-years.[254] As a result, there remains a substantial need for additional therapy or even effective prevention of esophageal cancer, particularly given the low 5-year survival rate of 13% to 17%.[505] Some investigators have shown unexpectedly large risk reductions of EAC, up to 70% by use of NSAIDs, PPIs, low-dose aspirin and statins. These results were however seen in selected populations and immortal time bias was present.[245, 261, 266] Whether such a chemopreventive effect of these drugs applies to an unselected population of newly diagnosed BE patients is unknown. We could not show a significant risk reduction of high-grade dysplasia (HGD) or EAC by use of these drugs as reported in this thesis. This indicates that for an unselected group of patients with BE, as is common in daily clinical practice in non-academic, non-specialized hospitals, chemoprevention of EAC by NSAIDs, PPIs, low-dose aspirin and statins should not be considered as routine care. There are several reasons why our study may have been unable to confirm results from previous studies. First we had less power than other studies, which impacts significance of effect sizes and demonstrates that previously observed effects are

likely to be much smaller. Second we were rigorous in addressing biases that may have been part of previous studies such as selective survival bias,[506] disease severity, time window bias or immortal time bias.[276, 277] Third, drug exposure may be misclassified in some of the studies; it is not clear what the correct exposure window should be for prevention of cancer, and what the shape an exposure-effect relation would be. If there would be a chemopreventive effect it could be in the stage of BE to EAC, but also occur at an earlier stage, such as; prevention of BE or dysplasia development rather than of adenocarcinoma.[507, 508] It is, however, difficult to disentangle drug exposure effects in three different risk periods: induction (dysplasia), latent (between dysplasia and cancer) and disease period (cancer). Ideally, this requires knowledge on exact timing of the first aberrant Barrett's cell and subsequent stages towards HGD and EAC develop, which in practice is not possible. The fourth explanation for not observing a preventive effect in our study is the exposure prevalence, as over-the-counter use of NSAIDs was not captured. Putting these considerations together leads us to conclude that based on current evidence unguarded use of statins, NSAIDs, PPIs and low-dose aspirin for the purpose of EAC prevention should not be started when a patient is newly diagnosed with BE. The benefit-risk assessment does not seem positive. Large sample studies are needed that avoid the biases as stated above and should consider overall and cancer-specific survival. Even though effects on survival may seem marginal on an individual basis (e.g. a risk reduction of 19% of dying from esophageal cancer by use of statins[509]), such a difference may potentially have large population impact. The risk-benefit balance and associated costs for prolonged survival of cancer patients should be taken into account as well.

NSAIDS AND THE RISK OF UPPER GASTROINTESTINAL BLEEDING

Although the pathophysiological effect of NSAIDs on the upper gastrointestinal (GI) tract is well-known, NSAID-related upper GI bleeding remains an important area of research. We know for several decades that particularly nonselective (ns) NSAIDs increase the risk of upper GI bleeding, ulcerations and complications by 2 to 4 fold, whereas selective COX-2 inhibitors are considered less harmful. However the effects of NSAIDs are not limited to the upper GI tract only, but extend to the lower GI tract as well.[82, 330] In order to mitigate the increased risk of upper GI bleeding among NSAID users with increased risk of these events, clinical guidelines[5, 99, 100, 315] suggest strategies as prescription of cyclo-oxygenase (COX)-2-selective inhibitors or concurrent use of gastroprotective agents (GPAs), such as proton pump inhibitors (PPIs). Although both preventive strategies aim to reduce the incidence of upper GI events, the risk of such complications cannot be eliminated completely; a considerable proportion of NSAID plus GPA users (6.3% to 8.5%) and COX-2 inhibitor users (3.7% to 8.9%) continues to experience upper GI events.[76-79] Most of the clinical trials were not able to show a difference between COX-2 inhibitor use or NSAIDs+GPA in terms of the frequency of GI events, although the results may not easily be extrapolated to clinical practice due to selective inclusion of patients in trials, use of supra-therapeutic doses and exclusion of patients with frequently

used concomitant medications as low-dose aspirin and corticosteroids.[76-78, 82] Comparison of nsNSAIDs and selective COX-2 inhibitors was also done through observational studies. However, such studies are challenging in an observational setting since COX-2 inhibitors are preferentially prescribed to persons at higher risk of GI events. This phenomenon is referred to as 'channeling' [290, 291] of certain drugs – in this instance selective COX-2 inhibitors – to patients at high risk.[294, 322, 510] This means that the baseline risk of developing the event of interest is not similar between the two groups of patients exposed to different drugs. This may arise due to differences in co-morbidity, which can cause confounding by indication. One way to deal with confounding by indication is the use of propensity scores, a method that is exponentially being used in (pharmaco)epidemiology studies as it allows in several ways to balance any of the baseline disproportionalities between the treatment groups and may mimic a randomized clinical trial.[297, 302] However, identifying which information should be considered in the propensity score model in large structured electronic health record databases is challenging. The high-dimensional propensity score was developed to empirically identify a large number of covariates that may be confounders or proxies for otherwise unmeasurable confounders.[302] Computerization of health care provides us with large amounts of electronic data and often these data are not recorded in a structured way, e.g. discharge letters, notes from physicians are composed of abbreviated words, incomplete phrases and medical acronyms. In general investigators use structured information for creation of propensity scores. In this thesis we explored whether we could create a PS model using both unstructured and structured information using data from the IPCI medical record database, that contains a lot of textual unstructured information. It was possible to generate a PS model with use of unstructured free text and relevant covariates for the PS model to be identified automatically.

