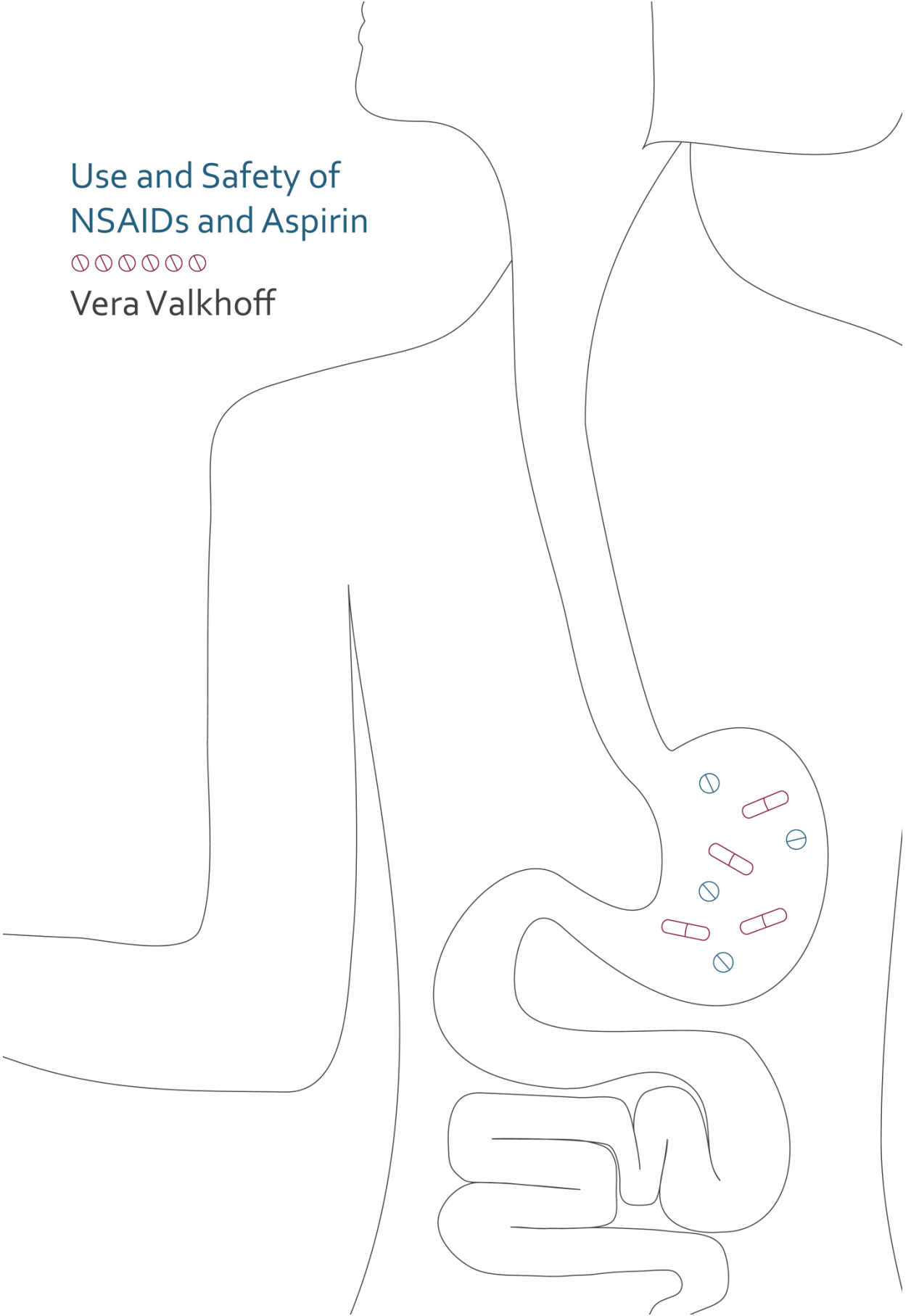
Use and Safety of NSAIDs and Aspirin

Vera Valkhoff



Use and Safety of Non-Steroidal Anti-Inflammatory Drugs and Aspirin

Vera Esther Valkhoff

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Use and Safety of Non-Steroidal Anti-Inflammatory Drugs and Aspirin

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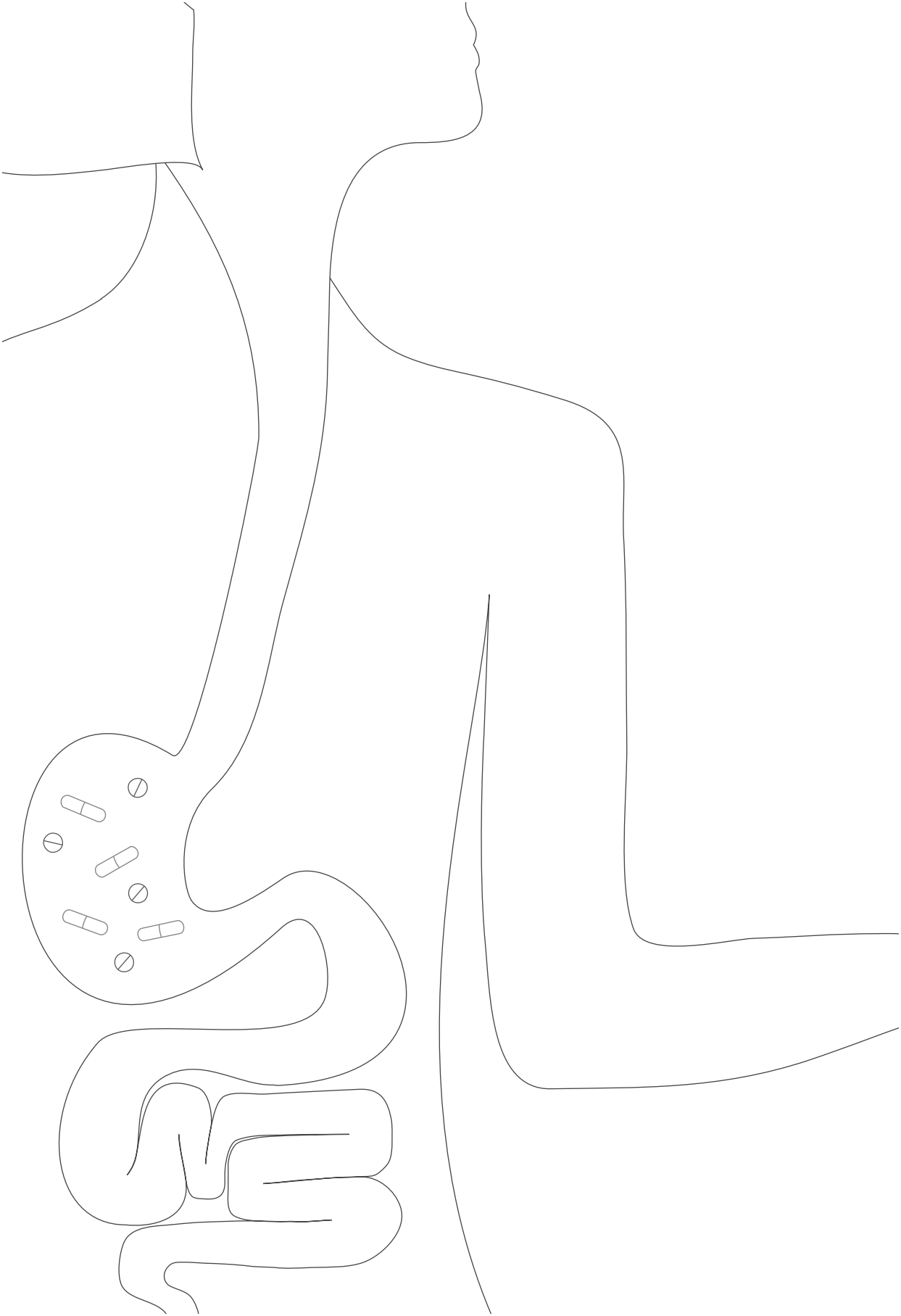
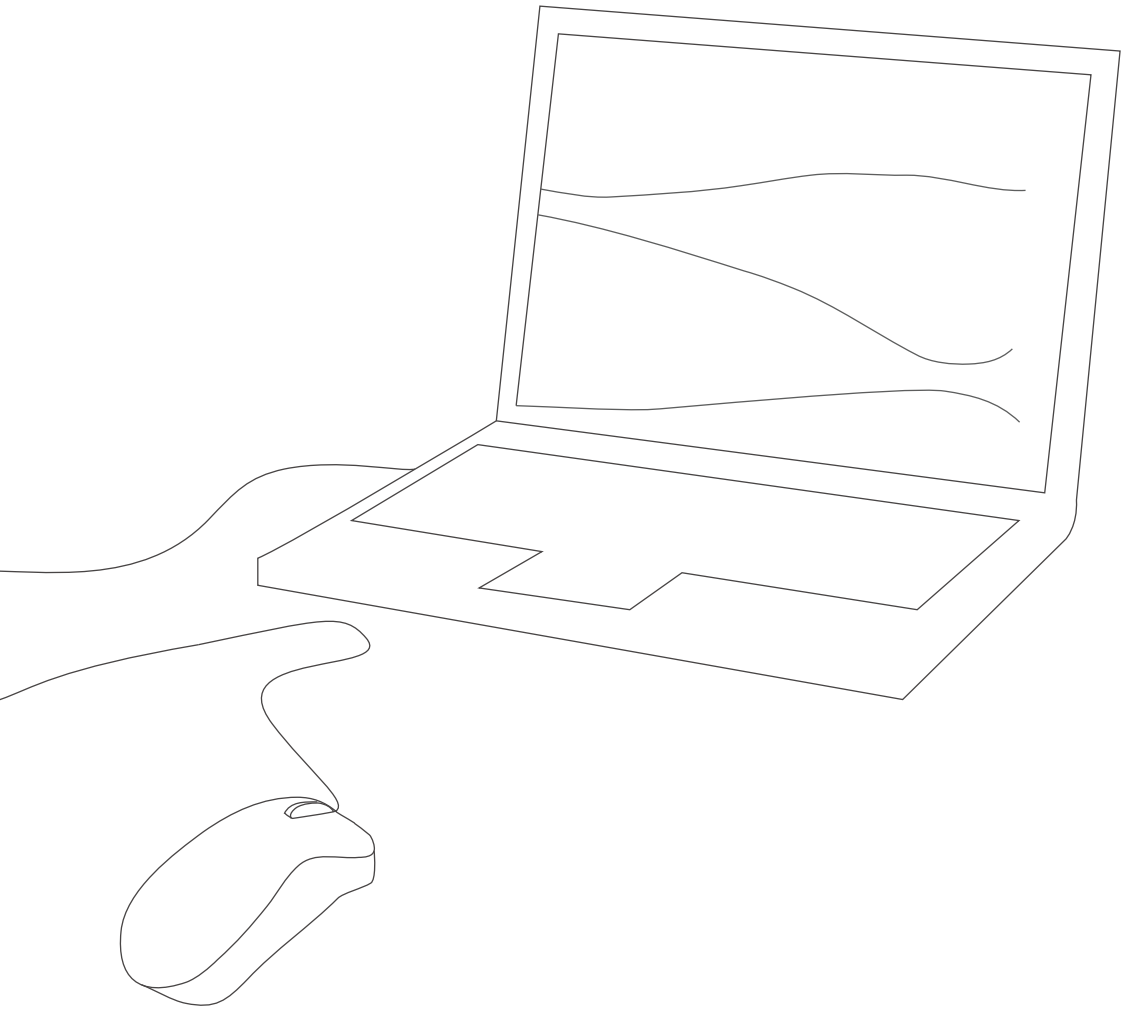
Contents



Introduction



Chapter 1

General Introduction

This introduction will provide a brief overview on two drugs investigated in this thesis, NSAIDs and aspirin. The use, indications, and harms for the gut will be discussed below and is followed by the outline of the thesis.

Aspirin and NSAID

The use of acetylsalicylic acid, better known as aspirin, dates back to the Egyptians in 1534 BC.[1] Aspirin-like compounds are naturally derived from willow tree bark and myrtle. At the end of the 19th century aspirin was patented by Bayer as the world's first synthetic drug. The recommended use was pain management. In 1968 it was shown that aspirin inhibited human platelet aggregation.[2] Since 1974 it has been recognized that aspirin use is beneficial in the secondary prevention of myocardial infarction and stroke.[3] As cardiovascular (CV) disease is the leading cause of morbidity and mortality in modern Europe and North-America[4], the use of aspirin has gained enormous popularity. It has been established that long term use of low-dose aspirin (between 75 to 100 mg per day) can reduce the risk of vascular events with 25%, primarily by acting as platelet aggregation inhibitor.[5-7] Aspirin is mostly recommended for secondary prevention[8], however is also considered for primary prevention of CV events in high-risk patients, depending on the number of CV risk factors such as age, sex, life-style and comorbidities.[7] Despite clear evidence supporting the preventive effects of aspirin, and despite the growing burden of CV disease worldwide, aspirin is reportedly underutilized in patients who are at high risk of developing CV events.[9] Approximately 9.6% of adults in the UK in 2006 were prevalent users of aspirin. This percentage was lower in younger subjects and increased with age to 35% of people over the age of 75.[10] In the Netherlands, which counts 16.5 million inhabitants, more than 1.1 million people treated with low-dose aspirin with 8 million aspirin prescriptions in 2010 (Figure 1.1). The annual related costs of aspirin use were 56 million euro's in the Netherlands also in 2010 (Figure 1.2).[11]

Although low-dose aspirin is currently most frequently used as anti-platelet therapy, aspirin at a higher dose (500-1000 mg per day) is still used as an analgesic agent, the original indication of aspirin. As derivatives of acetylsalicylic acid non-steroidal anti-inflammatory drugs (NSAIDs) were developed and have been marketed since 1969.[12, 13] The first non-aspirin NSAID was ibuprofen. NSAIDs have analgesic, anti-pyretic and anti-inflammatory properties, which make them among the world's most frequently prescribed medications. NSAIDs are indicated for a large variety of conditions. They are particularly valuable in the treatment of rheumatoid arthritis or other inflammatory conditions. They also play an important role in the management of pain in cancer. The World Health Organization has developed a so-called three-step "painladder" for cancer pain relief.[14] The first step in the painladder is to administer nonopioid drugs on a regular basis, such as paracetamol. NSAIDs might not be the first option, but should be considered in this stage. Other well-known indications for NSAID therapy include headache, migraine, postoperative pain, toothache, period cramps, osteoarthritis, and extra-articular disorders such as bursitis or tendinitis.[15]

Although not known under the general drug class name of NSAIDs, almost everyone is familiar with NSAID therapy due to their wide range of indications and effective pain relief. Recognized representatives of NSAIDs are ibuprofen, diclofenac, and naproxen. In 2010 around 6 million NSAID prescriptions were supplied in the Netherlands (Figure 1.1). This translates into 3,2 million people who were taking NSAIDs each year at an an-

nual cost of approximately €95,000,000 (Figure 1.2).[11] In the United States a quarter of persons over 65 years of age were reported to use NSAIDs at least once weekly in a self-reported questionnaire.[16]

There are around 70 different active substances or combinations that are licensed somewhere and belong to the class of NSAIDs. These drugs are predominantly available as prescription only medicine. The more traditional NSAIDs are also available without prescription either in the pharmacy or as over the counter drugs.

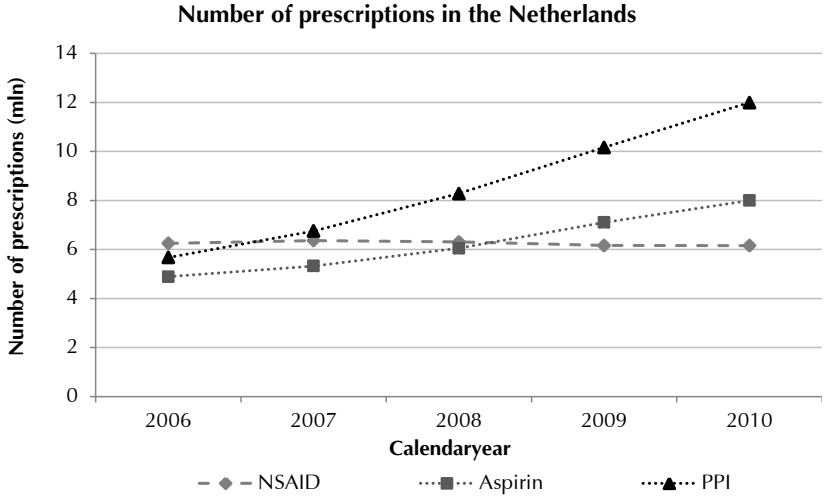


Figure 1.1: Number of prescriptions (in millions) for NSAIDs, aspirin, and Proton Pump Inhibitors in the Netherlands.[11]

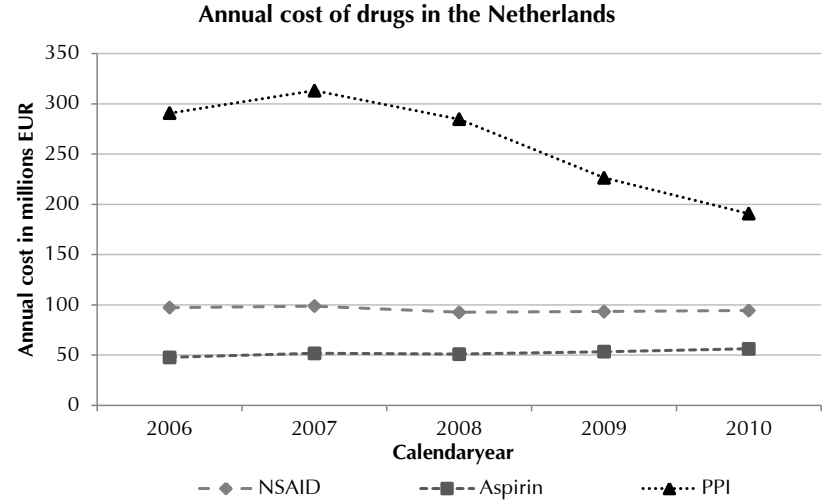


Figure 1.2: Annual cost (in millions euro's) for NSAIDs, Aspirin, and proton pump inhibitors in the Netherlands.[11]

Aspirin and NSAID-related gastroduodenal toxicity

Aspirin is an effective drug for prevention of CV events and NSAID in the management of pain. Yet, they are also known to cause serious adverse events of which upper gastrointestinal (UGI) complications are most pronounced. Already in 1938 it was demonstrated that aspirin induces gastric damage through rigid endoscopy.[17] The spectrum of aspirin and NSAID adverse drug events range from mild subjective UGI symptoms, such as dyspepsia, to gastroduodenal mucosal lesions, erosions, asymptomatic ulcers, and severe UGI complications. Patients with peptic ulcer disease, a defect in the gastric or duodenal mucosa, generally present themselves with abdominal pain, bloating, loss of appetite and weight loss. UGI complication is a composite medical term, referring to bleeding, perforation or obstruction of the UGI tract. Of these, bleeding occurs most often and is reported in a range of 0.5 to 1 per 1,000 person years (PY) in the general population.[18-26] Perforation of the UGI tract occurs in 0.03 to 0.08 per 1,000 PY.[19, 21, 22] Ulceration, edema due to inflammation and scarring with tissue deformation as result can lead to gastric outlet obstruction. This condition is uncommon and incidence rates are unknown. Dependent on the location, patients with a UGI bleed may present with hematemesis (vomiting of blood) or with tarry, blackened stool known as melena. In approximately half of all cases the cause of bleeding is a peptic ulcer bleed.[25] A UGI complication is considered a medical emergency and requires rapid diagnosis and treatment. Typically the management would consist of surgery in case of perforation, endoscopic treatment in combination with pharmacotherapy (profound acid suppression) for UGI bleeding and the treatment of gastric outlet obstruction will be mostly conservative with acid suppression as mainstay. The mortality of UGI bleeding is, despite major improvements in therapy over recent decades, still substantial and ranges from 5% to 14%.[20, 25, 27]

Patients on NSAID therapy have a 3 to 4 times higher risk of UGI complications than non-users.[28, 29] Compared to placebo or non-use, the relative risk of UGI complications in low dose aspirin users ranged from 1.5 to 2.5 in clinical trials [30-33] and from 2.6 to 3.3 in observational studies.[34, 35] Bleeding in general, including gastrointestinal bleeding, is the most common type of hospital admissions related to medicines (HARM), and almost half of them are judged as potentially avoidable. After oral anticoagulants, the two drugs most commonly associated with potentially avoidable hospitalizations for bleedings were found to be aspirin and NSAIDs.[36]

Mode of action

For a long time it has been unknown how NSAID use and aspirin use could cause these serious complications of the UGI tract. Despite centuries of aspirin use, the mode of action has only been elucidated in recent decades by, amongst others, John Robert Vane, Sune Bergström and Bengt Samuelsson. In 1982 these three researchers received the Nobel Prize in Physiology or Medicine for their work on prostaglandins.[37] They discovered that essentially, both aspirin and non-aspirin NSAIDs block the cyclooxygenase-1 (COX-1) pathway thereby attenuating the synthesis of prostaglandins. These drugs are therefore known as prostaglandinsynthase inhibitors. Prostaglandins maintain the gastric mucosal integrity by stimulation of the secretion of mucous and by inhibition of acid secretion. Apart from COX-1, a related isoform is described: COX-2. There are substantial differences in the expression of these enzymes. COX-1 can be referred to as a housekeeping enzyme, which is constitutively expressed in most tissues and functions as a physiological enzyme regulating normal cellular processes. COX-1 plays a role in vascular homeostasis, kidney function, and thus in maintenance of gastric mucosal integrity. COX-2, however,

is undetectable under normal physiological circumstances and is strongly inducible during states of inflammation, causing pain. As rule of thumb COX-1 can be considered the 'good cop' and COX-2 the 'bad cop'.

In order to reduce the UGI risk associated with NSAID use, the selective COX-2 inhibitors (coxibs) were developed in the 1990s. By preferentially inhibiting COX-2, and to a lesser extent the house-keeper isoform COX-1, coxibs are effective pain relievers and importantly, associated with a lower risk of UGI complications compared with traditional, non-selective (ns)NSAIDs.[38-41]

Prevention of NSAID-induced gastroduodenal toxicity

To minimize the risk of UGI complications associated with NSAIDs and aspirin use, several guidelines recommend avoiding prescribing NSAIDs to patients with a high risk of UGI complications. Paracetamol or opioids should be sought as alternative treatments. Factors that put patients at increased risk of UGI complications are advanced age, a history of UGI complications and concomitant use of oral steroids, antiplatelets or anticoagulants. Unfortunately not all guidelines list the same risk factors.[42]

If an NSAID is nevertheless prescribed in a high risk patient, it is advised to either co-prescribe acid suppressive therapy in the form of proton pump inhibitors (PPIs), histamine-2 receptor antagonists or misoprostol, which act as gastroprotective agents (GPAs). Alternatively, the traditional nsNSAID can be replaced by the newly developed coxib, which is a safer alternative to nsNSAIDs regarding UGI safety.[38-41]

These strategies have been found to be equally effective with respect to UGI safety.[43-45] Adherence to two single drugs can be problematic, potentially limiting the effectiveness of co-prescription of GPAs. Additionally, GPAs in itself can cause complaints or adverse drugs events. This may have led to the enormous popularity of coxibs and its use increased rapidly between 2000 and 2004 in the Netherlands.[46] However, shortly after the coxibs were launched, they came under scrutiny as data from clinical trials pointed towards an increased risk of serious CV events.[47, 48] Since then, evidence of an increased risk of ischemic CV events associated with coxib use but also with use of nsNSAIDs has accumulated.[49-51] This resulted in the advice to restrict NSAID use to patients without CV comorbidity.[52-54]

Prevention of aspirin-induced gastroduodenal toxicity

Also in aspirin users at a high risk of developing UGI complications, adequate gastroprotection is needed. One Dutch prescription guideline currently provides recommendations.[54] The following aspirin users should receive gastroprotection; patients at the age of 60 years or older who concomitantly use two or more drugs known to increase the risk of UGI complications, or patients at the age of 70 years or older who concomitantly use a second drug known to increase the UGI risk, and all patients older than 80 years of age or with a history of UGI complications. The relevant drugs are defined as anticoagulants, NSAIDs, clopidogrel, prasugrel, heparin, corticosteroids, selective serotonin reuptake inhibitors, and spironolactone.[55]

PPIs, the most common co-prescribed GPA with aspirin and NSAID therapy, are considered a true blockbuster drug. The use of PPIs is increasing over time, but as PPIs became generically available, the annual costs decreased from 300 million euro's in 2006 to 200 million euro's in 2010 in the Netherlands (Figure 1.1, Figure 1.2).[11]

Outline of the thesis

This thesis is divided into four sections. The first section of this thesis provides a short summary of what is known on the risk of UGI complications related to NSAID use and aspirin use and the recommended strategies to lower that risk. (**Chapter 1**)

Section 2 and section 3 encompass the main body of the thesis and addresses the following issues:

Section 2: Use of NSAIDs and gastroprotection

1) How often are NSAIDs prescribed in West-European children and is there a difference between countries?
2) Are NSAIDs withheld from patients considered at a high risk of ischemic CV events?
3) Are gastroprotective strategies considered in patients at increased risk of developing UGI complications while on NSAID therapy?

Section 3: Safety assessment and prediction

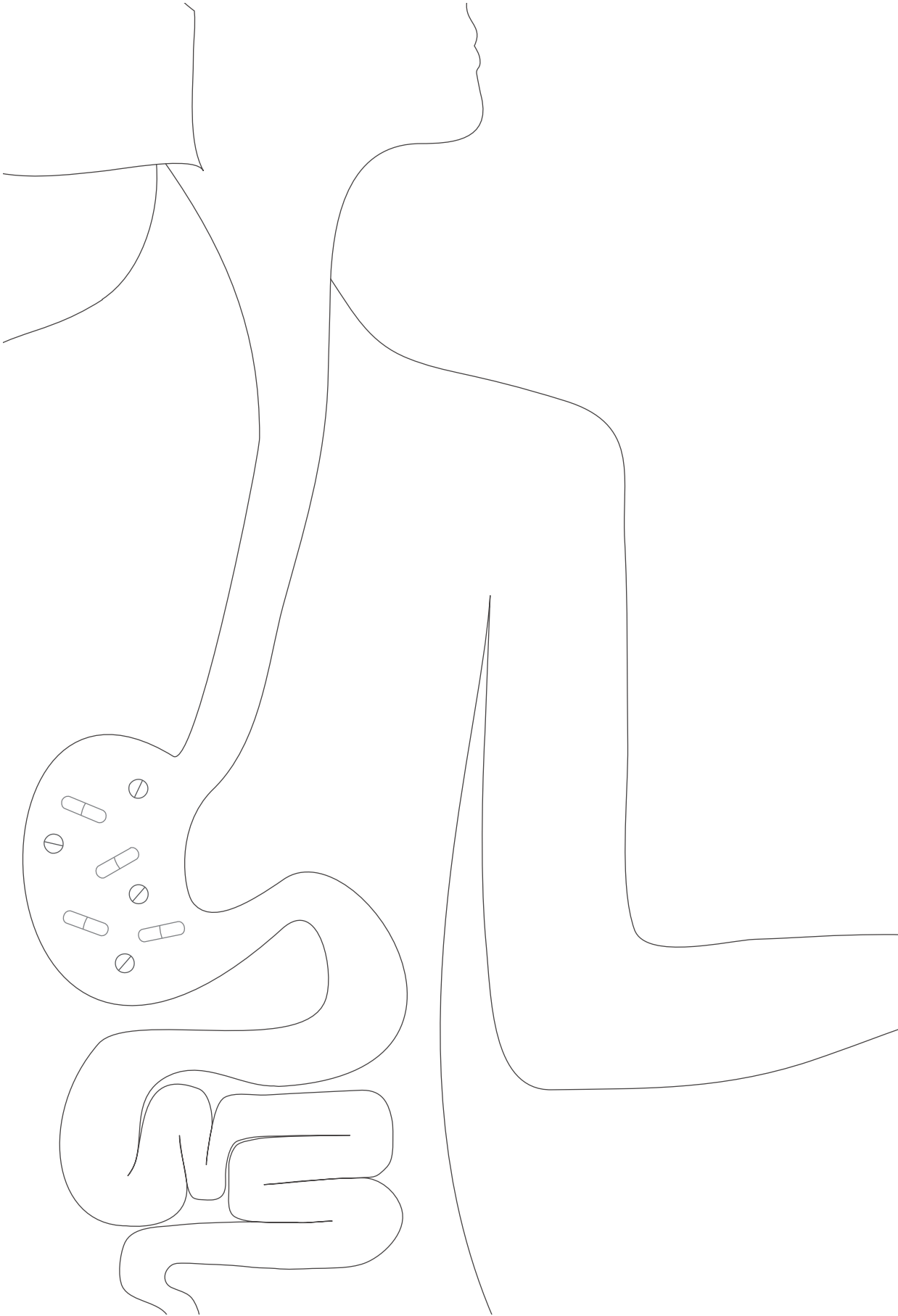
4) If gastroprotective agents are prescribed to NSAID users, what is the impact of being adherent to these agents?
5) Which of the two gastroprotective strategies is preferred for UGI safety; concomitant use of GPAs and nsNSAIDs or the sole use of coxibs?
6) What is the UGI risk for individual NSAIDs in daily clinical practice?
7) What are predictors for the occurrence of UGI complications among NSAID users?
8) What is the magnitude of UGI bleeding risk with low-dose aspirin use?
9) Is the interaction between PPIs and clopidogrel clinically relevant?
10) How does coding misclassification impact risk estimation of drug-related UGI bleeding?

In the second section of this thesis we explore the utilization patterns of NSAIDs and of gastroprotective strategies related to NSAID use. Drug utilization studies are an important mean to understand the prevalence of drug use in the population and in certain subpopulations. Understanding which drugs are highly consumed by which patients may allow for prioritization of resources and target studies into the efficacy and safety of these drugs. Drug utilization studies can thus provide insight in the public health impact of certain adverse drug events. In **Chapter 2** we describe the pattern of NSAID use in children and adolescents from four different countries in Europe and how NSAID use changes with age, gender and type of NSAID being used. In **Chapter 3** and **Chapter 4** an older population who receive NSAID prescriptions from their general practitioner (GP) is described. Risk factors for UGI complications were assessed for each NSAID user to determine which patients in the study were at an increased risk for NSAID-related UGI events. We then measured the prevalence of gastroprotective strategies in British, Dutch and Italian NSAID users to answer the question whether NSAID users at a high risk of developing UGI complaints were appropriately covered by gastroprotective strategies. The CV risk profile of patients consulting their GP with musculoskeletal (MSK) complaints was assessed as well as the UGI risk profile and the frequency of NSAID prescription. In patients at risk of CV events, the use of NSAIDs is contraindicated. In **Chapter 5** we looked at the influence of CV risk factors on the prescription and type of NSAIDs by Dutch GPs. In the

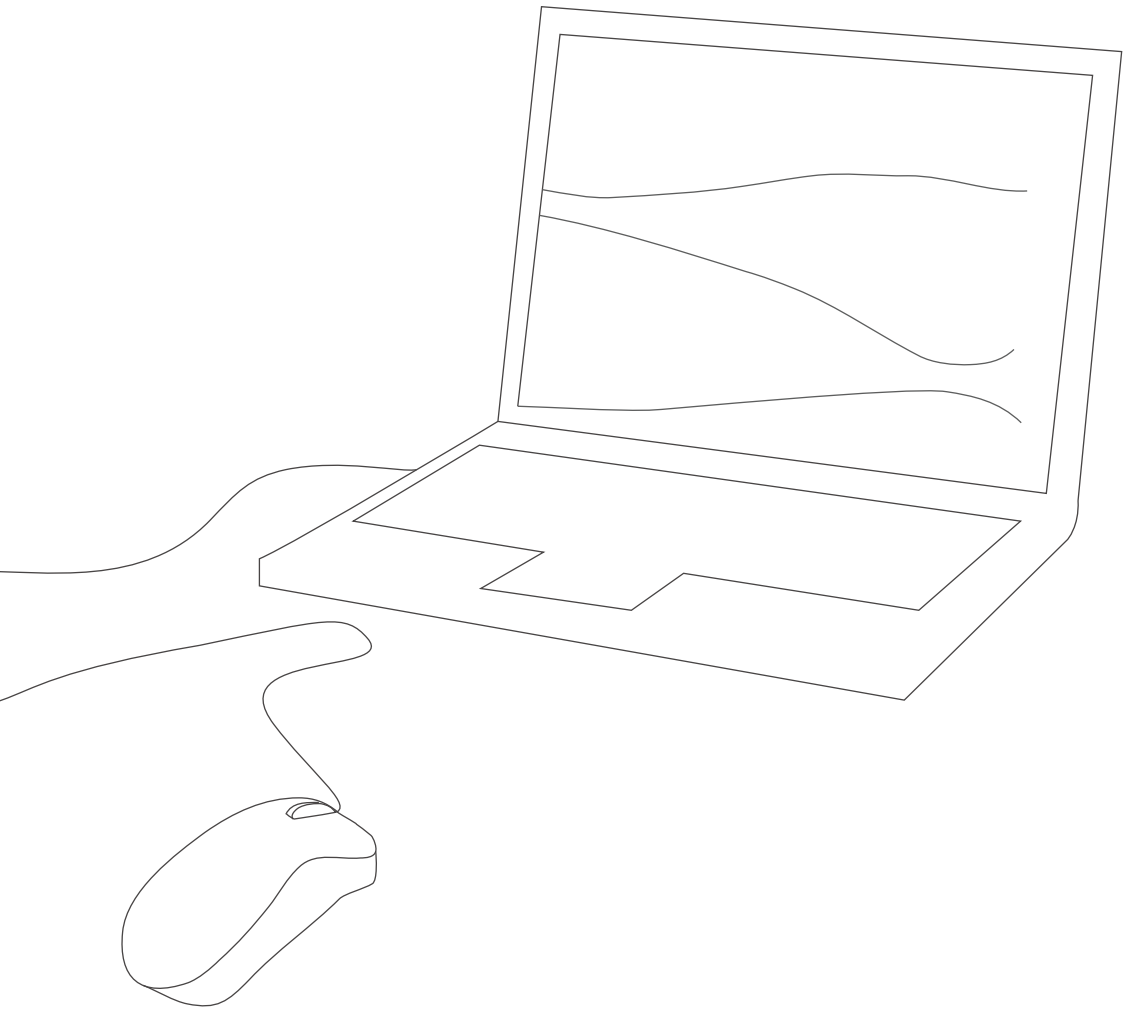
second section we shall see that many at risk NSAID users do not receive appropriate preventive strategies

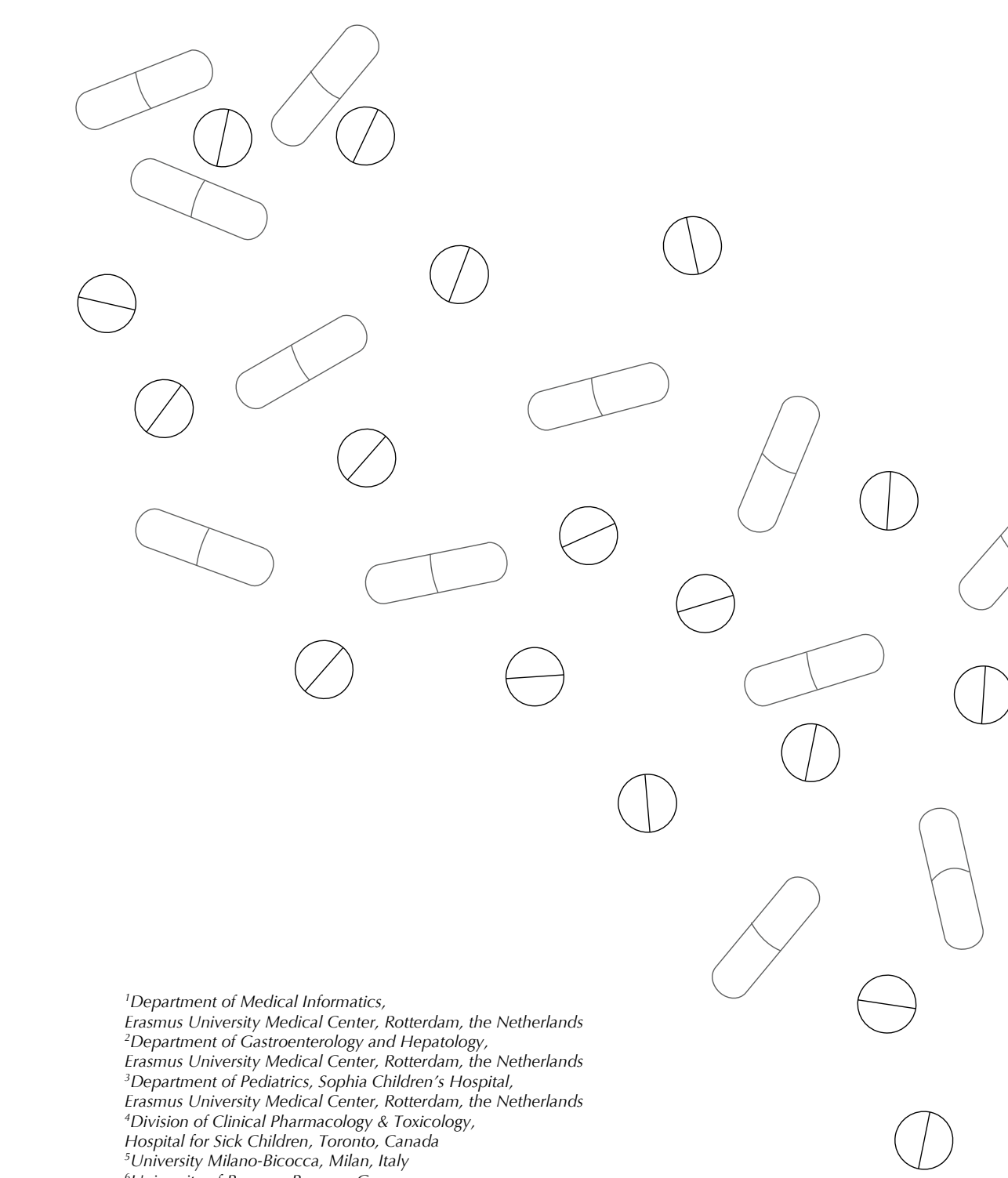
The third section explores the implications of not receiving the appropriate preventive prescribtions. Whether this is putting patients at risk for adverse drug events related to NSAID use. In the first chapters of the third section of the thesis we investigate to what extent therapy adherence influences the protective effect of gastroprotective agents (GPAs). The question is whether decreased adherence to GPAs increased the UGI risk attributable to non-selective (ns)NSAID use (**Chapter 6**) or coxib use (**Chapter 7**). In an additional study we explored the relative UGI safety of the two most commonly employed gastroprotective strategies: nsNSAIDs plus GPAs or the single use of coxibs. In **Chapter 8** we explore which identifiable subgroups of patients could benefit more from the first or the second gastroprotective strategy. Another area of interest is to understand which of the 70 individual NSAIDs yield the lowest risk regarding UGI complications. Prescribing NSAID compounds that have a better safety profile, thus less adverse UGI complications, but no loss of efficacy would be an easy intervention to decrease the UGI harm attributable to NSAID use. In **Chapter 9** we present data on individual NSAID UGI safety from a large nested case-control study. Numerous guidelines are published on gastroprotection with NSAIDs which all provide a risk stratification delineating whom to target with preventive strategies. In a prediction model presented in **Chapter 10** we sought to confirm the general believed risk factors of UGI complications in NSAID users. In addition we were interested in calculating the absolute risk of occurrence of UGI complications. In **Chapter 11** we summarize the current knowledge on the use of aspirin and the risk of UGI complications. A safety alert was given in 2009 by the European Medicines Agency (EMA) and the Federal Drug Agency concerning a potential relevant interaction between PPIs and clopidogrel, an antiplatelet agent. The hypothesis was that PPI co-administration with clopidogrel would lead to a reduction of the desired antiplatelet effect of clopidogrel. Subsequently this could result in an increased risk of CV endpoints, such a myocardial infarction (MI) or re-infarction. In the study described in **Chapter 12** we tested this hypothesis, and investigated whether a true association existed between the use of co-prescribed PPI and the risk of recurrent MI in clopidogrel users or whether the apparent association could be attributed to bias. Finally, we performed a validation study to determine the accuracy of codes used to identify patients with UGI bleeding. We performed this study using four electronic health care databases which use different coding terminologies. As second step, we implemented the results from the validation study and assessed whether the accuracy of codes could impact the risk estimate of UGI bleeding related to studied drugs, including low dose aspirin and the following two NSAIDs; indometacin and ibuprofen (**Chapter 13**).

The last and fourth section summarizes and discusses the main findings (**Chapter 14**). The studies in this thesis were conducted in large electronic healthcare record databases. The studies on adherence to GPAs and its impact on the risk of UGI complications with NSAID therapy described in Chapters 4, 6, 7 and 8 were conducted in the same primary care population originating from 3 GP databases located in the UK, the Netherlands and Italy. Three studies were performed within the framework of the Safety Of non-Steroidal anti-inflammatory drugs (SOS) project. This project was requested by the EMA with the aim of assessing the CV and UGI safety of NSAIDs in adults and children (Chapters 2, 9 and 10). The validation study was conducted in the context of the EU-ADR project(Chapter 13). This project aimed towards early safety detection to augment traditional pharmacovigilance systems by pro-active drug surveillance in a federation of eight European databases.



Use of NSAIDs and Gastroprotection





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Submitted

Chapter 2

Use of NSAIDs in children: the size of data platforms and their ability to assess potential serious safety issues

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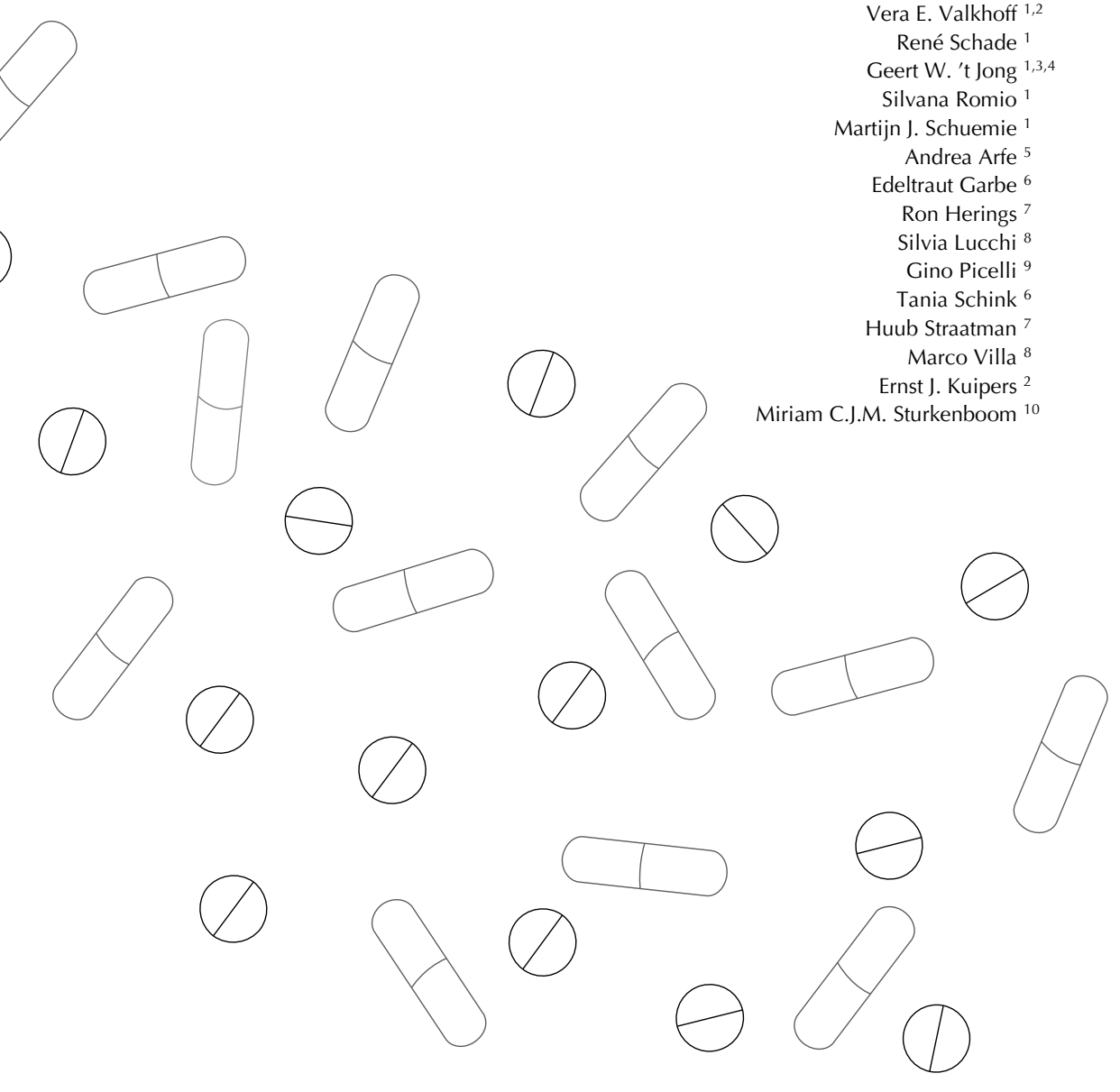

Abstract

Background

Little is known about the use and safety of non-steroidal anti-inflammatory drugs (NSAIDs) in children.

Aim

To investigate the utilization of NSAIDs in children from four European countries as part of the European-Commission funded Safety Of Non-Steroidal Anti-Inflammatory Drugs (SOS) project.

Methods

We calculated prevalence rates of NSAID use in children (0-18 years) from the following seven databases between 1999 and 2011: GePaRD (Germany), THIN (United Kingdom), IPCI and PHARMO (the Netherlands), OSSIFF, SISR, and PEDIANET (Italy). Prevalence rates of NSAID use were calculated as the number of users per 1000 persons per year and were stratified by age, sex, and calendar time. Sample size calculations were conducted to determine the amount of exposure time that would be required for NSAID safety studies in children.

Results

The source population in the SOS consortium comprised 7.7 million children with a total of 29.6 million person years of follow-up. Of those, 1.3 million children (17.3%) were exposed to at least one of 45 NSAIDs during follow-up. Overall prevalence rates of NSAID prescription in children differed across countries ranging between 4.4 (OSSIFF) to 197 per 1000 person years (GePaRD) in 2007. Two distinct patterns were observed. In three databases (GePaRD, THIN, Pedianet) NSAID prescriptions were most common below the age of four, and increased again from the age of 12 (GePaRD and THIN only). In the other databases the use of NSAIDs was low at young ages and increased beyond the age of eight in Germany, the United Kingdom and the Netherlands, but not in Italy. Only for ibuprofen (the most frequently used NSAID), enough exposure was available in the SOS platform to investigate a weak association - relative risk of 2 - between exposure and asthma exacerbation (the most common serious event).

Conclusions

Patterns of NSAID use in children were heterogeneous across the four European countries, with the highest prevalence of use in Germany. The SOS platform captures information on more than 1.3 million children who were exposed to NSAIDs. Nevertheless, the experienced exposure may not be enough to conclusively assess the safety of these drugs in children for many serious events of interest. Large-scale international collaboration is needed to increase sample size to study NSAID safety in children.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for their analgesic, antipyretic, and anti-inflammatory effects, even in children. NSAIDs were the tenth most frequently prescribed drug in the age group 2-11 years (33 users/1000 person years) and the sixth most frequently prescribed drug in age group 12-18 years (57 users/1000 person years) in a combined primary care database study conducted in Italy, the Netherlands and United Kingdom.[56]

The Safety of Non-steroidal Anti-inflammatory Drugs (SOS) project is a research and development project funded by the Health Area of the European Commission under the Seventh Framework Programme, with the aim to assess the cardiovascular and gastrointestinal safety of NSAIDs, in particular with respect to children. In the SOS project, data from clinical trials and observational studies have been investigated by literature review and meta-analysis. Furthermore, novel observational studies are conducted by linking seven databases from four European countries. The literature review revealed that safety of NSAIDs in children has not been adequately assessed in clinical trials nor post-marketing studies since most of these studies were too small and short to detect infrequent adverse events.[57, 58]

As one of the first steps in the SOS project we studied NSAID utilization in children to describe and compare patterns and assess power to study NSAID safety. For ten adverse events we investigated whether enough exposure was captured in the SOS platform to study NSAID safety in children and adolescents.

Methods

Data sources

Data for this study was obtained from seven longitudinal observational databases from four European countries involving more than 32 million patients. Three primary care databases and four hospital discharge or administrative databases provided data from Germany (DE), Italy (IT), the Netherlands (NL) and the United Kingdom (UK) (Table 2.1). All databases recorded demographics, diagnoses, and drug prescriptions. Participating databases contain a representative sample of the respective populations based on age and sex, and have been used previously for conducting scientific research on prescription patterns and disease frequency. The protocol for this drug-utilization study was approved by the databases' scientific and ethical advisory boards or regulatory agencies where applicable. The databases are described below and a brief overview of the participating databases is provided in Table 2.1.

German Pharmacoepidemiological Research Database (GePaRD)

GePaRD is a claims database and consists of claims data from four German statutory health insurance (SHI) providers. It covers about 14 million persons throughout Germany who have at any time between 2004 and 2008 been enrolled in one of the four SHIs. The database population represents approximately 17% of the German population. Available data contain demographic information and information on hospital discharges, outpatient physician visits, and outpatient dispensing of prescribed medications in the pharmacies. Hospital diagnoses are coded according to the German Modification of the International

Table 2.1: Characteristics of participating databases in SOS

Database	Country	Type of database	Diagnoses	Drugs	Study period	Pediatric study group (Age 0 to 18 years)	
						Persons	PY
GePaRD	Germany	Claims database	ICD-10-GM	ATC	2005 – 2008	2,992,087	7,056,919
THIN	United Kingdom	GP database	READ	BNF/ Multilex	1999 – 2008	1,261,668	5,198,351
IPCI	the Netherlands	GP database	ICPC and free text	ATC	1999 – 2011	250,296	618,479
PHARMO	the Netherlands	Record linkage system	ICD-9-CM	ATC	1999 – 2008	594,800	2,914,576
OSSIFF	Italy	NHS registry (claims)	ICD-9-CM	ATC	2000 – 2008	675,197	3,671,014
SISR	Italy	NHS registry (claims)	ICD-9-CM	ATC	2002 – 2009	1,744,525	9,111,635
Pedianet*	Italy	GP pediatric database	ICD-9-CM and free text	ATC	2000 – 2010	221,115	1,064,867
Total						7,739,688	29,635,841

**Age only up to 14 years.*
GP, general practice; NHS, National Health Service; 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;. PY, person years.

Classification of Diseases, 10th Revision (ICD-10 GM) with at least 4 digits.[59] Information on drug prescriptions is linked to a pharmaceutical reference database providing information on the World Health Organization's (WHO) anatomical-therapeutic-chemical (ATC) code[60], prescribed quantity (number of packages), prescription date, dispensation date, substance, product name, manufacturer, pack size, strength, defined daily dose (DDD), and pharmaceutical formulation.

The Health Improvement Network (THIN) database

THIN is a longitudinal database of primary care medical records from more than 10 million patients in the UK. Electronic medical records date back to 1985. Currently, the database has 3.6 million active patients registered. Data recorded in THIN include demographics, diagnoses, symptoms, life style information such as smoking or alcohol consumption, prescriptions, test results, height, weight, referrals to hospitals and specialists, and, on request, specialist letters and hospital discharge summaries. Diagnoses and symptoms are recorded using READ codes. Information on drug prescriptions is coded with MULTILEX product dictionary and British National Formulary (BNF) codes and is mapped to ATC codes.

Integrated Primary Care Information (IPCI) database

The IPCI database is a dynamic longitudinal primary care research database from NL initiated in 1992. Currently, it covers about one million people from 150 active general practices. Symptoms and diagnoses are recorded using the International Classification for Primary Care (ICPC[61]) and free text and hospital discharge summaries. Information on drug prescriptions comprises official label text, quantity, strength, prescribed daily dose and is coded according to the ATC classification.

PHARMO database

The PHARMO medical record linkage system is a population-based patient-centric data tracking system of 3.2 million community-dwelling inhabitants from NL. Data have been collected since October 1994. The drug dispensing data originate from out-patient-

pharmacies. Via the Dutch National Medical Register (LMR) hospital admissions are collected with ICD-9-clinically modified (CM). Information on drug prescriptions is coded according to the ATC classification.

OSSIFF database

In the Italian National Health Service (NHS), the Local Health Authority is responsible for the health of the citizens in a given geographical area, usually a province. In 2006, eight authorities have established a network named OSSIFF, accounting for a population of about 3.8 million people. Hospital diagnoses are coded according to ICD-9-CM. Prescriptions are coded according to the ATC coding system, and additionally prescription date, number of prescribed units, drug strength and the defined daily dose (DDDs) of the active entity are available.

Sistema Informativo Sanitario Regionale (SISR) database

In the Italian SISR database, data are obtained from the electronic healthcare databases of the Lombardy region. Lombardy is the largest Italian region with about nine million inhabitants, about 16% of the population of Italy. This population is entirely covered by a system of electronically linkable databases containing information on health services reimbursable by the NHS. The SISR database has complete population coverage and data is available from 2002. Via the ICD-9-CM dictionary and ATC classification, the database captures information on diagnoses from hospitalizations and drugs. Because OSSIFF covers a subset of patients covered by SISR, this database excluded the common subset of patients to avoid overlap.

Pedianet database

The Italian Pedianet database is a primary care pediatric database comprising the clinical data of about 160 family pediatricians (FPs) distributed throughout Italy. In Italy all children until the age of 14 years are registered with an FP. Pedianet has been built up since 1999. By December 2010, Pedianet database contained data on 370,000 children. Information on all drugs (date of prescription, ATC code, substance, formulation, quantity, dosing regimen, legend duration, indication, reimbursement status), symptoms and diagnoses are available in free text or coded by the ICD-9 system.[59]

Data extraction

Three defined data files were extracted from each database locally according to a prespecified format containing information on: (i) patient characteristics such as date of birth, sex, and registration date; (ii) NSAID prescriptions or dispensing (ATC code M01A) including duration of supply, and (iii) diagnoses and their corresponding date through ICD-10, READ, ICD-9, ICPC codes or free text.

Observation time

The observation time for each patient started 365 days after registration with a practice or health insurance system. For children who were born into the database, observation started at date of birth. The observation period ended at the earliest of the following dates: death, transfer out of the practice or insurance system, or last data collection. The study period varied between databases according to data availability (Table 2.1).

Data extraction from databases

In accordance with European data protection standards, neither personal identifiers nor other patient-level data were shared across countries. Data were extracted and processed locally by Jerboa© software, a software developed and validated at Erasmus University Medical Center in Rotterdam.[18] The Jerboa software calculated drug-utilization and disease-incidence measures for each database stratified by age, sex, and calendar time. The concept of a distributed data network with a common format of input files has been described previously.[18] The aggregated and de-identified data were stored centrally at a data warehouse (DW) in Milan, Italy. Assigned persons were allowed to gain access to the DW via a secured token, assigned to an Internet Protocol (IP)-address.

Events of interest for safety assessment

The pediatric part of the SOS project considered the following ten outcomes that are of clinical relevance in children: (i) asthma exacerbation; (ii) anaphylactic shock; (iii) upper gastrointestinal complications; (iv) stroke; (v) heart failure; (vi) acute renal injury; (vii) Stevens–Johnson syndrome; (viii) acute liver injury; (ix) acute myocardial infarction; and (x) Reye's syndrome.[62-70]

To extract the events of interest in the participating databases, the medical concepts were first mapped using the Unified Medical Language System (UMLS), a biomedical terminology integration system handling more than 150 medical dictionaries.[71] This process was needed as the clinical information captured by the different databases is collected using four different disease terminologies (ICPC, ICD-9, ICD-10, and READ codes) and free text in Dutch and Italian. For each medical concept, UMLS identified corresponding codes for each of the four terminologies. Subsequently, the codes were reviewed by a panel of medically trained investigators, feedback was obtained from the database holders, and the suggested list of codes was extracted in all databases. Extraction queries were reviewed in case of large, unexpected discrepancies. This iterative harmonization process enabled a more homogeneous identification of events across databases using different coding-based algorithms. This workflow was developed in the EU-ADR project and has been described in more detail elsewhere.[72]

Statistical analyses

Drug utilization measures

For each database, the prevalence rate of NSAID use was calculated by dividing the number of prevalent NSAID users by the person-time of observation, stratified by age, sex, calendar year, and calendar month. The reference calendar year was 2007. The person-time of NSAID exposure was calculated by using the duration of the prescription supply. Relative prevalence rates (in percentages) were calculated by dividing the absolute prevalence rate by the mean prevalence rate within each database for each calendar month and age year. Results were stratified by one-year and four-year age categories based on the guidelines of the International Conference of Harmonization: 0-< 2 years, 2-≤5 years; 6-≤11 years and 12-≤18 years.[73]

Incidence rates for events of interest

We calculated diagnosis incidence rates (IRs) per 100,000 person years for each of the events of interest for each database and performed direct standardization using the WHO World Standard Population as reference to account for age differences when comparing

the overall diagnosis rates (standardized IRs; SIRs).[74] We only considered the first recorded occurrence of the event of interest after a one year run-in period. When calculating the overall IR in the SOS platform the total number of events across databases was divided by the person time captured in all databases.

Required amount of drug exposure to detect safety signals

To determine the usability of the SOS database platform for the study of NSAID safety with respect to adverse events of interest in children, we calculated the person years of exposure required to detect a drug-event association over varying magnitudes of relative risks (RR), using RRs of 2 (weak association), 4 (moderate association), and 6 (strong association), a one-sided significance level $\alpha = 0.05$, and a power of 80% ($\beta = 0.2$). To estimate the required exposure for specific strengths of association we used a previously published sample size formula.[75] The required exposure time was compared with the person time exposed to ibuprofen to assess whether the database size is sufficient in current size, or expansion would be necessary for adequate evaluation of safety.

Results

Source population

The pediatric population of the SOS platform network comprised 7.7 million children and adolescents (0 to 18 years) contributing 29.6 million person years (PYs) of follow-up between 1999 and 2011 (Table 2.1). Of these PYs of follow-up, 11.5% were for children aged 0 to < 2 years, 20.8% for children aged 2 to ≤ 5 years, 31.5% for children aged 6 to ≤11 years and 36.3% for adolescents aged 12 to ≤ 18 years. Of the population, 51.4% was male. The database which contributed most person time was SISR, followed by GePaRD and THIN, although the period during which data were contributed varied considerably (Table 2.1).

Prevalence of NSAID use

Of the 7.7 million children and adolescents, 1,339,472 (17.3%) used NSAIDs for at least one day during the follow-up period. In GePaRD, 31% of children used NSAIDs, which is in contrast with lower percentages in SISR (2%), OSSIFF (3%), and IPCI (5%). A total of 45 NSAIDs were prescribed or dispensed with a total exposure of 61,739 PYs.

The prevalence rate of NSAID use per 1,000 person years was 56 - ranging from 4.4 (OSSIFF) to 197 (GePaRD) in 2007. Figure 2.1 shows that the annual prevalence of NSAID use varies extensively between age groups and countries. There were two distinct prescription patterns. The first pattern showed that the prevalence of NSAID use is relatively low in young children and substantially increased beyond 8 years of age for IPCI, PHARMO, OSSIFF and SISR. In contrast, the use of NSAIDs was most prevalent before the age of four in children for GePaRD, THIN and Pedianet. In GePaRD, prevalence rates reached values around 480 per 1000 PYs (48% of children) for three-year-olds in 2007. Prevalence rates decreased and were lowest for the age categories of thirteen and eight years for GePaRD and THIN, respectively. The prevalence rates increased thereafter. Figure 2.2 shows that the overall annual prevalence rates of NSAID use in 2007 were higher for females than for males, especially for THIN, IPCI and PHARMO. The sex distribution was equal for all databases until the age of ten, but the prevalence rates diverge after that age with higher rates for females in GePaRD, THIN, IPCI and PHARMO. Annual prevalence

of NSAID use was relatively stable over calendar time for most databases. There was a tendency of slightly decreasing prevalence rates after the year 2003 for OSSIF and SISR while prevalence rates were steadily increasing for THIN and GePaRD (data not shown).

Table 2.2: Required exposure time needed to investigate NSAID safety in children for ten potential adverse events with varying diagnosis incidence rates considering a weak, moderate or strong association

	IR	Weak association (RR = 2)			Moderate association (RR = 4)			Strong association (RR = 6)		
		Required exposure (PY)	Drugs n (%)	Expansion	Required exposure (PY)	Drugs n (%)	Expansion	Required exposure (PY)	Drugs n (%)	Expansion
Asthma exacerbation	82.12	9,788	1 (2.2)	0	1,499	4 (8.9)	0	669	6 (13)	0
Anaphylactic shock	4.29	187,358	0 (0)	4	28,687	1 (2.2)	1	12,809	1 (2.2)	0
Upper gastrointestinal complication	2.64	303,99	0 (0)	7	46,545	0 (0)	1	20,782	1 (2.2)	0
Stroke	2.07	388,41	0 (0)	9	59,471	0 (0)	1	26,554	1 (2.2)	1
Heart failure	1.57	511,927	0 (0)	12	78,384	0 (0)	2	34,998	1 (2.2)	1
Acute renal failure	1.40	573,919	0 (0)	13	87,875	0 (0)	2	39,236	1 (2.2)	1
Stevens–Johnson syndrome	0.56	1,438,097	0 (0)	34	220,194	0 (0)	5	98,315	0 (0)	2
Acute liver failure	0.46	1,741,369	0 (0)	41	266,629	0 (0)	6	119,048	0 (0)	3
Acute myocardial infarction	0.12	6,918,411	0 (0)	162	1,059,310	0 (0)	25	472,974	0 (0)	11
Reye's syndrome	0.02	42,663,537	0 (0)	998	6,532,413	0 (0)	153	2,916,676	0 (0)	68

IR, incidence rate (per 100,000 PYs); RR, relative risk; PY, Person years.
Drugs n (%): Number of drugs that have enough PY of exposure in the SOS platform to detect a potential signal for the respective event of interest (in brackets the proportion of NSAIDs with enough PY exposure of all 45 NSAIDs).
Expansion: magnitude of enlargement of PY exposure in the SOS platform necessary for assessment of each safety outcome for ibuprofen (exposed person time 42,768 PY) given the specified relative risk that should be detected with $\alpha < 0.05$ (one-sided) and $ß = 0.20$.

Monthly prevalence rates of NSAID use showed that prescriptions were most common in February and less frequent in summer months. This seasonal pattern of NSAID use in children and adolescents was especially seen in GePaRD (August: 19; February: 45), THIN (August: 7.5; February: 14), and Pedianet (August: 2.1; February: 10 – all numbers per 1000 person months in 2007) (Figure 2.1). Mean duration of NSAID prescription or dispensing was highest in THIN and SISR (15.4 and 15.8 days) and lowest in Pedianet (4.8 days).

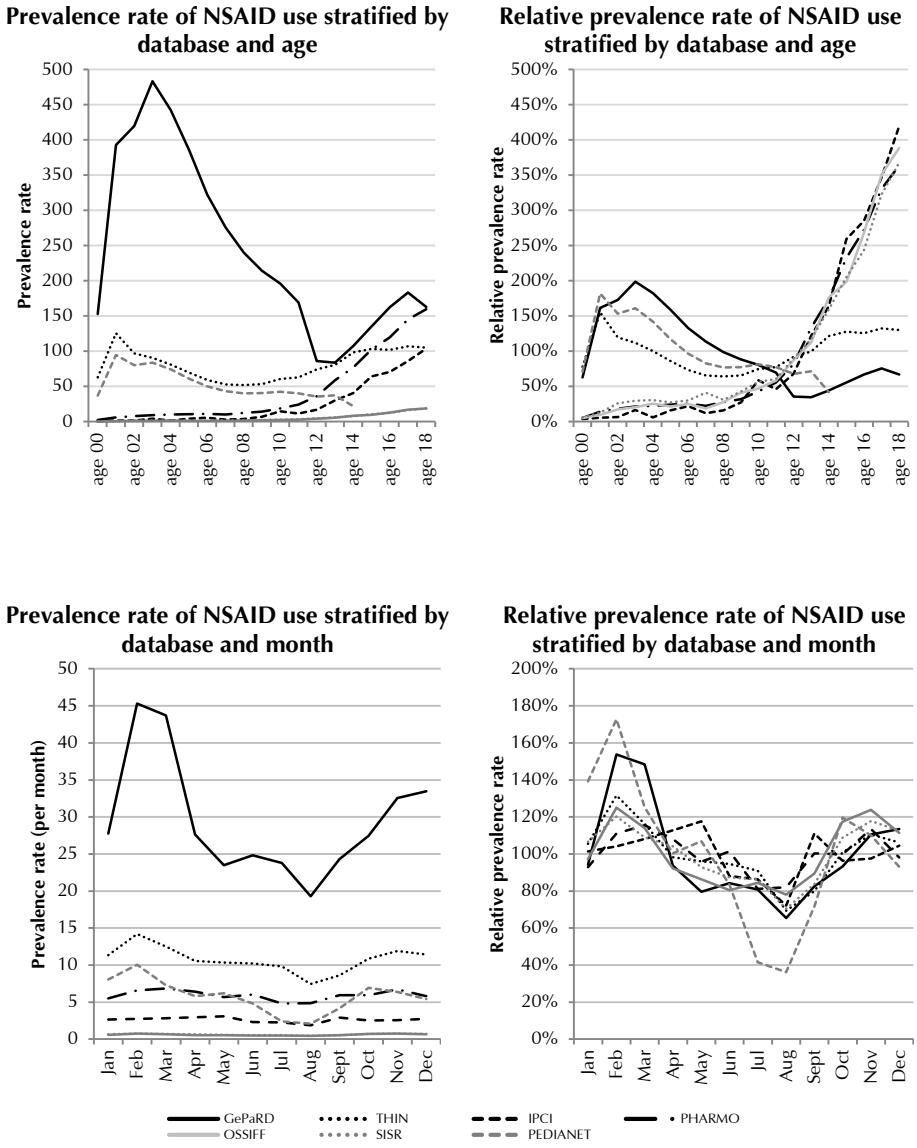

Figure 2.1: Prevalence rate and relative prevalence rate stratified by database and age. Prevalence rates are per 1000 person years for 2007 (upper panel). Prevalence rate and relative prevalence rate stratified by database and calendar month. Prevalence rates are per 1000 person months for 2007 (lower panel).

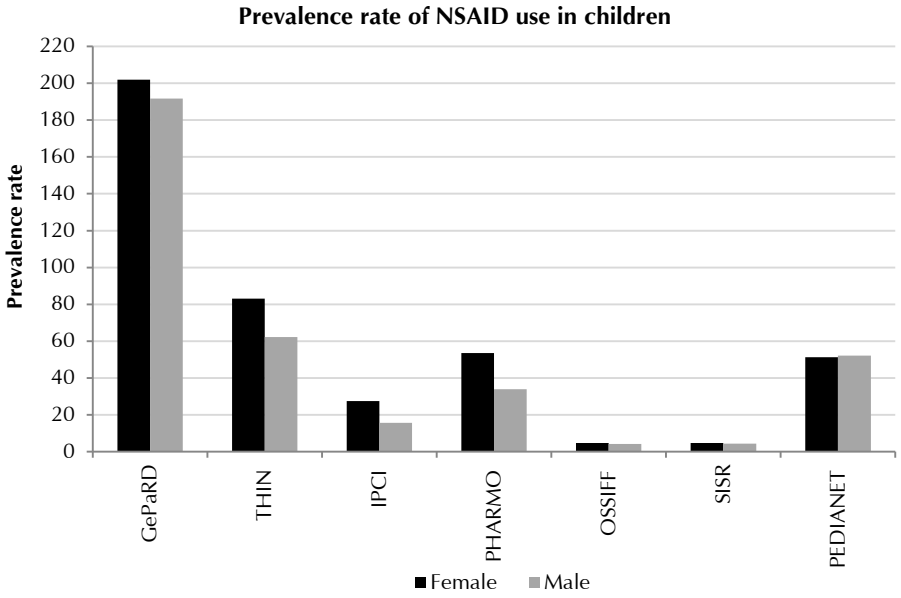

Figure 2.2: Prevalence rate of NSAID use, stratified by database and gender. Prevalence rates are per 1000 person years for 2007.

Specific NSAIDs

On average, 26 NSAIDs were prescribed or dispensed per database with a range between 19 for IPCI and 32 for OSSIFF. Of those, ibuprofen was the most frequently used NSAID, with 69.3% of total NSAID exposure. Diclofenac and naproxen were also available in all databases and captured respectively 13.0% and 6.3% exposed person years. Distribution of NSAID use was heterogeneous between countries. Ibuprofen was most frequent in GePaRD, THIN and Pedianet, but nimesulide was most frequent in the other two Italian databases, followed by ketoprofen and naproxen. Apart from ibuprofen and ketoprofen, morniflumate was common in Pedianet. In the Netherlands, diclofenac, naproxen and ibuprofen were most common. Nimesulide, morniflumate and niflumic acid were only available in Italy, while lonazolac and parecoxib were only available in the GePaRD database (Germany), and etodolac, fenbufen, and fenoprofen were only prescribed in THIN (UK). In IPCI and PHARMO (both from NL) a combination diclofenac and misoprostol (a prostaglandin E1 analogue used for gastroprotection) was frequently prescribed to adolescents, whereas this was not common in other databases (figure not shown). In all databases except OSSIFF and SISR, the top-3-used NSAIDs encompassed more than 80% of the total person years of NSAID exposure. Proprionic acid derivates (such as ibuprofen; ATC-5 digit level M01AE) were by far most common in all databases except OSSIFF and SIRS. These latter two showed relatively high prescription rates for coxibs (12% and 8.3% respectively, as compared with an average of 1.2% for the other database).

Required exposure time for NSAID safety assessment in children

Table 2.2 shows the number of NSAIDs that have enough exposure to detect weak (RR = 2), moderate (RR = 4) or strong (RR = 6) associations for the ten adverse events of interest. The stronger the association and the more common the event to be studied, the lower is

the required exposure time for a specific NSAID substance. Thus, the lower the required exposure time for a specific NSAID substance the higher is the number of drugs that can be studied, which is expected from the power calculations. Taking asthma exacerbation as example with the highest IR of 82/100 000 PYs, only one NSAID (ibuprofen) had enough person time exposure (9,788 person years or more) to detect a weak association (RR = 2). To assess a moderate (RR = 4) or a strong (RR = 6) association with asthma exacerbation, four and six NSAID substances had enough person time exposure, respectively. None of the drugs generated enough exposure time to detect a strong association for the following rare events: Stevens-Johnson syndrome, acute liver failure, acute myocardial infarction, and Reye's syndrome. The SOS platform would require 998 times as much exposed person time in order to study a weak association between ibuprofen (the most commonly used NSAID) and Reye's syndrome (the most infrequent adverse event) (Table 2.2). Table 2.3 shows for which events of interest sufficient person time is available to study a strong association (RR = 6) for the most frequently used NSAIDs.

Table 2.3: Is sufficient exposure time available in the SOS platform to investigate the particular event of interest given an expected relative risk of six stratified by NSAID substance?

			Strong association (RR=6)									
	Sum PYs	% PYs	Asthma exacer-bation	Anaphy-lactic shock	Upper gastro-intestinal complication	Stroke	Heart failure	Acute renal failure	Stevens–Johnson syndrome	Acute liver failure	Acute myocardial infarction	Reye's syndrome
Total NSAIDs	61,739	100	X	X	X	X	X	X				
Ibuprofen*	42,768	69.3	X	X	X	X	X	X				
Diclofenac#	8,000	13.0	X									
Naproxen^	3,878	6.3	X									
Mefenamic acid	2,297	3.7	X									
Ketoprofen&	946	1.5	X									
Nimesulide	925	1.5	X									
Piroxicam	519	0.8										
Indometacin	440	0.7										
Meloxicam	328	0.5										
Celecoxib	258	0.4										
Rofecoxib	247	0.4										
Etoricoxib	218	0.4										

PY, Person years.
X: indicates that enough person-time is available for detection of a RR of 6 with $\alpha < 0.05$ (one-sided) and $\beta = 0.20$.
**including combinations with ibuprofen; #including combinations with diclofenac; ^including combinations with naproxen; &including combinations with ketoprofen.*

Discussion

In the SOS project, the combined source population of children and adolescents (0 to 18 years of age) from seven databases from four European countries involved 7.7 million children and adolescents and generated 29.6 million person-years of observation between

1999 and 2011. Of these, 1.3 million children received NSAID prescriptions during the studied periods in the respective databases. Overall, 56 children/adolescents out of 1000 received an NSAID prescription per year. This varied largely between 4 per 1000 in OSSIFF to 197 per 1000 in GePaRD in the pediatric population. In general, one could conclude that the annual prevalence of prescribed NSAIDs is lowest in Italy, followed by the Netherlands, the United Kingdom and highest for Germany. Also, in all databases except the Italian ones, females received more NSAID prescriptions than males, mainly related to diverging prevalence rates in adolescence (Figure 2.2). When considering the age-specific prevalence rates, the high rates in the very young for the German database GePaRD compared with the other European countries are striking (Figure 2.1). For GePaRD values reach prevalence rates greater than 480 (48% of children in one year) for 3-year-olds. In Germany, United Kingdom and Italy, ibuprofen is the drug of choice beside paracetamol (acetaminophen) for fever in children[76-78], whereas in the Netherlands paracetamol is considered first.[79] In THIN and Pedianet prevalence rates were also higher in children below the age of 4, whereas for other databases prevalence rates were steadily increasing with age and peak at the age of 18. In the same three databases with high NSAID use in young children a clear seasonality is seen with highest NSAID use in winter, probably related to prescription of NSAIDs to young children for fever and fever-like symptoms (Figure 2.1). Between countries major differences exist in the type of NSAID that was used. Ibuprofen was the most frequently used NSAID (69.3%). Safety and efficiency of ibuprofen in children are much more extensively studied than (most) other NSAIDs.[64-67]

Two databases from the Netherlands were included in this study, allowing a comparison between populations that should have similar characteristics. Since PHARMO is a pharmacy dispensing database that captures over-the-counter (OTC) dispensations of NSAIDs, the prevalence of NSAID exposure was slightly higher for PHARMO than for IPCI, especially in adolescents. Three Italian databases participated in the SOS platform and the prevalence rates for different ages of NSAID use were very similar for OSSIFF and SISR, but not for Pedianet (Figure 2.1). This could be related to the fact that Pedianet captures all prescriptions, whether reimbursed or not, plus recommendations on NSAID treatment made by pediatricians, while OSSIFF and SISR contain only the reimbursed NSAID dispensing.

Although the SOS platform appears to provide a unique opportunity to study the safety of NSAIDs in a large number of children and adolescents, we showed that the data are still too limited to study the safety of specific NSAID substances or the safety of NSAIDs in general for rare adverse drug reactions. Only for ibuprofen enough exposure time was available in the platform to investigate the risk of asthma exacerbation (the most common event) for a 'weak association' with a RR of 2. Data accumulation in platforms like SOS and others is of utmost importance for the safety evaluation of drugs in adults and children. The coming decade is likely to bring enormous expansion of available health care records, and advancement of data mining and harmonization methods. Both the European Medicines Agency(EMA) and the US Food and Drug Administration(FDA) invest in infrastructure and knowledge expansion in this field. However, our study shows how difficult it is to study safety in children, when compared with adults. Because of lower drug consumption – fortunately – use of these platforms for adequate drug safety surveillance is more challenging, as are many aspects of drug research in children. This should emphasize the responsibility as researchers, clinicians, and policy makers to facilitate high quality research in this vulnerable patient group through funding, scholarship, education and collaboration.

Limitations

Firstly, our study may not have captured all NSAIDs, since they are also available as over-the-counter drugs in all four countries. Therefore, the consumption of NSAIDs will be underestimated in the current drug-utilization study. We assume, however, that the underestimation would be minor since most parents may be reluctant to administer drugs to their children without having consulted a health care professional. In addition, only prescribed NSAIDs are (partly) reimbursed, leading to the preference of prescribed NSAIDs over freely available NSAIDs. Our observation that rates were low in August could be related to the summer holiday season, in which children are not visiting the primary care physician or pharmacy. Secondly, we only used diagnosis codes for identification of pediatric events of interest. We did neither use laboratory values, medical images nor procedures for event measurement, therefore potentially missing some events. We expect the amount of misclassification very minor since most patients with a confirmed diagnosis from these examinations would have a diagnosis code entered in the participating databases, as this is important for reimbursement.

Thirdly, we may have overestimated the possibility of safety assessment by only considering the total person time of NSAID exposure, but not yet other study design issues such as gap lengths between subsequent NSAID prescriptions, switching between different substances, or a new, incident NSAID user-design which avoids hazards of biases related to prevalent users.[80] The incident NSAID user-design will further delete users from the cohort thereby further reducing exposure time for the NSAIDs. Therefore, for the SOS studies to overcome the 'limited' resources, we will consider case-only designs, such as case-crossover or self-controlled case series, to study the risks of pediatric outcomes of interest.[81] Besides eliminating confounding by fixed covariates, such as gender and genetics, such designs have potentially more power to detect safety issues than nested case control studies and are comparable to cohort studies when the exposed time is short compared with the observation period.[82] Moreover, when unmeasured time-independent confounders are present, self-controlled case series improve the estimates in terms of power when compared with cohort studies.

In conclusion, NSAID use is common in children and utilization patterns varied between Germany, Italy, United Kingdom, and The Netherlands. There is a clear need to study NSAID safety in children. Although the SOS platform captures information on a large number of young NSAID users (1.3 million) the data is very sparse to study NSAID safety of rare events. International collaboration is needed to adequately study NSAID safety in children.

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Chapter 3

Time-trends in gastroprotection with NSAIDs

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Abstract

Background

Preventive strategies are advocated in patients at risk of upper gastrointestinal (UGI) complications associated with non-steroidal anti-inflammatory drugs (NSAIDs).

Aim

To examine time-trends in preventive strategies.

Methods

In a study population comprising 50,126 NSAID users ≥ 50 years from the Integrated Primary Care Information database, we considered two preventive strategies: co-prescription of gastroprotective agents and prescription of a cyclooxygenase-2-selective inhibitor. In patients with ≥ 1 risk factor (history of UGI bleeding/ulceration, age > 65 years, use of anticoagulants, aspirin, or corticosteroids), correct prescription was defined as the presence of a preventive strategy, and under-prescription as the absence of one. In patients with no risk factors, correct prescription was defined as the lack of a preventive strategy, and over-prescription as the presence of one.

Results

Correct prescription rose from 6.9% in 1996 to 39.4% in 2006 (p-value < 0.01) in high-risk NSAID users. Under-prescription fell from 93.1% to 59.9% (p-value < 0.01). In the complete cohort, over-prescription rose from 2.9% to 12.3% (p-value < 0.01).

Conclusions

Under-prescription of preventive strategies has steadily decreased between 1996 and 2006; however, 60% of NSAID users at increased risk of NSAID complications still do not receive adequate protection.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the world's most frequently prescribed medications for arthritic and inflammatory conditions, but their use increases the risk of upper-gastrointestinal (UGI) toxicity. The effects range from mild UGI symptoms (e.g. dyspepsia) to severe complications, such as peptic ulcers and UGI hemorrhage, perforation or pyloric obstruction, which sometimes result in hospital admission and death. The incidence of these serious UGI adverse events is approximately 1.5% - 2.0% per year of therapy[83-85], four times higher than in non-users.[28, 29]

Several evidenced-based guidelines have been proposed to reduce the burden of UGI events attributable to NSAID use.[53, 86-89] Preventive strategies in particular include (i) substituting COX (cyclooxygenase)-2-selective inhibitors (coxibs) for a non-selective (ns)NSAID; and (ii) combining an NSAID with so-called gastroprotective agents (GPAs), including proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H_2RAs), and misoprostol, a synthetic E1 prostaglandin analogue.[53, 86-92]

The first method involves prescribing a coxib instead of a nsNSAID. The gastrointestinal toxicity caused by nsNSAIDs mainly arises from inhibition of COX-1 isoform.[93] Coxibs were developed to improve the UGI safety profile by preferentially inhibiting the inducible COX-2 isoform of the COX enzyme, which is involved in the desired anti-inflammatory effect. Although coxibs have been shown to be as effective as nsNSAIDs for relieving pain and do reduce the risk of UGI complications[38-41], cardiovascular toxicity emerged unexpectedly during their post-marketing studies[38, 47-49] This led to the voluntary withdrawal of two coxibs: rofecoxib in September 2004 and valdecoxib in April 2005.[94]

The second preventive method advocated in NSAID users is co-prescription of GPAs as they have been proven to reduce the incidence of NSAID-induced ulcer complications.[84, 91, 95]

Only patients with high risk of NSAIDs-related UGI complications require gastroprotective measures as a prophylactic intervention. Although different evidenced-based guidelines provide slightly different definitions of such high-risk patients, all designate advanced age, a medical history of UGI events, serious co-morbidity, and concurrent administration of anticoagulants and corticosteroids as considerable risk factors.[53, 86-88] The guidelines are less consistent with regard to some other possible risk factors, such as high doses or the use of multiple NSAIDs[53, 87, 88], infection with *Helicobacter pylori*[53, 88], or concurrent use of selective serotonin reuptake inhibitors (SSRIs).[87, 88]

Although the need for preventive strategies is recognized, correct adherence to this guidelines-supported advice remains low in daily clinical practice: a review showed that most patients (76%) with one or more risk factors had not been assigned a recommended preventive strategy.[96] This is presumed to be the major explanation for the observation that, even though the prevalence of *Helicobacter pylori* is steadily decreasing in Western countries, the incidence of peptic ulcer complications has not changed over the past 20 years.[24] Other studies have reported a tendency of prescribing preventive strategies to patients at low risk (up to 66%).[97-100] Although extensive data are available on the use of preventive strategies in NSAID users, little is known on how the prescription of these strategies was influenced by time (calendar year) and the withdrawal of rofecoxib.

The implementation of future guidelines would be improved by better insight into (i) the adherence of general practitioners to the guidelines, and (ii) how time and rofecoxib

withdrawal influenced the prescription behavior of preventive strategies by general practitioners. To examine time-trends in and predictors of preventive strategies in day-to-day practice among older NSAID users, we performed a population-based cohort-study, using data from a Dutch general practitioner database between 1996 and 2006. We also studied the possible influence of time and rofecoxib withdrawal on the observed trends.

Methods

Study design

A dynamic cohort study was conducted among incident NSAID users aged ≥ 50 years.

Source of data

The data used were contained in the Integrated Primary Care Information (IPCI) database, which is a dynamic general practitioner research database containing the longitudinal computer-based medical records of currently 1.2 million patients in the Netherlands. The IPCI database was set up in 1992 since when it has greatly expanded. The IPCI population has the same gender and age distribution as the Dutch general population.[101]

In the Dutch health care system, all citizens are registered at a GP practice, which acts as a gatekeeper in a two-way exchange of information with secondary care. The medical record of each individual patient can therefore be assumed to contain all relevant medical information. To ensure completeness of the data further, participating GPs are not allowed to use additional paper-based medical records.

Data held within the database comprise not only demographics, symptoms, and diagnoses (using the International Classification for Primary Care (ICPC[61]) and free text), but also referrals, clinical and laboratory findings, and hospitalizations. Information on drug prescriptions comprises their official label text, quantity, strength, ICPC-coded indication, prescribed daily dose, and the Anatomical Therapeutic Chemical (ATC[60]) classification code.

The IPCI database complies with European Union guidelines on the use of medical data for medical research and has been proven valid for pharmaco-epidemiological research. Extensive details on the database have been reported elsewhere.[102] The Scientific and Ethical Advisory Board of the IPCI project approved the study design and use of the data.

Study cohort

The source population consisted of all patients aged 50 years and over, whose data had been contributed to the IPCI database between January 1996 and December 2006, and who had at least one year of valid database history before the date of study entry. This 12-month period was required to allow assessment of baseline characteristics and inclusion and exclusion criteria of all study subjects at the time of prescription.

Within the source population, we identified all patients who newly started (no use in the previous six months) on nsNSAIDs, coxibs, or high dose aspirin (> 325 mg/day) during the study period and had no history of a gastrointestinal tract neoplasm, alcohol abuse, chronic liver disease, inflammatory bowel disease, or a coagulopathy. Patients using only topical NSAIDs were excluded based on the assumption that the UGI harm was limited. As the focus of this study was to evaluate the use of prophylactic strategies in naive

NSAID users, only the first NSAID prescription of a patient was considered. The first day of NSAID prescription was defined as the index date. To prevent overestimation of the number of patients receiving a preventive strategy, we excluded patients who had been given PPI, misoprostol, or H_2RA in the six months prior to the index date.

Identification of high-risk patients

Based on several international guidelines on the prevention of NSAID-related UGI complications[53, 86-89], five risk factors were used to identify NSAID users at high risk of UGI complications (risk set 1: (i) a history of UGI bleeding/ulceration; (ii) concurrent use of anticoagulants; (iii) concurrent use of antiplatelets (aspirin ≤ 325 mg/day); (iv) concurrent use of oral glucocorticoids (equipotent dose of ≥5 mg prednisone); and (v) age ≥ 65 years). As several additional risk factors can be of relevance in defining high-risk NSAID users, we extended this first list of risks with four extra conditions, identified by the Dutch guideline[88]: (i) diabetes mellitus; (ii) heart failure; (iii) a high NSAID dose (> two times the defined daily dosage (DDD)[60]); and (iv) concurrent use of SSRIs, effectively composing a second list (risk set 2). All risk factors were retrieved from the IPCI database by electronic searches in all data that was available before or at the index date. A previous medical history of UGI bleeding/ulceration was validated manually.

Outcome

We defined a preventive strategy as: (i) the use of a coxib, or (ii) co-prescription of GPAs (H_2RA, PPI, or misoprostol; either co-prescribed or the fixed combination with diclofenac (Arthrotec)) within two days of the index NSAID to proxy preventive use. This proxy has been shown to have a positive predictive value of approximately 85-90% in the IPCI database.[103]

The primary outcomes of interest were *correct prescription*, *over-prescription*, or *under-prescription* of preventive strategies at the index date. Correct prescription was defined as use of a preventive strategy in high-risk NSAID users and no use in low-risk patients. Under-prescription was defined as the absence of a preventive strategy in high-risk NSAID users. Over-prescription was defined as the presence of a preventive strategy in low-risk NSAID users. Consistent with evidence from randomized controlled trials, we considered co-prescription of a PPI with a coxib in high-risk users as correct prescription.[104, 105]

To avoid doubts about the need of preventive strategies in groups at the edge of the definitions, we also performed a subgroup analysis using only patients at high or very high risk of NSAID-related UGI complications. Patients with at least one risk factor were defined as high-risk NSAID users, whereas NSAID users at very high risk comprised persons ≥ 75 years *or* with a prior history of UGI complications. A further subgroup analysis was made in this cohort of very high risk persons by restricting to persons with a previous history of UGI complications.

To test whether the withdrawal of rofecoxib in 2004 was followed by an increase in under-prescription of preventive strategies in patients at risk of NSAID-related UGI complications, under-prescription rates were measured in three successive study periods: study period 1 (one year prior to the withdrawal of rofecoxib; 1 October 2003 - 31 September 2004), study period 2 (one year after the withdrawal of rofecoxib; 1 October 2004 - 31 September 2005), and study period 3 (1 October 2005 - 31 September 2006).