While dealing with channeling of COX-2 inhibitors, we observed in this thesis that the risk of an upper GI event and upper GI bleeding does not differ between users of nsNSAIDs in combination with adherent use of a GPA and COX-2 inhibitor users. In a further analysis of the EU-ADR data, we also investigated whether concomitant use of drugs that increase the risk of upper GI events are adding up or have synergistic effects. We noticed that the risk of upper GI bleeding was increased for the combination of glucocorticoids and nonselective NSAIDs, the combined effect was stronger than adding up the separate effects. There were also drug combinations with selective COX-2 inhibitors that in combination showed an excess risk that exceeded the sum of the individual risks. Patients may not know that when they buy a painkiller over-the-counter – as they would normally have done – they expose themselves to a hazardous risk of bleeding especially if they are concurrently using other drugs. Many drug combinations can increase the upper GI risk, while the use of the concomitant drugs is common and often for long-term, e.g. aldosterone antagonists, glucocorticoids, low-dose aspirin and selective serotonin reuptake inhibitors. When an NSAID is indicated personalized medicine is important to consider the 'safest' group of NSAIDs for the patient. We provided strong evidence that this issue should be addressed by physicians, pharmacists and patients. However, whether risks and drug-drug interactions differ per individual type of NSAIDs is unclear. Also, to which extent the newer oral anticoagulants (nOACs) cause interaction with

other drugs should deserve attention in future research.[511,512] The reach of scientific knowledge to the lay public is still an area that may deserve some attention. Despite news letters, radio interviews and guidelines, an interactive tool for patients to easily access and use may help towards a safer environment. By preventing upper GI bleedings through education, substantial reductions in health care costs can be achieved. Future studies should validate our findings and explore effects of subgroup interactions, such as aldosterone antagonists.

NSAIDS AND THE RISK OF MICROSCOPIC COLITIS

One of the most important functions of the colon is the resorption of water from the wastes that pass through. Inflammation of the colon interferes with this process and results in decreased water resorption and ultimately diarrhea. Microscopic colitis (MC) is a condition characterized by chronic watery diarrhea, normal radiological and endoscopic appearance, and microscopic inflammation of the colon. MC is recognized as a form of chronic inflammatory bowel diseases (IBD). IBD has been associated with an increased risk of colorectal cancer due to chronic inflammation.[397] In recent years several studies reported on an increasing incidence of MC.[371, 372, 395] Clinical awareness, more liberal use of colonoscopy, and routine random biopsy sampling in normal colonoscopies may have distorted the estimation of the 'true' incidence of the disease. These types of detection and diagnostic biases are, however, difficult to account for in incidence studies. In this thesis we dealt with this bias by estimating incidence not only on a general population level but also based on the number of colonoscopies. Our findings show that the actual incidence of MC remained fairly stable during a 10-year period in the Netherlands, and that increases that may be seen on the population level are due to increasing numbers of colonoscopies performed. The etiology of the disease is largely unknown, but because of its inflammatory character NSAIDs and PPIs have been suggested to alter MC development. Using a case-control design we showed that use of NSAIDs, PPIs, selective serotonin re-uptake inhibitors, low-dose aspirin, ACE-inhibitors, and beta-blockers were associated with an increased risk of MC. However, when taking confounding by indication, diagnostic delay and diagnostic bias into account (by comparing with subjects who have had a colonoscopy negative for colorectal cancer and MC), only PPIs and NSAIDs significantly increased the risk of MC. This finding was supported by dose-response analyses showing increasing estimates with higher cumulative doses used. The clinical implications of this study are that PPIs and NSAIDs should be avoided in subjects with a prior diagnosis of MC and careful evaluation about drug intake is needed when a patient is presenting with devastating watery diarrhea.

Continued chronic inflammation of the colon may result in changes of cell compositions in the colon predisposing to development of precancerous lesions and cancer. If one would be able to disentangle an increased risk, extensive surveillance strategies may be implemented for patients with MC. Therefore we investigated the risk of colorectal polyps, adenomas and cancer in MC patients. We found that MC patients did not have an increased

long-term risk of CRC as compared to the general population. MC patients are however more likely to develop colorectal polyps and adenomas on the long-term, which may resulted from prolonged colonic microscopic inflammation. Due to detection and diagnostic bias after MC diagnosis, more colorectal polyps, adenomas and CRC were diagnosed resulting in an increased risk of these outcomes in the first year following MC diagnosis. Nevertheless our findings did not suggest that a more extensive or tailored CRC screening program for MC patients than currently recommended for the general population should be considered.

There is a large amount of data that shows that MC is a common GI disease with an important impact on the patients' quality of life. Future research on MC should focus on shortening the diagnostic delay: e.g. primary care physicians, gastroenterologists and pathologists should be more aware of the disease. Unravelling the etiology of the disease and considering pharmacogenetic aspects may help educating physicians. Patients presenting to their physician with chronic diarrhea should be referred for colonoscopy or even only sigmoidoscopy [513, 514] with biopsy taking. As not all patients respond immediately to therapy and the disease is characterised by relapses careful monitoring of patients diarrhea symptoms and complaints is necessary. A follow-up colonoscopy for new MC patients after healing of the mucosal inflammation for assessment of colorectal polyps and cancer may be recommended,[342] though colonoscopy on long-term is not needed for CRC screening.