Analytic methods

Baseline characteristics were compared between high- and low-risk groups using a χ^2-test for dichotomous variables and independent t-test for age as a continuous variable. Within high-risk users, univariate and multivariate analyses of potential predictors (such as gender, UGI risk factors, number of UGI risk factors, year of index-prescription, number of co-medications, and type of NSAID) of receiving a preventive strategy were conducted to evaluate which risk factors are considered by general practitioners when deciding whether or not to prescribe a gastroprotective strategy. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analysis. Under-prescription rates in the different study periods around rofecoxib withdrawal (2 vs. 1 and 3 vs. 1) were compared using a χ^2-test. Linear regression was conducted to investigate the trend of correct, over- and under-prescription between 1996 and 2006. All analyses were performed using SPSS version 16 (SPSS Inc, Chicago, IL).

Results

Study cohort

Within the source population of 154,518 people aged 50 years and over, we identified 55,962 incident NSAID users without any of the exclusion criteria. Of these, 5,836 used GPAs in the previous six months and were excluded. In total, 50,126 patients were included in the cohort. The median age of the study population was 63.1 (SD: 10.7) years; 56.9% were women. Baseline characteristics are described in Table 3.1.

Twenty-six different types of NSAIDs were prescribed, diclofenac accounting for the highest number of prescriptions (38.8%), followed by ibuprofen (16.8%) and naproxen (15.7%).

Risk factors in NSAID users

Table 3.1 shows that 28,441 patients (56.7% of the study population) had no NSAID-related UGI risk factor and were therefore defined as low-risk NSAID users. Individuals with at least one risk factor (43.3%) were defined as high-risk NSAID users; 81.6% of them had one risk factor and 18.4% had two or more risk factors. Age above 65 years was the most frequent (39.7%) of the NSAID-related UGI risk factors, followed by concomitant use of antiplatelets (8.6%), and diabetes mellitus as co-morbid condition (7.5%).

Diabetes mellitus and heart failure were more prevalent among high-risk users than among low-risk users ($P < 0.001$). A high NSAID dose was rare, but significantly more prevalent among low-risk users than among high-risk users (2.4% vs. 1.7%, $P < 0.001$).

Preventive strategies

In total, 11.3% of all NSAID users received a preventive strategy in the form of a GPA. Excluding Arthrotec, PPIs were the most common co-prescribed GPAs (77.1%), followed by H_2RA (22.1%) and misoprostol (0.7%). Only 4.0% of 327 users of prophylactic H_2RAs were prescribed the recommended double dosages for UGI complication prophylaxis.

The use of coxibs and Arthrotec was more prevalent among high-risk users (coxibs: 7.5% vs. 4.0%, $P < 0.001$; Arthrotec: 10.6% vs. 6.7%, $P < 0.001$), whereas low-risk users were more likely to receive a nsNSAID (88.2% vs. 80.7%, $P < 0.001$). Nearly 17% of all NSAID users received a preventive strategy (GPA or coxib), which was significantly more

prevalent in NSAID users at high-risk than in low-risk NSAID users (21.9% vs. 12.7%, $P < 0.001$).

Of all high-risk patients, those with a history of UGI complications (OR 4.0; 95% CI 2.9-5.4) or who concomitantly used systemic steroids (OR 3.7; 95% CI 2.5-5.6) had the highest chance of being prescribed a preventive strategy (Table 3.2). Despite some guidelines identifying diabetes mellitus, heart failure, high NSAID dose, or the use of SSRI as risk factors for NSAID-related UGI complications, these risk factors did not increase the odds of receiving preventive strategies. The odds of receiving a preventive strategy increased with the number of NSAID prescriptions on the same day (data not shown), and over calendar time (Table 3.2). The likelihood of receiving a preventive strategy was the highest for prescriptions of indometacin (OR 3.1; 95% CI 1.9-5.2) and ketoprofen (OR 2.5; 95% CI 1.2-5.5) and the lowest for carbasalate calcium (OR 0.3; 95% CI 0.1-0.8) (Table 3.2).

Table 3.1: Baseline characteristics and index non-steroidal anti-inflammatory drug prescription of the study population

	Total n (%)	High-risk patients n (%)	Low-risk patients n (%)	P-value
Total	50,126 (100)	21,685 (43.3)	28,441 (56.7)	
Age (mean±sd)	63.14 (10.7)	72.99 (8.3)	55.62 (4.2)	<0.001
Gender (% male)	21,621 (43.1)	8666 (40.0)	12,955 (45.6)	<0.001
Type of index-prescription:				
Coxib	2778 (5.5)	1632 (7.5)	1146 (4.0)	<0.001
nsNSAID	42,584 (85.0)	17,509 (80.7)	25,075 (88.2)	<0.001
Arthrotec	4214 (8.4)	2297 (10.6)	1917 (6.7)	<0.001
Combinations	550 (1.1)	247 (1.1)	303 (1.1)	0.43
Individual UGI risk factors:				
Age ≥65 years*	19,898 (39.7)	19,898 (91.8)	0 (0.0)	
Prior UGI event*	661 (1.3)	661 (3.0)	0 (0.0)	
Use of antiplatelets*	4301 (8.6)	4301 (19.8)	0 (0.0)	
Use of anticoagulants*	678 (1.4)	678 (3.1)	0 (0.0)	
Use of glucocorticoids*	302 (0.6)	302 (1.4)	0 (0.0)	
Diabetes mellitus	3744 (7.5)	2392 (11.0)	1352 (4.8)	0.001
Heart failure	1172 (2.3)	1061 (4.9)	111 (0.4)	0.001
High NSAID dose (> 2x DDD)	1051 (2.1)	365 (1.7)	686 (2.4)	0.001
Use of SSRI	915 (1.8)	386 (1.8)	529 (1.9)	0.51
Number of UGI risk factors:				
0	28,441 (56.7)	0 (0.0)	28,441 (100)	
1	17,705 (35.3)	17,705 (81.6)	0 (0.0)	
2	3807 (7.6)	3807 (17.6)	0 (0.0)	
3	171 (0.3)	171 (0.8)	0 (0.0)	
4	2 (0.0)	2 (0.0)	0 (0.0)	
GPA	5667 (11.3)	3170 (14.6)	2497 (8.8)	0.001
Preventive strategy (GPA or coxib)	8370 (16.7)	4752 (21.9)	3618 (12.7)	0.001

GPA, gastroprotective agent; nsNSAID, non-selective non-steroidal anti-inflammatory drug; UGI, upper gastrointestinal; DDD, defined daily dosage; SSRI, selective serotonin reuptake inhibitors.
** Risk factors used to define high-risk NSAID users (risk set 1).*

Table 3.2: Predictors of prescription of preventive strategies in high-risk patients

	No preventive strategy n (%)	With preventive strategy n (%)	OR crude (95% CI)	OR adjusted* (95% CI)	P-value
Total (%)	16,933 (78.1)	4752 (21.9)			
Gender (% male)	6867 (40.6)	1799 (37.9)	1.12 (1.05-1.20)	1.08 (0.92-1.26)	0.35
Individual UGI risk factors:					
Age ≥65 years	15,511 (91.6)	4387 (92.3)	1.10 (0.98-1.24)	1.71 (1.30-2.23)	<0.001
Prior UGI event	443 (2.6)	218 (4.6)	1.79 (1.52-2.11)	3.98 (2.94-5.39)	<0.001
Use of antiplatelets	3272 (19.3)	1029 (21.7)	1.15 (1.07-1.25)	1.35 (1.13-1.61)	<0.001
Use of anticoagulants	504 (3)	174 (3.7)	1.24 (1.04-1.48)	1.89 (1.35-2.64)	<0.001
Use of glucocorticoids	203 (1.2)	99 (2.1)	1.75 (1.38-2.24)	3.72 (2.46-5.64)	<0.001
Diabetes mellitus	1821 (10.8)	571 (12)	1.13 (1.03-1.25)	0.86 (0.68-1.08)	0.20
Heart failure	770 (4.5)	291 (6.1)	1.37 (1.19-1.57)	1.00 (0.72-1.39)	0.98
High NSAID dose	196 (1.2)	26 (0.5)	0.47 (0.31-0.71)	0.57 (0.23-1.44)	0.24
Use of SSRI	281 (1.7)	105 (2.2)	1.34 (1.07-1.68)	1.38 (0.87-2.20)	0.17
Number of UGI risk factors:					
1	14,059 (83)	3646 (76.7)	1 (ref)		
2	2749 (16.2)	1058 (22.3)	1.48 (1.37-1.61)		
3	124 (0.7)	47 (1)	1.46 (1.04-2.05)		
4 or more	1 (0)	1 (0)	3.86 (0.24-61.66)		
Index -prescription in:					
1996	1246 (7.4)	93 (2)	1 (ref)	1 (ref)	
1997	1994 (11.8)	164 (3.5)	1.10 (0.85-1.44)	1.23 (0.66-2.31)	0.52
1998	2308 (13.6)	254 (5.3)	1.47 (1.15-1.89)	2.15 (1.22-3.81)	0.01
1999	2881 (17)	322 (6.8)	1.50 (1.18-1.90)	2.16 (1.23-3.78)	0.01
2000	2460 (14.5)	581 (12.2)	3.16 (2.52-3.98)	2.56 (1.46-4.48)	<0.001
2001	1516 (9)	584 (12.3)	5.16 (4.10-6.50)	2.83 (1.58-5.07)	<0.001
2002	1233 (7.3)	543 (11.4)	5.90 (4.67-7.45)	3.30 (1.83-5.96)	<0.001
2003	1167 (6.9)	651 (13.7)	7.47 (5.93-9.42)	5.40 (3.06-9.51)	<0.001
2004	1132 (6.7)	849 (17.9)	10.05 (7.99-12.63)	8.03 (4.62-13.95)	<0.001
2005	634 (3.7)	467 (9.8)	9.87 (7.75-12.57)	20.67(11.95-35.76)	<0.001
2006	362 (2.1)	244 (5.1)	9.03 (6.92-11.78)	23.92 (13.62-42.03)	<0.001
Type of index-prescription:					
Ibuprofen	3573 (21.1)	119 (2.5)	1 (ref)	1 (ref)	
Diclofenac	7194 (42.5)	392 (8.2)	1.64 (1.33-2.02)	1.28 (1.03-1.59)	0.03
Naproxen	2806 (16.6)	105 (2.2)	1.12 (0.86-1.47)	1.98 (0.75-1.29)	0.89
Indometacin	249 (1.5)	20 (0.4)	2.41 (1.48-3.94)	3.12 (1.87-5.18)	0.00
Piroxicam	707 (4.2)	30 (0.6)	1.27 (0.85-1.92)	1.48 (0.97-2.26)	0.07
Ketoprofen	115 (0.7)	8 (0.2)	2.09 (1.00-4.38)	2.54 (1.18-5.50)	0.02
Nabumetone	485 (2.9)	12 (0.3)	0.74 (0.41-1.36)	1.10 (0.59-2.04)	0.76
Carbasalate calcium	425 (2.5)	6 (0.1)	0.42 (0.19-0.97)	0.33 (0.14-0.77)	0.01
Acetylsalicylacid combi	86 (0.5)	1 (0)	0.35 (0.05-2.53)	0.34 (0.05-2.51)	0.29
Meloxicam	748 (4.4)	49 (1)	1.97 (1.40-2.77)	1.10 (0.77-1.58)	0.61
Other nsNSAIDs	367 (2.2)	12 (0.3)	0.98 (0.54-1.80)	0.95 (0.51-1.76)	0.86

nsNSAID, non-selective non-steroidal anti-inflammatory drug; UGI, upper gastrointestinal; SSRIs, selective serotonin reuptake inhibitors.

** Adjusted for known UGI risk factors (gender, age, prior UGI complication, use of antiplatelets, use of steroids, diabetes mellitus, heart failure, dose, use of SSRIs), year of cohort entry and type of nsNSAIDs.*

Correct, over- and under-prescription of preventive strategies in NSAID users

Risk set 1

Figure 3.1 shows the time-trend in prescription of preventive strategies in the 50,126 NSAID users, when the definition of high-risk users was based on risk set 1 (history of UGI complication, concurrent use of anticoagulants, antiplatelets, or oral glucocorticoids, and age ≥ 65 years). In the decade between 1996 and 2006, correct prescriptions of preventive strategies rose by 10.6% from 52.7% to 63.3% (R^2= 0.91, linear trend $P < 0.01$). Over the same period under-prescription fell from 44.4% to 24.4% (R^2= 0.94, linear trend $P < 0.01$). Over-prescription rose from 2.9% in 1996 to 12.3% in 2006 (R^2= 0.92, linear trend $P < 0.01$).

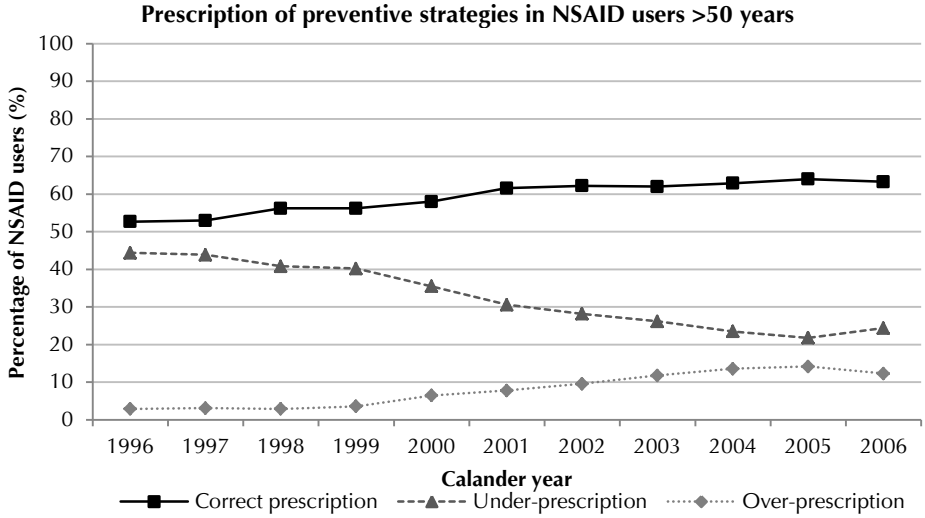

Figure 3.1: Prescription of preventive strategies in NSAID users > 50 years

Prescription of preventive strategies in NSAID users > 50 years (n = 50,126). Index prescriptions within a given calendar year were pooled. The denominator is the number of prescriptions per calendar year.

Risk set 2

When the broader criteria for NSAID-related UGI risk factors (risk set 2: adding diabetes mellitus, heart failure, high NSAID dose, and concomitant use of SSRIs to risk set 1) were used, more subjects were defined as high-risk users (48.4% vs. 43.3%). This did not strongly influence the appropriateness of prescription strategies; correct prescription rose from 48.9% in 1996 to 60.7% in 2006 (R^2 = 0.93, linear trend $P < 0.01$), under-prescription fell from 48.5% to 28.5% (R^2 = 0.94, linear trend $P < 0.01$), and over-prescription rose from 2.6% to 10.7% (R^2 = 0.91, linear trend $P < 0.01$) (data not shown).

Patients at high and very high risk of NSAID-related UGI complications

We performed three subgroup analyses to investigate whether subjects at high or very high risk of developing NSAID-related UGI complications had received proper preventive strategies.

For the 21,685 NSAID users with at least one UGI risk factor, under-prescription decreased from 93.1% to 59.9% (R^2 = 0.94, linear trend $P < 0.01$) and correct prescription rose from 6.9% to 39.4% (R^2 = 0.93, linear trend $P < 0.01$) between 1996 and 2006 (Figure 3.2a). When the cohort was restricted to 9,283 very high-risk NSAID users defined as being 75 years or older or having a previous history of UGI complications (mean age: 79.8±6.8; 34.1% male) the patterns were slightly different. Between 1996 and 2006, under-prescription in this group decreased from 90.8% to 50.6% (R^2 = 0.94, linear trend $P <$ 0.01) and correct prescription rose from 9.2% to 49.4% (R^2 = 0.94, linear trend $P < 0.01$) (Figure 3.2b).

As a history of UGI complications is widely assumed to be the risk factor most associated with an increased risk of developing UGI complications related to NSAIDs, we further

restricted the cohort of very high-risk patients to 661 subjects (1.3%) with a history of UGI bleeding/complication (mean age: 65.4±10.7; 54% male). During the study period, under-prescription in this subgroup decreased from 72.7% in 1996 to 51.5% in 2006 (R^2 = 0.75, linear trend $P < 0.01$). Correct prescription rose simultaneously from 27.3% in 1996 to 48.5% in 2006 ($R^2 = 0.77$, linear trend $P < 0.01$)(Figure 3.2c).

Influence of rofecoxib withdrawal on preventive strategies in high-risk users

In our study population, the use of coxibs increased from the time of their introduction in the Netherlands in 2000 to 17.5% of all first line NSAIDs in 2004. At that time, rofecoxib accounted for 39.6% of this share of the coxib market, followed by etoricoxib (33.3%) and celecoxib (26.3%). After the withdrawal of rofecoxib in September 2004, the overall coxib prescription rate decreased dramatically to 5.2% in 2006. In 2006, etoricoxib accounted for 76.9% of all coxibs prescribed and celecoxib for 21.8%.

To test whether the rapid decrease in coxib use after the withdrawal of rofecoxib had been followed by an increase in under-prescription, we compared under-prescription in study period 1 (one year before withdrawal of rofecoxib) with study period 2 (one year after withdrawal of rofecoxib) and study period 3 (1 October 2005 – 31 September 2006). In the group of patients at high risk (at least one risk factor), under-prescription increased significantly after rofecoxib withdrawal (from 56.6% before to 60.1% after rofecoxib withdrawal, $P = 0.04$), but it returned to period 1 levels quite rapidly again in period 3 (from 56.6% before to 58.0% two years after rofecoxib withdrawal, $P = 0.56$). Correct prescription decreased (from 43.0% to 39.4%, $P = 0.03$). In the very high-risk group, defined as being 75 years or older or having a previous history of UGI complications, under-prescription did not change after rofecoxib withdrawal (from 50.4% before to 50.1% after rofecoxib withdrawal, $P = 0.9$). This shows that the main effect was seen in patients at moderate risk (at least one risk factor, but no UGI complication and age < 75 years). Indeed, under-prescription increased significantly in this subgroup from 61.1% in study period 1 to 66.6% in study period 2 (P = 0.01).

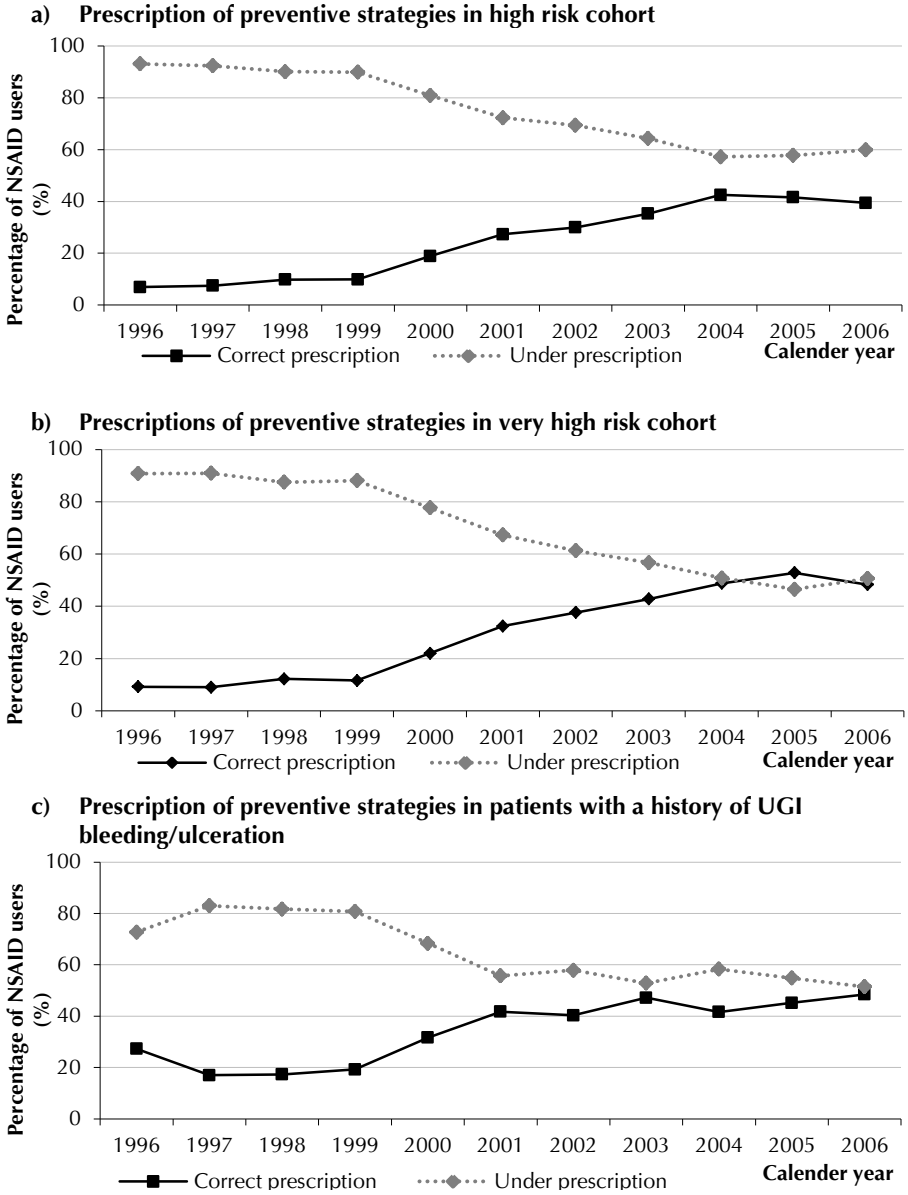

Figure 3.2: Prescription of preventive strategies

a) Prescription of preventive strategies in NSAID users with at least one risk factor (n = 21,685).
b) Prescription of preventive strategies in NSAID users > 75 years or with a history of UGI bleeding/ulceration (n = 9,283).
c) Prescription of preventive strategies in NSAID users with a history of UGI bleeding/ulceration (n = 661).
Index prescriptions within a given calendar year were pooled. The denominator is the number of prescriptions per calendar year.

Discussion

Preventive strategies (misoprostol, PPIs, H_2RAs, or coxibs) have been proposed to circumvent the well-recognized UGI-complications attributable to non-specific NSAIDs, especially in people at high risk. We have demonstrated in the past that under-prescription of preventive strategies was considerable.[103] The current study shows that under-prescription of preventive strategies by Dutch general practitioners decreased from 44% to 24% over a 10-year period. Despite this drop in under-prescription, in 2006, almost 60% of new NSAID users with at least one UGI risk factor and 52% of patients with a medical history of UGI events were not prescribed a proper preventive strategy. Over-prescription of preventive drugs was low, but rose from 3% in 1996 to 12% in 2006.

Our findings are consistent with other Dutch studies reporting under-prescription of preventive strategies in patients who would benefit from appropriate protection at a range of 43%-87%.[106-110] Consistently low rates of prescription of preventive strategies have also been reported in studies from other countries.[99, 111-114] In a recent pooled analysis of 11 studies related to the appropriate use of gastroprotective strategies in NSAID users, 76% of patients at high risk did not receive a preventive strategy.[96] Our analysis extended these data in the sense that we demonstrated that that figure depends largely on the time of measurement because we had data available of eleven subsequent calendar years.

Over-prescription of preventive strategies was low in our study-population: it has been reported in the range of 12-33%.[98, 99, 115, 116] However, these studies did not study over-prescription over time and in such a big study population.

As for our secondary aim, we showed that the withdrawal of rofecoxib may have had an effect on appropriate use of prophylactic strategies in moderately high-risk patients. Immediately after the withdrawal of rofecoxib we saw a significant increase in under-prescription in patients with a risk factor for NSAID related UGI complications, especially when we excluded persons at very high risk. However, this effect disappeared quickly and no causality between the date of rofecoxib withdrawal and the small increase in under-prescription could be attributed. This finding, however, is consistent with another Dutch study describing the effects of rofecoxib withdrawal where the authors showed that 34% of patients who stopped coxib therapy were switched to a nsNSAID without a PPI, whereas only 21% were switched to a nsNSAID with a co-prescription of a PPI.[117]

Some methodological aspects of this study require that our results should be interpreted carefully. First, because we used prescription data instead of more reliable proxies for drug use, we were unable to study actual drug utilization. Secondly, although it has been clearly demonstrated that only high-dose H_2RAs reduce the endoscopic ulcer rates associated with NSAIDs, we defined every H_2RA prescription, irrespective of dose, as a preventive strategy. Thirdly, we did not have any information about over-the-counter-use of NSAIDs. Some H_2RAs, such as ranitidine, were available over-the-counter as well. While these considerations are important, the aim of the study was to determine whether general practitioners' prescription of a preventive strategy to NSAID users reflected an intention to comply with (inter)national guidelines. As we have considered single H_2RA dose as a preventive strategy, we underestimated under-prescription of preventive strategies.

The strength of the present study is that, through ICPC-codes and free text, the IPCI-database contains complete information on all UGI risk factors and on drug prescriptions, including their quantity, strength, and prescribed daily dose. As it contains a large number

of eligible subjects and reflects the Dutch general population, the database also minimizes the potential for bias. Furthermore, we studied the influence of calendar year on prescription of GPAs among NSAID users. We also address issues of over-prescription, which have not been studied before over time and in such a big study population.

An additional finding of note is that physicians are not aware of the need for gastroprotective strategies when prescribing carbasalate calcium or acetylsalicylacid, as the likelihood of receiving a preventive strategy was lowest in patients using this type of medication.

In conclusion, we observed that physicians increase correct prescriptions of gastroprotection over a decade, which may be the result of guidelines, education, and probably the availability of generic PPIs. Despite the improvement, prescription of recommended strategies was still unacceptably low in 2006, especially in vulnerable populations. Non-adherence to gastroprotective measures lead to increased risk of NSAID-associated complications such as UGI-bleeds, as we have shown before.[118] The withdrawal of rofecoxib may have had a temporarily negative effect on gastroprotection, especially in the patients at risk, but below age of 75 years and without a history of UGI complications. This indicates that appropriate measures were not taken to protect at-risk NSAID users at the time of withdrawal. This is also important for regulators when risk minimization measures are taken such as removal of a drug from the market.

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Chapter 4

Prescription of non-selective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal

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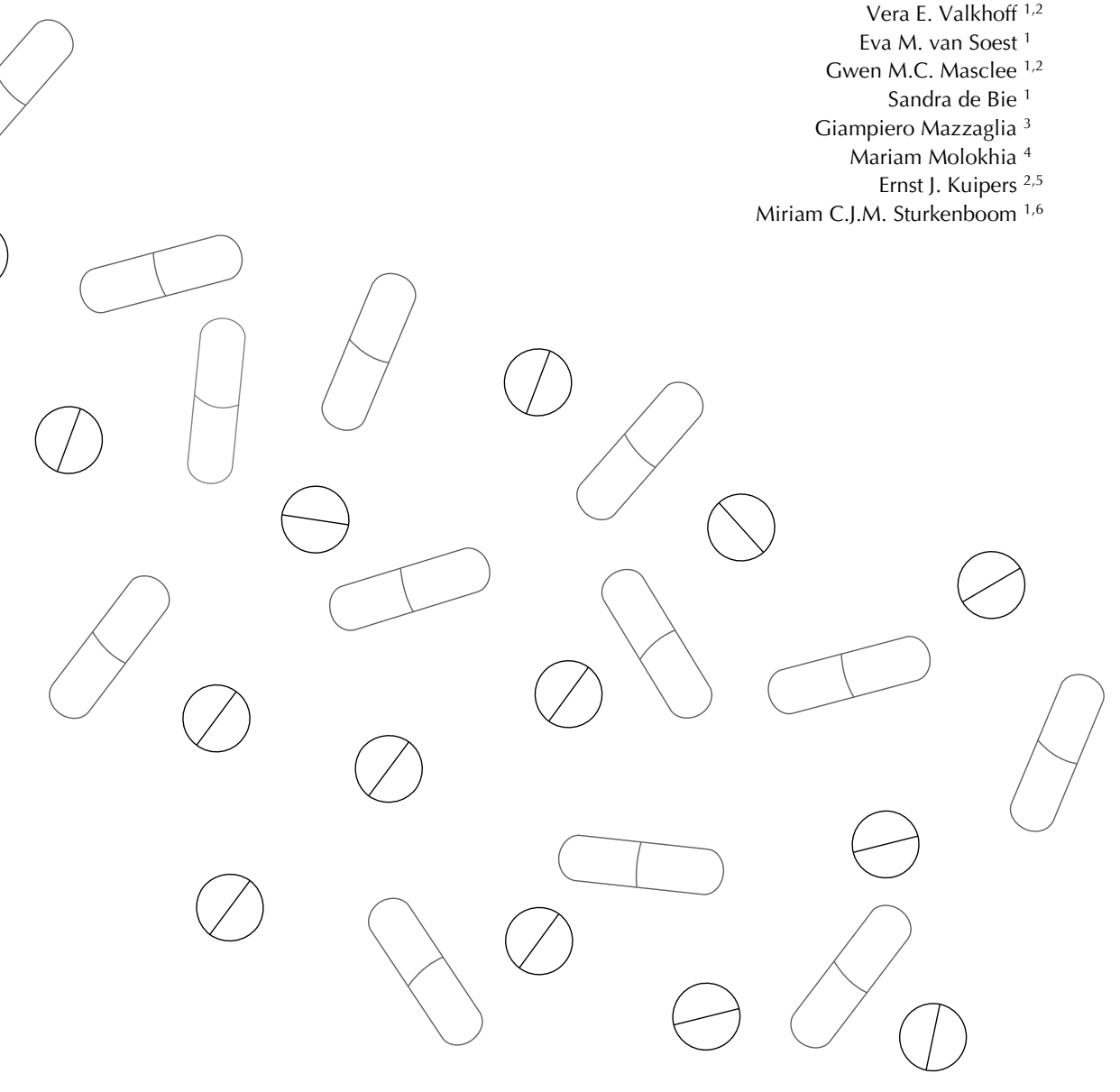


Abstract

Background

Gastroprotective strategies are recommended for non-steroidal anti-inflammatory drug (NSAID) users at risk of upper gastrointestinal (UGI) complications.

Aim

To compare use of gastroprotective strategies in NSAID users in 3 countries, and the subsequent impact of rofecoxib withdrawal.

Methods

We conducted a population-based cohort study in 3 general practice (GP) databases: (i) United Kingdom's (UK) GP Research Database (1998-2008), (ii) Italy's (IT) Health Search/CSD Longitudinal Patient Database (2000-2007), and (iii) the Dutch (NL) Integrated Primary Care Information database (1996-2006). Study cohorts comprised incident NSAID users ≥50 years. Gastroprotective strategies included: (i) co-prescription of gastroprotective agents, or (ii) use of a cyclooxygenase-2-specific inhibitor. Under-use was defined as no gastroprotection in patients with ≥1 UGI risk factor (history of UGI event, age ≥65 years, concomitant use of anticoagulants, antiplatelets, or glucocorticoids). Interrupted time-series analysis was performed to assess the impact of rofecoxib withdrawal on preventive strategies.

Results

The study populations consisted of 384,649 UK, 177,747 IT and 55,004 NL NSAID users. In UK, under-use of preventive strategies fell from 91% to 71% (linear trend (lt) $p = 0.001$), in NL from 92% to 58% (lt $p < 0.001$) and in IT from 90% to 76% (lt $p = 0.38$) in high-risk NSAID users. In 2000 and 2006, under-use was significantly lower in NL compared with UK and IT ($p < 0.001$) in high-risk users. After rofecoxib's withdrawal, a significant increase of under-use was shown for UK and NL, but not for IT.

Conclusions

The prescription of gastroprotective strategies with NSAIDs followed a similar pattern across three European countries. Despite a temporary negative effect of rofecoxib withdrawal on under-use, an improvement of gastroprotection with NSAIDs was observed.

Introduction

The risk of NSAID-related upper gastrointestinal (UGI) ulcers and haemorrhage can be reduced by preventive interventions such as concomitant prescription of gastroprotective agents (GPAs) or replacing non-selective (ns)NSAIDs by COX (cyclooxygenase)-2-selective inhibitors (coxibs).[53] GPAs include proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H_2RAs), and misoprostol.[53, 91, 92] Recommended interventions are especially beneficial for patients at high risk of NSAID-related UGI adverse events. NSAID users with the following risk factors are considered as such: advanced age, a medical history of a UGI event, serious co-morbidity, and concurrent administration of antiplatelets, anticoagulants or corticosteroids.[53]

Previously, we have shown that in the Netherlands adherence to these evidence-supported guidelines increased considerably over time.[46] However, even in 2006, 60% of patients with at least one UGI risk factor did not receive any gastroprotective measure. Data on the use of preventive strategies in NSAID users in several countries have been published, but all studies used different designs, outcome measures, populations, and definitions for at risk NSAID users.[96, 106, 108, 110, 115] Hence, it is impossible to compare adherence to preventive strategies across countries directly or to aggregate results. In the before-mentioned study from the Netherlands, we furthermore observed that there was a significant, but temporal, decrease in use of gastroprotection in at-risk NSAID-users after 2004. This observation was probably attributable to the cardiovascular (CV) safety concerns of coxibs, leading to rofecoxib withdrawal in September 2004.[94] In April 2005 valdecoxib was withdrawn for concerns on CV safety and serious skin reactions and lumiracoxib in December 2007 for reasons of hepatotoxicity.[119, 120] Although the effect of rofecoxib withdrawal on switches in classes of NSAID prescriptions has been studied before[117, 121], the impact on the accuracy of the prescription of preventive strategies remains unclear. Insight in switching to alternative appropriate measures after the withdrawal in the past may serve as important lesson for the future. Therefore, we aimed to compare prescription behavior and to assess predictors of preventive strategies among NSAID users by general practitioners (GPs) in three European countries, and to study the subsequent impact of rofecoxib withdrawal.

Methods

Data sources

Data for this study were obtained from three similar European population-based primary care databases[122]: (i) the *General Practice Research Database (GPRD; 1998-2008)* which was established in the United Kingdom (UK) in 1987. Symptoms and diagnoses are recorded using READ codes and drug prescriptions with the MULTILEX product dictionary and British National Formulary (BNF) codes; (ii) the *Integrated Primary Care Information (IPCI) database (1996-2007)* which was initiated in the Netherlands (NL) in 1992, and uses the International Classification for Primary Care (ICPC)[61] and free text to record symptoms and diagnoses. Information on drug prescriptions is coded according to the Anatomical Therapeutic Chemical (ATC) classification[60]; (iii) The *Health Search/CSD Longitudinal Patient Database (HSD; 2000-2007)* which was established in Italy (IT) in 1998. Symptoms and diagnoses are coded using the International Classification of Dis-

eases, 9th Revision, Clinical Modification (ICD-9-CM).[59] Information on drug prescriptions is coded according to the ATC classification.

In the British, Dutch and Italian health care systems, all citizens are registered with a primary care practice, which records all relevant medical information. Data recorded include demographics, symptoms and diagnoses, laboratory test results, drug prescriptions, specialist referrals, clinical diagnoses from outpatient visits and hospital discharge summaries.

The databases comply with European Union guidelines on the use of medical data for medical research and have been demonstrated valid for pharmaco-epidemiological research. The protocol of the present study was approved by the Scientific and Ethical Advisory Board of each database.

Study cohort

Patients were eligible for inclusion from the start of the study period, once reaching the age of 50 years, or once at least one year of valid enrollment data was obtained (whichever came latest). This 12-month period was required to allow assessment of baseline characteristics and inclusion and exclusion criteria of all study subjects at the time of NSAID prescription. Eligibility ended at death, last data supply, transferring out of the practice, or end of study period (whichever came first).

Within the source population, we identified all patients who newly started (no prescription in the previous six months) on nsNSAIDs, coxibs, or high dose aspirin (> 325 mg/day) during the study period. Patients with a history of a gastrointestinal tract neoplasm, alcohol abuse, chronic liver disease, inflammatory bowel disease, or a coagulopathy were excluded. As the focus of this study was to evaluate the use of prophylactic strategies in naive NSAID users at the time of NSAID prescription, only the first NSAID prescription of a patient was considered.

NSAIDs were arranged according to class [nsNSAID, coxib, or a fixed combination of diclofenac and misoprostol (diclofenac/misoprostol)] or a combination of the former classes. The nsNSAIDs were further classified by type, for example ibuprofen, diclofenac, or naproxen.

Identification of high-risk patients

To identify NSAID users at high risk of UGI events (i.e. presence of at least one risk factor), five risk factors were considered: (i) age $\geq$ 65 years; (ii) a history of UGI events (bleeding/ulceration); (iii) concurrent use of anticoagulants; (iv) concurrent use of antiplatelets (including aspirin $\leq$ 325 mg/day); and (v) concurrent use of glucocorticoids (equipotent dose of $\geq$ 5 mg prednisone).[53, 91] Risk factors were retrieved from the databases by electronic searches in all available data before (history of UGI bleeding/ulceration) or at the first day of NSAID prescription (age and concurrent medication). Low-risk patients were defined as having none of these risk factors.

Outcome

Preventive strategies were defined as: (i) the use of a coxib, or (ii) use of a GPA at start of nsNSAID prescription (double-doses H_2RAs, PPIs, or misoprostol (separately or as fixed combination with diclofenac)). The GPA could have been started prior to the NSAID prescription, but should at least have covered the first day of NSAID prescription. Prophylactic GPA use, a subgroup of preventive use, was defined as GPA started within two days of

the NSAID prescription and no use of a GPA in the six months prior to the first day of NSAID prescription.

Primary outcomes of interest were *appropriate use*, *over-use*, or *under-use* of preventive strategies at start of NSAID prescription. Appropriate use was defined as use of a preventive strategy in high-risk NSAID users and no use in low-risk patients. Under-use was defined as absence of a preventive strategy in high-risk NSAID users. Over-use was defined as presence of a preventive strategy in low-risk NSAID users. Consistent with recent evidence from randomized controlled trials, we considered co-prescription of a PPI with a coxib in high-risk users as appropriate use.[105]

Analytic methods

For each database, baseline characteristics were compared between high- and low-risk groups using a χ^2-test for dichotomous variables and independent t-test for age as a continuous variable. Primary outcomes between countries were compared using the χ^2-test in 2000 and 2006. To evaluate which risk factors were considered by GPs as increasing the risk of UGI events during NSAID use, univariate and multivariate analyses of potential predictors of receiving a preventive strategy were conducted within high-risk users. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analysis.

Linear regression by one-way ANOVA was conducted to investigate the time-trends of appropriate, over- and under-use and is expressed by R-squared (R^2) and a *p*-value for linear trend (lt). A value of 1 indicates a perfect linear fit, indicating the ability to predict the prescription trend based on prescriptions by calendar month.

To assess the effect of rofecoxib withdrawal on the accuracy of use of preventive strategies, interrupted time-series analyses were performed using an ARIMA (*a*uto-*r*egressive, *i*ntegrated, *m*oving *a*verage) (*p,d,q*) model[123] The outcome was the change in frequency of use of the preventive strategy due to the intervention (defined as rofecoxib withdrawal in September 2004) with a corresponding *p*-value. For estimating the impact on the use of preventive strategies, we hypothesized that rofecoxib withdrawal had an abrupt, temporary effect for one year (main analysis), and performed a sensitivity analysis for two years. All analyses were performed using SPSS version 15.0 (SPSS Inc, Chicago, Illinois).

Results

Study cohort

From United Kingdom (UK) 384,649 new NSAID users met the cohort inclusion criteria (source population 4,727,334 persons); from the Netherlands (NL) 55,004 (source population 154,518 persons) and from Italy (IT) 177,747 (source population 370,013 persons). Baseline characteristics by database and risk level are described in Table 4.1. Mean age and sex distribution of the study populations were similar in the three countries. Within each database all comparisons between high- and low-risk NSAID users were significantly different.

The most commonly prescribed NSAIDs differed across countries. In the UK ibuprofen accounted for 64%, naproxen for 13% and diclofenac for 8.3%. In NL, diclofenac accounted for the highest number of prescriptions (39%), followed by ibuprofen (17%) and

naproxen (16%). In IT, nimesulide accounted for 29%, diclofenac for 18% and ketoprofen for 11%. Carbasalate calcium in a dosage of 325 mg/day or more was prescribed exclusively in NL, accounting for 2.4% of all NSAID prescriptions (data not shown).

UGI risk factors in NSAID users

Table 4.1 shows that 186,188 (48% of the study population) in the UK, 31,433 (57%) in NL and 85,664 (48%) in IT had no NSAID-related UGI risk factors and were therefore defined as low-risk NSAID users. Individuals with at least one risk factor were defined as high-risk NSAID users. In all countries, most of the high-risk patients had one risk factor (UK 75%; NL 91%; IT 83%), with age above 65 years being the most frequently observed NSAID-related UGI risk factor, followed by concomitant use of antiplatelets and a prior UGI event.

Use of preventive strategies

In total, 15%, 18% and 17% of NSAID users received a preventive strategy (i.e. prescription of a GPA or coxib) in UK, NL and IT, respectively. Consistent for all countries, high-risk NSAID users were more likely to receive a preventive strategy compared with low-risk NSAID users ($p < 0.001$) (Table 4.1). Co-use of a GPA was highest in NL (13%) and lowest in IT (7.1%). The fixed combination of diclofenac/misoprostol accounted for 8.9% of all NSAID prescriptions in NL, compared with 3.3% in UK and 1.0% in IT. When excluding diclofenac/misoprostol, PPIs were the most common co-used GPAs (UK 99.5%; NL 96.9%; IT 95.5%), whereas double-dosed H_2RA (UK 0.2%; NL 2.3%; IT 0.1%) and misoprostol as a separate prescription (UK 0.3%; NL 0.8%; IT 4.4%) comprised the minority.

Prophylactic GPA prescriptions (i.e. no use of GPAs in 6 months prior to NSAID prescription and GPA within 2 days of NSAID prescription) comprised 40%, 53% and 42% of all co-used GPAs in UK, NL and IT, respectively.

Predictors of preventive strategies

Among high-risk NSAID users, those with a history of UGI events or who concomitantly used glucocorticoids had the highest chance of receiving a preventive strategy in all countries (Table 4.2). Age $\geq$ 65 years was a predictor of receiving a preventive strategy in UK and IT, but not in NL. Concurrent use of anticoagulants or antiplatelets was recognized as necessity for a preventive strategy for NSAID users in all. The likelihood of receiving a preventive strategy was highest for prescriptions of meloxicam in UK (OR 2.1; 95%CI 1.9–2.3), ketoprofen in NL (OR 2.7; 95%CI 1.6-4.7) and indometacin in IT (OR 2.6; 95%CI 1.8-3.7) (Table 4.2). Indometacin was the only nsNSAID recognized as predictor of preventive strategies in all countries. A new prescription of high-dosed aspirin was observed as a predictor of a preventive strategy exclusively in IT, whereas nimesulide was not (OR 0.6; 95%CI 0.5-0.8; $p< 0.001$). Compared with 2000, the likelihood for receiving a preventive strategy increased, resulting in an OR in 2006 of 4.3 in UK (95%CI 4.0–4.7), 7.9 in NL (95%CI 5.9–10.4) and 5.8 in IT (95%CI 5.1–6.4).

Appropriate, over- and under-use of preventive strategies in NSAID users

The time-trends in prescription of preventive strategies in all NSAID users by country are depicted in Figure 4.1. A similar pattern was observed across countries: appropriate use increased over time, whereas under-use decreased. All these trends were significant over

the entire study (p-value for linear trend (lt)< 0.001) with an R-squared (R^2) above 0.5 by one-way ANOVA, except for the trend in over-use in IT (R^2= 0.02, lt p = 0.18).

Within the subgroup of high-risk patients only, a decrease in under-use of a gastroprotective strategy was shown, from 91% to 71% in UK (R^2 = 0.70, lt p = 0.001), from 92% to 58% in NL (R^2 = 0.94, lt p < 0.001) and from 90% to 76% in IT (R^2 = 0.13, lt p = 0.38). In NL under-use was significantly less often observed than in UK or IT (p < 0.001) in high risk users, both in 2000 and in 2006. In addition, in 2000 and 2006 appropriate use was significantly more frequently observed in high risk users for NL compared with UK or IT (p< 0.001). In low-risk patients an increase in over-use was observed, from 5.3% to 13% (R^2 = 0.50, lt p = 0.014), from 6.2% to 22% (R^2 = 0.92, lt p < 0.001) and from 7.3% to 12% (R^2 = 0.01, lt p = 0.827), in UK, NL and IT, respectively.

Influence of rofecoxib withdrawal on NSAID class and preventive strategies

Since their introduction in 1999, the use of coxibs increased to 15%, 18% and 14% of all first line NSAIDs in 2004 in UK, NL and IT, respectively. In 2004, rofecoxib accounted for 37% (UK), 40% (NL) and 22% (IT) of the coxib market. After the withdrawal of rofecoxib in September 2004, the overall coxib prescription rate decreased dramatically to 1.4%, 5.5% and 4.8% in 2006 for UK, NL and IT respectively (Figure 4.2). After 2004, in NL mainly etoricoxib was prescribed, while in UK and IT also celecoxib was commonly prescribed. We compared the expected trend of appropriate, over- and under-use to the observed numbers to understand whether the rapid decrease in coxib use after the withdrawal of rofecoxib led to changes in the accuracy of use of preventive strategies. In UK, rofecoxib withdrawal resulted in a significant increase in under-use of preventive strategies (p = 0.038) and in a decrease of over-use (p < 0.001), whereas appropriate use was not significantly affected (p = 0.616) (Figure 4.1). In NL only a significant increase in under-use of preventive strategies was observed (p = 0.027) (appropriate use; p = 0.109, and over-use p = 0.753). In IT no significant effect on the accuracy of prescription of preventive strategies was seen after the withdrawal of rofecoxib. When conducting the sensitivity analyses with a temporary effect lasting for two years, the effect on under-use of preventive strategies in UK became non-significant while all further analyses remained similar.

Table 4.1: Baseline characteristics of study cohort by database and risk level

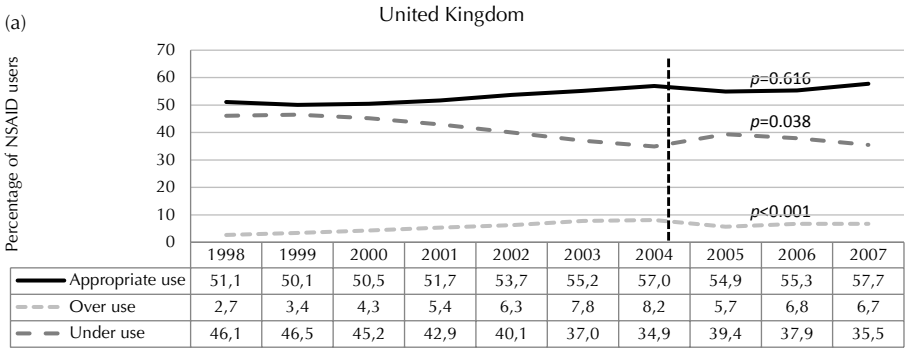
	United Kingdom			the Netherlands			Italy		
	Total n (%)	High-risk patients * n (%)	Low-risk patients ** n (%)	Total n (%)	High-risk patients * n (%)	Low-risk patients ** n (%)	Total n (%)	High-risk patients * n (%)	Low-risk patients ** n (%)
Total	384,649 (100)	198,461 (51.6)	186,188 (48.4)	55,004 (100)	23,571 (42.9)	31,433 (57.1)	177,747 (100)	92,083 (51.8)	85,664 (48.2)
Age in years (mean±sd)	64.8 (10.6)	72.7 (8.5)	56.3 (4.5)	63.4 (10.7)	73.7 (7.9)	55.7 (4.2)	64.6 (10.7)	72.6 (8.5)	56.1 (4.4)
Gender (n (%) male)	157,881 (41)	81,083 (40.9)	76,798 (41.2)	23,455 (42.6)	9,064 (38.5)	14,391 (45.8)	74,181 (41.7)	37,488 (40.7)	36,693 (42.8)
Class of NSAID:									
nsNSAID	353,601 (91.9)	178,712 (90)	174,889 (93.9)	46,777 (85)	19,023 (80.7)	27,754 (88.3)	156,810 (88.2)	79,310 (86.1)	77,500 (90.5)
Coxib	18,264 (4.7)	12,002 (6)	6,262 (3.4)	3,266 (5.9)	1,888 (8)	1,378 (4.4)	18,411 (10.4)	11,289 (12.3)	7,122 (8.3)
Diclofenac/misoprostol	12,581 (3.3)	7,604 (3.8)	4,977 (2.7)	4,885 (8.9)	2,611 (11.1)	2,274 (7.2)	1,725 (1)	1,036 (1.1)	689 (0.8)
Combinations	203 (0.1)	143 (0.1)	60 (0)	76 (0.1)	49 (0.2)	27 (0.1)	801 (0.5)	448 (0.5)	353 (0.4)
Individual UGI risk factors:									
Age ≥65 years	177,975 (46.3)	177,975 (89.7)	0 (0)	22,437 (40.8)	22,437 (95.2)	0 (0)	82,628 (46.5)	82,628 (89.7)	0 (0)
Prior UGI event	16,953 (4.4)	16,953 (8.5)	0 (0)	1,145 (2.1)	1,145 (4.9)	0 (0)	6,990 (3.9)	6,990 (7.6)	0 (0)
Use of antiplatelets	49,782 (12.9)	49,782 (25.1)	0 (0)	1651 (3)	1651 (7)	0 (0)	12,233 (6.9)	12,233 (13.3)	0 (0)
Use of anticoagulants	2,809 (0.7)	2,809 (1.4)	0 (0)	329 (0.6)	329 (1.4)	0 (0)	1,257 (0.7)	1,257 (1.4)	0 (0)
Use of glucocorticoids	4,169 (1.1)	4,169 (2.1)	0 (0)	252 (0.5)	252 (1.1)	0 (0)	3,779 (2.1)	3,779 (4.1)	0 (0)
Number of UGI risk factors:									
0	186,188 (48.4)	0 (0)	186,188 (100)	31,433 (57.1)	0 (0)	31,433 (100)	85,664 (48.2)	0 (0)	85,664 (100)
1	149,015 (38.7)	149,015 (75.1)	0 (0)	21,426 (39)	21,426 (90.9)	0 (0)	76,687 (43.1)	76,687 (83.3)	0 (0)
2	45,762 (11.9)	45,762 (23.1)	0 (0)	2,049 (3.7)	2,049 (8.7)	0 (0)	14,683 (8.3)	14,683 (15.9)	0 (0)
3	3,589 (0.9)	3,589 (1.8)	0 (0)	94 (0.2)	94 (0.4)	0 (0)	699 (0.4)	699 (0.8)	0 (0)
≥ 4	95 (0)	95 (0)	0 (0)	2 (0)	2 (0)	0 (0)	14 (0)	14 (0)	0 (0)
GPA	42,814 (11.1)	28,856 (14.5)	13,958 (7.5)	7,014 (12.8)	3,862 (16.4)	3,152 (10.0)	12,561 (7.1)	8,404 (9.1)	4,157 (4.9)
Preventive strategy (GPA or coxib)	57,845 (15.0)	38,494 (19.4)	19,351 (10.4)	10,078 (18.3)	5,632 (23.9)	4,446 (14.1)	30,281 (17.0)	19,064 (20.7)	11,217 (13.1)

nsNSAID, non-selective non-steroidal anti-inflammatory drug; UGI, upper gastrointestinal; GPA, gastroprotective agent.
**High-risk patient: patient with ≥ 1 UGI risk factor.*
***Low-risk patient: patient with no UGI risk factors.*
All comparisons between high- and low-risk NSAID users were significantly different by database.

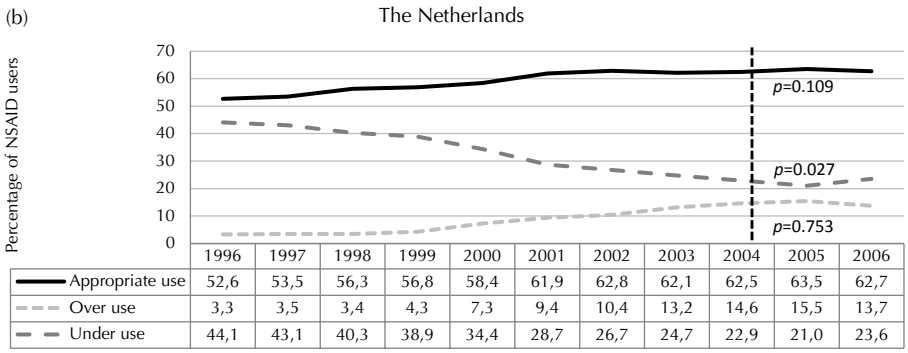
Table 4.2: Predictors for prescription of preventive strategies in high-risk patients

	United Kingdom			the Netherlands			Italy		
	No preventive strategy n (%)	With preventive strategy n (%)	OR adjusted * (95% CI)	No preventive strategy n (%)	With preventive strategy n (%)	OR adjusted * (95% CI)	No preventive strategy n (%)	With preventive strategy n (%)	OR adjusted * (95% CI)
Total (%)	159,967 (100)	38,494 (100)		17,939 (100)	5,632 (100)		73,019 (100)	19,064 (100)	
Gender (% male)	67,030 (41.9)	14,053 (36.5)	1.23 (1.19 - 1.27)	7,025 (39.2)	2,039 (36.2)	1.30 (1.14 - 1.49)	30,157 (41.3)	7,331 (38.5)	**0.97 (0.92 - 1.03)**
Individual UGI risk factors:									
Age ≥ 65 years	144,502 (90.3)	33,473 (87.0)	1.19 (1.13 - 1.25)	17,123 (95.5)	5314 (94.4)	**1.06 (0.82 - 1.36)**	65,780 (90.1)	16,848(88.4)	1.28 (1.18 - 1.39)
Prior UGI event	10,926 (6.8)	6,027 (15.7)	3.80 (3.63 - 3.98)	765 (4.3)	380 (6.7)	3.16 (2.53 - 3.96)	4,510 (6.2)	2,480 (13)	4.65 (4.31 - 5,01)
Use of antiplatelets	37,832 (23.6)	11,950 (31.0)	1.78 (1.72 - 1.84)	1,197 (6.7)	454 (8.1)	2.39 (1.97 - 2.88)	9,531 (13.1)	2,702 (14.2)	1.59 (1.48 - 1.70)
Use of anticoagulants	2,046 (1.3)	763 (2.0)	1.72 (1.54 - 1.93)	230 (1.3)	99 (1.8)	2.35 (1.58 - 3.51)	959 (1.3)	298 (1.6)	1.84 (1.53 - 2,20)
Use of glucocorticoids	2,673 (1.7)	1,496 (3.9)	3.39 (3.12 - 3.68)	153 (0.9)	99 (1.8)	4.96 (3.40 - 7.24)	2,692 (3.7)	1,087 (5.7)	3.25 (2.94 - 3.58)
Number of UGI risk factors:									
1	124,051 (77.5)	24,964 (64.9)		16,469 (91.8)	4,957 (88.0)		61,752 (84.6)	14,935(78.3)	
2	33,853 (21.2)	11,909 (30.9)		1,412 (7.9)	637 (11.3)		10,869 (14.9)	3,814 (20)	
3	2,032 (1.3)	1,557 (4.0)		57 (0.3)	37 (0.7)		391 (0.5)	308 (1.6)	
≥ 4	31 (0)	64 (0.2)		1 (0)	1 (0)		7 (0)	7 (0)	
Type of nsNSAID prescription: #									
Ibuprofen	100,044 (62.5)	9,906 (25.7)	1 (ref)	3,809 (21.2)	181 (3.2)	1 (ref)	1,537 (2.1)	161 (0.8)	1 (ref)
Diclofenac	10,529 (6.6)	1,221 (3.2)	1.55 (1.44 - 1.66)	7,628 (42.5)	531 (9.4)	**1.17 (0.97 - 1.40)**	3,900 (5.3)	428 (2.2)	1.19 (0.98 - 1.46)
Naproxen	14,758 (9.2)	2,311 (6)	1.48 (1.40 - 1.57)	2,962 (16.5)	156 (2.8)	**0.91 (0.71 - 1.17)**	404 (0.6)	35 (0.2)	**1.00 (0.63 - 1.49)**
Indometacin	1,702 (1.1)	180 (0.5)	1.59 (1.35 - 1.87)	271 (1.5)	22 (0.4)	2.04 (1.27 - 3.28)	283 (0.4)	56 (0.3)	2.60 (1.84 - 3.67)
Ketoprofen	779 (0.5)	87 (0.2)	1.50 (1.19 - 1.90)	135 (0.8)	17 (0.3)	2.70 (1.55 - 4.71)	2,032 (2.8)	244 (1.3)	1.35 (1.08 - 1.68)
Aspirin	153 (0.1)	9 (0)	**0.92 (0.47 - 1.83)**	556 (3.1)	17 (0.3)	**0.65 (0.39 - 1.10)**	353 (0.5)	36 (0.2)	1.55 (1.04 - 2.30)
Meloxicam	3,174 (2)	599 (1.6)	2.09 (1.90 - 2.30)	850 (4.7)	87 (1.5)	1.37 (1.04 - 1.81)	818 (1.1)	93 (0.5)	**1.29 (0.97 - 1.71)**
Nimesulide	0 (0)	0 (0)	0.00	0	0	0.00	5,345 (7.3)	266 (1.4)	0.64 (0.52 - 0.79)
Other nsNSAIDs	4,253 (3.1)	17,583 (55.1)		1,724 (9.6)	4,621 (82.0)		4,514 (23.5)	4,816 (78.5)	

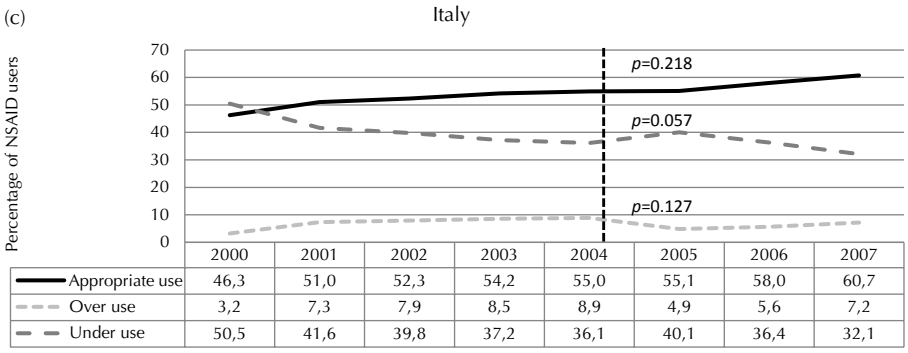
nsNSAID, non-selective non-steroidal anti-inflammatory drug; UGI, upper gastrointestinal.
Depicted in bold are non-significant values.
**Adjusted for known UGI risk factors (age, prior UGI event, use of antiplatelets, anticoagulants, and glucocorticoids) year of cohort entry and type of nsNSAIDs.*
#Also adjusted for dose. Patients were only included when dose was available (UK: 84.3%; NL: 99.9%; IT: 27.5%).



	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007
Appropriate use	51,1	50,1	50,5	51,7	53,7	55,2	57,0	54,9	55,3	57,7
Over use	2,7	3,4	4,3	5,4	6,3	7,8	8,2	5,7	6,8	6,7
Under use	46,1	46,5	45,2	42,9	40,1	37,0	34,9	39,4	37,9	35,5



	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006
Appropriate use	52,6	53,5	56,3	56,8	58,4	61,9	62,8	62,1	62,5	63,5	62,7
Over use	3,3	3,5	3,4	4,3	7,3	9,4	10,4	13,2	14,6	15,5	13,7
Under use	44,1	43,1	40,3	38,9	34,4	28,7	26,7	24,7	22,9	21,0	23,6



	2000	2001	2002	2003	2004	2005	2006	2007
Appropriate use	46,3	51,0	52,3	54,2	55,0	55,1	58,0	60,7
Over use	3,2	7,3	7,9	8,5	8,9	4,9	5,6	7,2
Under use	50,5	41,6	39,8	37,2	36,1	40,1	36,4	32,1

Figure 4.1: Accuracy of preventive strategy in all NSAID users by country

Accuracy of preventive strategies in NSAID users ≥ 50 years by country over entire study period ((a) UK: 1998-2008; (b) NL: 1996-2006; (c) IT: 2000-2007). NSAID prescriptions within a given calendar year were pooled. The denominator is the number of prescriptions per calendar year. Rofecoxib withdrawal (September 2004) is depicted by vertical squared line. The p-values of the interrupted time-series analyses reflect whether subsequent observations per month after rofecoxib withdrawal were significantly affected with a temporarily duration of one year and are depicted next to the vertical squared line.

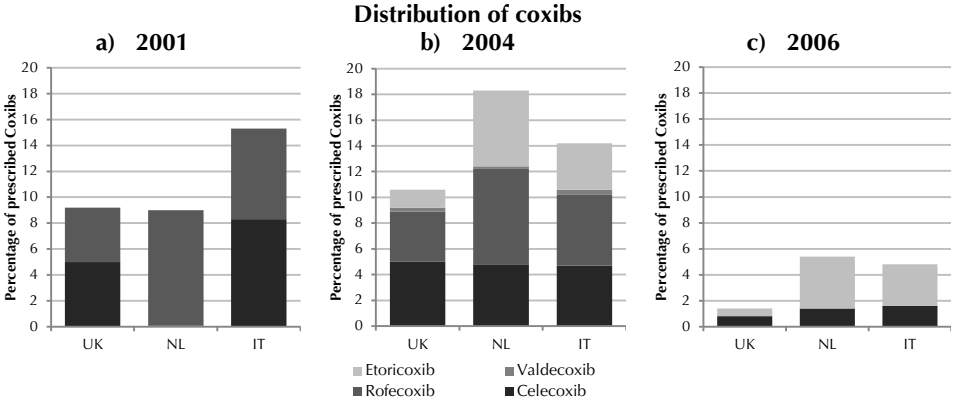


Figure 4.2: Distribution of prescribed coxibs in percentage of all NSAIDs by country and year.

Discussion

Guidelines recommend gastroprotective strategies, such as prescription of COX-2 inhibitors (coxibs) or co-prescription of gastroprotective agents to reduce NSAID-related UGI events, especially in high-risk NSAID users. We previously demonstrated that adherence to these evidence-supported guidelines was suboptimal in the Netherlands.[46] In order to compare prescription behavior and define predictors of use of gastroprotective strategies across countries, we now extended these data with primary care data from the United Kingdom and Italy, while using the same definitions to identify high-risk NSAID users and to determine appropriate, over- and under-use of gastroprotective strategies. In general, we found a very analogous usage pattern of preventive strategies in elderly NSAID users across three European countries. Although an evident improvement was seen in the use of preventive strategies over a 7 to 10-year period, still a substantial proportion of new high risk NSAID users, in need of a preventive strategy, lacked one. At the end of the study period, 71%, 58% and 76% of new NSAID users with at least one UGI risk factor did not receive an adequate preventive strategy in UK, NL and IT, respectively.

In addition, we assessed the effect of the withdrawal of rofecoxib from the market in September 2004 on the use of preventive strategies in each country. After rofecoxib was withdrawn, an abrupt change in NSAID prescriptions was observed. In line with previous reports[117, 124-126], the number of coxib prescriptions dropped while the number of non-selective NSAIDs prescriptions increased. Despite the shift in drug classes, this abrupt change did not significantly impacted the accurate use of preventive strategies in IT. In UK and NL however, a significant temporary increase in under-use of preventive strategies was observed. Thus, GPs in UK and NL did not immediately replace appropriate alternative gastroprotective strategies after rofecoxib withdrawal, but regained appropriate prescription of gastroprotective strategies with NSAIDs after one year. Besides the increase in under-use directly after the withdrawal, over-use decreased significantly in UK, but not in NL and IT. The increase in under-use can probably be explained by the observation that coxib users switched more frequently to a nsNSAID without co-prescription of a GPA than to another coxib[117], although coxibs were more likely to be prescribed to high risk patients.[124] We were unable to assess the impact of valdecoxib or lumiracoxib withdrawal on use of preventive strategies due to low number of users.

Consistent with previous reports[108, 110, 115], a history of UGI complications and concomitant glucocorticoid use were the strongest predictors of receiving a preventive strategy across countries. Although advanced age is a generally accepted risk factor for UGI complications attributable to NSAIDs, age of 65 years and older did not increase the odds of receiving preventive strategies in NL.

Our study has the following limitations. First, no information was available about over-the-counter (OTC)-use of NSAIDs, which may have led to an underestimation of NSAIDs used. However, only prescribed NSAIDs are (partly) reimbursed whereas OTC NSAIDs are not which results in a preference for prescribed drugs. Some H_2RAs, such as ranitidine, were available OTC as well, but it is highly unlikely that patients use doses that are high enough to be classified as gastroprotection. PPIs became available OTC only after the study period has ended in IT and NL, but not for UK (omeprazole). This may have led to underestimation of GPA use in UK. However again, only prescribed PPIs are partly reimbursed in UK, thereby leading to a preference for receiving prescribed PPIs. Furthermore, up to date no overall consensus is available in Europe describing which NSAID users would benefit most from gastropreventive measures. We therefore selected the five risk factors most frequently recognized in national and international guidelines.[53, 88, 127, 128] However, this conservative approach in recognizing UGI risk factors could have resulted in an underestimation of patients at UGI risk, thereby possibly underestimating the frequency of under-use of preventive strategies or overestimating over-use. This could also have happened in patients who apparently lacked documented UGI risk factors, but had other reasons for co-prescription of acid-suppressive therapy, such as self-reported dyspeptic symptoms. Also, all guidelines concerning gastroprotection with NSAIDs were published in or after 2000, whereas we have included prescription data from 1996 onwards. In line with this, there has been a considerable increase in the use of gastroprotective agents itself, especially PPIs.[129]

The strength of the present study is that all three general practice databases contain a large number of patients and reflect the underlying general population. Complete information on drug prescriptions and all UGI risk factors are encoded in the databases through either READ codes, ICPC codes or ICD-9 codes and free text. Furthermore, we compared three primary care populations, while using the same data work-up and definitions, which has not been done before, thereby creating the possibility to directly compare prescription behavior across countries. We included data from several subsequent calendar years, enabling trend analysis over a fair period of time.

In conclusion, general practitioners in three European countries follow a similar pattern in prescription of gastroprotective strategies with NSAIDs over several years. Although appropriate use improved over time, prescription of recommended preventive strategies in patients at risk for UGI events is still not fully succeeded. The withdrawal of rofecoxib had a negative effect on correct prescription of gastroprotective strategies. Our results indicate that there is room for considerable improvement with regard to use of gastroprotective strategies during NSAID therapy in Western Europe.

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Chapter 5

Prescription of NSAIDs in a primary care population with musculoskeletal complaints and ischemic cardiovascular risk

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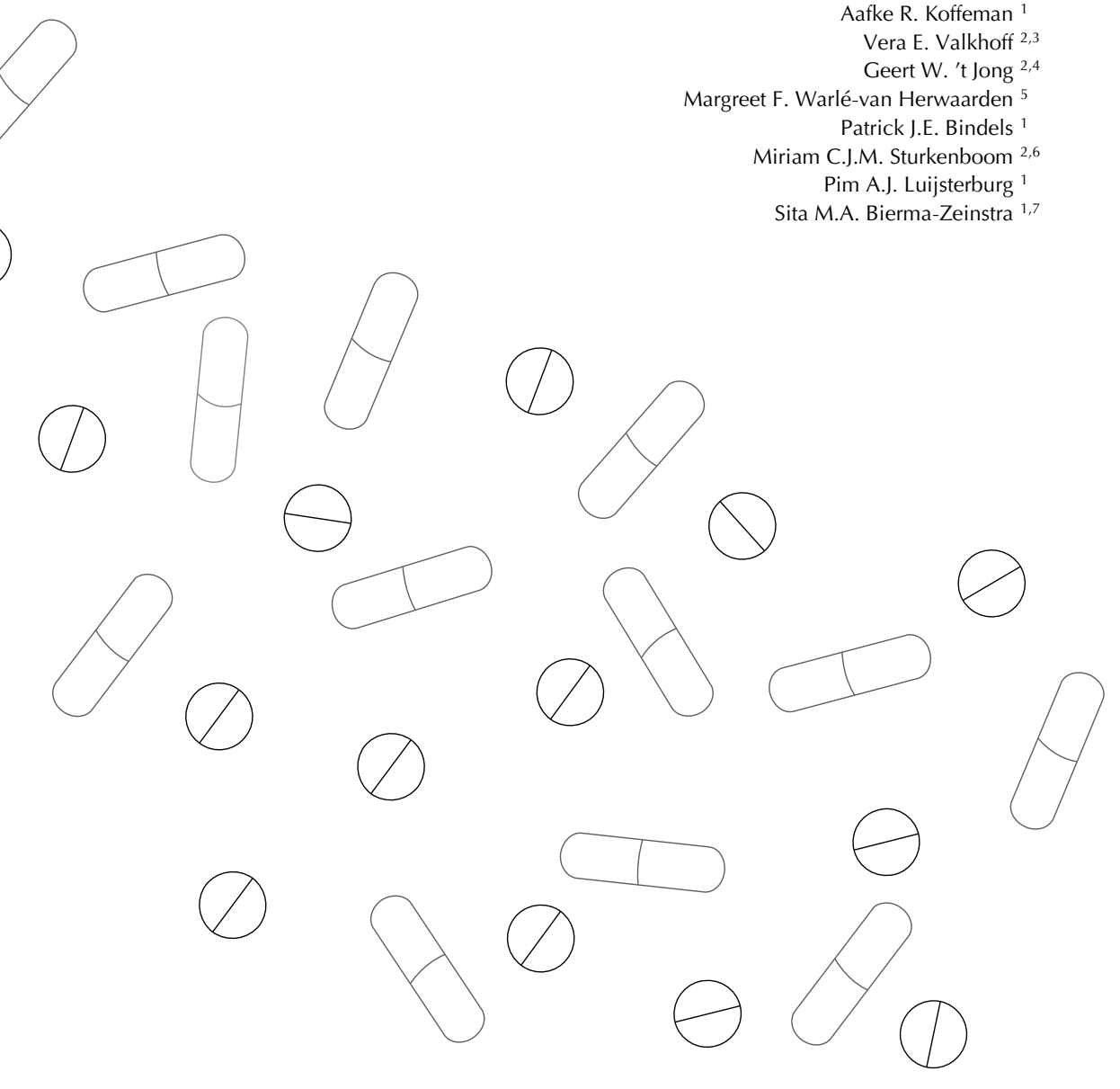


Abstract

Background

Non-steroidal anti-inflammatory drugs (NSAIDs), including both selective cyclooxygenase-2 inhibitors (coxibs) and traditional, non-selective NSAIDs (nsNSAIDs), are often prescribed in the treatment of musculoskeletal (MSK) complaints. These drugs are known to be associated with adverse ischemic cardiovascular (CV) events.

Aim

To examine the influence of ischemic cardiovascular risk on the prescription of nsNSAIDs and coxibs by general practitioners (GPs) in patients with MSK complaints.

Methods

Data were retrieved from the Integrated Primary Care Information (IPCI) database. In a study population comprising 474,201 adult patients presenting with a MSK complaint between 2000 and 2010, we assessed the cardiovascular risk profile and the frequency of coxib and nsNSAID prescription. Patients were considered at a high risk of ischemic CV events if they had a history of myocardial infarction (MI), angina pectoris (AP), stroke, transient ischemic attack (TIA) or peripheral arterial disease (PAD). Patients without any CV risk factors were considered to have a low risk of CV events. The influence of demographic factors, the type of MSK complaint presented and the risk of upper gastrointestinal (UGI) complications were also assessed.

Results

Of the 474,201 patients presenting with a MSK complaint, 24.4% were treated with a nsNSAID and 1.4% were prescribed a coxib. A total of 41,483 patients (8.8%) were found to have a high ischemic CV risk, of which 19.9% received a nsNSAID and 2.2% a coxib. These high CV risk patients were more likely to be prescribed a coxib than low CV risk patients (OR 1.88, 95% CI 1.75-2.02). The prescription of nsNSAIDs decreased over time in all risk groups and was lower in patients with a high CV risk than in patients with a low CV risk throughout the study period (OR 0.8, 95% CI 0.7-0.8). CV risk and UGI risk were strongly correlated, and patients with a high UGI risk were more likely to be prescribed a coxib (OR 2.8; 95% CI 2.7-3.0) and less likely to be prescribed a nsNSAID (OR 0.8, 95% CI 0.8-0.8) than patients with a low UGI risk.

Conclusions

Patients with musculoskeletal complaints and a high CV risk were more likely to be prescribed a coxib than patients with a low CV risk, although prescription of coxibs was low in both groups with less than two percent of patients receiving a coxib overall. High CV risk patients were less likely to be prescribed a nsNSAID than low CV risk patients. Nevertheless, one in five high CV risk patients received a nsNSAID, indicating that there is still room for improvement.

Introduction

Musculoskeletal (MSK) complaints are the most commonly presented complaints in the primary care population, with an incidence of 267 and a prevalence of 397 per 1000 patients in Dutch general practitioner (GP) practices in 2001.[130] Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in the treatment of MSK complaints because of their analgesic and anti-inflammatory properties. Their use is known to be associated with peptic ulcer disease and its complications, most notably upper gastrointestinal (UGI) bleeding, obstruction and perforation.[28, 29] The need to limit these UGI complications led to the development of selective cyclooxygenase-2 inhibitors (coxibs), which are associated with a significantly lower incidence of UGI complications when compared with traditional, non-selective NSAIDs (nsNSAIDs).[38-41]

However, shortly after the introduction of coxibs, concerns were raised regarding their cardiovascular (CV) safety profile. In September 2004, rofecoxib was withdrawn from world markets after a randomized controlled trial showed the incidence of stroke, myocardial infarction, or sudden cardiac death in patients taking rofecoxib was two times that of patients taking placebo.[47] An increased risk of ischemic CV events was also observed in studies of other coxibs, leading the European Medicines Agency to contraindicate the use of any coxib in patients with established ischemic heart disease, stroke or peripheral arterial disease in 2005.[131] Since then, there is increasing evidence that the risk of ischemic CV events is increased not only by the use of coxibs but also by the use of nsNSAIDs.[49-51] Recent guidelines and consensus therefore recommend avoiding the prescription of NSAIDs in general in patients at high CV risk.[53, 54, 132]

A previous study examining the use of coxibs between 2000 and 2004 found that coxib use increased at the expense of nsNSAID use during this time period, particularly in patients with a high risk of UGI complications, and that patients with cardiovascular disease were more likely to receive a coxib than those without cardiovascular disease.[133] It is not clear whether since then GPs take the cardiovascular risk profile into account when prescribing coxibs or nsNSAIDs in the treatment of MSK complaints. To examine the influence of ischemic cardiovascular risk on the prescription of nsNSAIDs and coxibs in patients with MSK complaints, we conducted a population-based cohort study in a large Dutch GP registration database between 2000 and 2010. In addition, we aimed to examine the influence of demographic factors, the type of MSK complaint presented and the presence of UGI risk factors on NSAID prescription in this group of patients.

Methods

Setting

A retrospective cohort study was conducted in the Integrated Primary Care Information (IPCI) database. This longitudinal observational GP research database contains the patient records of over one million patients throughout the Netherlands. In the Netherlands, all citizens are registered with a GP practice, which forms the first point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical record of each patient can therefore be assumed to contain all relevant medical information, including medical findings and diagnoses from secondary care. To further maximize the completeness of data, GPs contributing data to the IPCI database are not allowed to main-

tain a system of paper based records separate from the electronic medical records. The electronic records contain coded and anonymous data on patient demographics, symptoms (in free text), diagnoses using the International Classification for Primary Care 1 (ICPC-1[61]) and free text, clinical findings, referrals, laboratory findings and hospitalizations. Furthermore, there is a complete record of all drug prescriptions, their dosage regimen and the Anatomical Therapeutic Chemical (ATC) classification code.[60] Further details of the database have been described elsewhere.[102, 134]

Study cohort

The study population comprised all patients ≥ 18 years of age newly diagnosed with a MSK complaint between 1st January 2000 and 31st December 2010. Diagnoses were considered new if the patient had not been diagnosed with the same MSK complaint in the six months prior to consultation. Only patients with at least 12 months of valid database history prior to study entry were included, as this period was required to allow assessment of baseline characteristics. Diagnoses of MSK complaints were identified based on ICPC-1 coding. Included were symptomatic diagnoses of the back and neck (ICPC-1 code L01-L03), upper extremity (code L08-L12 and L92-L93), and lower extremity (code L13-L17), generalized and other symptoms of the musculoskeletal system (code L04-L07 and L19-L20), arthritis, including all forms of inflammatory arthritis, osteoarthritis and gout (code L84, L88-L91 and T92), radiculopathy (code L83 and L86), trauma (code L72-L81 and L96-L97), and other diseases of the musculoskeletal system (L29, L70-L71, L82, L85, L87, L95, L98-L99 and N93). If the patient consulted their GP again with the same complaint within six months of initial diagnosis, this consultation was considered part of the same MSK complaint episode. For each patient, only the first newly diagnosed complaint episode was included.

Cardiovascular and upper gastrointestinal risk

The age, gender and medical history of all included patients were assessed on the date of initial consultation. In line with clinical practice recommendations on the prescription of NSAIDs[54, 132], patients were considered at high CV risk if they had a history of myocardial infarction (MI), angina pectoris (AP), stroke, transient ischemic attack (TIA) or peripheral arterial disease (PAD). They were considered at moderate CV risk if they did not have one of the risk factors described above but did have a history of diabetes, hypertension or hyperlipidemia. Patients without any of these CV risk factors were considered at low CV risk.

In addition, risk factors for the occurrence of NSAID-related upper gastrointestinal (UGI) complications were identified. Based on the most recent Dutch national guideline on the prescription of NSAIDs[135], patients were considered at high UGI risk if they had a history of upper gastrointestinal bleeding or ulceration, were aged over 70 years or had two or more of the following risk factors: age 60-70 years, history of heart failure, diabetes or severe rheumatoid arthritis, use of antithrombotics, corticosteroids, or selective serotonin reuptake inhibitors. They were considered at moderate UGI risk if only one of the latter risk factors was present. In the absence of any of these risk factors patients were considered to have a low UGI risk.

The history of the diseases and conditions described above were assessed based on ICPC-1 coding and free text search strings. In the case of diabetes, hyperlipidemia and severe rheumatoid arthritis, the use of specific types of medication, identified based on ATC

classification code, was taken into account in addition to ICPC-1 coding as proxy for the identification of these three comorbidities.

NSAID prescription

For all included patients, the first NSAID prescription issued during the complaint episode was identified based on ATC classification code. Only NSAID prescriptions issued on the day of a consultation for the MSK complaint were included, to ensure that they were most likely intended as treatment for the MSK complaint. It has been suggested that the use of naproxen is less likely to increase cardiovascular risk than the use of other nsNSAIDs, and that the prescription of naproxen may be warranted in patients at a high CV risk.[53, 132, 136] To examine whether GPs take this possibility into account, a sensitivity analysis was conducted excluding naproxen, thereby only assessing the prescription of other types of nsNSAIDs.

Statistical analysis

Baseline characteristics were compared between high and low CV risk groups and between moderate and low CV risk groups using a χ^2-test for dichotomous variables and independent t-test for age as a continuous variables. Univariate analyses of potential predictors of NSAID prescription such as age, gender, CV risk and UGI risk were conducted and odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated by performing logistic regression analyses. All analyses were performed using SPSS version 17 (SPSS, Chicago, IL).

Results

Study cohort

Between 2000 and 2010, 804,261 adult patients aged over 18 years contributed data to the IPCI database. Of these, 474,201 patients presented with a MSK complaint and were included in the cohort. Baseline characteristics of included patients are described in Table 5.1. The most frequent MSK complaints were symptoms of the back and neck (22.8%), upper extremity (17.3%) and lower extremity (13.9%). Of the included patients, 67,184 (14.2%) had a moderate CV risk and 41,483 (8.8%) had a high CV risk. Within the moderate CV risk group, hypertension was the most frequent CV risk factor (68.6%). In the high CV risk group the most frequent CV risk factor was a history of myocardial infarction/angina pectoris (65.4%). Patients with CV risk factors were far more likely to have a high UGI risk: 60.3% of patients at a high CV risk were also at a high UGI risk, vs. 35.9% of patients at a moderate CV risk and only 7.0% of patients at a low CV risk ($P < 0.001$).

NSAID prescription

In total, 122,169 (25.8%) of all MSK complaint episodes were treated with a nsNSAID or a coxib (Table 5.2). The most commonly prescribed NSAIDs were diclofenac (54.6%), ibuprofen (12.2%) and naproxen (11.7%). Coxibs formed 5.3% of all NSAID prescriptions. Of these, rofecoxib was prescribed most frequently (49.1% of all coxib prescriptions). Patients in the high CV risk group were significantly more likely to receive a coxib than patients in the low CV risk group (2.2% vs. 1.1%, $P < 0.001$). The opposite was true for nsNSAIDs, which were prescribed less frequently in patients with a high CV risk than in those with a low CV risk (19.9% vs. 24.8%, $P < 0.001$). In the moderate CV risk group,

patients were more likely to receive both coxibs and nsNSAIDs than patients in the low CV risk group (2.0% vs. 1.1%, $P < 0.001$ and 25.1% vs. 24.8%, $P < 0.001$, respectively).

Table 5.1: Baseline characteristics in the study population

	Total		Low CV risk		Moderate CV risk		P-value*	High CV risk		P-value*
	n	(%)	n	(%)	n	(%)		n	(%)	
Total	474,201,	(100)	365,534,	(100)	67,184,	(100)		41,483,	(100)	
Age (mean ± SD)	46.6,	±,17.4	42.2,	±,15.5	58.9	±14.7	<0.001	65.3,	±,14.5	<0.001
Age category (years):										
18-35	144,797	(30.5)	138,809	(38.0)	4,532	(6.7)	<0.001	1,456	(3.5)	<0.001
36-50	147,497	(31.1)	127,403	(34.9)	14,773	(22.0)	<0.001	5,321	(12.8)	<0.001
51-65	108,132	(22.8)	69,526	(19.0)	25,735	(38.3)	<0.001	12,871	(31.0)	<0.001
> 65	73,775	(15.6)	29,796	(8.2)	22,144	(33.0)	<0.001	21,835	(52.6)	<0.001
Female	256,015,	(54.0)	196,550,	(53.8)	38,906	(57.9)	<0.001	20,559,	(49.6)	<0.001
NSAID prescription in 6 months prior to diagnosis	37,637	(7.9)	26,472	(7.2)	6,831	(10.2)	<0.001	4,334	(10.4)	<0.001
MSK complaint episode:										
Symptomatic diagnosis										
Back/neck	108,213	(22.8)	86,957	(24.1)	12,641	(18.8)	<0.001	7,615	(18.4)	<0.001
Upper extremity	82,026	(17.3)	63,366	(17.3)	11,810	(17.6)	0.126	6,850	(16.5)	<0.001
Lower extremity	66,107	(13.9)	49,802	(13.6)	10,003	(14.9)	<0.001	6,302	(15.2)	<0.001
Generalized/other	59,986,	(12.6)	46,572	(12.7)	8,035	(12.0)	<0.001	5,379	(13.0)	0.191
Arthritis	21,529	(4.5)	11,548	(3.2)	5,739	(8.5)	<0.001	4,242	(10.2)	<0.001
Inflammatory arthritis	4,676	(1.0)	2,874	(0.8)	1,045	(1.6)	<0.001	757	(1.8)	<0.001
Osteoarthritis	11,211	(2.4)	5,944	(1.6)	3,056	(4.5)	<0.001	2,211	(5.3)	<0.001
Gout	5,642	(1.2)	2,730	(0.7)	1,638	(2.4)	<0.001	1,274	(3.1)	<0.001
Radiculopathy	25,409	(5.4)	19,180	(5.2)	3,822	(5.7)	<0.001	2,407	(5.8)	<0.001
Trauma	55,211	(11.6)	45,586	(12.5)	6,064	(9.0)	<0.001	3,561	(8.6)	<0.001
Other	55,720	(11.8)	41,523	(11.4)	9,070	(13.5)	<0.001	5,127	(12.4)	<0.001
Individual CV risk factors†:										
Diabetes	28,597,	(6.0)	-	-	20,847	,(31.0)	-	7,750	(18.7)	-
Hypertension	63,841,	(13.5)	-	-	46,077	,(68.6)	-	17,764,	(42.8)	-
Hyperlipidemia	30,600,	(6.5)	-	-	18,129	,(27.0)	-	12,471	(30.1)	-
MI/AP	27,118,	(5.7)	-	-	-	-	-	27,118,	(65.4)	-
Stroke/TIA	14,118,	(3.0)	-	-	-	-	-	14,118	(34.0)	-
PAD	5,715,	(1.2)	-	-	-	-	-	5,715,	(13.8)	-
UGI risk group:										
Low UGI risk	335,556,	(70.8)	305,168	(83.5)	22,003	(32.8)	<0.001	8,385	(20.2)	<0.001
Moderate UGI risk	63,843,	(13.5)	34,692,	(9.5)	21,058	(31.3)	<0.001	8,093	(19.5)	<0.001
High UGI risk	74,802	(15.8)	25,674	(7.0)	24,123	(35.9)	<0.001	25,005	(60.3)	<0.001

CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drug; MSK, musculoskeletal; MI, myocardial infarction; AP, angina pectoris; TIA, transient ischemic attack; PAD, peripheral arterial disease; UGI, upper gastrointestinal.
** vs. low CV risk.*
† Risk factors used to define low, moderate and high CV risk groups.

Table 5.2: Prescription of nsNSAIDs and coxibs

	Total		Low CV risk		Moderate CV risk		*P*-value*	High CV risk		*P*-value*
	n	(%)	n	(%)	n	(%)		n	(%)	
Total	474,201,	(100)	365,534,	(100)	67,184,	(100)		41,483,	(100)	
Coxib prescription	6,456,	(1.4)	4,161,	(1.1)	1,362	(2.0)	<0.001	933	(2.2)	<0.001
Rofecoxib	3,173,	(0.7)	2,155,	(0.6)	574	(0.9)	<0.001	444	(1.1)	<0.001
Celecoxib	1,155,	(0.2)	693	(0.2)	275	(0.4)	<0.001	187	(0.5)	<0.001
Etoricoxib	2,117,	(0.4)	1,308,	(0.4)	511	(0.8)	<0.001	298	(0.7)	<0.001
Valdecoxib	11	(0.002)	5	(0.001)	2	(0.003)	0.666	4	(0.01)	0.004
nsNSAID prescription	115,713,	(24.4)	90,615,	(24.8)	16,852	(25.1)	0.107	8,246,	(19.9)	<0.001
Diclofenac	66,724,	(14.1)	53,234,	(14.6)	9,412	(14.0)	<0.001	4,087	(9.8)	<0.001
Ibuprofen	14,855,	(3.1)	12,078,	(3.3)	1,843	(2.7)	<0.001	934	(2.3)	<0.001
Naproxen	14,337,	(3.0)	11,437,	(3.1)	1,930	(2.9)	<0.001	970	(2.3)	<0.001
Other	19,797,	(4.2)	13,866,	(3.8)	3,667	(5.5)	<0.001	2,264	(5.5)	<0.001

CV, cardiovascular; nsNSAID, non-selective non-steroidal anti-inflammatory drug.
** vs. low CV risk.*

Predictors of nsNSAID and coxib prescription

Table 5.4 describes these and other predictors of nsNSAID and coxib prescription in more detail. The individual CV risk factors were all associated with a higher chance of coxib prescription and a lower chance of nsNSAID prescription. Patients with a history of MI/AP were most likely to receive a coxib (OR 2.0; 95% CI 1.8-2.2 coxib vs. no NSAID), followed by patients suffering from diabetes (OR 1.9; 95% CI 1.8-2.1 coxib vs. no NSAID). Prescription of nsNSAIDs was lowest in patients with a history of stroke/TIA (OR 0.7; 95% CI 0.7-0.7 nsNSAID vs. no NSAID).