NSAIDS AND THE RISK OF CARDIOVASCULAR EVENTS

After successful market introduction of the selective COX-2 inhibitors [10, 75] concerns were raised about their cardiovascular safety resulting in the voluntary withdrawal of rofecoxib in 2004.[11] Though the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) concluded that selective COX-2 inhibitors increased the risk of cardiovascular events[362] and posted the recommendation that these should be avoided in patients with ischemic heart disease, stroke or peripheral arterial disease[89, 94, 95], it remained unclear what the cardiovascular risk of the traditional nsNSAIDs was. As part of the European Commission funded Safety of NSAIDs (SOS) Study we report on the risk of acute myocardial infarction with use of individual NSAIDs. We noticed that among twenty-eight individual NSAID compounds the risk of acute myocardial infarction varied with each individual agent, 13 of them were associated with a significant risk increase of small size. It appeared that the degree of COX-2 inhibition is not the unique feature determining the cardiovascular safety of NSAIDS. Patients with cardiovascular comorbid diseases often require co-prescriptions for comorbid conditions. This may challenge the physician for NSAID prescribing given the fact he needs to incorporate cardiovascular and gastrointestinal risk profiles, availability of drugs in his country and concomitant medications used. As we learned that risk of acute myocardial infarction, but upper GI bleeding as well, may differ per individual NSAID compound, it is important to balance and weigh individual patient risk to consider the relative safest NSAID for an individual patient. Despite some guidance from the clinical guidelines, it remains difficult for a physician

to tailor NSAID-therapy and appropriate gastric protection for an individual patient. As part of the SOS project we assessed for an individual patient given his/her upper GI and cardiovascular risk profile which individual NSAID should be preferred. We built an overall decision tool to assess on individual patient-level which individual NSAID is the preferred choice. Over a range of different scenarios we noticed that only a few NSAIDs always were considered the relative safest NSAIDs. Despite the fact that patient characteristics alter the risk of adverse events, such as age, sex and presence of comorbid diseases, this apparently did not affect the choice which NSAID yielded the lowest risk of upper GI complication, ischemic stroke, acute myocardial infarction and heart failure. However, as is common in pharmacoepidemiology, discrete ranking levels considering the 'safest' choice may not be clinically applicable as for some scenarios absolute differences are very small. However, since many of the NSAIDs included in the decision model are available world-wide over the counter, it may be an even safer strategy to take all NSAIDs off-the-counter. Also, considering the interactions with other chronically used drugs this would result in reductions of healthcare costs, an aspect currently highly important for government and medical decision makers.

Prior studies have suggested that PPIs may reduce the efficacy of clopidogrel in patients with a history of acute coronary syndrome.[515, 516] The clinical impact of these observations remains unclear. More recent studies did not observe a difference in mortality or ischemic cardiovascular events.[169, 517, 518] There has been a recent signal that PPIs may adversely impact vascular function and increase the risk of acute myocardial infarction.[519] Before conclusions on this data-mining study can be drawn, further investigation towards any interaction or channeling of PPIs should be performed.

POOLING OF DATA FROM MULTIPLE DATA SOURCES

Scientific studies in the medical field using 'big data' are gaining popularity, as if the terminology by itself assigns scientific plausibility and importance to the study. There are currently many projects using 'big data' with a common data model or distributed network, for example the SOS study was performed using the model. Other projects with such networks include Mini-Sentinel,[490, 493] HMO Research Network,[494] the Observational Medical Outcomes Partnership (OMOP),[489] the EU-ADR project[346] and IMI-PROTECT.[459] One of the key reasons that such widely distributed networks have been developed is the ambition to conduct large-scale epidemiologic studies meanwhile guaranteeing data privacy and legacy issues.[346] Within these networks it is possible that data partners contribute summary data or results while keeping individual-level data locally and thereby account for security issues. However, the 'optimal' way to pool and aggregate site-, population- and study-specific estimates is an area that does not include fully developed and validated methods, let alone our assumption there should be an optimal way. We and others have shown that one-stage analyses (individual patient-level pooled data) and two-stage analyses (regular meta-analysis on site-specific estimates) perform very similar to each other in a setting where a common data model is used.[485-487] How to

proceed with these methods and to integrate this information in the field of observational studies and clinical trials when a common data model is not applied needs further exploration. For instance, whether factors as the differences in prevalence, associations between varying confounders and outcome in different study designs can affect the results of pooling in the two different methods should be clarified. Although it is assumed that clinical trials are free of confounding, combining of data from different trials may however be problematic, as study populations with very specific in- and exclusion criteria likely differ between trials.

FUTURE PERSPECTIVES

In general

Scientific research in all areas of interest is growing rapidly and requires close collaboration between research groups. In this thesis the focus is directed towards drugs (NSAIDs and PPIs) and their effects on the gastrointestinal and cardiovascular system, and we have studied the effects by using several electronic health care databases. When looking at the aspect of 'combining' databases, data and results; not only are studies being designed across countries but also data from different cohorts and countries are being aggregated or 'pooled' to obtain more robust estimates. Statistical models that allow a certain degree of heterogeneity between the studies are often considered standard, though individual patient-level pooling without taking the site-specific effects into account is often used nowadays. Whether the latter method may be applied in pooling results of randomized clinical trials, observational studies and clinical cohorts should be investigated. By pooling on individual patient-level main advantages are the availability of more flexible analyses and investigation of rare exposures. Site-specific elements such as confounders, differences in prescribing behaviors, health care and most importantly study populations, analysis and design may contribute to a substantial degree of heterogeneity. Different techniques to adjust for the 'best' confounders or selecting these automatically need more exploration in the area of medical healthcare records from hospitals and primary care practices where more unstructured data is available. Data mining techniques will allow for better characterization of data and covariates than currently used methods for identification of covariables. A large amount of data is stored and entered into medical records and there is an enormous gap between availability and our ability to use these data. Despite many efforts to 'automate' the use of this data and our ability to create more sophisticated models, clinical and a-priori knowledge remains an important pillar in all research facets.