The odds of receiving a coxib increased with age (OR 5.6; 95% CI 5.0-5.9 for oldest vs. youngest age group). For nsNSAIDs, the odds of prescription increased in middle age, but decreased in old age (OR 0.9; 95% CI 0.9-0.9 for oldest vs. youngest age group). The frequency of NSAID prescription varied depending on the type of MSK complaint diagnosed. Patients suffering from arthritis, symptoms of the back or neck, or radiculopathy were most likely to receive NSAID treatment (35.2%, 34.9% and 34.3%, respectively). The prescription of coxibs was particularly high in patients suffering from arthritis. The odds of receiving a coxib were 14 times higher in patients with arthritis than in patients with MSK complaints after trauma, which was set as the reference group. When corrected for age and gender, this difference was still tenfold (adjusted OR 9.8; 95% CI 8.4-11.5, not shown in table).

UGI risk was also a strong predictor of coxib prescription (OR 2.3; 95% CI 2.2-2.5 for high UGI risk vs. low UGI risk and OR 2.8; 95% CI 2.7-3.0 for moderate UGI risk vs. low UGI risk). A moderate UGI risk was associated with a slightly higher chance of nsNSAID prescription when compared with a low UGI risk (OR 1.1; 95% CI 1.1-1.1), whereas a high UGI risk was associated with a lower chance of nsNSAID prescription (OR 0.8; 95% CI 0.8-0.8).

Prescription of nsNSAIDs and coxibs over time

The prescription of nsNSAIDs decreased significantly over time, from 29.1% in 2000 to 19.0% in 2010 (OR 0.6; 95% CI 0.6-0.6 for 2010 vs. 2000). This decrease occurred mainly during the first four years and last two years of the time period, with a temporary increase between 2004 and 2005. For coxibs, prescription initially increased until 2004, by which point 13.2% of all NSAID prescriptions concerned a coxib. In these first five years of the study period, rofecoxib was the most frequently prescribed (74.3% of all coxib prescriptions). In 2005 a decrease in coxib prescriptions occurred, followed by a slight temporary increase in nsNSAID prescriptions.

Figure 5.1 shows the percentage of patients at a high and at a low CV risk prescribed a nsNSAID or a coxib over time. The drop in coxib prescription in 2005 occurred not only in patients with a high CV risk, but also in patients with a low CV risk. As reported in Table 5.3 the odds of coxib prescription were significantly higher in patients at high CV risk than in patients at low CV risk, not only between 2000 and 2004 (OR 2.0; 95% CI 1.8-2.2), but also between 2005 and 2010 (OR 1.9; 95% CI 1.7-2.2). The odds of nsNSAID prescription remained significantly lower in patients at high CV risk than in patients at low CV risk in both time periods (OR 0.8; 95% CI 0.8-0.8 and OR 0.8; 95% CI 0.7-0.8, respectively). In a sensitivity analysis in which naproxen was excluded, the odds of prescription of a nsNSAID vs. no NSAID in high CV risk patients vs. low CV risk patients were the same as that of all nsNSAIDs vs. no NSAIDs in both time period (OR 0.8; 95% CI 0.8-0.9 and OR 0.8, 96% CI 0.7-0.8, for 2000-2004 and 2005-2010 respectively).

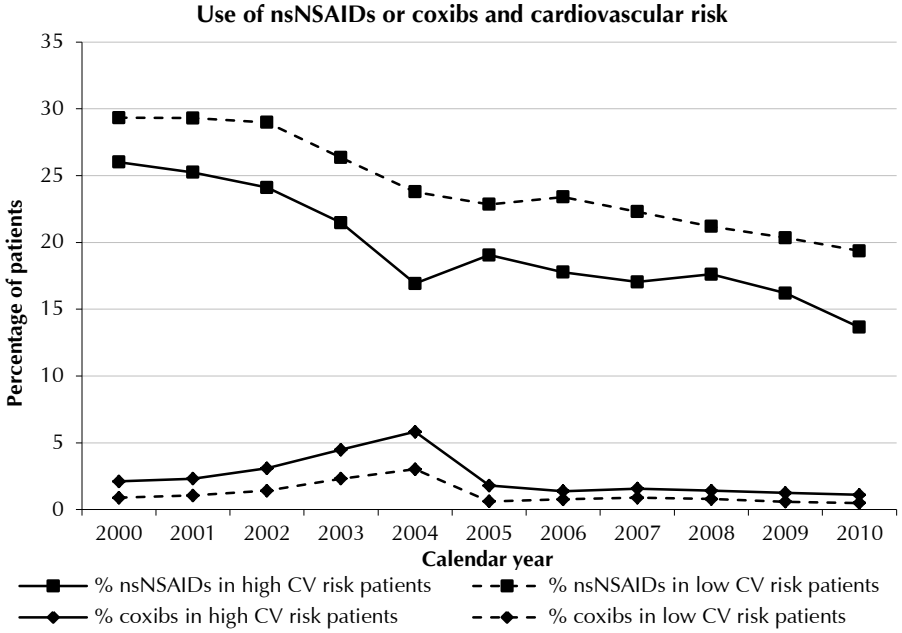


Figure 5.1: Percentage of patients with a high CV risk and with a low CV risk prescribed a nsNSAID or coxib per year

Table 5.3: Prescription of coxibs and nsNSAIDs vs. no NSAID in moderate and high CV risk patients vs. low CV risk patients per time period

Time period	CV risk group	Number of patients		No NSAID		nsNSAID		Coxib		nsNSAID vs. no NSAID† adj. OR (95% CI)		Coxib vs. no NSAID† adj. OR (95% CI)	
		n	(%)	n	(%)	n	(%)	n	(%)				
2000-2004	Low CV risk	181 443	(100)	127 912	(70.5)	50 670	(27.9)	2 861	(1.6)	1.0	(ref.)	1.0	(ref.)
	Moderate CV risk	27 421	(100)	18 939	(69.1)	7 703	(28.1)	779	(2.8)	1.0	(1.0-1.1)	1.9	(1.7-2.1)
	High CV risk	18 574	(100)	13 619	(73.3)	4 349	(23.4)	606	(3.3)	0.8	(0.8-0.8)	2.0	(1.8-2.2)
2005-2010	Low CV risk	184 091	(100)	142 846	(77.6)	39 945	(21.7)	1 300	(0.7)	1.0	(ref.)	1.0	(ref.)
	Moderate CV risk	39 763	(100)	30 031	(75.5)	9 149	(23.0)	583	(1.5)	1.1	(1.1-1.1)	2.3	(1.9-2.4)
	High CV risk	22 909	(100)	18 685	(81.6)	3 897	(17.0)	327	(1.4)	0.8	(0.7-0.8)	1.9	(1.7-2.2)

CV, cardiovascular; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug.
† adjusted for year of MSK complaint episode within the time period.

Table 5.4: Predictors of prescription of nsNSAIDs and coxibs

	No NSAID prescribed		nsNSAID prescribed		Coxib prescribed		nsNSAID vs. no NSAID		Coxib vs. no NSAID	
	n	(%)	n	(%)	n	(%)			OR (95% CI)	
Age category (years):										
18-35	114,077	(78.8)	29,948	(20.7)	772	(0.5)	1	(ref)	1	(ref)
36-50	105,154	(71.3)	40,815	(27.7)	1,528	(1.0)	1.5	(1.5-1.5)	2.2	(1.97-2.34)
51-65	76,359	(70.6)	29,688	(27.5)	2,085	(1.9)	1.5	(1.5-1.5)	4.0	(3.71-4.38)
> 65	56,442	(76.5)	15,262	(20.7)	2,071	(2.8)	1.0	(1.0-1.1)	5.4	(4.99-5.89)
Gender:										
Male	159,766	(73.2)	55,909	(25.6)	2,511	(1.2)	1	(ref)	1	(ref)
Female	192,266	(75.1)	59,804	(23.4)	3,945	(1.5)	0.9	(0.9-0.9)	1.3	(1.24-1.37)
MSK complaint:										
Trauma	49,345	(89.4)	5,605	(10.2)	261	(0.5)	1	(ref)	1	(ref)
Symptomatic diagnosis										
Back/neck	70,464	(65.1)	36,477	(33.7)	1,272	(1.2)	4.6	(4.4-4.7)	3.4	(3.0-3.9)
Upper extremity	56,150	(68.5)	24,558	(29.9)	1,318	(1.6)	3.9	(3.7-4.0)	4.4	(3.9-5.1)
Lower extremity	54,211	(82.0)	11,109	(16.8)	787	(1.2)	1.8	(1.7-1.9)	2.8	(2.4-3.2)
Generalized/other	46,926	(78.2)	12,308	(20.5)	752	(1.3)	2.3	(2.2-2.4)	3.0	(2.6-3.5)
Arthritis	13,943	(64.8)	6,545	(30.4)	1,041	(4.8)	4.1	(4.0-4.3)	14.1	(12.3-16.2)
Inflammatory arthritis	3,027	(64.7)	1,386	(29.6)	263	(5.6)	4.0	(3.8-4.3)	16.4	(13.8-19.6)
Osteoarthritis	8,239	(73.5)	2,349	(21.0)	623	(5.6)	2.5	(2.4-2.6)	14.3	(12.3-16.6)
Gout	2,677	(47.4)	2,810	(49.8)	155	(2.7)	9.2	(8.7-9.8)	10.9	(8.9-13.4)
Radiculopathy	16,699	(65.7)	8,269	(32.5)	441	(1.7)	4.4	(4.2-4.5)	5.0	(4.3-5.8)
Other	44,294	(79.5)	10,842	(19.5)	584	(1.0)	2.2	(2.1-2.2)	2.5	(2.2-2.9)
Individual CV risk factors:										
No CV risk factors	270,758	(74.1)	90,615	(24.8)	4,161	(1.1)	1	(ref)	1	(ref)
Diabetes	21,113	(73.8)	6,864	(24.0)	620	(2.2)	1.0	(1.0-1.0)	1.9	(1.8-2.1)
Hypertension	28,368	(64.6)	14,261	(32.5)	1,312	(3.0)	0.9	(0.9-0.9)	1.8	(1.7-1.9)
Hyperlipidemia	23,118	(75.5)	6,853	(22.4)	629	(2.1)	0.9	(0.9-0.9)	1.8	(1.6-1.9)
MI/AP	21,113	(77.9)	5,356	(19.8)	649	(2.4)	0.8	(0.7-0.8)	2.0	(1.8-2.2)
Stroke/TIA	11,209	(79.4)	2,626	(18.6)	283	(2.0)	0.7	(0.7-0.7)	1.6	(1.5-1.9)
PAD	4,484	(78.5)	1,117	(19.5)	114	(2.0)	0.7	(0.7-0.8)	1.7	(1.4-2.0)
CV risk group:										
Low CV risk	270,758	(74.1)	90,615	(24.8)	4,161	(1.1)	1	(ref)	1	(ref)
Moderate CV risk	48,970	(72.9)	16,852	(25.1)	1,362	(2.0)	1.0	(1.0-1.1)	1.8	(1.7-1.9)
High CV risk	32,304	(77.9)	8,246	(19.9)	933	(2.2)	0.8	(0.7-0.8)	1.9	(1.8-2.0)
UGI risk group:										
Low UGI risk	248,705	(74.1)	83,753	(25.0)	3,098	(0.9)	1	(ref)	1	(ref)
Moderate UGI risk	45,724	(71.6)	16,792	(26.3)	1,327	(2.1)	1.1	(1.1-1.1)	2.3	(2.2-2.5)
High UGI risk	57,603	(77.0)	15,168	(20.3)	2,031	(2.7)	0.8	(0.8-0.8)	2.8	(2.7-3.0)
Year of MSK complaint:										
2000	44,787	(69.8)	18,648	(29.1)	688	(1.1)	1	(ref)	1	(ref)
2001	35,363	(69.7)	14,757	(29.1)	639	(1.3)	1.0	(1.0-1.0)	1.2	(1.1-1.3)
2002	28,836	(69.8)	11,790	(28.5)	689	(1.7)	1.0	(1.0-1.0)	1.6	(1.4-1.7)
2003	25,604	(71.2)	9,362	(26.0)	988	(2.7)	0.9	(0.9-0.9)	2.5	(2.3-2.8)
2004	25,880	(73.3)	8,165	(23.1)	1,242	(3.5)	0.8	(0.7-0.8)	3.1	(2.8-3.4)
2005	28,009	(76.7)	8,195	(22.5)	298	(0.8)	0.7	(0.7-0.7)	0.7	(0.6-0.8)
2006	32,930	(75.9)	10,046	(23.2)	408	(0.9)	0.7	(0.7-0.8)	0.8	(0.7-0.9)
2007	38,280	(76.8)	10,992	(22.1)	566	(1.1)	0.7	(0.7-0.7)	1.0	(0.9-1.0)
2008	35,997	(77.9)	9,772	(21.1)	452	(1.0)	0.7	(0.6-0.7)	0.8	(0.7-0.9)
2009	32,684	(79.0)	8,394	(20.3)	296	(0.7)	0.6	(0.6-0.6)	0.6	(0.5-0.7)
2010	23,662	(80.4)	5,592	(19.0)	190	(0.6)	0.6	(0.6-0.6)	0.5	(0.5-0.6)

NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; CV, cardiovascular; MSK, musculoskeletal; MI, myocardial infarction; AP, angina pectoris; TIA, transient ischemic attack; PAD, peripheral arterial disease; UGI, upper gastrointestinal.

Discussion

In this study, we examined the prescription of NSAIDs in the treatment of musculoskeletal complaints by general practitioners, over the course of the last decade in which evidence emerged regarding the cardiovascular risks of these drugs. We found that one quarter of all patients presenting with a MSK complaint were treated with an NSAID. Prescription varied widely depending on the type of MSK complaint diagnosed. Patients suffering from arthritis and back or neck disorders were most likely to receive NSAID treatment, whilst NSAID prescription for symptoms of the lower extremity and MSK complaints after trau-

ma was relatively low. Diclofenac, ibuprofen and naproxen together accounted for four fifths of all NSAID prescriptions. Overall, only one in twenty NSAID prescriptions concerned a coxib. In patients suffering from arthritis, however, coxibs were prescribed far more frequently than in patients presenting with other types of MSK complaints. In this group of patients, one in seven NSAID prescriptions was a coxib.

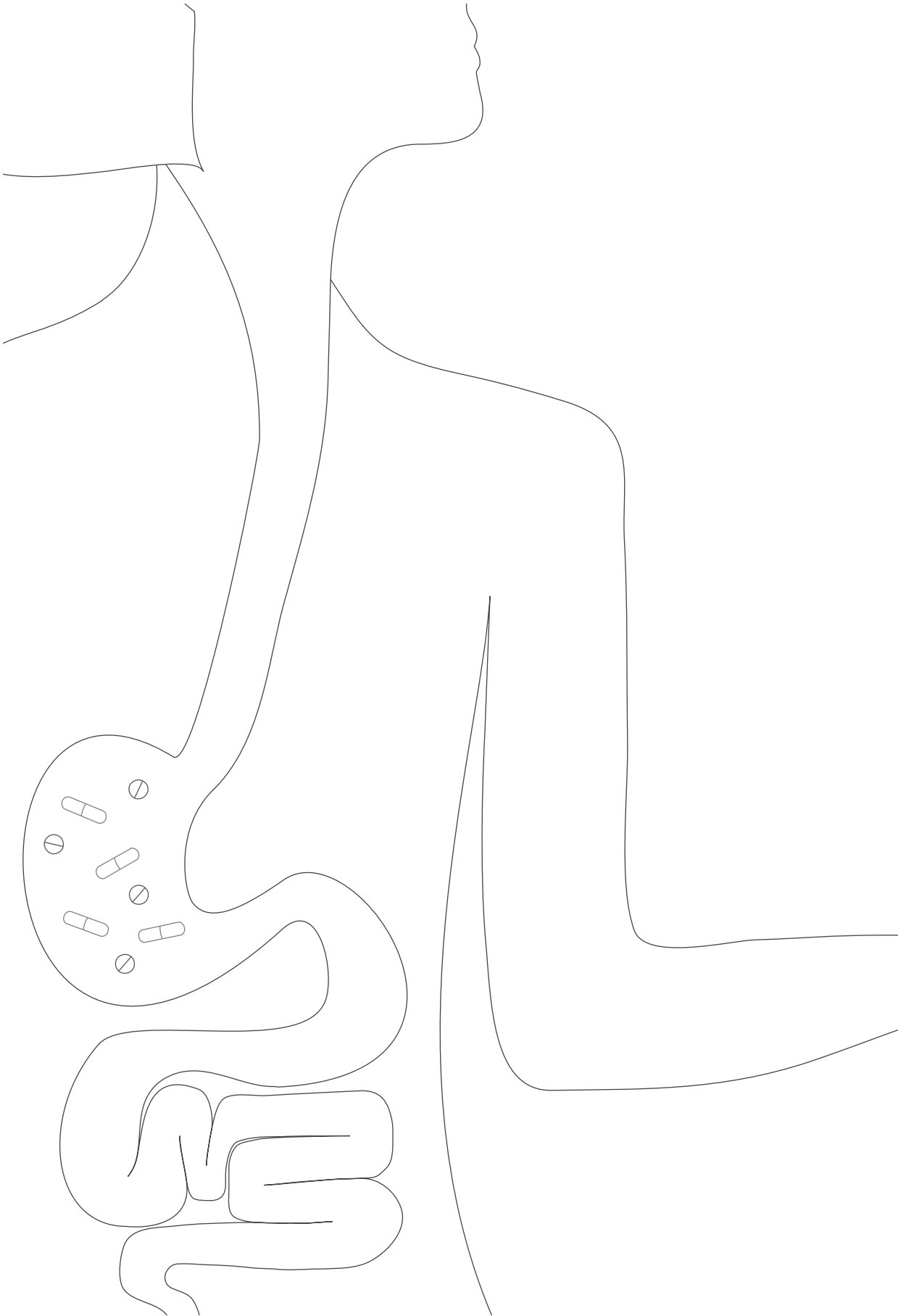
In line with previous reports[46, 117, 133], we found that coxibs gained in popularity during the first five years of marketing in the Netherlands, followed by a decrease after rofecoxib was withdrawn from the market. The increase in coxib prescription at the beginning of the decade was accompanied by a decrease in nsNSAID prescription. Prescription of nsNSAIDs showed a temporary increase after the withdrawal of rofecoxib in 2004, and subsequently remained steady until 2008, after which a decrease was again observed. Patients with a high CV risk presenting with musculoskeletal complaints were more likely to be treated with a coxib than patients with a low risk of developing CV events. Interestingly, the decrease in coxib prescription observed after 2004 occurred not only in patients with a high CV risk, but equally in patients with a low CV risk. So although prescription of rofecoxib was eliminated in this group after withdrawal of this drug from the market, celecoxib, etoricoxib and valdecoxib continued to be prescribed to high CV risk patients. Prescription of coxibs remained almost twice as high in patients with a high CV risk than in patients with a low CV risk, even after their use was contraindicated in these patients by the European Medicines Agency in 2005.[131] Conversely, nsNSAIDS were prescribed less frequently in high CV risk patients than in low CV risk patients throughout the study period. This difference in nsNSAID prescription between high and low CV risk patients was already present over the first part of the decade, before evidence of an association between nsNSAID use and cardiovascular events first emerged.[49, 50]

A strong overlap was found between CV risk and UGI risk. The percentage of patients with a high UGI risk profile was over eight times higher in the high CV risk group than in the low CV risk group, which can be explained by the fact that patients with a high CV risk were older, were more likely to suffer from diabetes or heart failure and were more likely to use antithrombotics, all of which are related to an increased UGI risk. It therefore seems likely that the observed differences in coxib and nsNSAID prescription in patients with a high CV risk vs. patients with a low CV risk, which remained present throughout the study period, are explained by the fact that GPs base their choice of NSAID therapy on the patient's UGI risk profile, rather than taking their CV risk profile into account. When corrected for UGI risk using a multivariate logistic regression analysis, the odds of coxib prescription vs. no NSAID prescription were no longer significantly higher in high CV risk patients than in low CV risk patients (adjusted OR 0.95; 95% CI 0.87-1.03), whilst the odds of nsNSAID prescription remained significantly lower (adjusted OR 0.84; 95% CI 0.82-0.87). However, the results of these multivariate analyses should be interpreted with caution, as CV risk and UGI risk were highly correlated variables.

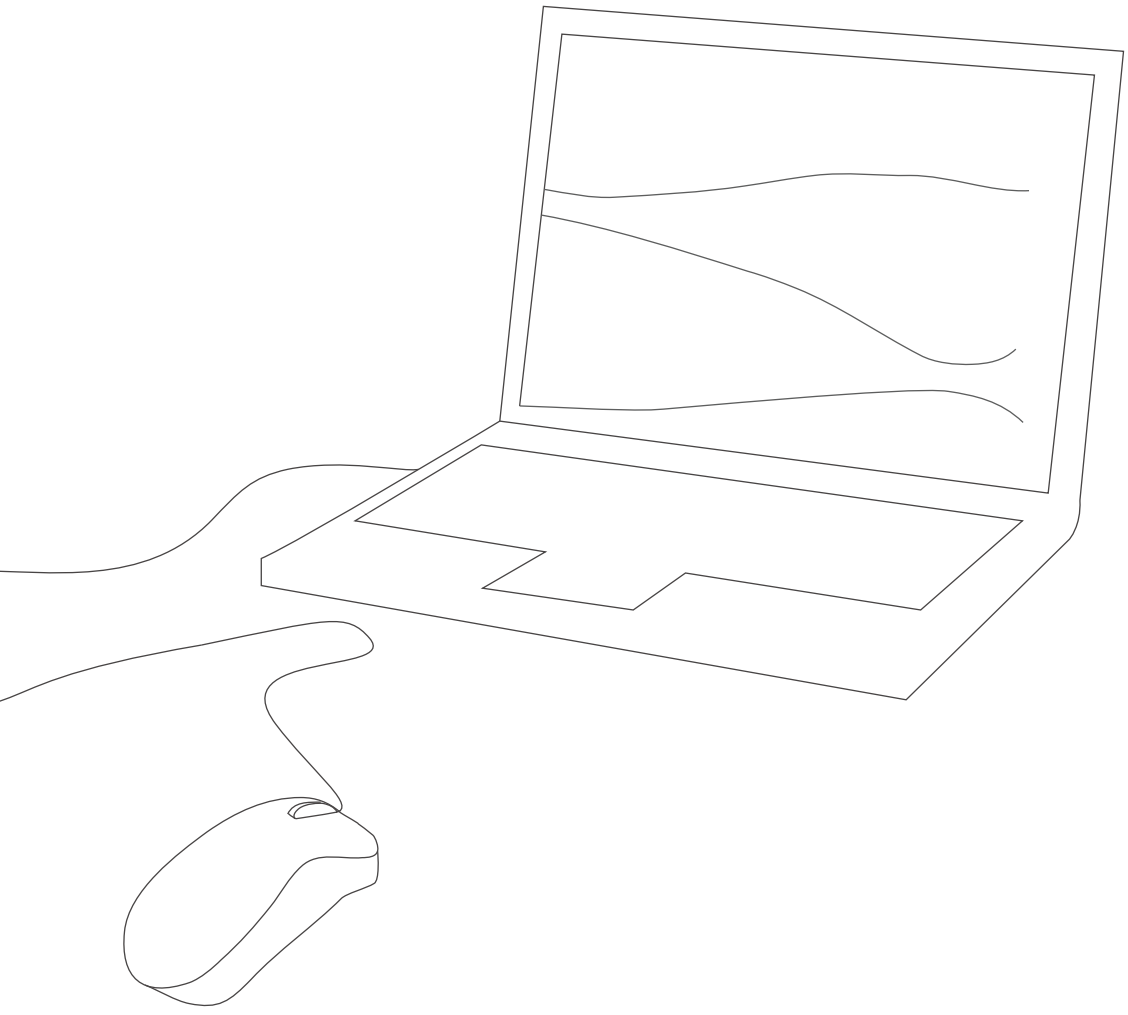
The strength of this study is that it was conducted in a database containing a large number of patients reflecting the Dutch general population. By conducting free text searches in addition to assessing ICPC codes and medication use, we were able to accurately identify all relevant CV and UGI risk factors. Nonetheless, there are several potential limitations that should be considered when reviewing the results. First, only patients presenting with an ICPC coded MSK complaint were included in the cohort. As some GPs may apply the ICPC coding more diligently than others, this may have led to an underestimation or overestimation of NSAID treatment, if the prescribing behavior of GPs is in any way related to their tendency to apply the ICPC coding. Secondly, we had to make certain assumptions in determining whether the NSAID prescribed was intended as treatment for the

MSK complaint. We only considered NSAID prescriptions to be intended as treatment of the MSK complaint if the first NSAID prescription issued during a MSK complaint episode was issued on the day of a consultation for that complaint. Thus, if an NSAID was prescribed at another point in time, this prescription was not taken into account. In order to test whether doing so was likely to lead to an underestimation of the percentage of MSK complaints treated with NSAIDs, we assessed the probability of NSAID prescription on days on which a consultation occurred and on the 30 days following consultation. On a consultation day, the probability of NSAID prescription was 0.258, whereas the maximum probability on any of the subsequent 30 days did not exceed 0.004. It therefore seems unlikely that an underestimation occurred. As patients may present more than one complaint when consulting their GP, the assumption that an NSAID prescribed on the day of a MSK complaint is intended as treatment for this complaint could also potentially lead to an overestimation. We therefore also assessed whether the patients presented any other, non-musculoskeletal complaints associated with pain on the day of an NSAID-treated MSK complaint, for which the NSAID prescription may have be intended. We found this to be the case in only 0.7% of all NSAID prescriptions. Finally, we did not have any information on over-the-counter (OTC) use of analgesics. Although coxibs are not available without prescription in the Netherlands, nsNSAIDs and other analgesics such as paracetamol are freely available. As the IPCI database only contains information on medication prescribed by physicians, we were unable to assess whether any additional OTC nsNSAIDs or paracetamol were used by patients. While this consideration is important, our objective in this study was to determine the association between cardiovascular risk and NSAID prescription by the GP.

In conclusion, patients with a high CV risk consulting their GP for a musculoskeletal complaint were more likely to be prescribed a coxib than patients with a low CV risk. Conversely, they were less likely to be prescribed a nsNSAID. It seems likely that the observed differences in prescription in patients with a high CV risk vs. patients with a low CV risk may be explained by GPs basing their choice of NSAID therapy on the patients' UGI risk profile, which is strongly correlated with their CV risk profile. Although international guidelines have provided recommendations on NSAID prescription in patients with CV risk factors[53, 132], as of yet no national Dutch guideline has been published specifically on this topic. The most recent Dutch guideline specifically on NSAID prescription was published in 2003[135], at which point in time little was known about the cardiovascular risks associated with NSAID use. Since then, however, other general prescription guidelines and consensus have been published by the Dutch College of General Practitioners and the Dutch Ministry of Health containing recommendations and warnings regarding the prescription of coxibs and nsNSAIDs in patients with CV risk factors.[54, 137] It appears that over time GPs have grown more cautious when prescribing NSAIDs. The prescription of coxibs has remained very low since 2005, with less than one percent of all patients being prescribed a coxib. The prescription of nsNSAIDs, although much higher, has decreased over time in both high and low CV risk patients. Nonetheless, it appears that GPs do not fully consider the CV risks associated with NSAID use when prescribing NSAIDs in patients presenting with MSK complaints, indicating that there is still room for improvement.



Safety Assessment and Prediction



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Chapter 6

Suboptimal gastroprotective coverage of NSAID use and the risk of upper gastrointestinal bleeding and ulcers: an observational study using three European databases

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Abstract

Background

Gastro-protective agents (GPAs) are co-prescribed with NSAIDs to lower the risk for upper gastrointestinal (UGI) events. It is unknown to which extent the protective effect is influenced by therapy adherence.

Aim

To study the association between GPA adherence and UGI events among non-selective (ns)NSAID users.

Methods

The General Practice Research Database (United Kingdom: 1998-2008), the Integrated Primary Care Information database (the Netherlands: 1996-2007) and the Health Search/CSD Longitudinal Patient Database (Italy: 2000-2007) were used. A nested case-control design was employed within a cohort of nsNSAID users aged ≥ 50 years, who also used a GPA. Cases with a UGI event (UGI bleeding and/or symptomatic UGI ulcer with/without obstruction/perforation) were matched to event-free members of the cohort on age, sex, database, and calendar time. Adherence to GPAs was calculated as the proportion of nsNSAID treatment days covered by a GPA prescription. Adjusted odds ratios (OR) with 95%-confidence intervals (CI) were calculated.

Results

The cohort consisted of 618,684 NSAID users, generating 1,107,266 nsNSAID episodes. Of these, 117,307 (10.6%) were (partly) covered by GPAs, 4.9% of which with a GPA coverage lower than 20% (non-adherence), and 68.1% with a GPA coverage over 80% (full adherence). We identified 339 patients with an event. Among non-adherers, the OR was 2.39 (95%CI:1.66-3.44) for all UGI events and 1.89 (95%CI:1.09-3.28) for UGI bleeding alone, compared with full adherers.

Conclusions

The risk of UGI events was significantly higher in nsNSAID users with GPA non-adherence. This underlines the importance of strategies to improve GPA adherence.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties, and are indicated mainly for pain management in musculoskeletal injury, osteoarthritis and rheumatoid arthritis. The use of NSAIDs may lead to upper gastrointestinal (UGI) symptoms such as dyspepsia, and to more severe events such as gastroduodenal ulcers or UGI bleeding. The incidence of such clinically significant UGI events during NSAID use has been estimated at 1-2.5/100 person years[83, 138] and is associated with substantial mortality.[139] Non-selective NSAIDs (nsNSAIDs) inhibit the cyclooxygenase (COX) 1 enzyme more strongly than COX-2 selective inhibitors (coxibs).[140] As COX-1 is involved in gastroprotection, nsNSAIDs are believed to increase the risk of UGI events to a higher degree than coxibs.[39]

To prevent UGI events during nsNSAID use, evidence-based guidelines recommend the concomitant use of gastroprotective agents (GPAs)[141], mostly in nsNSAID users with one or more risk factors. The guidelines differ slightly in their definition of risk factors, but most consider advanced age, the history of a UGI event, and the use of antiplatelet agents, anticoagulants, or corticosteroids as risk factors.[53, 88, 142] Some guidelines also mention other factors, including the use of selective serotonin reuptake inhibitors (SSRIs), infection with *Helicobacter pylori* (*H. pylori*) or the presence of heart failure.[53, 88, 142]

The actual concomitant use of GPAs with nsNSAIDs can be problematic for two reasons: suboptimal prescription by the physician and suboptimal use by the patient. Although the situation has been recently improving[46], even recent observational studies estimated that 67-90% of the nsNSAID users with at least one risk factor did not receive GPAs as recommended.[96, 98, 103, 113, 143] Two other studies showed that 25-50% of the patients did not use their GPA on a daily basis.[144, 145]

Lack of adherence to concomitant GPAs was shown to be associated with an increased risk of nsNSAID-induced UGI events, but the studies concerned were limited by lack of power especially to detect an effect on the risk of UGI bleeding.[118, 144] To investigate the extent of suboptimal GPA adherence during nsNSAID use and the consequences thereof, a case-control study nested within a cohort of nsNSAID plus GPA users aged 50 years or older drawn from three similar European population-based primary care research databases was conducted. Combining data from comparable medical record databases in different countries (United Kingdom, the Netherlands and Italy) enabled increased statistical power and expanded the inclusion to a wide variety of NSAIDs, resulting in increased generalizability.

Methods

Data sources

Data for this study were obtained from three similar population-based primary care registries from the United Kingdom (UK), the Netherlands (NL) and Italy (IT). In the British, Dutch and Italian national healthcare systems, all citizens are registered with a primary care practice, which records all relevant medical information. Data recorded include demographics, symptoms and diagnoses, laboratory test results, drug prescriptions, specialist referrals, clinical diagnoses from outpatient visits and hospital discharge summaries. The databases comply with European Union guidelines on the use of medical data for

medical research and have been demonstrated valid for pharmacoepidemiology research. In the EU-ADR project it was shown that primary care databases from Italy, the Netherlands and the UK were very similar in terms of UGI event rates.[18] The databases are briefly described below.

General Practice Research Database (GPRD) (1998-2008)

The General Practice Research Database (GPRD) is a dynamic longitudinal primary care research database from the UK that was established in 1987. Currently, there are more than 500 active practices and 4.4 million active patients who are demographically representative of the UK population. Symptoms and diagnoses are recorded using the thesaurus of clinical terms used in the UK (READ codes) and information on drug prescriptions is coded using the Multilex product dictionary and British National Formulary codes. When available, we requested additional information on hospitalizations from Hospital Episode Statistics (HES) data including procedures coded according to the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th revision and diagnoses coded according to the International Classification of Diseases, 10th revision.

Integrated Primary Care Information database (1996-2007)

The Integrated Primary Care Information (IPCI) database is a dynamic longitudinal primary care research database from the Netherlands that was set up in 1992. The database covers approximately 800,000 patients from 150 active practices. Symptoms and diagnoses are recorded using the International Classification for Primary Care (ICPC[61]) and free text; drug prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC[60]) classification.

Health Search/Cegedim Strategic Data Longitudinal Patient Database (2000-2007)

The Health Search/Cegedim Strategic Data Longitudinal Patient Database (HSD) is a dynamic longitudinal primary care database from Italy that was established in 1998. The HSD currently contains data from over 900 general practitioners and covers approximately 1.6 million patients.[146] Symptoms and diagnoses are recorded using the International Classification of Diseases, 9th revision, Clinical Modification (ICD-9-CM). Information on drug prescriptions is coded according to the ATC classification.

The protocol of the present study was approved by the Scientific and Ethical Advisory Board of each database.

Source population

For each database, patients were eligible for inclusion in the source population from the start of the study period, at 50 years of age or the date on which at least 1 year of valid enrollment data were obtained (whichever was latest). Eligibility ended at death, last data supply, transferring out of the practice, or end of the study period, whichever came first.

Study cohorts and exposure assessment

Two types of exposure cohorts were created: (i) NSAID cohort (nsNSAIDs plus coxibs) and (ii) nsNSAID plus GPA sub-cohort, which was selected from the NSAID cohort. For each database, the NSAID cohort included all patients from the source population who received at least one NSAID prescription (ATC codes (or equivalent BNF code): M01AA - M01AX, or ATC codes N02BA01, N02BA15 or N02BA51 at a dose > 325 mg/day) during

the eligibility period, and who did not receive any NSAID prescription during the 6 months previously. All identified new users of NSAIDs were followed from the start of NSAID therapy to the end of the eligibility period or occurrence of the study outcome (whichever came earliest). Patients with a neoplasm of the gastrointestinal tract, alcohol abuse, chronic liver disease, Crohn's disease, ulcerative colitis or a coagulopathy recorded before or during follow-up were excluded from the cohort.

Within the NSAID cohort, episodes of NSAID use were defined as consecutive NSAID prescriptions with gaps not exceeding the duration of the previous NSAID prescription. For each prescription, duration 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 episode was defined as the end of the last NSAID prescription within that episode or the end of follow-up (whichever came earliest). There was no lower limit for consecutive NSAID use, in order to increase generalizability and to avoid exclusion of events that occurred with a first prescription. Patients could have more than one episode of NSAID use during follow-up, but eligible episodes were only those that had at least a 180-day NSAID-free period before the start of the episode.

From the NSAID cohort we selected the nsNSAID plus GPA subcohort, which comprised all nsNSAID users who received GPAs for at least one day during an eligible nsNSAID episode. The beginning of the nsNSAID plus GPA episode was based on the beginning of the nsNSAID prescription; the GPA could have started earlier, on the same day or later during the episode. Patients could have more than one eligible episode of nsNSAID plus GPA use and re-enter the cohort. All episodes that included Arthrotec (fixed combination of diclofenac with misoprostol; ATC code: M01AB55) or coxibs (ATC code: M01AH) or a combination of products (combination of nsNSAIDs, coxibs and/or Artrotec) were excluded (Figure 6.1).In this cohort, follow-up started at the beginning of the nsNSAID plus GPA episode and ended 60 days after the end of the last nsNSAID prescription in that episode (or the end of eligibility if earlier). This carry-over period was added because the nsNSAID-associated elevated risk of UGI events is believed to return to baseline approximately 2 months after stopping treatment.[28]

Among GPAs we included PPIs (ATC codes: A02BC and A02BD), high-dosed H_2RAs (ATC codes: A02BA)[141] and misoprostol (ATC code: A02BB01). The duration of GPAs was calculated as described above for NSAIDs.

Adherence calculation

Within the nsNSAID plus GPA cohort, each particular nsNSAID day within an eligible episode was classified as being or as not being covered with a GPA prescription. Adherence estimates were created on the basis of the percentage of nsNSAID days covered (PDC) by a GPA. Adherence was expressed as both a continuous and a categorical variable: (i) non-adherence (PDC< 20%); (ii) moderate adherence (PDC 20-80%); and (iii) full adherence (PDC > 80%). This categorization separates extremes and is based on previous studies on treatment adherence.[118, 147]

Case and control definition

Cases were members from the nsNSAID plus GPA cohort who had a UGI event, which was defined as UGI bleeding and/or symptomatic UGI ulcer with or without perforation or obstruction, during follow-up. UGI events were identified by a sensitive electronic search and were subsequently manually (IPCI) or electronically (GPRD, HSD) validated considering all relevant information available in each database (i.e. histology reports,

specialist letters, endoscopy results, clinical notes as free text). Different systems for coding and recording clinical details prompted us to consider different search and validation algorithms for each database. In general, cases were classified as definite if: (i) an endoscopy record confirming the UGI event was available; (ii) the event was mentioned together with the exact location (for example: 'acute duodenal ulcer with hemorrhage'); (iii) there was a recording of a hospital admission or anemia within one month of the event. Cases were classified as probable if the occurrence of a UGI event was mentioned, but was unconfirmed or non-specific (for example: 'blood in vomit'). Angiodysplasias, esophageal varices and Mallory Weiss syndrome were excluded as a case. The index date was defined as the start of the sign/symptom leading to the diagnosis of the UGI event, if present; otherwise it was defined as the date of diagnosis.

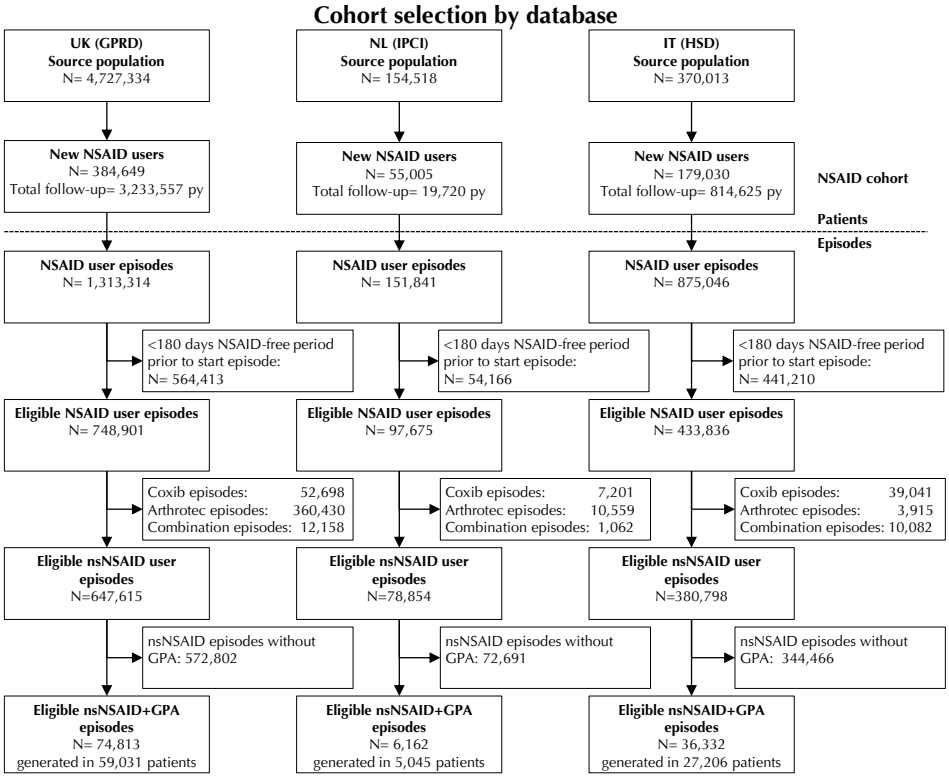


Figure 6.1: Cohort selection by database

GPA, gastroprotective agent; GPRD, general practice research database; HSD, health search/CSD longitudinal patient database; IPCI, integrated primary care information; IT, Italy; NSAID, non-steroidal anti-inflammatory drug; nsNSAID, non-selective non-steroidal anti-inflammatory drug; NL, the Netherlands.

To each case we matched all eligible persons from the nsNSAID plus GPA cohort who were at the index date of the corresponding case: alive, at risk of a nsNSAID-related UGI event (i.e. being in follow-up), of similar age (± 3 years) and the same sex, and were present in the same database as the case. This matching method samples from person time rather than persons and the controls should be regarded as person moments, similarly to a

cohort approach. Adherence was calculated for the most recent episode of nsNSAID use (with censoring at the event) before the event.

Covariates

As covariates we evaluated the presence of risk factors for NSAID-related UGI events as commonly described in guidelines on the prevention of NSAID-related UGI events[53, 88, 142]: (i) age 65 years or greater; (ii) history of UGI event; (iii) concomitant use of antiplatelets; (iv) concomitant use of anticoagulants; or (v) concomitant use of systemic steroids greater than 5 mg daily. In the nested case-control analysis, covariates were assessed before the index date. Concomitant use was defined as drug use overlapping the index date.

We additionally evaluated the presence of dyspepsia/gastro-esophageal reflux in the year before the nsNSAID episode, (history of) smoking, presence of heart failure or diabetes, the concomitant use of SSRIs, spironolactone[26, 148] or calcium channel blockers, calendar year, the length of the NSAID episode, and the density of NSAID use (number of NSAID prescription days divided by episode length) within the episode.

Statistical analyses

Baseline characteristics of the NSAID and nsNSAID plus GPA cohort were described by database. The database-specific and pooled crude incidence rates of UGI events within the NSAID cohort were estimated together with 95%-confidence intervals (95%CI) based on the Poisson distribution, and expressed per 1,000 NSAID user years. Events that occurred during or within 60 days after an eligible NSAID episode were counted. In a subanalysis we calculated separately the incidence rate of UGI bleeding. Exposure time was censored at the occurrence of the outcome of interest.

GPA adherence in the nsNSAID plus GPA cohort was described by database and by the presence of the five major risk factors as described under 'Covariates'. To estimate the risk of nsNSAID-related UGI events and UGI bleeding according to GPA adherence we calculated pooled adjusted matched odds ratios (OR) with 95% CIs through conditional logistic regression analyses, while adjusting for all covariates that changed the estimated risk in any of the exposure categories by more than 10%. Statistical heterogeneity across databases was tested by using a Cochran's Q statistic, and no significant results were found.

The analyses were stratified by type of first used nsNSAID, duration of nsNSAID episode and the presence of the major risk factors (assessed at the index date). To test the robustness of our findings, sensitivity analyses were performed by restricting the analysis to definite cases only, to cases and controls using nsNSAIDs for at least 30 or 60 days or to only the first nsNSAID episode per patient.

We calculated the number-needed-to-treat (NNT) within the nsNSAID plus GPA cohort based on the risk estimate in patients with full adherence compared with patients with non-adherence, and the UGI event rate in the non-adherent group. The NNT expresses the number of nsNSAID years during which patients need to be fully adherent to the GPA to prevent one UGI event.[149] This calculation was done separately for patients with no UGI risk factors and patients with at least one UGI risk factor.

All analyses were performed using SPSS 15.0 for Windows (SPSS Inc, Chicago, Ill). A two-sided p-value of less than 0.05 was considered to be statistically significant.