Besides these concerns, international collaboration between groups and cohorts linking different registries will enable future research efforts to gain transatlantic knowledge and improve health care. In such way, otherwise unknown and remaining research questions can be addressed. Personalized medicine, public health and prevention are important targets

for future research in helping to focus more specifically on the 'best' and 'safest' care. However, in case large study populations are needed the results should be interpreted with caution by the general public. As high relative risks do not necessarily mean a clinically meaningful increase in absolute terms for the general population.

Topic specific

Clinical practice on Barrett's esophagus and esophageal adenocarcinoma would benefit if research on this topic would focus on identifying optimal risk stratification models and markers for individual patients predictions on progression rates and prevention. Collaboration between large cohorts of BE patients across countries would offer large sample sizes for estimation of risk reductions on cancer and cancer-related mortality.

Upper GI bleeding is a traditional area of research with respect to drug-related adverse events. With the newer oral anticoagulants on the market, future research should identify interactions with these drugs and the clinical impact of other important interactions such as aldosterone antagonists with NSAIDs. Risk factors for patients on chronic therapies such as low-dose aspirin in need of gastroprotective agents but not being adherent to these should be identified.

Microscopic colitis in increasingly being recognized by physicians as well as a disease that significantly impacts quality of life of patients. Lack of knowledge resulting in diagnostic delay remains an important issue. When the etiology of the disease and the long-term consequences of MC are better understood such aspects may be encountered. Development of clinical decision models may aid the physician.

Much more clinical and observational research should distinguish between the effects of individual drugs or the effects of a group of drugs. As we showed for NSAID-related AMI, the risk of the outcome of interest may be different by individual drugs. One way to achieve this is the combination and pooling of data taking the above mentioned considerations into account.

8

APPENDICES

NEDERLANDSE SAMENVATTING

Een overzicht van de belangrijkste resultaten van studies beschreven in dit proefschrift is te zien in Tabel 1.

Niet-steroïdale anti-inflammatoire medicijnen (NSAID's) worden veelvuldig gebruikt voor pijnstilling en ontstekingsremming. Ze worden vaak gelijktijdig gebruikt met proton pomp remmers (PPI's) die de belangrijkste middelen zijn om productie van maagzuur te remmen en zo de kans op complicaties van NSAID gebruik zoals maag-darm bloedingen, verder bovenste tractus digestivus bloedingen, te verkleinen. In dit proefschrift is het gebruik en de veiligheid van NSAID's en PPI's bestudeerd. Na een algemene introductie in sectie 1 vervolgen we in sectie 2 met een review van het gebruik van PPI's bij ouderen. PPI's worden vaak gegeven aan mensen die NSAID's gebruiken om zo het risico op NSAID-gerelateerde bovenste tractus digestivus erosies en ulcera te voorkomen. Echter, het gebruik van PPI's geeft ook bijwerkingen, zoals beschreven in *hoofdstuk 2.1*. Het bewijs dat deze bijwerkingen ondersteunt is desalniettemin inconsistent en van matige sterkte.

In sectie 3 wordt gekeken naar de frequentie van twee slokdarm aandoeningen, zoals Barrett slokdarm en slokdarm adenocarcinoom. Deze aandoeningen kunnen mogelijk worden voorkomen door gebruik van NSAID's of PPI's. De pathogenese van Barrett slokdarm bestaat uit langdurige gastroesofageale reflux vanuit de maag naar het onderste deel van de slokdarm. Vervolgens kan er door stapsgewijze progressie van Barrett slokdarm via laaggradige en hooggradige dysplasie uiteindelijke kwaadaardige groei van cellen (neoplasie) ontstaan. Momenteel worden patiënten met een Barrett slokdarm behandeld middels een PPI. In *hoofdstuk 3.1* laten we zien dat de incidentie van Barrett slokdarm steeg in Nederland en het Verenigd Koninkrijk tot 2003 maar in de jaren daarna gelijk bleef. Dit in tegenstelling tot de incidentie van slokdarm adenocarcinoom die juist bleef stijgen tot nu toe. Slechts 0,3% van de patiënten met een Barrett slokdarm bleek uiteindelijk na verloop van tijd een slokdarm adenocarcinoom te ontwikkelen. Ondanks het lage risico op progessie is er gezien de nog steeds matige overleving van patiënten met slokdarm adenocarcinoom een hoge noodzaak om preventieve therapieën te ontdekken. In *hoofdstuk 3.2* hebben we gekeken naar de preventieve werking van NSAID's en PPI's op het ontwikkelen van slokdarm adenocarcinoom bij patiënten met een Barrett slokdarm. Gebruik van NSAID's en PPI's bleek echter het risico op slokdarm adenocarcinoom niet te verlagen.