Results

NSAID cohort

Within the source population of 5,251,865 patients, we identified 618,684 patients who newly started on NSAIDs at least once during the eligibility period (Figure 6.1).The mean eligibility time per patient was 8.4 years in the UK, 3.6 years in the Netherlands and 4.6 years in Italy.

Table 6.1 shows characteristics of the NSAID cohort by database. Most patients in the NSAID cohort started on nsNSAIDs (n = 557,907; 90.2%). The most commonly prescribed nsNSAIDs were ibuprofen in UK (69.8%), diclofenac in NL (38.6%) and nimesulide in IT (28.5%). The mean age in the NSAID cohort was 64.6 ± 10.7 years and 41.4% were men. Most patients had no (n = 310,028; 50.1%) or one (n = 259,668; 42.0%) risk factor for NSAID-induced UGI bleeding or ulcer. The most common risk factor was age 65 years or greater (n = 283,994; 45.9%).

Table 6.1: Cohort characteristics for the NSAID cohort (at cohort entry) and for the nsNSAID+GPA cohort (at start of each eligible episode) by database

	NSAID cohort			nsNSAID+GPA cohort		
	UK n (%)	NL n (%)	IT n (%)	UK n (%)	NL n (%)	IT n (%)
Total	384,649	55,005	179,030	74,813	6,162	36,332
Age (mean ± sd)	64.8±10.6	63.4±10.7	64.6±10.7	68.9±10.6	65.4±10.9	68.6±10.5
Male	157,881 (41.0)	23,897 (42.7)	74,571 (41.7)	28,047 (37.5)	2,257 (36.6)	14,397 (39.6)
Individual UGI risk factors:						
Age ≥65 years	177,975 (46.3)	22,845 (40.8)	83,174 (46.5)	45,807 (61.2)	2,954 (47.9)	22,024 (60.6)
Prior UGI event	16,953 (4.4)	1,134 (2.0)	7,056 (3.9)	9,040 (12.1)	385 (6.2)	3,704 (10.2)
Use of antiplatelets	49,782 (12.9)	1,682 (3.0)	13,629 (7.6)	20,043 (26.8)	853 (13.8)	6,034 (16.6)
Use of anticoagulants	2,809 (0.7)	334 (0.6)	1,274 (0.7)	1,191 (1.6)	148 (2.4)	553 (1.5)
Use of systemic steroids	4,169 (1.1)	260 (0.5)	3,797 (2.1)	2,539 (3.4)	117 (1.9)	2,302 (6.3)
Number of UGI risk factors:¶						
0	186,188 (48.4)	32,029 (57.2)	86,331 (48.2)	21,080 (28.2)	2,689 (43.6)	10,582 (29.1)
1	149,015 (38.7)	21,805 (38.9)	77,198 (43.1)	31,947 (42.7)	2,556 (41.5)	17,595 (48.4)
2	45,762 (11.9)	2,083 (3.7)	14,785 (8.3)	18,820 (25.2)	852 (13.8)	7,460 (20.5)
3	3,589 (0.9)	92 (0.2)	702 (0.4)	2,834 (3.8)	63 (1.0)	6,78 (1.9)
≥4	95 (0.0)	2 (0.0)	14 (0.0)	132 (0.2)	2 (0.0)	17 (0.0)
Type of NSAID:						
nsNSAIDs	353,036 (91.8)	46,778 (85.0)	158,093 (88.3)	74,813 (100.0)	6,162 (100.0)	36,332 (100.0)
Coxibs	18,261 (4.7)	3,266 (5.9)	18,411 (10.3)	excluded	excluded	excluded
Arthrotec	12,581 (3.2)	4,885 (8.9)	1,725 (1.0)	excluded	excluded	excluded
Combinations	771 (0.2)	76 (0.1)	801 (0.5)	excluded	excluded	excluded

UGI, upper gastrointestinal; UK, United Kingdom; NL, the Netherlands; IT, Italy.
¶ Included in the count were prior UGI event (in any prior history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids > 5 mg daily and age > 65 years.

During follow-up of the NSAID cohort, 2,340,201 NSAID user episodes were counted, 1,280,412 of which were eligible (i.e. had at least a 180-day NSAID-free period before the start of the episode) (Figure 6.1). The mean duration per NSAID episode was 27.5 ± 71.5 days.

Incidence rates

In total, we identified 2,056 patients with a UGI event (1,182 UGI bleedings and 874 symptomatic ulcers) which occurred during or within 60 days of an eligible NSAID episode. The incidence rates are described in Table 6.3. The incidence rate was 6.7 (95%CI:

6.4-7.0) per 1,000 NSAID user years for UGI events and 3.8 (95%CI: 3.5-4.1) per 1,000 NSAID user years for UGI bleedings.

Of all UGI events that occurred during an NSAID episode or within 60 days thereafter, 413 (20.1%) concerned an NSAID episode with concomitant GPA. For UGI bleeding, this percentage was similar (18.4%, n = 217). The crude incidence rates of UGI events and UGI bleeding were significantly higher among GPA users than among non-GPA users (Table 6.3). For UGI events, the crude incidence rates among coxib users were significantly higher as compared with nsNSAID users.

nsNSAID+GPA cohort

After exclusion of episodes that included the use of coxibs (n = 98,940) or Arthrotec (n = 50,904) or a combination of products (n = 23,302), 1,107,266 eligible nsNSAID episodes remained (Figure 6.1). The mean number of eligible nsNSAID episodes per patient was 1.9. The mean length of the eligible nsNSAID episodes was 31.1 days (sd: 73.5).

In 117,307 (10.6%) of the eligible nsNSAID episodes a GPA was prescribed (UK: 11.6%; NL: 7.8%, IT: 9.5%) and these episodes were the basis for the nsNSAID plus GPA cohort, comprising of 91,282 patients(Figure 6.1). The characteristics of this cohort are described in Table 6.5.

Adherence to GPAs in the eligible nsNSAID episodes is described in Table 6.4. Overall, mean adherence was 81% ± 28% (UK: 83% ± 27%; NL: 88% ± 24%; IT: 74% ± 30%), and 79,869 patients (68.1%) (UK: 71.8%; NL: 80.5%; IT: 58.3%) were fully adherent.

Nested case-control study

In the nsNSAID plus GPA cohort 339 UGI events occurred during follow-up, 187 of which were UGI bleeds. All patients with a UGI event during follow-up were included as cases and 71,380 controls were matched. The characteristics of the cases and controls at the index date are described in Table 6.5.

Table 6.2: Association between adherence to gastroprotective agents during non-selective NSAID use and the risk of UGI events

	Cases	Controls	ORmatched (95% CI)	ORadjusted* (95% CI)	P for trend
UGI events (UGI bleeding and ulcer)					
Continuous: with every 10% decline in adherence	339	71 380	1.08 (1.04-1.12)	1.09 (1.05-1.13)	
Categorical:					
GPA adherence PDC > 80%	205 (60.5)	50 309 (70.5)	1 (ref)	1 (ref)	< 0.001
GPA adherence PDC 20-80%	94 (27.7)	16 808 (23.5)	1.31 (1.02-1.67)	1.35 (1.05-1.73)	
GPA adherence PDC < 20%	40 (11.8)	4263 (6)	2.15 (1.53-3.03)	2.39 (1.66-3.44)	
UGI bleeding					
Continuous: with every 10% decline in adherence	187	39 571	1.04 (0.99-1.10)	1.06 (1.01-1.12)	
Categorical:					
GPA adherence PDC > 80%	120 (64.2)	28 160 (71.2)	1 (ref)	1 (ref)	0.02
GPA adherence PDC 20-80%	51 (27.3)	9091 (23)	1.26 (0.91-1.75)	1.30 (0.93-1.82)	
GPA adherence PDC < 20%	16 (8.6)	2320 (5.9)	1.56 (0.93-2.64)	1.89 (1.09-3.28)	

UGI, upper gastrointestinal; PDC, percentage of nsNSAID days covered with GPA.
**Adjusted for length of NSAID episode, density of NSAID use within episode.*

Table 6.3: Incidence rates of UGI events during eligible NSAID episodes in the NSAID cohort

	UGI events (UGI bleeding and ulcer)			UGI bleeding		
	n	NSAID user years	Incidence (95%CI)	n	NSAID user years	Incidence¶ (95%CI)
Total	2 056	306 281	6.7 (6.4-7.0)	1 182	307 507	6.8 (3.5-4.1)
Age (years):						
50-65	598	152 903	3.9 (3.6-4.2)	272	153 362	1.8 (1.6-2.0)
65-75	595	87 061	6.8 (6.3-7.4)	330	87 491	3.8 (3.4-4.2)
> 75	863	66 318	13.0 (12.2-13.9)	580	66 654	8.7 (8.0-9.4)
Gender:						
Male	967	120 532	8.0 (7.5-8.5)	562	121 092	4.6 (4.3-5.0)
Female	1 089	185 749	5.9 (5.5-6.2)	620	186 414	3.3 (3.1-3.6)
Individual UGI risk factors:						
Age ≥65 years	1 458	153 379	9.5 (9.0-10.0)	910	154 145	5.9 (5.5-6.3)
Prior UGI event	209	12 041	17.4 (15.1-19.8)	128	13 121	9.8 (8.2-11.6)
Use of antiplatelets	537	41 558	12.9 (11.9-14.1)	350	41 781	8.4 (7.5-9.3)
Use of anticoagulants	40	2 652	15.1 (10.9-20.3)	32	2 667	12.0 (8.4-16.7)
Use of systemic steroids	58	4 895	11.9 (9.1-15.2)	38	4 930	7.7 (5.5-10.5)
Number of UGI risk factors:*						
0	464	135 939	3.4 (3.1-3.7)	203	135 988	1.5 (1.3-1.7)
1	960	128 922	7.5 (7.0-7.9)	552	129 342	4.3 (3.9-4.6)
2	557	38 728	14.4 (13.2-15.6)	378	39 305	9.6 (8.7-10.6)
3	72	2 624	27.4 (21.6-34.3)	46	2 795	16.5 (12.2-21.8)
4 or more	3	67	44.6 (12.3-118.9)	3	76	39.5 (10.9-105.3)
Type of first NSAID:**						
nsNSAIDs:	1 800	275 695	6.5 (6.2-6.8)	1 051	276 703	3.8 (3.6-4.0)
Ibuprofen	721	121 784	5.9 (5.5-6.4)	495	122 052	4.1 (3.7-4.4)
Diclofenac	289	41 419	7.0 (6.2-7.8)	159	41 601	3.8 (3.3-4.5)
Naproxen	263	31 192	8.4 (7.5-9.5)	182	31 271	5.8 (5.0-6.7)
Nimesulide	129	26 568	4.9 (4.1-5.8)	27	26 740	1.0 (0.7-1.5)
Others/combinations	398	54 733	7.3 (6.6-8.0)	188	55 039	3.4 (3.0-3.9)
Coxibs:	256	30 586	8.4 (7.4-9.4)	131	30 804	4.3 (3.6-5.0)
Celecoxib	99	13 337	7.4 (6.1-9.0)	49	13 435	3.7 (2.7-4.8)
Rofecoxib	115	12 859	8.9 (7.4-10.7)	58	12 933	4.5 (3.4-5.8)
Other/combinations	42	4 391	9.6 (7.0-12.8)	24	4 436	5.4 (3.6-7.9)
Origin of database:						
United Kingdom	1 392	198 581	7.0 (6.7-7.4)	927	199 163	4.7 (4.4-5.0)
the Netherlands	128	19 341	6.6 (5.5-7.8)	92	19 373	4.8 (3.9-5.8)
Italy	536	883 593	6.1 (5.6-6.6)	163	889 712	1.8 (1.6-2.1)
No GPAs	1 643	266 887	6.2 (5.9-6.5)	965	267 479	3.6 (3.4-3.8)
With GPAs	413	39 395	10.5 (9.5-11.5)	217	40 027	5.4 (4.7-6.2)
GPA adherence						
PDC < 20%	47	4 126	11.4 (8.5-15.0)	19	4 181	4.5 (2.8-7.0)
PDC 20-80%	120	11 735	10.2 (8.5-12.2)	58	11 909	4.9 (3.7-6.3)
PDC > 80%	246	23 533	10.5 (9.2-11.8)	140	23 937	5.9 (4.9-6.9)

UGI, upper gastrointestinal; GPA, gastroprotective agents; PDC, percentage of NSAID days covered with GPA.

¶ Incidence per 1000 NSAID user years.

** Included in the count were prior UGI event (in any prior history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids > 5 mg daily and age > 65 years*

***Episodes with Arthrotec use or with a combination of nsNSAIDs with coxibs were excluded.*

Table 6.4: GPA adherence during nsNSAID use (in nsNSAID+GPA cohort)

		GPA adherence (PDC)			
	n	PDC Mean ± SD*	< 20% n (%)	20-80% n (%)	> 80% n (%)
Total	117 307	81 ± 28	5723 (4.9)	31 715 (27.0)	79 869 (68.1)
Age (years):					
50-65	4522	80 ± 28	2350 (5.1)	12 776 (27.5)	31 396 (67.5)
65-75	35 973	81 ± 28	1785 (5.0)	9658 (26.8)	24 530 (68.2)
> 75	34 812	81 ± 27	1588 (4.6)	9281 (26.7)	23 943 (68.8)
Gender:					
Male	44 701	81 ± 28	2129 (4.8)	11 956 (26.7)	30 616 (68.5)
Female	72 606	81 ± 28	3594 (5.0)	19 759 (27.2)	49 253 (67.8)
Individual UGI risk factors:					
Age ≥65 years	70 785	81 ± 28	3373 (4.8)	18 939 (26.8)	48 473 (68.5)
Prior UGI event	13 129	84 ± 25	447 (3.4)	3002 (22.9)	9680 (73.7)
Use of antiplatelets	26 930	83 ± 26	1092 (4.1)	6355 (23.6)	19 483 (72.3)
Use of anticoagulants	1892	85 ± 25	64 (3.4)	423 (22.4)	1405 (74.3)
Use of systemic steroids	4958	82 ± 27	238 (4.8)	1280 (25.8)	3440 (69.4)
No. of UGI risk factors:¶					
0	34 351	79 ± 29	1871 (5.4)	9869 (28.7)	22 611 (65.8)
1	52 098	80 ± 28	2611 (5.0)	14 476 (27.8)	35 011 (67.2)
2	27 132	83 ± 27	1122 (4.1)	6617 (24.4)	19 393 (71.5)
3	3575	86 ± 24	117 (3.3)	723 (20.2)	2735 (76.5)
4 or more	151	89 ± 19	2 (1.4)	30 (20.3)	119 (78.8)
Type of first NSAID:					
Ibuprofen	47 782	83 ± 26	2070 (4.3)	11 251 (23.5)	34461 (72.1)
Diclofenac	19 936	81 ± 28	876 (4.4)	5452 (27.3)	13 608 (68.3)
Nimesulide	8784	73 ± 31	654 (7.4)	3012 (34.3)	5118 (58.3)
Naproxen	14 253	83 ± 26	550 (3.9)	3517 (24.7)	10 186 (71.5)
Others/combinations	26 552	77 ± 29	1573 (5.9)	8483 (31.9)	16 496 (62.1)
Type of GPA:					
PPI	115 937	81 ± 28	5645 (4.9)	31 286 (27.0)	79006 (68.1)
H_2RA	3	94 ± 10	0	0	3 (100)
Misoprostol	999	76 ± 30	51 (5.1)	313 (31.3)	635 (63.6)
Combination of GPAs	371	76 ± 30	27 (7.3)	116 (31.3)	228 (61.5)
Duration of episode:*					
< 1 month	68 519	87 ± 24	2086 (3.0)	13 659 (19.9)	52 774 (77.0)
1-6 months	43 843	73 ± 29	2500 (5.7)	16 608 (37.9)	24 735 (56.4)
6-12 months	2599	65 ± 34	473 (18.2)	826 (31.8)	1300 (50.0)
> 12 months	2346	58 ± 38	664 (28.3)	622 (26.5)	1060 (45.2)

UGI, upper gastrointestinal; GPA, gastroprotective agents; PDC, percentage of nsNSAID days covered with GPA; PPI, proton pump inhibitor; H_2RA, histamine-2 receptor antagonist.
¶ Included in the count were prior UGI event (in any prior history), concomitant antiplatelet use, concomitant anticoagulant use, concomitant use of systemic steroids > 5 mg daily and age > 65. P for trend = 0.00.
** P for trend < 0.001.*

The mean GPA adherence (PDC) of cases and controls was 74% ± 33% and 82% ± 28%, respectively. The p-value for the Cochran's Q statistic was 0.13, indicative for statistical homogeneity across databases. With every 10% decline in PDC, the risk of a UGI event increased by 9% (95%CI: 5-13%) (Table 6.2). NsNSAID users who were non-adherent to GPAs had a 2.4-fold increased risk of UGI events (95%CI: 1.7-3.4) as compared with patients who were fully adherent. Upon restriction to definite cases (n = 91), the association became stronger; with every 10% decline in PDC, the risk of a UGI event increased by 16% (95%CI: 9-25%). Upon restriction to patients with at least 30 (174 cases) or 60 (100 cases) days nsNSAID use during the episode or to only the first nsNSAID episode per patient, the results were similar to those of the original analysis (data not shown). Analyses stratified by the type of nsNSAID, duration of nsNSAID episode and the presence of risk factors are shown in Table 6.6.

Table 6.5: Association between patient characteristics and UGI events (nested case-control analysis in nsNSAID+GPA cohort)

	Cases n (%)	Controls n (%)	$OR_{matched}$ (95% CI)
Total	339	71,380	
Age (mean±sd) ¶	71.6 ± 10.7	71.0 ± 9.0	-
Male gender ¶	137 (40.4)	21631 (30.3)	-
Type of first NSAID:*			
Ibuprofen	89 (38.5)	25768 (53.8)	1 (ref)
Diclofenac	38 (16.5)	4421 (9.2)	1.87 (1.24-2.82)
Nimesulide	4 (1.7)	240 (0.5)	2.04 (0.60-6.90)
Naproxen	53 (22.9)	8772 (18.3)	2.00 (1.39-2.87)
Others/combinations	47 (20.3)	8683 (18.1)	1.32 (0.91-1.91)
Individual UGI risk factors:			
Prior UGI event	69 (20.4)	6340 (8.9)	2.19 (1.67-2.87)
Use of antiplatelets	92 (27.1)	18924 (26.5)	1.04 (0.81-1.32)
Use of anticoagulants	16 (4.7)	1228 (1.7)	2.79 (1.68-4.63)
Use of systemic corticosteroids	23 (6.8)	2861 (4.0)	1.67 (1.09-2.55)
Dyspepsia/reflux prior to NSAID start	21 (6.2)	3335 (4.7)	1.24 (0.80-1.94)
Smoking	123 (36.3)	28423 (39.8)	0.94 (0.74-1.18)
Chronic heart failure	32 (9.4)	3132 (4.4)	1.71 (1.17-2.50)
Diabetes mellitus	58 (17.1)	10280 (14.4)	1.20 (0.90-1.59)
Use of SSRIs	37 (10.9)	5053 (7.1)	1.79 (1.27-2.54)
Use of spironolactone	2 (0.6)	616 (0.9)	0.61 (0.16-2.62)
Use of calcium channel antagonists	57 (16.8)	11879 (16.6)	1.11 (0.83-1.48)
Number of UGI risk factors:**			
0	180 (53.1)	45162 (63.3)	1 (ref)
1	124 (36.6)	23214 (32.5)	1.30 (1.03-1.65)
2	29 (8.6)	2874 (4.0)	2.29 (1.53-3.42)
3	6 (1.8)	129 (0.2)	10.39 (4.50-24.00)
4	0	1 (0.0)	-

UGI, upper gastrointestinal .

¶ Matching variables.

** Adjusted for dose. Patients were only included when dose was available (67.7%).*

*** Included in the count were prior UGI event (in any prior history), concomitant antiplatelet use, concomitant anticoagulant use and concomitant use of systemic steroids > 5 mg daily. Excluding age > 65 because age was a matching variable. P for trend was 0.00.*

No major heterogeneity was observed, with the exception of patients with concomitant use of anticoagulants or corticosteroids, in whom the association between GPA adherence and nsNSAID-related UGI events was no longer present.

When analyzing the subset of UGI bleeding cases, mean adherence of the cases and the controls was 78% ± 30% and 82% ± 28%, respectively. The p-value for the Cochran's Q statistic was 0.62 for UGI bleeding, indicative for statistical homogeneity across databases. With every 10% decline in PDC, the risk of developing a UGI bleeding increased by 6% (95%CI: 1-12%) (Table 6.2). NsNSAID users who were non-adherent to their GPA had a 1.9-fold increased risk of UGI bleeding (95%CI: 1.1-3.3) compared with patients who were fully adherent (Table 6.2).

For calculation of the NNT, we calculated the nsNSAID-related UGI event rate in non-adherent patients with no UGI risk factor and with at least one UGI risk factor, being 7.7/1000 nsNSAID user years (95%CI: 3.8-14.0) and 18.9/1000 nsNSAID user years (95%CI: 3.7-25.5) respectively. In the patients with no risk factors, patients with full adherence were at a risk of 0.52 (95%CI: 0.22-1.26) of developing a UGI event compared with non-adherers. In the patients with at least one risk factor, patients with full adherence were at a risk of 0.44 (95%CI: 0.29-0.67) compared with non-adherers. Based on these numbers, we calculated that for patients with no risk factors, 274 nsNSAID user years with GPA non-adherence needed to be covered with full GPA adherence to prevent one nsNSAID-related UGI event. For patients with at least one risk factor, this was 96 nsNSAID user years.

Table 6.6: Risk of UGI events with every 10% decline in GPA adherence during non-selective NSAID use: stratified analyses

	Cases	Controls	$OR_{matched}$ (95% CI)	$OR_{adjusted*}$ (95% CI)
Total	339	71380	1.08 (1.04-1.12)	1.09 (1.05-1.13)
Type of first NSAID:†				
Ibuprofen	89	25768	1.02 (0.94-1.11)	1.04 (0.95-1.13)
Diclofenac	38	4421	1.20 (1.08-1.33)	1.19 (1.06-1.33)
Nimesulide	4	240	1.08 (0.71-1.63)	1.05 (0.66-1.69)
Naproxen	53	8772	1.08 (0.98-1.19)	1.10 (0.99-1.22)
Others/combinations	47	8683	1.11 (1.01-1.21)	1.15 (1.05-1.27)
Duration of NSAID episode:¶				
< 1 month	162	33556	1.09 (1.02-1.16)	1.09 (1.02-1.16)
1-6 months	126	26612	1.07 (1.00-1.14)	1.06 (1.00-1.13)
6-12 months	20	4440	1.17 (1.01-1.35)	1.20 (1.03-1.41)
> 12 months	31	6772	1.07 (0.97-1.18)	1.07 (0.97-1.17)
Age (years):				
50-65	95	19047	1.10 (1.03-1.17)	1.11 (1.04-1.19)
65-75	107	27321	1.08 (1.01-1.15)	1.08 (1.01-1.15)
> 75	137	25012	1.07 (1.01-1.13)	1.08 (1.02-1.15)
Risk level:				
No UGI risk factors	65	14246	1.11 (1.02-1.20)	1.12 (1.03-1.21)
≥ 1 UGI risk factor	274	57134	1.07 (1.03-1.11)	1.08 (1.03-1.12)
Prior UGI event:				
No	270	65040	1.09 (1.05-1.13)	1.10 (1.06-1.15)
Yes	69	6340	1.07 (0.98-1.17)	1.07 (0.98-1.18)
Concomitant drug use:				
Antiplatelets	92	18924	1.03 (0.96-1.11)	1.04 (0.81-1.32)
Anticoagulants	16	1228	0.98 (0.80-1.20)	0.95 (0.75-1.20)
Corticosteroids	23	2861	1.00 (0.85-1.18)	0.99 (0.83-1.17)
SSRIs	37	5053	1.08 (0.96-1.22)	1.09 (0.96-1.23)

UGI, upper gastrointestinal.
**Adjusted for length of NSAID episode, density of NSAID use within episode.*
† Additionally adjusted for dose. Patients were only included when dose was available (67.7%).
¶ Only adjusted for density of NSAID use within episode.

Discussion

This large, population-based, multiple database study shows that, during nsNSAID use, non-adherence to GPAs is associated with a 2.4-fold increased risk of UGI bleeding and ulcers and a 1.9-fold increased risk of UGI bleeding alone. With every 10% decrease in GPA adherence, the risk increased by 9% for UGI bleeding and ulcers and 6% for UGI bleeding alone. From the stratified analysis, it appears that full GPA adherence is important in both nsNSAID users with risk factors for developing a UGI event and nsNSAID users without any risk factor.

The results of this study are in line with two previous observational studies, one from USA[144] and one from Europe[118], which also showed an increased risk of UGI events associated with low GPA adherence. As a result of the low use of GPAs and the relatively rare incidence of serious UGI events, the impact of both studies was limited because of the small number of exposed cases. In the present study we were able to include more than 300 exposed cases as we combined together three large primary care databases. This allowed the conduction of several sub-analyses. Randomized controlled trials (RCTs) on the subject are not available. This is understandable since in RCTs adherence to the study drug is often well controlled. To study effects of drug adherence, real-world variability of use is needed.

In our study the overall incidence of UGI events was 6.7/1000 NSAID users years. The incidence was higher among patients using GPAs as compared with patients who did not. This can be explained by channeling, i.e. patients who are at higher risk of UGI events are more likely to be prescribed GPAs or coxibs. To minimize channeling bias, we created the nsNSAID plus GPA cohort, excluding non-GPA users and coxib users. Nevertheless, in nsNSAID plus GPA users only, it is conceivable that patients who are at higher risk of developing UGI events will be more adherent to their GPA. This is confirmed by the high crude incidence rate among full adherers compared with patients who were moderately adherent.

This study showed that mean GPA adherence is relatively high (81%). Although the number of nsNSAID users that received a GPA prescription was lowest in the Netherlands, adherence was highest in this country. In this study (1996-2007), adherence in the Netherlands was slightly higher (88%) than in a previous study (82%) from the same database (1996-2002).[145] Lowest adherence was found in Italy.

The strength of this study is the large amount of data from three European countries. It describes real world prescription and patient behavior in the general population. As with all observational database studies, however, selection bias, information bias, and confounding need to be considered. Selection bias is limited because in the cohort we included all eligible patients available in the prospectively collected population-based data from the three databases. The data in these databases is collected for clinical use, irrespective of any research question.

Information bias includes misclassification of exposure and misclassification of outcome. With regard to misclassification of exposure, recall bias was avoided by using prescription data but precise information on actual dispensing and intake is not available. Also, over-the-counter (OTC) drug use is not recorded in the databases. In all three countries, OTC NSAIDs are available. OTC omeprazole (a PPI) is available in the UK (for short-term use). In all three countries only prescription NSAIDs and PPIs are (partly) reimbursed. OTC NSAIDs and PPIs are therefore usually for short-term use, but an underestimation of NSAID and PPI use in our study is conceivable. Low-dosed H_2RAs are available OTC in all three countries, but it is unlikely that patients use doses that are high enough to classify as gastroprotection. Misclassification of the outcome was reduced by manual/electronic validation of the records after sensitive electronic searches based on both codes and key words in free text. A sensitivity analysis that included only definite cases strengthened the study findings. Heterogeneity was seen in the incidence of UGI bleeding, whereas there was homogeneity in the incidence of UGI events in the databases. The incidence of UGI bleeding was substantially lower in Italy than in the Netherlands and the UK. An explanation could be that the most frequently used nsNSAID in Italy is nimesulide, a drug that may lead to less UGI bleeding due to higher COX-2 specificity[150], and also variations in coding systems or health seeking behavior may have contributed. The common case definition is however that all outcomes were symptomatic UGI events.

As a result of low numbers, the estimated risks differed between databases, but the conclusions were consistent across databases (data not shown) and heterogeneity was not significant.

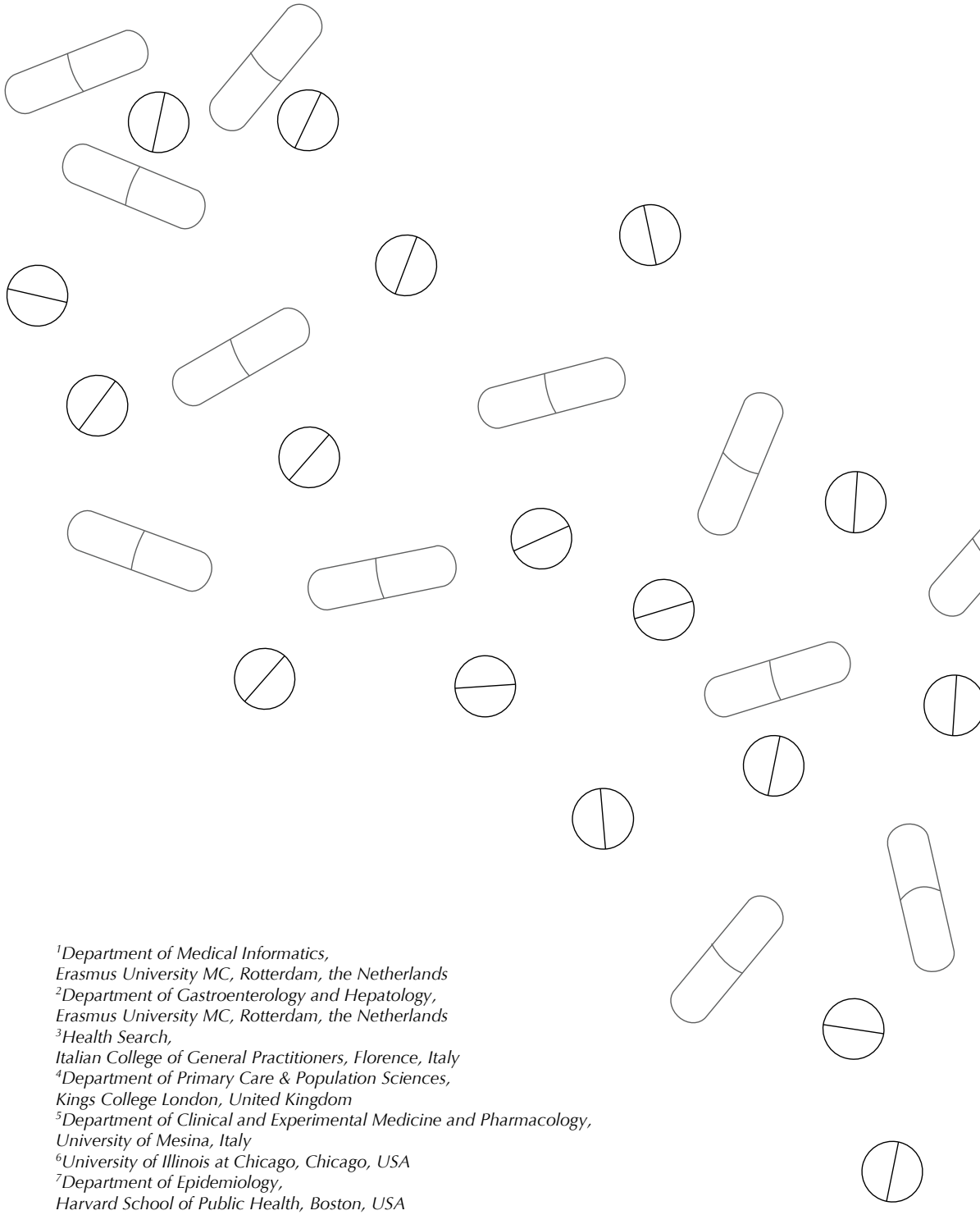
Protopathic bias would be introduced if patients start the study drug (GPAs) for treatment of early symptoms of the outcome of interest (UGI events). In this particular study, this is an obvious threat to validity. Especially when GPAs are started later in the nsNSAID episode, the association between low GPA adherence and UGI events would be overestimated. In order to avoid protopathic bias, we defined the index date as the start of symp-

toms leading to the diagnosis of the UGI event rather than the date of diagnosis, whenever possible, and determined the exposure before rather than at the index date.

Residual confounding might have been introduced by the *H. pylori* status of patients, on which we had no information. If a positive *H. pylori* status was to lead to a higher GPA adherence and to a higher risk of UGI events, this would lead to an underestimation of the true association between GPA adherence and UGI events.

As a result of the fact that the databases contain prescription data and no data on intake, we cannot make a distinction between physician-induced or patient-induced non-adherence. We calculated the risk associated with a suboptimal prescription pattern, irrespective of the cause. Most likely both prescriber and patient non-adherence play a role.

In conclusion, we observed a strong association between GPA adherence and the risk of nsNSAID-related UGI events. The results highlight the importance of GPA use during nsNSAID therapy and suggest that an improvement of GPA adherence could be beneficial in reducing the risk of nsNSAID-related UGI events.



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Chapter 7

Adherence to gastroprotection during cyclooxygenase-2 inhibitor use and the risk of upper gastrointestinal events: a population-based study

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Abstract

Background

Guidelines recommend co-prescription of gastroprotective agents (GPAs) in users of cyclooxygenase-2 inhibitors (coxibs) at high risk (i.e. those with a previously complicated ulcer, or with multiple risk factors) of upper gastrointestinal (UGI) complications. Suboptimal GPA adherence has been shown to diminish the gastroprotective effect during non-selective NSAID use, but little is known about the effect of GPA adherence during coxib use.

Aim

To study the association between GPA adherence and UGI events among coxib users.

Methods

We used primary care data from three European databases. We conducted a case-control study within a cohort of newly started coxib users aged 50 years and older, who concomitantly used GPAs. Cases with a UGI event (bleeding or symptomatic ulcer) were matched to event-free controls on age, sex, database, and calendar date. Adherence to GPAs was calculated as the Proportion of coxib treatment Days Covered by a GPA prescription (PDC). Odds ratios (OR) were calculated using conditional logistic regression analysis.

Results

The cohort consisted of 14,416 coxib+GPA users, generating 16,442 coxib+GPA episodes. Most patients used coxibs for less than 30 days. Seventy-four patients had a UGI event during or shortly after these episodes, with an incidence rate of 11.9 (95%CI 9.4-14.8) per 1000 coxib user years. The risk of UGI events was 1.97 (95%CI 0.84-4.60) for low GPA adherers (PDC < 20%) compared with full adherers (PDC > 80%). For every 10% decrease in GPA adherence, the risk of UGI events increased by 9% (OR 1.09, 95%CI 1.00-1.18).

Conclusions

Decreasing GPA adherence among coxib users is associated with an increased risk of UGI events.

Introduction

Non-steroidal anti-inflammatory drug (NSAID) therapy is one of the mainstays of pain treatment, especially in patients with chronic conditions such as osteoarthritis. Since NSAIDs are known for negative upper gastrointestinal (UGI) effects, new NSAIDs (referred to as coxibs) were developed possessing less gastrotoxic properties by preferentially inhibiting the inducible isoenzyme cyclooxygenase 2 (COX-2).

By sparing isoenzyme COX-1, it was postulated that selective inhibition of the COX-2 isoform by COX-2 selective inhibitors (coxibs) would still lead to effective pain relief but to a lower risk of NSAID-related UGI events, such as bleeding, obstruction, or perforation. Indeed it was shown that coxibs were associated with a significantly lower incidence of gastric and duodenal ulcer complications when compared with traditional, non-selective (ns)NSAIDs (which inhibit both COX isoenzymes at a similar level).[38-41]

In patients receiving nsNSAIDs who are at high risk of UGI tract complications, it is common practice to coprescribe gastroprotective agents (GPAs). GPAs include proton pump inhibitors (PPIs), high-dose histamine-2 receptor antagonists (H_2RAs) and misoprostol, and they reduce the incidence of nsNSAID-induced UGI ulcer complications.[84, 91] The effects of GPA coprescriptions in coxib users were addressed by two randomized studies and two observational studies.[95, 104, 105, 151] One key study was done by Chan et al. who randomly assigned 441 patients hospitalized for nsNSAID-related UGI tract bleeding to receive coxib plus PPI or coxib plus placebo. After a median follow-up of 13 months, no patients (0%) in the coxib plus PPI treatment group compared with 12 patients (8.9%) in the coxib plus placebo-treated group had recurrent ulcer bleeding ($p = 0.0004$).[104] The results of the other three studies are in keeping with those of that randomized study, consistently showing that NSAID-related UGI tract events are further reduced when PPIs are added to coxibs, also in patients without risk factors receiving coxibs.[95, 105, 151]

Evidence-based guidelines now recommend GPA co-prescription in coxib users at high-risk of developing NSAID-related ulcer complications.[53, 152] Previously we reported the importance of GPA adherence to lower the risk of nsNSAID-induced UGI events in clinical practice.[153] However, little is known about the specific effect of GPA non-adherence during coxib treatment.

To investigate whether decreased GPA adherence during coxib use is associated with an increased risk of UGI tract events, we conducted a case-control study nested within a cohort of patients age 50 years and older who were receiving coxibs plus GPAs, originating from three population-based primary care research databases (in the United Kingdom, the Netherlands and Italy).

Methods

Data sources

Data were obtained from dynamic population-based primary care registries in the United Kingdom (UK) from 1998 to 2008, the Netherlands (NL) from 1996 to 2007, and Italy (IT) from 2000 to 2007. In these countries, all citizens are registered with a primary care practice that records all medical information, including demographics, symptoms and diagno-

ses, drug prescriptions, specialist referrals, clinical diagnoses from outpatient visits, and hospital discharge summaries.

The databases comply with European Union guidelines on the use of medical data for medical research and have been demonstrated to be valid for pharmacoepidemiologic research. The protocol of the present study was approved by the Scientific and Ethical Advisory Board of each database. The databases are briefly described below.

General Practice Research Database (GPRD)

The GPRD was established in the United Kingdom in 1987 and currently includes more than 500 general practitioners (GPs) and 4.4 million patients. Symptoms and diagnoses are recorded by using READ codes (the thesaurus of clinical terms used in the UK). Information on drug prescriptions is coded with MULTILEX product dictionary and British National Formulary (BNF) codes. We requested additional information on hospitalizations from the Hospital Episode Statistics (HES) database including procedures coded according to the Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th Revision (OPCS-4), and diagnoses coded according to the International Classification of Diseases, 10th Revision (ICD-10).

Integrated Primary Care Information (IPCI) database

The IPCI database was initiated in the Netherlands in 1992. Currently, the database covers about 1 million patients from practices of 300 GPs. Symptoms and diagnoses are recorded using the International Classification for Primary Care (ICPC[61]) and string search, drug prescriptions are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[60]

Health Search/Cegedim Strategic Data Longitudinal Patient Database (HSD)

The HSD was established in Italy in 1998. The HSD currently contains data from 900 GPs and covers about 1.6 million patients.[146] Symptoms and diagnoses are recorded using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM). Information on drug prescriptions is coded according to the ATC classification.

Source population

Patients were eligible for inclusion in the source population from the start of the study period, the date of reaching 50 years of age, or the date by which at least one year of valid enrollment data were obtained (whichever came latest). Eligibility ended at death, last data supply, transferring out of the practice, or end of the study period (whichever came earliest).

Study cohorts and exposure assessment

Three types of exposure cohorts were created. The first was the total cohort of coxib-treated patients (the coxib cohort), which was split into the other two cohorts. The second cohort consisted of patients who received a coxib prescription but who received no GPAs (the coxib minus GPA cohort). The third cohort consisted of patients who received a coxib prescription and who had at least one day of GPA (the coxib plus GPA cohort). The coxib cohort included all patients from the source population who received at least one coxib prescription (ATC code M01AH (or equivalent BNF code)) during the eligibility period, and who did not receive any type of NSAID (nsNSAID or coxib) prescription dur-

ing the previous six months. All identified new coxib users were followed up from the start of coxib therapy to the end of the eligibility period or occurrence of the outcome of interest (whichever came earliest). Patients with a GI neoplasm, alcohol abuse, chronic liver disease, Crohn's disease, ulcerative colitis, or a coagulopathy were excluded from the cohort.

Episodes of coxib use were defined as consecutive coxib prescriptions with intervening gaps not exceeding the duration of the previous coxib prescription. The duration of each prescription was calculated by dividing the prescribed quantity by daily dose regimen (GPRD/IPCI) or defined daily dose (HSD). The end of an episode was defined as the end of the last coxib prescription within that episode or the end of follow-up (whichever came earliest). Patients could have more than one episode of coxib use during follow-up, but the only eligible episodes were those that were preceded by at least 180 days without any NSAIDs.

From the coxib cohort we selected the coxib plus GPA sub-cohort, which comprised all coxib users who received GPAs for at least one day during an eligible coxib episode. The beginning of the coxib episode was based on the beginning of the coxib prescription; the GPA could have started earlier, on the same day, or later during the episode. Patients could have more than one eligible episode of coxib plus GPA use and re-enter the cohort. In this cohort, follow-up started at the beginning of the eligible coxib plus GPA episode and ended 60 days after the end of the last coxib prescription in that episode (or end of eligibility if earlier). This carry-over period was added because the NSAID-associated elevated risk of UGI events is believed to return to baseline approximately two months after stopping treatment.[28] Episodes with a combination of coxib plus nsNSAIDs (ATC codes M01AA-M01AG and M01AX, or ATC codes N02BA01, N02BA15 or N02BA51 at a dose > 325 mg/day) were excluded.

Among GPAs we included PPIs (ATC codes A02BC and A02BD), double-dose H_2RAs (ATC codes A02BA)[91] and misoprostol (ATC code A02BB01). Duration of GPAs was calculated as described above for coxibs.

Adherence calculation

Within the coxib plus GPA cohort, each particular coxib day within an eligible episode was classified as being covered or not with a GPA prescription. Adherence estimates were created on the basis of the Percentage of (coxib) Days Covered by a GPA (PDC). Adherence was expressed as both continuous and categorical variables: Non-adherence was defined as < 20% of days covered (PDC < 20%), moderate adherence was defined as 20-80% of days covered (PDC 20-80%), and full adherence as >80% of days covered (PDC > 80%).[147] Adherence was calculated for the most recent episode of coxib use (with censoring at a UGI tract event) prior to the event.

Case and control definition

Cases were members of the coxib plus GPA cohort who had a UGI event, which was defined as UGI tract bleeding or symptomatic UGI ulcer both with or without perforation or obstruction either during the coxib episode, or a maximum of 60 days thereafter. UGI tract events were identified by a sensitive electronic search and were subsequently manually (IPCI) or electronically (GPRD, HSD) validated considering all relevant information available in each database (histology reports, specialist letters, endoscopy results, clinical notes as free text). Different systems for coding and recording clinical details prompted us to consider different search and validation algorithms for each database. In general, cases

were classified as definite if: (i) an endoscopy record was available confirming the UGI event; (ii) the event was mentioned together with the exact location (for example: 'acute duodenal ulcer with haemorrhage'); or (iii) there was a recording of a hospital admission or anaemia within 1 month of the event. Cases were classified as probable if the occurrence of a UGI event was mentioned, but was unconfirmed or non-specific (for example: 'blood in vomit'). Angiodysplasias, esophageal varices and Mallory Weiss syndrome were excluded as case criteria. The index date was defined as the start of the sign/symptom leading to the diagnosis of the UGI event, if present; otherwise it was defined as the date of diagnosis.

To each case we matched all eligible persons from the coxib plus GPA cohort who were, at the index date of the corresponding case, alive, at risk of a coxib-related UGI event (i.e. being in follow-up), of similar age (± 3 years) and same sex, and present in the same database as the case. This matching method samples from the person-time distribution of each person to estimate the exposure distribution (in a manner similar to a cohort), and the number of controls reflects person-moments.

Covariates

For covariates, we evaluated the presence of the risk factors for NSAID-related UGI events as commonly described in guidelines on the prevention of NSAID-related UGI events.[53, 152] These were (i) age 65 years and older; (ii) a prior UGI event; (iii) concomitant use of antiplatelets (including low-dose aspirin of 325 mg/day or less); (iv) concomitant use of anticoagulants; or (v) concomitant use of systemic steroids > 5 mg/day. In the nested case-control analysis, covariates were assessed prior to the index date. Concomitant treatment was defined as drug use overlapping the index date. We additionally evaluated the length of coxib episode and the density of coxib use (number of coxib prescription days divided by episode length) within the episode.