Sectie 4 bekijkt het risico op bovenste tractus digestivus bloedingen en complicaties bij gebruik van NSAID's. NSAID's remmen het enzym cyclo-oxygenase (COX)-1 en COX-2. Nadat er nieuwere en potentieel veiligere NSAID's ontwikkeld waren, de zogenoemde

selectieve COX-2 remmers, werden deze nieuwere middelen met name voorgeschreven aan patiënten met een hoog risico op een bovenste tractus digestivus complicatie. In *hoofdstuk 4.1* demonstreren we dat het gebruik van een propensity score door middel van informatie uit een elektronisch patiënten dossier rekening kan houden met het selectief voorschrijven van de selectieve COX-2 remmers aan hoog risico patiënten. Bij patiënten met even hoog risico op bovenste tractus digestivus complicaties bleek dat gelijktijdig gebruik van een traditioneel niet-selectief (ns) NSAID met een PPI een even hoog risico op bovenste tractus digestivus complicaties gaf als gebruik van een selectieve COX-2 remmer (*hoofdstuk 4.2*). Het risico op een bovenste tractus digestivus complicatie is mede afhankelijk van patiënt karakteristieken en gelijktijdig gebruik van medicijnen. Alhoewel in richtlijnen beschreven staat dat sommige medicijncombinaties vermeden dienen te worden, was het onduidelijk in hoeverre het risico op een bovenste tractus digestivus bloeding is toegenomen en of er hierbij een verschil is tussen de klasse nsNSAID's en klasse selectieve COX-2 remmers. In *hoofdstuk 4.3* tonen we aan dat bij gelijktijdig gebruik van medicijnen met nsNSAID's, selectieve COX-2 remmers of cardiovasculair aspirine het risico op een bovenste tractus digestivus bloeding verschilt tussen deze middelen en hoger is dan het risico dat we verwachtten op basis van de som van de individuele risico's.

In sectie 5 onderzoeken we effecten van NSAID's en PPI's op het onderste deel van het maag-darm stelsel, namelijk de dikke darm. Eerst bekijken we in *hoofdstuk 5.1* de frequentie van microscopische colitis in Nederland en tonen aan dat de toename in nieuwe diagnoses van microscopische colitis in Nederland niet verklaard kan worden door een toename in het totale aantal colonoscopieën in de laatste tien jaar. Een colonoscopie is een diagnostische procedure om microscopische colitis te diagnosticeren. Vervolgens laten we in *hoofdstuk 5.2* zien dat NSAID's en PPI's de kans op het ontwikkelen van microscopische colitis verhogen. In *hoofdstuk 5.3* onderzoeken we de prognose van patiënten met microscopische colitis door gebruik te maken van nationale pathologie registers van Denemarken en Nederland. Patiënten met microscopische colitis werden vaker gediagnosticeerd met colorectale poliepen en adenomen dan in vergelijking met de algemene bevolking gedurende follow-up.

We onderzoeken ook de effecten van NSAID's op het cardiovasculaire systeem in sectie 6. We konden het risico op het ontwikkelen van een acuut myocard infarct (hartaanval) voor gebruik van 28 verschillende NSAID's schatten binnen een multi-nationaal project. Het risico op een acuut myocard infarct was verhoogd voor dertien verschillende NSAID's zoals we laten zien in *hoofdstuk 6.1*. Door integratie van gegevens van NSAID's en het risico op het maag-darm stelsel en het cardiovasculaire systeem ontwikkelden we een beslissingsmodel om voor een individuele patiënt, op basis van specifieke karakteristieken, te beoordelen welk individueel NSAID relatief gezien het veiligste is

(*hoofdstuk 6.2*). Bij verschillende karakteristieken bleken celecoxib en ketoprofen relatief gezien het vaakst het veiligste, terwijl ketorolac en etoricoxib het minst te prefereren waren.

Aangezien alle hoofdstukken in de eerdere secties gebaseerd zijn op gebruik van elektronische patiënten dossiers in databases van één of meerdere landen beschrijven we in sectie 7 (*hoofdstuk 7.1*) een methode om informatie, resultaten en data van verschillende databronnen te combineren. Individuele patiënt-level data analyse gaf vergelijkbare resultaten als de reguliere methode om resultaten te combineren namelijk meta-analyse.

Table 1. Overzicht van belangrijkste resultaten van studies beschreven in dit proefschrift.

Hoofdstuk	Onderwerp	Resultaat
2.1	Gebruik en veiligheid van proton pomp remmers bij ouderen	Gebruik van PPI's onder ouderen toonde inconsistent bewijs met een zwakke associatie voor medicijn interactie met clopidogrel, cardiovasculair aspirine, levothyroxine; bot fracturen, pneumonie en vitamine B12 absorptie. Matige associatie was gevonden voor *Clostridium difficile* infectie en andere maag-darm infecties. Onbekende sterkte associatie was gevonden voor ijzer absorptie, hypomagnesiëmie en acute interstitiële nefritis.
3.1	Incidentie van Barrett slokdarm en slokdarm adenocarcinoom bij patiënten met Barrett slokdarm	Incidentie van Barrett slokdarm in Verenigd Koninkrijk en Nederland steeg tot 2003, maar bleef gelijk daarna. In tegenstelling, de incidentie van slokdarm adenocarcinoom bleef stijgen tot nu toe, echter slechts 0,3% van de patiënten met Barrett slokdarm ontwikkelden slokdarm adenocarcinoom.
3.2	Chemopreventie van slokdarm adenocarcinoom bij patiënten met Barrett slokdarm	Gebruik van NSAID's, PPI's, cardiovasculair aspirine en statines verminderden het risico op hooggradige dysplasie en slokdarm adenocarcinoom bij patiënten met Barrett slokdarm in een populatie gebaseerd cohort niet.
4.1	Genereren van een propensity score model op ongestructureerde informatie van een elektronisch patiënten dossier database	Het was mogelijk om een propensity score model te ontwikkelen met ongestructueerde medische informatie en automatisch relevante covariaten te identificeren.
4.2	Selectieve COX-2 remmers of niet-selectieve NSAID's plus maagbeschermers en het risico op een bovenste tractus digestivus bloeding	Het risico op een bovenste tractus digestivus bloeding was even hoog voor gebruikers van nsNSAID's+maagbeschermer en selectieve COX-2 remmers. Bij gelijktijdig gebruik van corticosteroïden moet aan selectieve COX-2 remmers de voorkeur gegeven worden.
4.3	Gelijktijdig gebruik van medicijnen met nsNSAID's, selectieve COX-2 remmers en cardiovasculair aspirine en het risico op bovenste tractus digestivus bloeding	Bij gelijktijdig gebruik van nsNSAID's, selectieve COX-2 remmers of cardiovasculair aspirine met SSRIs neemt het risico op een bovenste tractus digestivus bloeding toe. Bij gelijktijdig gebruik van nsNSAID's of cardiovasculair aspirine, maar niet selectieve COX-2 remmers, met corticosteroïden, aldosteron antagonisten of anticoagulantia is er een sterk verhoogd risico en versterkt effect op een bovenste tractus digestivus bloeding.
5.1	Incidentie van microscopische colitis in relatie tot het aantal colonoscopieën	De incidentie van microscopische colitis bleef stabiel gedurende 10 jaar in Nederland en een toename van het aantal patiënten met microscopische colitis op populatie niveau kan worden verklaard door toename van het aantal colonoscopieën.
5.2	Risico op microscopische colitis bij gebruik van medicijnen	NSAID's en PPI's verhogen het risico op microscopische colitis, terwijl de associatie met gebruik van andere medicijnen waarschijnlijk wordt verklaard door verergering van diarree/symptomen.
5.3	Risico op colorectale neoplasie in microscopische colitis	Patiënten met microscopische colitis hebben geen verhoogd risico op colorectaal carcinoom in vergelijking met de algemene bevolking in Denemarken en Nederland. Het hoge aantal colorectale poliepen en adenomen en carcinoom in het eerste jaar na diagnose van microscopische colitis komt waarschijnlijk door betere en veelvuldigere screening en behandeling van precursor lesies.
6.1	Risico op acuut myocard infarct bij gebruik van individuele NSAID's	Het risico op acuut myocardinfarct wisselt tussen 28 individuele NSAID's. Het risico was het hoogste voor ketorolac maar was ook verhoogd voor verschillende andere selectieve COX-2 remmers en nietselectieve NSAID's. Het risico was hoger bij een hogere dosis van een NSAID.
6.2	Beslissingsmodel voor NSAID's per individu op basis van cardiovasculaire en maag-darm risicoprofielen	We creëerden een beslissingmodel op basis van cardiovasculaire en maag-darm risico's voor individuen die een NSAID nodig hebben. Bij verschillende karakteristieken bleken celecoxib en ketoprofen relatief gezien het vaakst het veiligste, terwijl ketorolac en etoricoxib het minst te prefereren waren.
7.1	Samenvoegen van data en resultaten van meerdere data bronnen	Individuele patiënt-level data analyse gaf vergelijkbare resultaten als de reguliere methode om resultaten te combineren namelijk meta-analyse bij gebruik van data van het SAFEGUARD project.

PPI, proton pomp remmer; NSAID, niet-steroïdaal anti-inflammatoir medicijn; COX, cyclo-oxygenase; SSRIs, selectieve serotonine heropname remmers

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ABBREVIATIONS

5-ASA	5-Aminosalicylic Acid
AIN	Acute Interstitial Nephritis
AMI	Acute Myocardial Infarction
AP	proportion attributable to interaction
ATC	Anatomical Therapeutic Chemical
BE	Barrett's esophagus
BIFAP	Base de Datos para la Investigación Farmacoepidemiologica en Atención Primaria
BMD	Bone Mineral Density
BMI	Body Mass Index
BNF	British National Formulary
CC	Collagenous Colitis
CD	Crohn's Disease
CDI	*Clostridium difficile* infection
CI	Confidence Interval
COX	Cyclo-oxygenase
CPRD	Clinical Practice Research Datalink
CRC	Colorectal Cancer
CV	Cardiovascular
CYP	Cytochrome P-450
DDD	Defined Daily Dose
DK	Denmark
DNPR	Danish National Patient Register
EAC	Esophageal Adenocarcinoma
EHR	Electronic Healthcare Record
EMA	European Medicines Agency
ES	Spain
EU	European Union
EU-ADR	Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge
FDA	Food and Drug Administration
GE	Germany
GERD	Gastroesophageal Reflux Disease
GePaRD	German Pharmacoepidemiological Research Database
GI	Gastrointestinal
GP	General Practitioner
GPA	Gastroprotective Agent
GPRD	General Practitioner Research Database

H2RA	Histamine-2 Receptor Antagonists
Hd-PS	High Dimensional-Propensity Score
HF	Heart Failure
HGD	High-grade dysplasia
H. pylori	*Helicobacter pylori*
HSD	Health Search/CSD Longitudinal Patient Database
IBD	Inflammatory Bowel Disease
ICD	International Classification of Diseases
ICPC	International Classification for Primary Care
IPCI	Integrated Primary Care Information
IQR	Interquartile Range
IR	Incidence Rate
IRR	Incidence Rate Ratio
IS	Ischemic Stroke
IT	Italy
LC	Lymphocytic Colitis
LDA	Low-dose Aspirin
MC	Microscopic Colitis
MI	Myocardial Infarction
N adh	Non adherent
NA	Not Applicable
NIBLGD	Non-insulin blood glucose lowering drug
NL	the Netherlands
NSAID	Non-Steroidal Anti-Inflammatory Drugs
nsNSAID	Nonselective Non-Steroidal Anti-inflammatory Drug
OR	Odds Ratio
OSSIFF	Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia
OTC	Over-the-counter
PPIs	Proton Pump Inhibitors
PS	Propensity Score
PYs	Person-Years
RERI	Relative Excess Risk due to Interaction
S	Synergy index
Safeguard	Safety Evaluation of Adverse Reactions in Diabetes
SIBO	Small Intestinal Bacterial Overgrowth
SIR	Standardized Incidence Rate
SISR	Sistema Informativo Sanitario Regionale
SNOMED	Systematized Nomenclature of Medicine
SOS	Safety Of non-Steroidal anti-inflammatory drugs
SSRI	Selective Serotonin Reuptake Inhibitor