Statistical analyses

Baseline characteristics of the coxib cohort, the coxib minus GPA-cohort, and the coxib plus GPA cohort were described by database. The database-specific and pooled crude incidence rates of UGI events within the coxib cohort and subcohorts were estimated together with 95% confidence intervals (95% CI) based on the Poisson distribution and expressed per 1,000 years of coxib use. Exposure time was calculated on the basis of actual use plus the carry-over period and censored upon the earliest of the end of the carry-over period, the occurrence of the outcome of interest, or the end of the eligibility period.

GPA adherence in the coxib plus GPA cohort was described by database, type of coxib, type of GPA, episode length, and the presence of the five major risk factors for UGI tract events. To estimate the risk of coxib-related UGI events according to GPA adherence, we calculated adjusted matched odds ratios (OR) with 95% CIs through conditional logistic regression analyses, while adjusting for all covariates that changed the estimated risk in any of the exposure categories by more than 10%.

The analyses were stratified by the presence of important UGI risk factors, including concomitant use of low-dose aspirin or a prior UGI event. Interaction terms were tested to investigate whether effect modification occurred by age, risk level, type of coxib, or duration of coxib episode. In a subanalysis we calculated the risk of UGI bleeding only (excluding symptomatic UGI ulcers). To test the robustness of our findings, a sensitivity analysis was performed including only definite cases (excluding probable cases).

Two methods were used to pool data across databases. The first method was to pool the data on the study level by obtaining three estimates of the risk of coxib-related UGI events according to continuous GPA adherence per database, then to pool the three obtained risk estimates using a meta-analysis approach, resulting in an overall risk estimate (inverse variance model) using a random-effects model. The second method was to pool the data on the patient level. The latter method is only appropriate when there is no heterogeneity.

All analyses were performed using SPSS 15.0 for Windows. A two-sided p-value less than 0.05 was considered significant.

Results

Characteristics of total coxib cohort and subcohorts

Within the source population of 5,251,865 patients, we identified 81,000 coxib users generating 98,940 eligible episodes for the overall coxib cohort. In 16,442 of these episodes (16.6%), a GPA was co-prescribed (UK: 21.2%; NL: 13.4%, IT: 11.0%) and these episodes were the basis for the coxib plus GPA cohort, comprising of a total of 14,416 patients. The mean number of eligible coxib plus GPA episodes per patient was 1.14, and the median duration of the coxib episode was 30 days (IQR 20-61 days) in the coxib plus GPA cohort.

Table 7.1 shows the characteristics of the total coxib cohort and the corresponding subcohorts for each database. Within the coxib cohort, the most commonly prescribed coxibs were celecoxib (43.1%), rofecoxib (40.9%), and etoricoxib (15.1%). Patients within the coxib plus GPA sub-cohort had more reported UGI risk factors compared with the coxib minus GPA cohort (73.8% vs. 63.4%).

Incidence rates in coxib cohort

We identified a total of 256 patients with a symptomatic UGI event (131 UGI bleedings and 125 symptomatic ulcers) which occurred during or within 60 days of an eligible coxib episode. The pooled crude incidence rate of UGI events was 8.4 (95% CI: 7.4-9.4) per 1,000 years of coxib use (UK: 9.5 (95% CI: 8.2-11.0), NL: 6.8 (95% CI: 3.8-11.4), IT 6.2 (95% CI: 4.7-8.0)). In a sub-analyses the incidence rate for UGI bleedings was 4.3 (95% CI: 3.6-5.0) per 1,000 years of coxib treatment.

The pooled crude incidence rates of UGI events were significantly higher among patients receiving GPAs than among those not receiving GPAs, which shows channeling of GPAs towards persons at high-risk of UGI tract events. The crude incidence rates of UGI events were higher among patients who were adherent to the prescribed GPA (PDC > 80%) than among those who were non-adherent (PDC < 20%) (Table 7.2).

Adherence to gastroprotective agents in the coxib plus GPA cohort

PPIs were the most commonly used GPAs (99.2%), whereas double-dose H_2RAs were not prescribed. Overall, adherence was 76% ± 30% (UK: 79% ± 29%; NL: 85% ± 27%; IT: 66% ± 30%), and 9,817 patients (59.7%) (UK: 66.6%; NL: 76.2%; IT: 38.1%) were fully adherent. The level of adherence increased with the presence of an increasing number of risk factors (P for trend < 0.001), but decreased with increased duration of the episodes (P for trend < 0.001) (Table 7.5).

Table 7.1: Cohort characteristics for the coxib cohort (at cohort entry) and for the coxib+GPA cohort (at start of each eligible episode) by database

	Coxib cohort			Coxib-GPA cohort			Coxib+GPA cohort		
	UK	NL	IT	UK	NL	IT	UK	NL	IT
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total	52,698	7,201	39,041	41,519	6,233	34,746	11,179	968	4,295
Age, mean±SD (years)	68.6±10.4	66.1±11.2	68.2±10.4	68.5±10.4	66.0±11.3	68.0±10.4	69.2±10.3	66.8±11.1	70.1±10.2
Male	16,349 (31.0)	2,461 (34.2)	12,675 (32.5)	12,953 (31.2)	2,162 (34.7)	11,260 (32.4)	3,396 (30.4)	299 (30.9)	1,415 (32.9)
Individual UGI risk factors:									
Age ≥65 years	31,876 (60.5)	3,645 (50.6)	23,197 (59.4)	24,792 (59.7)	3,110 (49.9)	20,331 (58.5)	7,084 (63.4)	535 (55.3)	2,866 (66.7)
Prior UGI event	4,214 (8.0)	223 (3.1)	1,988 (5.1)	2,431 (5.9)	132 (2.1)	1,468 (4.2)	1,783 (15.9)	91 (9.4)	520 (12.1)
Use of antiplatelets	10,708 (20.3)	776 (10.8)	3,609 (9.2)	7,791 (18.8)	660 (10.6)	3,031 (8.7)	2,917 (26.1)	116 (12.0)	578 (13.5)
Use of anticoagulants	631 (1.2)	144 (2.0)	310 (0.8)	438 (1.1)	120 (1.9)	268 (0.8)	193 (1.7)	24 (2.5)	42 (1.0)
Use of systemic steroids	1,186 (2.3)	71 (1.0)	878 (2.2)	759 (1.8)	48 (0.8)	624 (1.8)	427 (3.8)	23 (2.4)	254 (5.9)
Number of UGI risk factors:[¶]									
0	17,172 (32.6)	3,253 (45.2)	14,072 (36.0)	14,294 (34.4)	2,906 (46.6)	12,991 (37.4)	2,878 (25.7)	347 (35.8)	1,081 (25.2)
1	23,707 (45.0)	3,078 (42.7)	20,182 (51.7)	18,933 (45.6)	2,611 (41.9)	17,914 (51.6)	4,774 (42.7)	467 (48.2)	2,268 (52.8)
2	10,593 (20.1)	830 (11.5)	4,567 (11.7)	7,627 (18.4)	689 (11.1)	3,717 (10.7)	2,966 (26.5)	141 (14.6)	850 (19.8)
3	1,182 (2.2)	39 (0.5)	214 (0.5)	636 (1.5)	27 (0.4)	122 (0.4)	546 (4.9)	12 (1.2)	92 (2.1)
≥4	44 (0.1)	1 (0.0)	6 (0.0)	29 (0.1)	-	2 (0)	15 (0.1)	1 (0.1)	4 (0.1)

UGI, upper gastrointestinal; GPA, gastroprotective agents; UK, United Kingdom; NL, the Netherlands; IT, Italy.
¶ Included in the count were prior UGI event, concomitant use of antiplatelets, anticoagulants, or steroids, and age ≥65 years.

Table 7.2: Incidence rates of UGI events (UGI bleeding and symptomatic ulcer) during eligible coxib episodes (in total coxib cohort) by database

	Total		UK		NL		IT	
	n	Incidence* (95%CI)	n	Incidence* (95%CI)	n	Incidence* (95%CI)	n	Incidence* (95%CI)
Total	256	8.4 (7.4-9.4)	187	9.5 (8.2-11.0)	13	6.8 (3.8-11.4)	56	6.2 (4.7-8.0)
Age, (years):								
50-65	55	4.6 (3.5-5.9)	37	4.9 (3.5-6.6)	1	1.3 (0.1-6.0)	17	4.7 (2.9-7.4)
65-75	80	8.4 (6.7-10.4)	56	9.1 (6.9-11.7)	4	7.8 (2.6-18.5)	20	7.1 (4.5-10.8)
> 75	121	13.3 (11.1-15.8)	94	16.1 (13.1-19.6)	8	13.2 (6.2-24.9)	19	7.2 (4.5-11.0)
Gender:								
Male	90	9.5 (7.7-11.7)	68	11.5 (9.0-14.5)	5	8.2 (3.1-18.0)	17	5.8 (3.5-9.1)
Female	166	7.9 (6.7-9.1)	119	8.7 (7.2-10.4)	8	6.2 (2.9-11.7)	39	6.3 (4.6-8.6)
Individual UGI risk factors:								
Age ≥65 years	201	10.8 (9.4-12.4)	150	12.5(10.6-14.6)	12	10.7 (5.9-18.1)	39	7.1 (5.2-9.7)
Prior UGI event	28	14.7 (10.0-21.0)	24	17.5 (11.5-25.6)	1	17.8 (1.6-83.1)	3	6.4 (1.8-17.0)
Use of antiplatelets	90	17.8 (14.4-21.7)	75	18.9 (15.0-23.6)	7	27.2 (12.1-53.4)	8	9.4 (4.5-17.8)
Use of anticoagulants	4	10.6 (3.5-25.1)	2	7.9 (1.6-25.3)	0	-	2	26.1 (5.2-83.7)
Use of systemic steroids	9	12.2 (6.7-9.1)	9	18.5 (9.2-33.8)	0	-	0	-
Number of UGI risk factors:¶								
0	42	4.1 (3.0-5.5)	25	4.0 (2.6-5.8)	1	1.4 (0.1-6.6)	16	5.0 (3.0-8.0)
1	109	7.5 (6.2-9.0)	76	8.5 (6.7-10.6)	4	4.4 (1.5-10.5)	29	6.1 (4.2-8.7)
2	92	17.3 (14.0-21.1)	74	18.7 (14.8-23.3)	8	28.6 (13.5-53.9)	10	9.2 (4.7-16.4)
3	13	28.80 (16.1-47.9)	12	31.3 (17.1-53.1)	0	-	1	18.5 (1.7-86.3)
No GPAs (Coxib-GPA cohort)	182	7.5 (6.5-8.6)	127	8.6 (7.2-10.2)	11	6.8 (3.6-11.8)	44	5.5 (4.0-7.3)
With GPAs (Coxib+GPA cohort)	74	11.9 (9.4-14.8)	60	12.3 (9.5-15.7)	2	6.8 (1.4-21.8)	12	11.5 (6.3-19.4)
GPA adherence:								
PDC < 20%	7	8.4 (3.7-16.4)	7	10.0 (4.4-19.6)	0	-	0	-
PDC 20-80%	26	13.0 (8.7-18.8)	17	12.6 (7.6-19.7)	1	14.2 (1.3-66.0)	8	13.9 (6.6-26.3)
PDC > 80%	41	12.1 (8.8-16.2)	36	12.7 (9.0-17.4)	1	5.1 (0.5-23.7)	4	11.0 (3.7-26.1)

UGI, upper gastrointestinal; GPA, gastroprotective agents; PDC, percentage of coxib days covered with GPA.

* *Incidence per 1000 coxib use years.*

¶ *Included in the count were prior UGI event, concomitant use of antiplatelets, anticoagulants, or steroids, and age ≥65 years.*

Table 7.3: Association between patient characteristics and UGI events (nested case-control analysis in coxib+GPA cohort) by database

	UK		IT		Total		
	Cases	Controls	Cases	Controls	Cases	Controls	$OR_{matched}$
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	(95% CI)
Total	60 (100)	4,891 (100)	12 (100)	260 (100)	74 (100)	5,156 (100)	
Age, mean±SD (years)*	72.6±11.0	71.5±8.5	72.6±7.7	70.4±6.7	73.0±10.6	71.4±8.5	-
Male gender*	16 (26.7)	684 (14.0)	4 (33.3)	47 (18.1)	21 (28.4)	733 (14.2)	-
Type of first coxib:†							
Celecoxib	24 (48.0)	1,902 (45.7)	3 (60.0)	39 (42.4)	28 (49.1)	1,942 (45.6)	1 (ref)
Rofecoxib	21 (42.0)	1,920 (46.1)	1 (20.0)	37 (40.2)	23 (40.4)	1,961 (46.0)	0.78 (0.42-1.44)
Etoricoxib	5 (10.0)	305 (7.3)	1 (20.0)	16 (17.4)	6 (10.5)	321 (7.5)	0.98 (0.36-2.66)
Valdecoxib	0 (0)	38 (0.9)	0 (0)	0 (0)	0	38 (0.9)	-
Other/combinations	0 (0)	1 (0.0)	0 (0)	0 (0)	0	1 (0)	-
Individual UGI risk factors:							
Prior UGI event	13 (21.7)	601 (12.3)	2 (16.7)	35 (13.5)	16 (21.6)	637 (12.4)	1.77 (1.00-3.12)
Use of antiplatelets	20 (33.3)	1,167 (23.9)	2 (16.7)	38 (14.6)	23 (31.1)	1,207 (23.4)	1.45 (0.86-2.45)
Use of anticoagulants	0 (0)	83 (1.7)	1 (8.3)	3 (1.2)	1 (1.4)	86 (1.7)	0.80 (0.11-5.94)
Use of systemic steroids	5 (8.3)	230 (4.7)	0 (0)	13 (5.0)	5 (6.8)	244 (4.7)	1.26 (0.49-3.22)
Number of UGI risk factors:¶							
0	29 (48.3)	3,039 (62.1)	8 (66.7)	180 (69.2)	37 (50.0)	3,221 (62.5)	1 (ref
1	24 (40.0)	1,631 (33.3)	3 (25.0)	71 (27.3)	29 (39.2)	1,704 (33.0)	1.45 (0.87-2.40)
2	7 (11.7)	213 (4.4)	1 (8.3)	9 (3.5)	8 (10.8)	223 (4.3)	2.63 (1.17-5.88)
3	0 (0)	8 (0.2)	0 (0)	0 (0)	0 (0)	8 (0.2)	-

UGI, upper gastrointestinal.
NL only had two exposed cases. NL is included in the total amount.
** Matching variables .*
¶Included in the count were prior UGI event and concomitant use of antiplatelets, anticoagulants, or steroids. Age was excluded as a matching variable. P for trend was 0.02.
† Adjusted for dose. Patients were only included when dose was available (82.6%).

Table 7.4: Association between adherence to gastroprotective agents during coxib use and the risk of UGI events (UGI bleeding and symptomatic ulcer)

	Cases	Controls	$OR_{matched}$ (95% CI)	$OR_{adjusted}$* (95% CI)	P for trend
Continuous: with every 10% decline in adherence	74	5,156	1.05 (0.97-1.14)	1.09 (1.00-1.18)	0.045
Categorical:					
GPA adherence PDC > 80%	41 (55.4)	3,348 (64.9)	1 (ref)	1 (ref)	0.045
GPA adherence PDC 20%-80%	26 (35.1)	1,375 (26.7)	1.41 (0.84-2.37)	1.55 (0.91-2.62)	
GPA adherence PDC < 20%	7 (9.5)	433 (8.4)	1.43 (0.63-3.26)	1.97 (0.84-4.60)	

UGI, upper gastrointestinal; PDC, percentage of coxib days covered with GPA.
** Adjusted for length of coxib episode, density of coxib use within episode.*

Table 7.5: Adherence to gastroprotective agents during coxib use (in coxib+GPA cohort)

		GPA adherence (PDC)			
		PDC	< 20%	20-80%	> 80%
	n	Mean ± SD*	n (%)	n (%)	n (%)
Total	16,442	76 ± 30	1,188 (7.2)	5,437 (33.1)	9,817 (59.7)
Age (years):					
50-65	5,957	76 ± 30	442 (7.1)	2,001 (33.6)	3,534 (59.3)
65-75	5,257	75 ± 30	421 (8.0)	1,750 (33.3)	3,086 (58.7)
> 75	5,228	77 ± 29	345 (6.6)	1,686 (32.2)	3,197 (61.2)
Gender:					
Male	5,110	76 ± 30	380 (7.4)	1,707 (33.4)	3,023 (59.2)
Female	11,332	76 ± 30	808 (7.1)	3,730 (32.9)	6,794 (60.0)
Individual UGI risk factors:					
Age ≥65 years	10,485	76 ± 30	766 (7.3)	3,436 (32.8)	6,283 (59.9)
Prior UGI complication	2,394	79 ± 27	121 (5.1)	729 (30.5)	1,544 (64.5)
Use of antiplatelets	3,436	79 ± 28	227 (6.6)	947 (27.6)	2,262 (65.8)
Use of anticoagulants	259	83 ± 26	12 (4.6)	60 (23.2)	187 (72.2)
Use of systemic steroids	704	75 ± 28	36 (5.1)	266 (37.8)	402 (57.1)
Number of UGI risk factors:¶					
0	4,329	75 ± 30	334 (7.7)	1,509 (34.9)	2,486 (57.4)
1	7,591	75 ± 30	569 (7.5)	2,580 (34.0)	4,442 (58.5)
2	3,899	78 ± 29	263 (6.7)	1,195 (30.6)	2,441 (62.6)
3	603	84 ± 24	21 (5)	144 (23.9)	438 (72.6)
4 or more	20	74 ± 27	1 (5.0)	9 (45.0)	10 (50.0)
Type of first coxib:					
Celecoxib	7,209	75 ± 29	523 (7.3)	2,464 (34.2)	4,222 (58.6)
Rofecoxib	6,185	77 ± 30	454 (7.3)	1,945 (31.4)	3,786 (61.2)
Etoricoxib	2,861	76 ± 30	200 (7.0)	974 (34.0)	1,687 (59.0)
Valdecoxib	151	77 ± 29	11 (7.3)	44 (29.1)	96 (63.6)
Other/combinations	36	82 ± 26	0 (0)	10 (27.8)	26 (72.2)
Type of GPA:					
PPI	16,314	76 ± 30	1,175 (7.2)	5,379 (33.0)	9,760 (59.8)
H_2RA	0	-	-	-	-
Misoprostol	84	62 ± 33	12 (14.3)	38 (45.2)	34 (40.5)
Combination	44	73 ± 30	1 (2.3)	20 (45.5)	23 (52.3)
Duration of episode:*					
< 1 month	10,107	81 ± 27	445 (4.4)	2,960 (29.3)	6,702 (66.3)
1-6 months	4,667	70 ± 30	375 (8.0)	1,999 (42.8)	2,293 (49.1)
6-12 months	828	66 ± 33	144 (17.4)	271 (32.7)	413 (49.9)
> 12 months	840	60 ± 38	224 (26.7)	207 (24.6)	409 (48.7)

UGI, upper gastrointestinal; GPA, gastroprotective agents; PDC, percentage of coxib days covered with GPA; PPI, proton pump inhibitor; H_2RA, histamine-2 receptor antagonist.
¶ Included in the count were prior UGI event, concomitant use of antiplatelets, anticoagulants, or steroids, and age ≥65 years. P for trend< 0.001.
** P for trend< 0.001.*

Nested case-control study in the coxib plus GPA cohort

In the coxib plus GPA cohort, all 74 patients with a UGI event during follow-up were included as cases, and 5,156 event-free controls were matched. The characteristics of the cases and controls at the index date are described in Table 7.3.

GPA adherence (PDC) of cases and their controls was 72% ± 32% and 78% ± 30%, respectively. Coxib users who were non-adherent to GPAs had a non-significant 2-fold increased risk of UGI events (OR: 1.97; 95% CI: 0.84-4.60) and those who were moderately adherent a 1.5-fold increased risk (OR: 1.55; 95% CI: 0.91-2.62), compared with patients who were fully adherent (Table 7.4). With every 10% decline in GPA adherence, the risk of a UGI event increased significantly by 9% (OR: 1.09; 95% CI: 1.00-1.18; p-value: 0.045). Upon restriction to definite cases only (n = 20), the association became stronger. With every 10% decline in GPA adherence, the risk of a UGI event increased by 20% (OR: 1.20; 95% CI: 1.03-1.39). Pooling on the basis of random effects (being the most conservative approach) yielded a similar estimate (OR: 1.09; 95% CI: 1.01-1.19; p-value: 0.03). Analyses stratified by concomitant use of low-dose aspirin, the presence of a UGI risk factor, the type of coxib, and duration of the coxib episode are shown in Table 7.6. None of the interaction terms was significant, although the power to detect statistically significant effect modification was low. A decreasing trend in the association between GPA adherence and the risk of UGI events was observed with increasing coxib episode length.

Table 7.6: Risk of UGI events with every 10% decline in GPA adherence during coxib use: stratified analyses

	Cases	Controls	$OR_{matched}$ (95% CI)	$OR_{adjusted*}$ (95% CI)
Original	74	5,156	1.05 (0.97-1.14)	1.09 (1.00-1.18)
UGI bleed alone	30	2,189	1.03 (0.90-1.17)	1.07 (0.93-1.22)
Origin of database:				
The United Kingdom	60	4,891	1.06 (0.97-1.15)	1.10 (1.01-1.20)
The Netherlands	2	5	1.28 (0.49-3.34)	2.76 (0.00-4489)
Italy	12	260	1.01 (0.81-1.26)	1.07 (0.85-1.34)
Type of first coxib:†				
Celecoxib	28	1,942	0.96 (0.81-1.13)	0.96 (0.81-1.14)
Rofecoxib	23	1,961	1.12 (0.99-1.27)	1.17 (1.02-1.34)
Other/combinations	6	360	1.14 (0.66-1.98)	1.20 (0.67-2.15)
Duration of coxib episode:¶				
< 1 month	35	1,937	1.13 (1.00-1.28)	1.13 (1.00-1.28)
1-6 months	29	1,721	1.02 (0.88-1.19)	1.02 (0.88-1.18)
6-12 months	6	637	0.96 (0.73-1.28)	1.00 (0.72-1.26)
> 12 months	4	861	0.92 (0.62-1.36)	0.94 (0.62-1.42)
Age (years):				
50-65	19	1,168	1.03 (0.88-1.21)	1.10 (0.93-1.29)
65-75	21	2,128	1.0 (0.85-1.17)	1.03 (0.87-1.21)
> 75	34	1,860	1.11 (0.99-1.24)	1.14 (1.01-1.29)
Risk level:				
No UGI risk factors	12	849	0.89 (0.69-1.14)	0.93 (0.72-1.19)
≥ 1 UGI risk factor	62	4,307	1.08 (0.99-1.18)	1.11 (1.02-1.22)
Low dose aspirin:				
With low dose aspirin	22	1,057	1.12 (0.96-1.30)	1.15 (0.98-1.36)
Without low dose aspirin	52	4,099	1.03 (0.94-1.14)	1.08 (0.97-1.19)
Prior UGI event:				
Yes	16	637	1.08 (0.87-1.34)	1.10 (0.87-1.38)
No	58	4,519	1.05 (0.96-1.15)	1.08 (0.99-1.19)

UGI, upper gastrointestinal.

**Adjusted for length of coxib episode, density of coxib use within episode.*

† Additionally adjusted for dose. Patients were only included when dose was available (82.6%).

¶ Only adjusted for density of coxib use within episode.

When restricting the cases to UGI bleeding only, the risk of a UGI bleed increased by 7% (OR: 1.07; 95% CI: 0.93-1.22) for every 10% decline in GPA adherence (Table 7.6). Coxib users who did not adhere to their GPAs had a 2.2-fold increased risk of UGI bleeding (OR: 2.24; 95% CI: 0.62-8.10) compared with patients who were fully adherent. The number of patients was too small to allow a sensitivity analysis with definite cases only.

Discussion

This population-based, multiple database study shows that with every 10% decrease in GPA adherence during coxib use, the risk of UGI events increased significantly by 9% for all UGI events. In other words, with every three-day reduction of GPA coverage per 30 days of coxib use, the risk of UGI events increases by 9%. GPA non-adherence (PDC < 20%, meaning that a GPA was on average only taken every one out of five days of coxib use, or less) was associated with a non-significant two-fold increased risk of UGI events, as compared with coxib users who were fully adherent to GPAs (PDC > 80%, meaning that a GPA was on average taken four out of five days of coxib use, or more).

These results are consistent with results from our previous study on GPA adherence in patients receiving non-selective NSAIDs, using the same protocol and databases, providing similar risk estimates.[153] This suggests that GPA adherence is of similar importance in nsNSAID and coxib users. However, to our knowledge, our results are in contrast with those from the only study that investigated associations of GPA adherence both in nsNSAID users and in coxib users.[144] In that study from the United States (US), the likelihood of UGI events decreased as adherence to GPA increased among nsNSAID users, but remained relatively constant for coxib users (mostly rofecoxib and celecoxib) across all adherence levels. A possible explanation for the difference between the study by Goldstein et al and ours is that a younger and healthier subgroup of coxib plus PPI users was selected in the referred study (mean age 50.2 years vs. 69.3 years in our study). Also, rofecoxib dosages are generally higher in Europe than in the US. As such, the study population was at a relatively low risk, and conceivably the incremental benefit of PPIs was less pronounced. In our study we demonstrated a tendency toward a stronger association between GPA adherence and UGI events in coxib users who had at least one UGI risk factor (OR 1.11; 95% CI: 1.02-1.22). The effect was absent in patients receiving coxibs who were at low risk (OR: 0.93; 95% CI: 0.72-1.19), confirming that GPA non-adherence is more harmful in high risk coxib users.

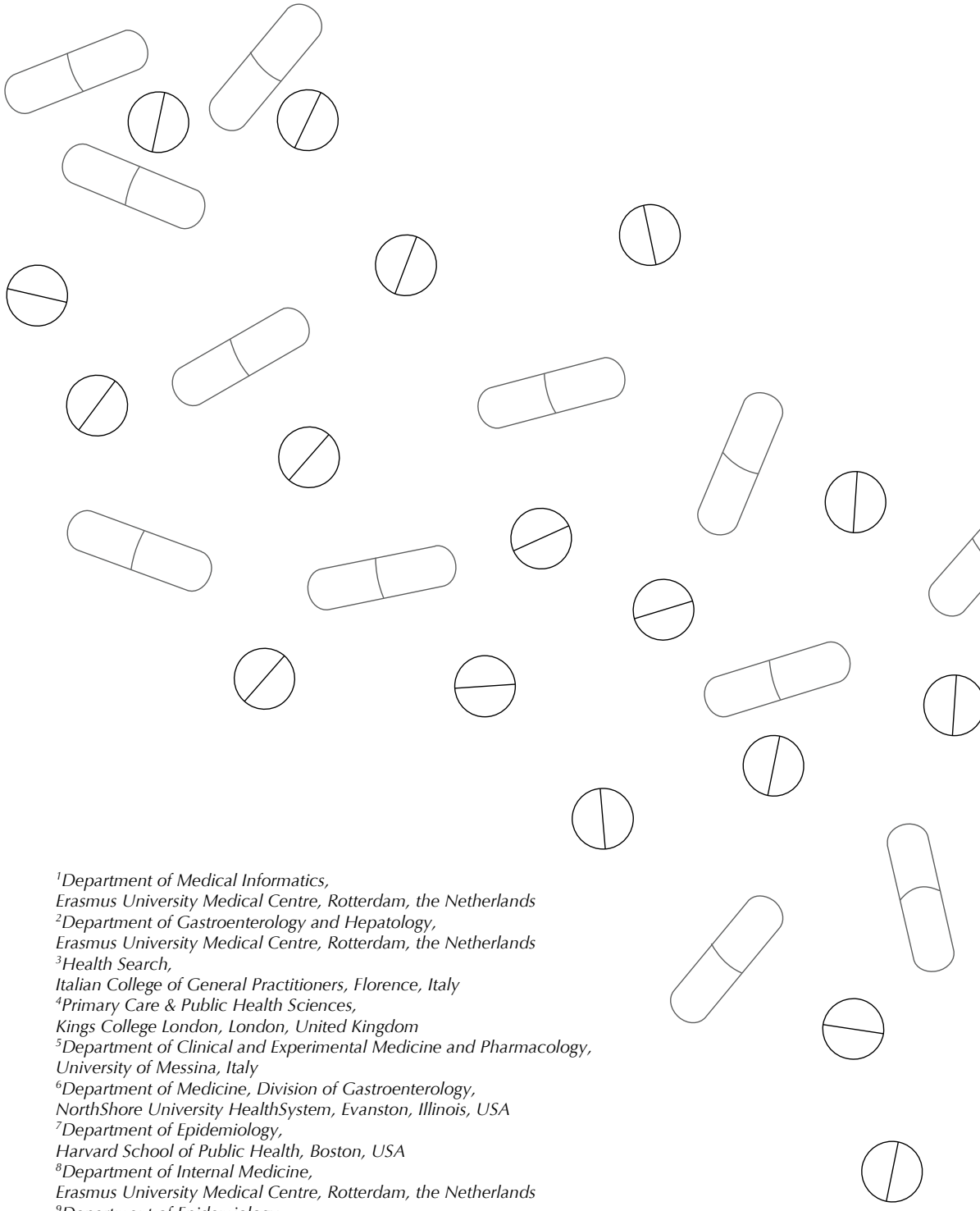
The strength of this study is that it describes real-world patient and physician behavior regarding prescriptions in the general population originating from a large amount of data from three countries. Of the coxibs included in this study, only celecoxib is still available in the US, while celecoxib, etoricoxib, and parecoxib are available in Europe. As with all observational database studies, selection bias, information bias, and confounding need to be considered. Data were gathered prospectively for clinical use and irrespective of the hypothesis studied, this minimized the threat of selection bias. Information bias includes misclassification of exposure and outcome. The databases capture information on prescription data only, as information on drug dispensing or actual drug intake is not available. The actual adherence pattern may be different from the prescription pattern, which may have led to misclassification of exposure and an attenuation of the association. Due to small numbers, we had limited possibilities to distinguish between different types of coxibs. Although coxibs are not available over-the-counter (OTC), omeprazole (one of the

PPIs) is available OTC in the UK for short-term use only (not reimbursed), whereas PPIs were not available OTC in NL or IT during the study period. Misclassification of the outcome was probably minimal, as we manually and/or electronically validated all cases. Some non-differential misclassification remained, since restriction of the analyses to definite cases strengthened the association.

We have attempted to minimize confounding by design (restriction to the coxib plus GPA cohort) and by analysis (multivariable adjustments on comorbidity, UGI risk factors, and concomitant drug use). Restriction was decided upon beforehand, but we were strengthened in this decision as the observed incidence of UGI events was higher among patients taking GPAs than among patients not taking GPAs (Table 7.2). This can be explained by channeling (i.e. patients with a worse prognosis with regard to UGI events are more likely to receive GPAs than are healthier patients). By restricting our study to only those patients receiving coxibs concomitant with GPAs, we have mitigated this. Nevertheless, within the group of patients receiving coxibs plus GPAs, it is conceivable that patients at higher risk of developing UGI events will be more adherent to their GPA. This is confirmed by the high crude incidence rate among moderate and full adherers as compared with patients who were non adherent (Table 7.2). These results indicate that the healthy adherer effect (i.e. patients who adhere well to any medical or lifestyle regimen have better outcomes) is not of major concern in this particular study.

A potential explanation for the observation that the association of GPA adherence with the risk of UGI events decreased with increasing coxib episode length, beyond chance, is depletion of susceptibles. Subjects resistant to UGI events continue to take the drug, while those who are susceptible to drug-related UGI events select themselves out of the population at risk by withdrawing from the drug. This phenomenon is well known in observational studies on NSAIDs and UGI events.[154]

In conclusion, GPA adherence seems to be a major factor in reducing the risk of UGI tract events in coxib-treated patients, as GPA non-adherence is as important a risk factor as other conventional risk factors (Table 7.3 and Table 7.4). This is relevant since non-adherence to GPAs is a modifiable risk factor, whereas most conventional risk factors are not. This study supports the hypothesis that improvement of GPA adherence could be beneficial in reducing the risk of coxib-related UGI events.



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Submitted

Chapter 8

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

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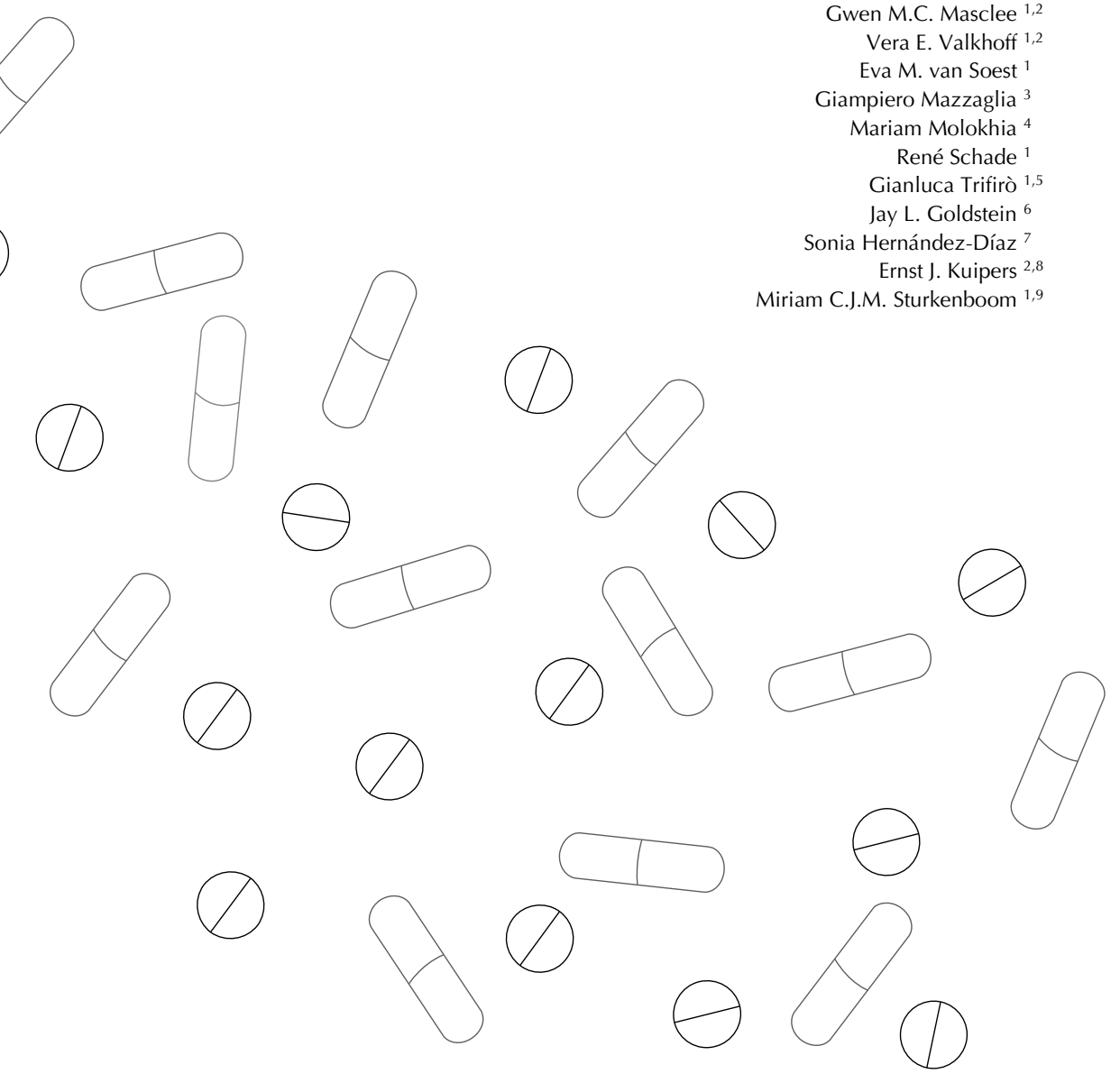

Abstract

Background

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

Aim

The aim of our study was to identify whether and in whom either of these strategies should be preferred in daily clinical 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 coxib users (without GPA use) aged ≥ 50 years. Cases with a UGI event (i.e. symptomatic UGI ulcer or bleeding (UGIB)) were matched to cohort members without a UGI event based on age, sex and number of individual UGI risk factors (i.e. history of a UGI event, 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 all potential confounders.

Results

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

Conclusions

The risk of UGI events was similar in nsNSAID+GPA (≥ 80% adherence) and coxibs users. In patients concurrently using aspirin a significant increase in the risk of UGI events for coxibs was observed, whereas in concurrent glucocorticoid use nsNSAID+GPA users are at increased risk.

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 (UGI) ulcers and bleeding. To mitigate the increased risk among long term NSAID users, guidelines have been developed and strategies are recommended[53, 87, 88, 142] including prescription of cyclo-oxygenase (COX)-2-selective inhibitors (coxibs) or concurrent use of gastroprotective agents (GPAs), such as proton pump inhibitors (PPIs). Although both gastroprotective strategies aim to reduce the incidence of UGI events, the risk of such complications is not eliminated; a considerable proportion of NSAID plus GPA users (6.3-8.5%) and coxib users (3.7-8.9%) continues to experience UGI events.[43-45, 155]

Defining which of the two gastroprotective strategies is preferred in terms of UGI safety has been the scope of recent studies. Most of the randomized clinical trials showed no superiority for one of the gastroprotective strategies over the other.[43-45, 156] Only one large randomized clinical trial showed a beneficial effect in favor of celecoxib. In this 6 month trial patient randomized to celecoxib, as compared with 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.[157] 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 coxibs or included a selected group of high-risk patients (i.e. those with a recent UGI event).[43-45, 157] Alternatively in some of the prospective trials, the presence of co-morbid diseases such as ischemic heart disease, peripheral arterial disease[157], or congestive heart failure[45] were considered as exclusion criterion, thereby preferentially selecting patients at lower risk of UGI events. Additionally, the exclusion of patients with frequently used co-medication (e.g. low-dose aspirin[45], anticoagulant agents[44, 45] and corticosteroids[44]) in some of the studies might be an important issue, considering that the use of low-dose aspirin clearly influences the efficacy of UGI protection in coxibs.[41, 158] Finally, as a consequence of protocol driven inclusion of patients with recent or past UGI bleeding and in some studies, the recruitment of patients from a hospital-setting[45, 157] or endoscopy centers[43, 44], a substantial number of enrolled subjects may have had NSAID-associated complications and as such at higher risk.

Apart from the clinical studies, one population-based cohort study concluded that coxibs alone were not superior to nsNSAID combined with PPI in the prevention of hospitalization for a perforated or bleeding ulcer.[159] 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 UGI events, but it did not address the lack of adherence to PPIs.[151] 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[107] and associated with significantly increased risk of nsNSAID-related upper GI events.[118, 144, 153]

Thus, whether coxibs and nsNSAIDs plus GPA are similarly effective in preventing incident NSAID-related UGI events in daily clinical practice is still unknown. Therefore, we conducted a case-control study to compare the risk of UGI events between coxib 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.

Methods

Description of data sources

Three similar European population-based primary care registries served as data sources: (i) the General Practice Research Database (GPRD) from the United Kingdom (UK, 1998 – 2008), (ii) the Integrated Primary Care Information database (IPCI) from the Netherlands (1996 – 2007), and (iii) 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, who 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. We have previously shown the validity to combine and to compare data from the three European databases.[122, 153] For GPRD, the READ dictionary was used to identify medical diagnosis and symptoms, whereas the International Classification for Primary Care[61] and the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) were used for that purpose in IPCI and HSD, respectively. In IPCI and HSD information on drug prescription was coded according to the Anatomical Therapeutical Chemical (ATC) classification. 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.[153] 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, and 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. A cohort of patients who newly started (i.e. no NSAID prescriptions within 6 months prior to inclusion) on either coxibs 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 a 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. 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 pre-

scription 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, non-selective 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). The GPA adherence calculation has been described previously.[144]

NSAID episodes during which patients switched between classes of NSAIDs (from nsNSAID to coxib or vice versa) were excluded. Episodes during which coxibs were used concurrently with a GPA were also excluded, resulting in a cohort including only nsNSAID plus GPA (≥ 80 % adherence) and coxib (alone) users.

Cases and controls selection

Outcomes of interest were a composite of UGI events (including symptomatic ulceration, UGI bleeding (UGIB), perforation or obstruction) and UGIB alone. Identification of the outcomes has been described in more detail elsewhere.[153] The date of outcome (i.e. index date) was determined as the date of the start of symptoms leading to the diagnosis of the UGI event, or if this date was unknown, the date of diagnosis. Events occurring within 60 days after the end of an NSAID episode were attributed to the previous NSAID use.[28]

A nested case-control study was conducted. To each case experiencing a UGI 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 UGI event at the index date of the corresponding case and were at the index date alive, using an NSAID within 60 days prior to the event date, had equal number of UGI risk factors (see below) as the case and had similar age (±3 years) and same gender.

Covariates

We considered as risk factors for UGI events those that are commonly reported in literature: (i) age ≥ 65 years; (ii) a history of UGI 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 channel antagonists) at the time of 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 UGI events and UGI bleeding among nsNSAID + GPA users (≥ 80% adherence) in comparison to coxib users, matched and adjusted odds ratios (OR) with 95% confidence interval (CIs) were calculated using conditional logistic regression analyses for each database separately and as pooled analysis. The pooling of data across

databases was performed by two methods: (i) on patient-level (respecting matched cases and controls from the original database); and (ii) on study-level by estimating the risk of UGI events for nsNSAID + GPA (≥ 80% adherence) use vs. coxib 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%.

Subsequent analyses evaluated the risk of UGI events and UGI bleeding stratified by the presence of individual risk factors: age ≥ 65 years, history of UGI 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 UGI 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 a UGI event (194 with UGI bleeding). In the Netherlands 17 cases with a UGI event (14 with UGI bleeding) were identified from 55,004 new users of NSAIDs and in Italy 74 cases with a UGI event (17 with UGI bleeding) were identified from 177,747 new NSAID users. Overall, 57,568 event-free controls were matched to these 398 UGI 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 8.1. In the UK, the most commonly prescribed nsNSAID was ibuprofen (56% of nsNSAIDs), while celecoxib and rofecoxib were the most commonly prescribed coxibs (48% and 40% of coxibs, respectively). In NL, the most commonly prescribed coxib 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 coxibs. 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, UGI event cases reported more often a history of UGI 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, UGI 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). UGI 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 UGIB cases and controls in the Netherlands and Italy.

From all UGI event cases in the UK, the Netherlands and Italy, respectively 11.7%, 11.8% and 32.4% had no documented UGI risk factor. The majority of cases were identified as having one or two documented UGI 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.

Risk of UGI events and UGI bleeding

To compare the risk of UGI event between use of coxibs alone vs. highly adherent nsNSAID+GPA use, a nested case-control study was conducted. Using the adjusted model, no statistically significant decreased or increased risk was observed for nsNSAID + GPA users (≥ 80% adherence) as compared with coxib users (Table 8.2). This holds true for the three countries separately and as pooled estimates on patient level (Table 8.2). Regarding UGIB specifically, similar results were observed. For both outcomes, a trend towards a more protective effect for nsNSAID+GPA (≥ 80% adherence) as compared with coxibs was observed in the Netherlands and Italy (Table 8.2), but the adjusted model did not show a significant benefit (Table 8.2).

Meta-analysis of studies conducted at individual database-level using a random effects model (no significant heterogeneity between databases was shown) did not report different results from pooling on patient-level. Using this meta-analytic approach, adjusted ORs for UGI events and UGI bleeding in association to nsNSAID+GPA (≥ 80% adherence) as compared with coxib use were equal to 1.00 (95% CI: 0.73-1.33) and 1.11 (95% CI: 0.76-1.63), respectively.