T2DM	Type 2 Diabetes Mellitus
THIN	The Health Improvement Network
TSH	Thyroid-stimulating Hormone
UC	Ulcerative Colitis
UK	United Kingdom
WHO	World Health Organization of the United Nations

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Oral Presentations

Risk of colorectal polyps, adenomas and cancer in Microscopic Colitis

- *United European Gastroenterology Week, Barcelona, Spain 2015*

Individualized NSAID prescribing based on gastrointestinal and cardiovascular risks: a decision model in the SOS project

- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, MA, USA 2015*

Incidence of Barrett's esophagus and esophageal adenocarcinoma in the United Kingdom and the Netherlands are leveling off

- *Digestive Disease Week, Chicago, ILL, USA 2014*
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- *United European Gastroenterology Week, Berlin, Germany 2013*
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Incidence of Microscopic Colitis in the Netherlands

- *United European Gastroenterology Week, Vienna, Austria 2014, awarded as 'Oral Free Paper Prize' in the Free Paper Session: IBD: Epidemiology and disease outcomes*

Comparison of Incidence Rates of Acute Pancreatitis and Pancreatic Cancer among the general population and type 2 Diabetes Mellitus patients between different Databases in the SAFEGUARD project

- *Digestive Disease Week, Chicago, ILL, USA 2014*
- *Dutch Gastroenterology Society, Veldhoven, the Netherlands 2014*

NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study

- *Dutch Gastroenterology Society, Veldhoven, the Netherlands 2014*

Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily clinical practice?

- *Dutch Gastroenterology Society, Veldhoven, the Netherlands 2013*
- *Digestive Disease Week, Orlando ,FL, USA 2013*

Risk of Upper Gastrointestinal Bleeding from Different Drug Combinations

- *Digestive Disease Week, Orlando ,FL, USA 2013*
- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada 2013*

Poster Presentations

Risk of acute myocardial infarction during use of individual NSAIDs: a nested case-control study in the SOS project

- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Boston, MA, USA 2015*

Increased risk of Microscopic Colitis with use of Proton Pump Inhibitors and Non-Steroidal Anti-Inflammatory Drugs

- *United European Gastroenterology Week, Vienna, Austria 2014. Poster of Excellence and awarded as 'Poster Champ'*
- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Taipei, Taiwan 2014*

Incidence of Microscopic Colitis in the Netherlands

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Harmonization of Acute Pancreatitis diagnoses from different Databases in the SAFEGUARD project.

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Harmonization of Acute Myocardial infarction identifications from different Databases in the SAFEGUARD project.

- *International Conference on Pharmacoepidemiology and Therapeutic Risk Management, Montreal, Canada 2013*

Workshops lecturing

Workshop 'Safety of novel diabetes drugs from the SAFEGUARD project. In memoriam: Prof. Diamant'

- *European Association for the Study of Diabetes, Vienna, Austria 2014*

NSAIDs and risk profiling

- *Symposium 'What's new in Gastrointestinal Bleeding', Rotterdam, 2014*

Membership

Dutch Society of Gastroenterology, 2012
International Society of Pharmacoepidemiology, 2013

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Alimentary Pharmacology & Therapeutics
Sir Henry Welcome Postdoctoral Fellowship, grant application
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International Journal of Clinical Practice
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2015	Course Study Design, presentations, NIHES, Rotterdam
2014	Course Study Design, presentations, NIHES, Rotterdam
2014-2015	Kartini Gadroen, Caitlin Dodd, PhD students, project 'Measles and infections'
2014-2015	Kartini Gadroen, PhD student, project 'Hepatitis vaccination and multiple sclerosis'
2013-2015	Zubair Afzal, PhD student, project 'Propensity scores and upper gastrointestinal bleeding'

LIST OF PUBLICATIONS

Manuscripts related to this thesis

1. **Masclee GMC**, Coloma PM, Kuipers EJ, Sturkenboom MCJM.
   Letter: Incidence of Microscopic Colitis.
   American Journal of Gastroenterology 2015; 110:749-759.

2. **Masclee GMC**, Coloma PM, Kuipers EJ, Sturkenboom MCJM.
   Increased risk of Microscopic Colitis with use of Proton Pump Inhibitors and Non-Steroidal Anti-Inflammatory Drugs.
   American Journal of Gastroenterology 2015; 110:749-759.

3. **Masclee GMC,** Coloma PM, Spaander MCW, Kuipers EJ, Sturkenboom MCJM**.**
   NSAIDs, statins, low-dose aspirin and PPIs, and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus: a population-based case-control study.
   BMJ Open. 2015 Jan 29;5(1):e006640.

4. **Masclee GMC**, Valkhoff VE, Coloma PM, de Ridder M, Romio S, Schuemie MJ, Herings R, Gini, R, Mazzaglia G, Picelli G, Scotti L, Pedersen L, Kuipers EJ, van der Lei J, Sturkenboom M.
   Risk of Upper Gastrointestinal Bleeding from Different Drug Combinations.
   Gastroenterology. 2014 Oct;147(4):784-792.e9.

5. **Masclee GMC,** Coloma PM, de Wilde M, Kuipers EJ, Sturkenboom MCJM**.**
   Letter: Incidence rates of Barrett's esophagus and esophageal adenocarcinoma in the United Kingdom and the Netherlands are leveling off.
   Alimentary Pharmacology & Therapeutics. 2014 Aug;40(4):404.

6. **Masclee GMC,** Coloma PM, de Wilde M, Kuipers EJ, Sturkenboom MCJM**.**
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   Alimentary Pharmacology & Therapeutics. 2014 Jun;39(11):1321-30.

7. **Masclee GMC**, Sturkenboom MCJM, Kuipers EJ.
   A Benefit-Risk assessment of the use of proton pump inhibitors in the elderly.
   Drugs & Aging. 2014 Apr;31(4):263-82.

8. **Masclee GMC,** Valkhoff VE, van Soest EM, Schade R, Mazzaglia G, Molokhia M, Trifirò G, Goldstein JL, Hernández-Díaz S, Kuipers EJ, Sturkenboom MCJM.
Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily practice?
Alimentary Pharmacology & Therapeutics. 2013 Jul;38(2):178-89.

9. **Masclee GMC**, Varas-Lorenzo C, Castellsague J, Arfe A, Garbe E, Herings E, Lucchi S, Perez-Gutthann, Romio S, Schuemie MJ, Schade R, Schink T, Straatman H, Valkhoff VE, Villa M, Sturkenboom MCJM.
Risk of acute myocardial infarction during use of individual NSAIDs: a nested case-control study in the SOS project.
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10. Afzal MZ, **Masclee GMC**, Sturkenboom MCJM, Kors JA, Schuemie MJ
Generating and evaluating a propensity model using textual features from electronic medical records.
Submitted.

11. **Masclee GMC**, Pedersen L, Coloma PM, Erichsen R, Toft Sørensen, van Kemenade FJ, Verhaegh BPM, Pierik MJ, Kuipers EJ, Sturkenboom MCJM.
Risk of colorectal neoplasia in patients with microscopic colitis.
Submitted.

Other Publications

12. Valkhoff VE, Coloma PM, **Masclee GMC**, Gini R, Innocenti F, Lapi F, Molokhia M, Mosseveld M, Schou Nielsson M, Schuemie M, Thiessard F, van der Lei J, Sturkenboom MCJM, Trifiro G, on behalf of the EU-ADR Consortium.
Validation study in four health-care databases: upper gastrointestinal bleeding misclassification affects precision but not magnitude of drug-related upper gastrointestinal bleeding risk.
Journal of Clinical Epidemiology. 2014 Aug;67(8):921-31.

13. Valkhoff VE, van Soest EM, **Masclee GMC**, de Bie S, Mazzaglia G, Molokhia M, Kuipers EJ, Sturkenboom MCJM.
Prescription of non-selective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal - a 617,400-patient study.
Alimentary Pharmacology & Therapeutics. 2012 Oct;36(8):790-9.

14. **Masclee GMC**
Anti-inflammatory and antipyretic analgesics and drugs used in gout.
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16. **Masclee GMC**
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17. **Masclee GMC**, Penders J, Pierik M, Wolffs P, Jonkers D.
Enteropathogenic viruses: Triggers for exacerbation in IBD? A prospective cohort study using real-time quantitative polymerase chain reaction.
Inflammatory Bowel Diseases. 2013 Jan;19(1):124-31.

18. **Masclee GMC**, Penders J, Jonkers D, Wolffs P, Pierik M.
Is Clostridium difficile associated with relapse of inflammatory bowel disease? A combined retrospective and prospective cohort study using real-time quantitative polymerase chain reaction.
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BMC Gastroenterology. 2012 Sep 5;12:121.

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Risk of upper gastrointestinal complications during the use of individual NSAIDs: a nested case-control study in the SOS project.
Submitted.

DANKWOORD

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Gwen

ABOUT THE AUTHOR

Gwen Marilou Cootje Masclee was born on December 11th 1987 in Nijmegen, the Netherlands. She attended the Stedelijk Gymnasium Leiden in Leiden in 2000 where she graduated in 2005 (*cum laude*) with a combined profile in both biology and science. In the same year, she started medical school at Maastricht University. During her study she completed two internships at the University Hospital of Leuven in Leuven, Belgium. She performed one internship at the department of Gastroenterology and Hepatology and one at the department of Internal Medicine. Furthermore, she became interested in scientific research and conducted a scientific internship within the laboratory of Medical Microbiology in collaboration with the department of Gastroenterology and Hepatology at the University Hospital Maastricht. In 2011 she obtained her Master of Science degree in Medicine. Directly following, she started her PhD traject as described in this thesis. Gwen was tutored by Prof. Miriam Sturkenboom, Prof. Ernst Kuipers and dr. Preci Coloma. During her PhD traject she obtained a Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES) in Rotterdam. She has collaborated in the SAFEGUARD project and conducted research as a research fellow at the Department of Pharmacoepidemiology and Pharmacoeconomics (DoPE) at the Brigham and Women's Hospital (Harvard Medical School) in Boston (Massachusetts, USA) under supervision of John Seeger.

As of October 2015 she started her Internal Medicine residency (Sint Franciscus Hospital, Rotterdam, program director dr. A.P. Rietveld) as part of the formal training in Gastroenterology and Hepatology at Erasmus University Medical Center in Rotterdam. She will also follow residency in Deventer (Deventer Hospital, program director dr. F. ter Borg) and finalize her training at the Erasmus Medical Center (head of Gastroenterology and Hepatology department prof. dr. M. Bruno and program director prof. dr. R.A. de Man).