Subgroup group analyses

Stratification according to the predefined individual UGI risk factors was performed to identify a possible preference for either strategy to prevent a UGI event or UGI bleeding in specific UGI risk groups (Table 8.3). In non-antiplatelet users a trend towards an increased risk both for symptomatic UGI events and UGI bleeding was observed for nsNSAID+GPA (≥ 80% adherence), whereas the opposite was found for antiplatelet users. This interaction term was significant.

When we compared coxib use with highly adherent nsNSAID+GPA use in glucocorticoid users, the use of nsNSAID+GPA increased the risk for UGI 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). 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. Therefore, stratification according to time period was performed. A decrease in percentage of cases and controls using a coxib was noticed, but this did not impact on the risk of a UGI event for nsNSAIDs+GPA vs. coxibs.

Table 8.1: Baseline characteristics of cases with symptomatic UGI events (UGI bleeding and symptomatic ulcer) and matched controls by database

	United Kingdom			the Netherlands			Italy		
	cases n (%)	controls n (%)	P-value	cases n (%)	controls n (%)	P-value	cases n (%)	controls n (%)	P-value
Total	307	48,860		17	374		74	8,334	
Age (years) (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:*(years)			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
UGI risk factors:									
Age ≥ 65 years	247 (80.5)	36,638 (75.0)	0.243	15 (88.2)	311 (83.2)	-	48 (64.9)	4,949 (59.4)	0.67
Prior UGI 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 UGI 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)	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
Concomitant use of other medication:									
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 antagonists	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

SSRIs, selective serotonin reuptake inhibitors.

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

NA, Not applicable; matching criteria.

Table 8.2: The risk of symptomatic UGI events and UGI bleeding in users of nsNSAID+GPA (≥ 80% adherence) as compared with coxib users

		Symptomatic UGI events (UGI bleeding and symptomatic ulcer)						UGI bleeding					
		Cases n (%)	Controls n (%)	ORmatched (95%CI)	P-value	ORadj† (95%CI)	P-value	Cases n (%)	Controls n (%)	$OR_{matched}$ (95%CI)	P-value	$OR_{adjusted}$† (95%CI)	P-value
United Kingdom	Coxib	128 (41.7)	24,722 (50.6)	1.00		1.00		86 (44.3)				1 (ref)	
	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)			0.568	1.20 (0.80-1.80)	0.375
the Netherlands*	Coxib	13 (76.5)	243 (65.0)	1.00		1.00		10 (71.4)	172 (60.4)	1 (ref)		1 (ref)	
	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	Coxib	44 (59.5)	6,201 (74.4)	1.00		1.00		6 (35.3)	1,124 (64.6)	1 (ref)		1 (ref)	
	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
Total pooled on patient level	Coxib	185 (46.5)	31,166 (54.1)	1.00		1.00		102 (45.3)	16,131 (51.9)	1 (ref)		1 (ref)	
	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 UGI 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%).

Table 8.3: Risk factors for symptomatic UGI events and UGI bleeding; stratified analyses on data pooled on patient level

		Symptomatic UGI events (UGI bleeding and symptomatic ulcer)				UGI bleeding			
		Cases n (%)	$OR_{matched}$* (95% CI)	P-value	P-value§	Cases n (%)	$OR_{matched}$* (95% CI)	P-value	P-value §
Age < 65 years	Coxib	34 (38.6)	1 (ref)			11 (31.4)	1 (ref)		
	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 years	Coxib	151 (48.7)	1 (ref)			91 (47.9)	1 (ref)		
	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 UGI event	Coxib	171 (50.6)	1 (ref)			93 (50.0)	1 (ref)		
	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 UGI event	Coxib	14 (23.3)	1 (ref)			9 (23.1)	1 (ref)		
	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	Coxib	120 (44.4)	1 (ref)			59 (41.0)	1 (ref)		
	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	Coxib	65 (50.8)	1 (ref)			43 (53.1)	1 (ref)		
	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	Coxib	182 (47.5)	1 (ref)			99 (46.7)	1 (ref)		
	nsNSAID+GPA	201 (52.5)	0.99 (0.76-1.27)	0.904	0.078	113 (53.3)	0.91 (0.65-1.28)	0.603	0.085
Use of anticoagulants	Coxib	3 (20.0)	-			3 (23.1)	-		
	nsNSAID+GPA	12 (80.0)				10 (76.9)			
No use of glucocorticoids	Coxib	180 (47.7)	1 (ref)			99 (46.5)	1 (ref)		
	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	Coxib	5 (23.8)	1 (ref)			3 (25.0)	1 (ref)		
	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†	Coxib	162 (62.5)	1 (ref)			91 (64.1)	1 (ref)		
	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‡	Coxib	23 (16.5)	1 (ref)			11 (13.3)	1 (ref)		
	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 and number of individual UGI risk factors.*
 # 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.
§ P-value interaction term.

Discussion

In this case-control study we demonstrate that the risk of a UGI event or UGI bleeding is equal between users of non-selective (ns)NSAIDs in combination with adherent use of a gastroprotective agent (GPA) and coxib users.

Lowering the risk of NSAID-related UGI events can be achieved by concomitant use of GPAs. In particular increasing adherence to GPAs is important in reducing the risk nsNSAID-related UGI events.[118, 144, 153] 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 UGI events or concomitantly using anticoagulants, antiplatelets or corticosteroids. After the introduction of coxibs, it was shown that they indeed were associated with less gastrointestinal toxicity as compared with the traditional non-selective NSAIDs.[38, 40, 41, 160] In order to investigate which strategy is superior with regard to UGI safety, head-to-head comparisons between coxibs and NSAIDs combined with GPAs have been performed in randomized studies. These studies showed no preference of one strategy over the other.[43-45, 156, 157] However, most clinical studies do not allow generalization of their results to daily clinical practice in Western countries, since many studies included selected categories of patients (i.e. high-risk patients with a known endoscopically documented UGI bleed/ulcer- or with specific disease, in particular rheumatoid arthritis), were performed in non-Caucasian persons, and in persons at very high risk of a UGI event.

Our results are in keeping with another observational study by Targownik et al. showing no superiority of nsNSAID combined with PPI use to coxibs in the prevention of NSAID-related UGI events.[151] Although the efficacy of both gastroprotective strategies overall seems equivalent for the upper gastrointestinal tract in the CONDOR study, the coxib-treated patients appeared to have a reduced risk of lower GI events as compared with nsNSAID plus PPI use.[157, 161] However, results from other studies evaluating lower GI tract events as an outcome were conflicting.[162-165] A post hoc analysis of a prospective study showed a lower rate of serious lower GI events for rofecoxib compared with naproxen[164], whereas this was not confirmed in a cross-sectional capsule enteroscopy study showing comparable small-bowel damage between long-term NSAID and coxib users.[166] Mechanistically, whether the impact of NSAIDs on lower GI events reflect a reduction in risk by use of a coxib or an increase in risk by use of a PPI due to altered intestinal bacteria and increased susceptibility to small intestinal bacterial overgrowth is still under debate.[167]

Another area of potential benefit of coxibs over nsNSAID plus GPA use might be in selected high-risk patient groups. In the present study, we found that in glucocorticoid users, adherent use of an nsNSAID plus GPA was associated with a nine times higher UGI event risk compared with coxib users. 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 coxib and nsNSAID plus GPA use in glucocorticoid users separately. Although data on glucocorticoids as an independent risk factor for UGI events are scarce, prior studies have shown a two-fold increased risk of UGI bleeding during glucocorticoid use alone.[166, 168-170] When glucocorticoids are used in combination with NSAIDs, the risk of UGI bleeding is estimated higher as compared with NSAID use alone or glucocorticoid use alone.[166, 168-170] 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[171, 172] as well as NSAIDs do, although the mecha-

nism of inhibition differs. Alternatively, gastric bacterial overgrowth due to acid-suppression such as occurs by PPI use[173, 174] might aggravate gastric mucosal damage by increased exposure time of gastric flora to the mucosal surface or by delayed gastric emptying caused by PPIs.[175] The combination of nsNSAIDs and PPIs therefore may have led to the observed increased risk in concurrent glucocorticoid users. Future studies are needed to further explore these mechanisms of potential interactions.

To reduce the risk of NSAID-related UGI events in certain risk groups, one might prefer one preventive strategy over the other. Although not significant, we found a tendency towards an increased UGI event risk in patients with a history of a UGI event among nsNSAID plus adherent GPA users as compared with coxib users. In this particular high-risk patient group, one might consider the addition of a GPA to a coxib. This combination has been shown to reduce the risk of NSAID-related UGI events to a higher degree than coxibs alone or nsNSAIDs plus PPIs.[151]

In line with previous studies, concomitant use of low-dose aspirin seems to eliminate the UGI risk benefit of coxibs.[40, 158, 160, 176] We observed a trend towards an increased UGI risk among nsNSAID plus adherent GPA compared with coxib users who did not concomitantly use aspirin, whereas the opposite was true for concomitant aspirin users. The interaction term was significant, pointing to a significant increase in risk of UGI events for coxibs 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 coxib users.[53, 122, 151]

The strength of the current study is that 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.[43-45]

Some limitations of this study should be acknowledged. By performing observational studies, certain forms of biases can be introduced of which confounding-by-indication is one of the most important one to discuss with respect to the current study. Confounding-by-indication could have been introduced as the general practitioner's awareness of the UGI risk profile of the individual patient might have influenced the prescribed preventive strategy. After the introduction of coxibs, high-risk patients were more likely to receive a coxib instead of co-prescription of a GPA to NSAIDs.[124] Nevertheless, the preference for preventive strategies changed after warnings for an increased cardiovascular risk related to coxibs were released by regulatory agencies. We have tried to address confounding-by-indication by matching on the number of UGI 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). From previous studies we know that patients being adherent to the prescribed GPA are at the highest risk of nsNSAID related UGI events.[144, 153] In addition, we selected patient groups with a similar UGI risk profile, by matching on the number of UGI risk factors, as well as gender and age. Confounding was also dealt with by adjusting for several co-morbid conditions. Nevertheless, residual confounding cannot be ruled out in this, and every other, observational study.

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 UGI events between the use of coxibs and use of nsNSAIDs plus adherent GPA in daily clinical practice. Neither strategy was superior in the prevention of a first or a recurrent UGI event or UGI bleeding. A significant increase in the risk of UGI events for coxibs was observed when aspirin is used concurrently, whereas nsNSAID plus GPA users concomitantly using glucocorticoids are at increased risk of a UGI event compared with coxib users.

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Chapter 9

Risk of upper gastrointestinal complications and the use of individual NSAIDs: a nested case-control study in the SOS project

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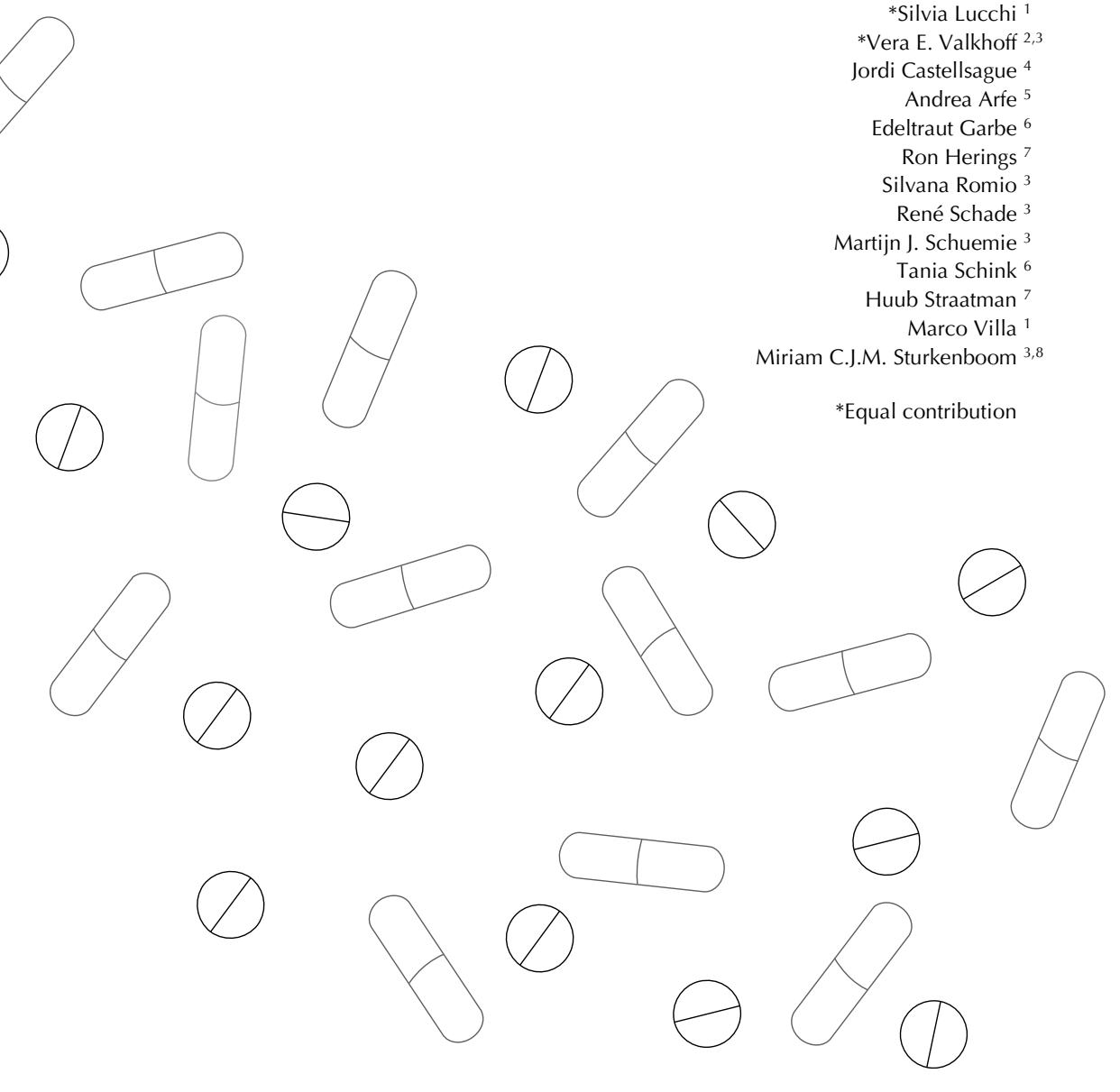

Abstract

Background

The use of non-steroidal anti-inflammatory drugs (NSAIDs) has been linked to an increased relative risk of upper gastrointestinal complications (UGIC) of around two to four. However, each individual NSAID will have a particular gastrointestinal safety profile.

Aim

To estimate the risk of upper gastrointestinal complications (UGIC) associated with use of individual NSAIDs as part of the European Commission funded project on Safety Of Non-Steroidal Anti-Inflammatory Drugs (SOS).

Methods

A matched case-control study was performed nested in a cohort of new NSAID users of 18 years and older between 1999 and 2011. Data were retrieved from 6 databases participating in the SOS project: IPCI and PHARMO (Netherlands), SISR and OSSIFF (Italy), GePaRD (Germany) and THIN (United Kingdom), covering a source population of 32 million subjects. Cases were identified with a common harmonized definition for complication of the UGI tract during follow-up. UGIC cases were matched to up to 100 controls on database, sex, age, and date of UGIC diagnosis (i.e. index date). Demographic information, co-morbidities and concomitant drug use were considered as potential confounders. Adjusted odds ratios (ORs) and their 95% confidence intervals were estimated per database using conditional logistic regression comparing current use of individual NSAIDs vs. past use of any NSAID. Pooled NSAID-specific ORs were obtained by a random effects model that was applied to the individual patient level data to account for heterogeneity across databases.

Results

In the overall cohort, 28.567 UGIC cases were matched to almost 2.7 million controls. Current use of NSAIDs increased the risk of UGIC especially for those taking ketorolac, oxaprozin and lornoxicam (pooled OR greater than 4). Pooled OR estimates were between 2 and 4 for naproxen, diclofenac, indometacin, ketoprofen, etoricoxib, meloxicam, tenoxicam and piroxicam, and between 1 and 2 for celecoxib, aceclofenac, nimesulide, ibuprofen, rofecoxib and the fixed combination between diclofenac and misoprostol. Heterogeneity between databases was substantial.

Conclusions

Current use of individual NSAID increases the risk of UGIC. Compared to past users, the risk can be six times higher, depending on the drug used. Findings for frequently used NSAIDs were in line with past studies. The collaboration between six European databases to increase size facilitates that infrequently used NSAIDs, for which little prior knowledge is available, can be studied with respect to their risk of UGIC.

Introduction

NSAIDs are a class of medication, with around 60 different compounds. NSAIDs are effective in terms of analgesic, antipyretic, and anti-inflammatory effects, but their use has been associated with serious adverse events, such as gastrointestinal (GI) and cardiovascular (CV) events.[53] To date it is unclear what the magnitude of that risk is for each of those individual NSAIDs. In addition, the effect of individual NSAIDs by dose, duration of use, and in patients at high risk is scarce. Recent guidelines have introduced restrictions in the use of some individual NSAIDs and particularly for selective COX (cyclooxygenase)-2 inhibitors.[131] Information on current patterns of use and on the effect of these restrictions on the CV and GI safety is limited.

The SOS (Safety of Non-steroidal Anti-inflammatory Drugs) project is a research and development project funded and requested by the Health Area of the European Commission (EC) under the Seventh Framework Programme, which aims to asses and compare the risk of cardiovascular (CV) and gastrointestinal (GI) events with the use of individual non-steroidal anti-inflammatory drugs (NSAIDs) by conducting novel observational studies on linked electronic healthcare databases in four European countries.

Within the SOS study we conducted a nested case-control study to assess and compare the risk of upper gastrointestinal complications associated with the use of individual NSAIDs in each of the six electronic health care databases from four European countries. Collaboration between multiple databases from different countries that worked with a common protocol, common definitions for outcome, confounder and exposure, and common data elaboration scripts enabled us to study a wide variety of individual NSAIDs with a substantial amount of exposed cases, resulting in the ability to provide stable risk estimates also for infrequently used NSAIDs.

Methods

Study design and data sources

Nested case-control studies were conducted within a cohort of new users of NSAIDs during the study period. Data for this study was obtained from six different longitudinal population-based health care databases from four European countries (Germany (DE), Italy (IT), Netherlands (NL) and United Kingdom (UK)) covering a source population of around 32 million subjects. Data were derived from four hospital discharge / administrative databases and two medical record databases from primary care. The databases have all been used for pharmacoepidemiological research and have been described in Chapter 2. A brief overview of main characteristics is provided in Table 2.1.

In short, the German Pharmacoepidemiological Research Database (GePaRD) is a claims database and covers about 14 million insurants throughout Germany, who represent approximately 17% of the German population. The Health Improvement Network (THIN) database is a database of primary care medical records in the UK and the database currently captures 2.7 million active patients. The Integrated Primary Care Information (IPCI) database is also a primary care research database but from NL and covers about 1 million people from 150 active practices. The Dutch PHARMO database is a medical record linkage system of 3.2 million community-dwelling inhabitants from NL. The administrative Italian database called OSSIFF (Osservatorio Interaziendale per la Farmacoepidemio-

logia e la Farmacoeconomia) accounts for a population of about 3.8 million people. The second Italian database is SISR (Sistema Informativo Sanitario Regionale) that obtain data from the electronic healthcare databases of the Lombardia region, the largest Italian region with about nine million inhabitants (approximately 16% of the national population). Because OSSIFF captures a subset of patients covered by SISR, SISR excluded the common subset of patients to avoid overlap.

All databases contain information on demographics, diagnoses, and drug prescriptions. The clinical information captured by the different databases was collected using four different disease terminologies, such as the International Classification of Diseases (ICD) 9th or 10th revision[59], International Classification for Primary Care (ICPC[61]), or READ codes.[178] This prompted us to map medical concepts using the Unified Medical Language System (UMLS), a biomedical terminology integration system handling more than 150 medical dictionaries.[71] This workflow was developed in the EC funded EU-ADR project and has been described in more detail elsewhere.[72] Information on drug prescriptions is mapped to or coded using the World Health Organization's (WHO) classification of Anatomical Therapeutic Chemical (ATC) in all databases.[60] Due to regulatory and governmental actions, only completely de-identified data were centrally stored and shared at a data-warehouse in Milan, Italy, a remote environment in which the data was analyzed. Details have been described previously.[18]

Study cohort

For each database, we identified a cohort of patients 18 years of age and older who received at least one NSAID prescription (ATC codes (or equivalent BNF code): M01AA to M01AX, excluding M01AX05, M01AX12, M01AX14, M01AX21, M01AX24, M01AX25, and M01AX26) during the database-specific study period which started at the first of January 1999 or later. The date of first NSAID prescription or dispensing during the study period was defined as the date of cohort entry. Subjects receiving any NSAID prescription during the one 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 (i.e. under detection of events after short-term therapy). Patients were required to have had at least one year of continuous database history, to allow uniform assessment of potential confounding factors and exclusion criterion. All subjects with a cancer diagnoses except non-melanoma skin cancers during the 12 months preceding cohort entry were excluded from the cohort. The study cohort was followed from the date of cohort entry until the date of UGIC diagnosis, exclusion criterion (cancer), death, last data supply, transferring out of the database, or end of the database-specific study period, whichever came first.

Case definition

The study outcome was a first or recurrent hospitalization for a UGI complication (GePaRD, PHARMO, OSSIFF, and SISR) or a first or recurrent diagnosis of a UGI complication (THIN and IPCI) during follow-up. A case of UGI complication was defined as a patient with peptic ulcer disease or gastritis complicated by bleeding, perforation and/or obstruction, during follow-up. Uncomplicated 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 endpoint. The date of diagnosis of the UGIC was used as index date.

Selection of controls

Within each databases, a total of 100 controls per each case were randomly selected from the new-NSAID users cohort and matched on age at index date (± 1 year), sex, index-date and follow-up time in cohort (± 25 days).

Definition of exposure

Exposure to individual NSAIDs was obtained from either prescriptions by general practitioners (THIN and IPCI) or from (reimbursement files from) outpatient drug dispensings of community pharmacies (GePaRD, PHARMO, OSSIFF, and SISR). Duration of a single NSAID dispensing or NSAID prescription (which is defined as 'therapy' onwards) was obtained by dividing total units dispensed or prescribed by the daily number of units prescribed (THIN, IPCI, and PHARMO) or the national defined daily dose (GePaRD, OSSIFF, and SISR). Classification of exposure to each individual NSAID was based on the days between the index date and the end of the most recent NSAID episode before the index date. NSAID therapy was classified as either 'current' use (the exposure period overlapped the index date or ended within the 14-day period before the index day), 'recent' use (the exposure period ended between 15 and 183 days before the index day), or 'past' use (the exposure period ended 184 or more days before the index day).

Covariates

Risk factors and confounders were measured at baseline (i.e. in the year before cohort entry) or at the index date (i.e. within 90 days before index day) and were divided into a-priori defined confounders or potential confounders. As a-priori defined confounders measured at cohort entry we selected the following factors: (i) history of complicated UGI disease; (ii) history of uncomplicated UGI disease; (iii) rheumatoid arthritis and inflammatory polyarthritis; (iv) alcohol abuse. A-priori defined confounders measured within 90 days of index date were: (v) concomitant use of platelet aggregation inhibitors, excluding heparin and aspirin; (vi) concomitant use of long-term aspirin; (vii) concomitant use of anticoagulants; (viii) concomitant use of systemic glucocorticosteroids; (ix) concomitant use of proton pump inhibitors, or; (x) concomitant use of other gastroprotective agents (GPA). As potential confounders measured at baseline, we additionally assessed the presence of diabetes mellitus, cardiovascular disease, chronic liver disease, kidney failure, smoking, obesity, blood coagulation disorder, iron deficiency anemia, osteoarthritis, other gastrointestinal disease, and drug use related to cardiovascular disease. Potential confounders assessed at the index date were: concomitant use of selective serotonin reuptake inhibitors (SSRIs), bisphosphonates, nitrates, *Helicobacter pylori* eradication therapy, and medications inducing or inhibiting cytochrome P450 (CYP) enzymes (i.e. CYP2C19) as NSAIDs are metabolized via these liver enzymes.

Statistical analyses

Baseline characteristics of cases and controls are described by database. To estimate the risk for UGI complications among current use of an individual NSAID in comparison to past users of any NSAID, matched odds ratios (OR_m) and adjusted odds ratios (OR_a) with 95% CIs were applied using conditional logistic regression analyses for each database separate. Applying an active reference category (i.e. past users of any NSAID) effectively deals in part with confounding by indication and was considered more appropriate as reference categories such as 'no use of NSAIDs' or 'current use of acetaminophen'. Only if 10 or more exposed cases per database were available, an association measure was calculated, which should result in more stable risk estimates and to avoid non-

convergence of the models. Pooled NSAID-specific ORs (OR_p) were obtained by a random effects meta-analysis method to account for heterogeneity across databases. Statistical heterogeneity across databases was tested by using a Cochran's Q statistic. For this test, a *P* value of 0.10 (two sided) and below was considered to indicate heterogeneity. To measure the degree of heterogeneity an I^2 value was recorded, with I^2 values above 75% representing a high level of heterogeneity. To be as conservative as possible, a random-effects model was always applied, regardless of the Cochran's Q statistic.

Additionally, pooling of data across databases was performed by combining the data sources on patient-level, regardless of the number of exposed cases. This provides that one combined risk measure (OR_c) can be estimated (only for NSAIDs with a minimum of 10 or more exposed cases in combined dataset).

A stepwise approach for confounder selection was applied. Firstly, the a-priori selected confounders were always included in the model for each database, regardless of statistically significance. Second, identification of the potential confounders was performed by entering the potential confounders into the model and were considered for the final model only if the *p*-value of the Wald test was smaller than 0.05. All variables from the a-priori list and all potential confounders selected in step 2 were included in the model. Then a backward elimination procedure was performed in which all a-priori specified confounders were forced to stay in the model and other confounders were removed from the model step by step if the Wald test was not significant (i.e. *p*-value > 0.05). Important statistical interactions were also selected through this backward elimination procedure.

In order to estimate a class effect, the risk of UGIC was estimated by comparing the current use of coxibs, the current use of nsNSAIDs, and the combination of the current use of nsNSAIDs with coxibs, with no use of nsNSAIDs or coxibs as reference category. All analyses were performed using SAS Cary, NC version 9.2. Statistical significance was defined as a two-sided p-value lower than 0.05.

Results

Study population

The SOS population comprised 8,573,580 patients who were taking NSAIDs during follow-up. Of the population, 46% were men (in a range from 42.6% for SISR to 51.6% for GePaRD). The median age of the Italian databases (OSSIFF: 55 years and SISR: 58 years) was higher than the median age in the other databases (median age in the range of 44 years for PHARMO to 47 years for IPCI).

Exposure distribution

In GePaRD, THIN, IPCI and PHARMO, the most commonly prescribed NSAIDs were diclofenac and ibuprofen. In Italy, nimesulide attributed for the greater part of NSAIDs (OSSIFF: 3.6%; SISR: 4.3%), followed by diclofenac (OSSIFF: 2.3%; SISR: 2.6%). Per database an average of 25 NSAIDs were prescribed or dispensed with a range between 14 for IPCI and 31 for THIN.

Nested case-control study in new NSAID users cohort on risk of UGIC per database

Within the study cohort, 28,567 patients developed an upper gastrointestinal (UGI) complication. To these, 2,675,558 controls without UGIC in the same database were matched with a median number of controls of 93.7 per case (IPCI lowest with 44.7 controls per case and SISR highest with 98.9 controls per case). Baseline characteristics of the cases and matched controls are shown in Table 9.3. The population in the Italian databases was older compared with the other databases. In general, cases had more documented comorbidities associated with an increased risk of UGIC, such as a prior history of UGI complication. Additionally, use of PPIs and other gastroprotective drugs was more frequent among cases than among controls at baseline. The mean total time in the cohort was less than 2 years for IPCI and GePaRD and between 2 and 4 years for SISR (2.2 years), OSSIFF (3.3 years), PHARMO (3.6 years) and THIN (3.7 years).

For 20 individual NSAIDs risk estimates were calculated, of which for only the risk estimate related to diclofenac was available in all databases studied. For etodolac (THIN), flurbiprofen (SISR) and mefenamic acid (THIN) only one risk estimate was available in the participating databases. With past use of any NSAID as reference category, we found no association between UGIC and recent use of any NSAID (OR_p: 1.1, 95%CI: 1.0-1.2) (Table 9.3). The risk of UGIC associated with current use of celecoxib was lowest (OR_p: 1.0, 95%CI: 0.8-1.3) and highest for current use of ketorolac (OR_p: 6.5, 95%CI: 5.7-7.4) compared with past use of any NSAID. Besides celecoxib, pooled OR were between 1 and 2 for aceclofenac, nimesulide, ibuprofen, rofecoxib and the fixed combination between diclofenac and misoprostol. Pooled OR estimates were between 2 and 4 for the following individual NSAIDs in an ascending order: naproxen, diclofenac, indometacin, ketoprofen, etoricoxib, meloxicam, tenoxicam and piroxicam. Pooled OR estimates were more than 4 for lornoxicam, oxaprozin and ketorolac, indicating a four to six-fold increased risk of UGIC associated with the current use of these NSAID compounds. As can be derived from Table 9.3, heterogeneity between databases was mostly high with p-values for the Cochrane Q-statistic of less than < 0.001, therefore a random effect approach was used in pooling the datasets. However, when only the risk estimates for the two Italian databases OSSIFF and SISR were pooled, no heterogeneity was present (aceclofenac, ketorolac, lornoxicam, nimesulide, oxaprozin and tenoxicam). For etoricoxib (5 risk estimates) and for ketoprofen (3 risk estimates) no heterogeneity was present. In general, the risk estimates in the PHARMO database were higher and showed less variability than in the Italian databases. In Figure 9.1 we have ranked the NSAID compounds and we show the point estimates in an ascending order for the pooled risk estimates.

A class effect was also studied by grouping the coxibs and the nsNSAIDs. When applying no current use of NSAIDs as the reference category, an increasing UGIC risk was seen for current use of coxib alone (OR_p: 1.5, 95%CI: 1.4-1.7), for current use of nsNSAID alone (OR_p: 2.2, 95%CI: 2.2-2.3) and for the combination of current use of nsNSAIDs and coxibs (OR_p: 4.1, 95%CI: 3.6-4.8).

Nested case-control study in new NSAID users cohort on risk of UGIC in the entire SOS platform

In order to estimate the UGIC risk associated with infrequently used NSAIDs we combined all 6 datasets on patient-level. This allowed to study 4 more individual NSAIDs (acemetacin, dexibuprofen, nabumetone and valdecoxib) as the sum of exposed cases combined was more than 10. The results are depicted in Table 9.3. The use of valdecoxib (sum of 19 exposed cases) was associated with UGIC risk (OR_c: 2.3, 95%CI: 1.4-3.7). For

other NSAIDs the point estimate was not substantially different when comparing the combined or the pooled estimate, with smaller confidence intervals in the combined dataset than in the pooled data. Only for flurbiprofen which had 10 exposed cases in SISR, 6 exposed cases in OSSIFF and 3 exposed cases in THIN the OR derived from SISR was higher than the OR on the combined set (OR_{SISR}: 4.6, 95%CI: 2.4-8.8 vs. OR_c: 2.8, 95%CI: 1.8-4.5).

Table 9.1: Baseline characteristics of cases with UGI complications and matched controls by database

	Germany		United Kingdom		the Netherlands				Italy			
	GePaRD		THIN		IPCI		PHARMO		OSSIFF		SISR	
	cases %	controls %	cases %	controls %	cases %	controls %	cases %	controls %	cases %	controls %	cases %	controls %
Total (number)	4,763	450,529	10,593	983,266	585	26,138	1,871	162,834	4,691	452,914	6,064	599,907
Age in years (mean±sd)*	63.9 (16.0)	62.9 (15.3)	64.5 (16.1)	63.2 (15.4)	58.7 (15.2)	55.1 (12.7)	67.2 (16.1)	64.6 (15.3)	71.5 (13.2)	70.9 (13.0)	72.3 (13.2)	72.1 (13.0)
Gender*												
Male	59.1	59.7	49.7	49.0	46.5	47.0	54.7	54.3	52.4	52.1	50.9	50.7
Female	40.9	40.3	50.3	51.0	53.5	53.0	45.3	45.7	47.6	47.9	49.1	49.3
A-priori selected UGI risk factors:												
Before cohort entry:												
Prior UGI complication	7.3	1.5	1.1	0.3	9.4	5.2	0.3	0.1	1.3	0.2	1.3	0.2
Prior UGI disease	19.7	10.1	4.6	1.9	7.0	2.1	0.3	0.0	1.2	0.4	0.9	0.3
Rheumatoid arthritis	3.9	3.0	0.7	0.3	14.7	9.5	0.1	0.1	0.4	0.2	0.5	0.2
Alcohol abuse	7.3	1.1	12.8	10.2	2.7	6.3	0.2	0.1	1.0	0.1	1.0	0.1
At index-date:												
Use of antiplatelets	5.9	2.0	5.2	2.4	3.4	1.3	5.7	2.6	6.0	3.7	7.8	5.0
Use of aspirin	10.9	5.5	30.1	18.8	6.2	4.2	19.0	10.5	23.8	15.8	28.3	19.7
Use of anticoagulants	10.5	4.9	3.3	2.3	7.2	2.3	12.6	5.5	10.0	5.1	9.5	5.3
Use of glucocorticoids	8.0	4.3	6.1	4.0	6.2	2.8	8.6	4.5	6.2	3.5	6.0	3.8
Use of PPIs	27.8	12.1	42.2	14.4	37.6	19.0	26.6	14.6	19.3	11.8	22.6	15.8
Use of other GPAs	3.6	1.4	16.9	4.9	5.5	2.5	8.1	3.6	14.3	6.7	0.5	0.3
Potential confounders:												
Before cohort entry:												
Diabetes mellitus	4.3	2.6	2.2	1.3	2.7	1.7	2.1	1.5	3.5	2.5	6.9	4.7
Cardiovascular disease	47.7	33.3	7.1	4.5	11.8	8.4	4.4	2.8	11.2	7.8	14.8	10.4
Chronic liver disease	16.6	9.4	0.8	0.1	3.4	1.6	0.3	0.0	1.8	0.5	2.1	0.5
Kidney failure	8.9	3.6	0.3	0.1	0.0	0.2	0.0	0.0	0.1	0.1	0.3	0.1
Smoking	0.0	0.0	3.4	2.3	16.1	17.8	0.1	0.0	0.0	0.0	0.0	0.0
Obesity	13.8	10.5	0.8	0.6	2.1	1.4	0.2	0.1	0.5	0.1	0.9	0.3
Coagulation disorder	5.4	2.2	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.0	0.3	0.1
Iron deficiency anemia	3.7	0.9	2.5	1.5	2.2	1.1	2.1	1.3	1.5	0.7	-	-
Osteoarthritis	24.1	22.4	11.0	8.3	4.8	2.8	2.0	1.2	1.4	1.2	1.6	1.2
Other GI disease	16.0	12.2	3.0	1.6	3.8	3.7	0.4	0.2	0.9	0.4	1.1	0.5
Cardiovascular drugs	36.7	26.9	17.1	13.2	11.3	9.9	15.3	12.1	30.0	24.6	44.9	38.2
At index-date:												
Use of SSRIs	4.6	2.0	9.7	5.7	1.2	3.7	4.4	3.4	7.6	4.7	9.1	5.7
Use of bisphonates	2.7	1.9	5.1	3.7	3.1	2.1	4.0	3.3	1.6	1.4	2.7	2.5
Use of nitrates	5.8	3.3	9.3	5.1	2.2	1.3	11.6	5.7	11.3	8.1	12.5	8.6
Use of *H. pylori* eradication therapy	0.3	0.1	-	-	0.5	0.1	0.7	0.1	-	-	-	-
Use of CYP2C19 inhibitor	0.7	0.4	0.5	0.5	0.0	0.1	0.5	0.7	2.1	2.2	2.2	2.4
Use of CYP2C19 inducer	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	-	-

UGI, upper gastrointestinal; PPIs, proton pump inhibitors; GPAs, gastroprotective agents; SSRIs, selective serotonin reuptake inhibitors; H. pylori, Helicobacter pylori.
**Age and gender are matching criteria.*
Values are percentages.

Table 9.2: Association between current use of individual NSAID use and risk of UGIC compared with any use of past NSAID stratified by database

	Germany		United Kingdom		the Netherlands				Italy			
	GePaRD		THIN		IPCI		PHARMO		OSSIFF		SISR	
	ORm (95%CI)	ORa (95%CI)	ORm (95%CI)	ORa (95%CI)	ORm (95%CI)	ORa (95%CI)	ORm (95%CI)	ORa (95%CI)	ORm (95%CI)	ORa (95%CI)	ORm (95%CI)	ORa (95%CI)
Past use of any NSAID	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Recent use of any NSAID	1.0 (0.9-1.1)	1.2 (1.1-1.2)	1.3 (1.2-1.4)	1.3 (1.2-1.3)	0.9 (0.7-1.2)	0.9 (0.7-1.2)	1.0 (0.9-1.1)	1.2 (1.0-1.3)	1.1 (1.0-1.2)	1.1 (1.0-1.2)	1.0 (1.0-1.1)	1.0 (1.0-1.1)
Current use of:												
Aceclofenac									1.3 (0.8-2.0)	1.4 (0.9-2.2)	1.0 (0.8-1.4)	1.1 (0.8-1.6)
Celecoxib	2.2 (1.4-3.5)	1.8 (1.1-2.9)	1.0 (0.8-1.2)	0.8 (0.7-1.0)					1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.8-1.2)	1.0 (0.9-1.3)
Diclofenac	2.4 (2.2-2.7)	2.6 (2.4-2.9)	1.8 (1.7-2.0)	1.8 (1.6-1.9)	1.2 (0.9-1.7)	1.1 (0.8-1.5)	4.3 (3.7-5.0)	4.7 (4.1-5.4)	3.1 (2.7-3.5)	3.2 (2.8-3.6)	3.0 (2.7-3.3)	3.1 (2.8-3.5)
Diclofenac, combi			1.2 (1.0-1.5)	1.3 (1.0-1.5)	3.3 (2.2-5.1)	2.4 (1.5-3.9)	2.8 (2.2-3.6)	3.8 (2.9-4.8)	1.3 (0.8-2.2)	1.5 (0.9-2.6)	1.1 (0.7-1.9)	1.2 (0.7-2.1)
Etodolac			1.4 (1.0-2.0)	1.1 (0.8-1.6)								
Etoricoxib	2.8 (2.1-3.7)	2.6(2.0-3.4)	3.2 (2.6-3.9)	2.6 (2.1-3.2)			3.9 (2.5-5.9)	4.0 (2.6-6.1)	2.5 (1.9-3.3)	2.3 (1.8-3.1)	2.8 (2.3-3.3)	2.8 (2.3-3.3)
Flurbiprofen											4.1(2.2-7.6)	4.6 (2.4-8.8)
Ibuprofen	1.9 (1.7-2.1)	2.1 (1.8-2.3)	0.8 (0.8-1.0)	1.0 (0.9-1.1)			0.8 (0.6-1.2)	1.3 (0.9-1.7)	1.3 (0.9-1.8)	1.3 (0.9-1.9)	1.2(0.9-1.5)	1.3 (1.0-1.6)
Indometacin	2.6 (1.6-4.2)	3.0 (1.8-4.9)	1.4 (1.0-1.9)	1.4 (1.0-2.0)			3.6 (2.0-6.4)	4.0 (2.2-7.3)	3.0 (2.0-4.7)	2.5 (1.6-4.0)	3.0(2.2-4.3)	2.8 (2.0-4.0)
Ketoprofen			4.2 (2.8-6.5)	3.6 (2.3-5.6)					2.5 (2.1-3.0)	2.4 (2.0-2.9)	2.3 (2.0-2.7)	2.4 (2.1-2.8)
Ketorolac									8.1 (6.8-9.7)	6.9 (5.8-8.3)	7.1 (6.0-8.5)	6.1 (5.1-7.2)
Lomoxicam									4.4 (2.3-8.4)	4.7 (2.4-9.0)	4.3 (2.9-6.6)	4.6 (3.0-7.1)
Mefenamic acid			1.8 (1.2-2.7)	1.9 (1.3-2.9)								
Meloxicam	3.2 (2.2-4.7)	3.5 (2.3-5.1)	2.1 (1.8-2.4)	1.7 (1.5-2.0)			3.7 (2.9-4.8)	4.3 (3.3-5.6)	2.0 (1.5-2.7)	2.2 (1.7-2.9)	2.3 (1.8-2.8)	2.5 (2.0-3.1)
Naproxen	2.2 (1.4-3.6)	2.1 (1.3-3.5)	2.4 (2.1-2.8)	2.2 (1.9-2.5)			3.1 (2.4-3.9)	3.6 (2.9-4.6)	1.7 (1.2-2.4)	1.8 (1.3-2.6)	2.0 (1.5-2.6)	2.0 (1.5-2.7)
Nimesulide									1.1 (1.0-1.3)	1.2 (1.1-1.4)	1.1 (1.0-1.2)	1.2 (1.1-1.4)
Oxaprozin									5.1 (3.1-8.5)	5.2 (3.1-8.7)	5.0 (3.4-7.4)	5.5 (3.7-8.2)
Piroxicam	3.7 (2.6-5.2)	4.4 (3.1-6.3)	2.7 (1.9-3.9)	2.3 (1.6-3.3)			3.0 (1.6-5.6)	4.1 (2.2-7.6)	3.9 (3.4-4.5)	4.2 (3.7-4.8)	3.7 (3.3-4.2)	4.2 (3.7-4.8)
Rofecoxib			1.4 (1.2-1.8)	1.2 (1.0-1.5)			2.4 (1.8-3.3)	3.0 (2.2-4.1)	1.7 (1.4-2.1)	1.8 (1.5-2.2)	1.2 (0.9-1.6)	1.4 (1.1-1.9)
Tenoxicam									3.1 (1.8-5.4)	3.4 (1.9-6.1)	2.0 (1.1-3.7)	2.4 (1.3-4.4)

ORm, matched odds ratio; ORa, adjusted odds ratio. Values presented are OR with corresponding 95%CI.

Table 9.3: Association between current use of individual NSAID use and risk of UGIC compared with any use of past NSAID in combined dataset and pooled by a random effects meta-analysis approach

	Combined dataset			Pooled (random effect)		
	Cases	Controls	ORc	ORp	P-value	I^2
	n	n	(95% CI)	(95% CI)	Q-stat	%
Total	28,567	2,675,588				
Past use of any NSAID	12,655	1,543,045	1 (ref)	1 (ref)		
Recent use of any NSAID	8,309	747,058	1.1 (1.1-1.2)	1.1 (1.0-1.2)	<0.001	84.3
Current use of:						
Aceclofenac	65	6,071	1.1 (0.9-1.4)	1.2 (0.9-1.6)	0.49	0
Acemetacin	11	632	1.6 (0.9-2.9)	NA		
Celecoxib	304	28,745	1.0 (0.9-1.1)	1.0 (0.8-1.3)	0.023	68.4
Dexibuprofen	11	864	1.2 (0.7-2.2)	NA		
Diclofenac	2,488	110,922	2.4 (2.3-2.6)	2.5 (1.9-3.4)	<0.001	97.5
Diclofenac, combi	240	13,444	1.7 (1.5-2.0)	1.9 (1.1-3.2)	<0.001	92
Etodolac	34	2,185	1.3 (0.9-1.9)	1.1 (0.8-1.6)*	NA	NA
Etoricoxib	368	12,488	2.6 (2.3-2.9)	2.7 (2.4-3.0)	0.33	13.3
Flurbiprofen	19	717	2.8 (1.8-4.5)	4.6 (2.4-8.8)[#]	NA	NA
Ibuprofen	828	63,434	1.4 (1.3-1.5)	1.3 (0.9-2.0)	<0.001	95.2
Indometacin	115	4,805	2.2 (1.8-2.6)	2.5 (1.8-3.6)	0.01	68.4
Ketoprofen	371	15,239	2.4 (2.2-2.7)	2.5 (2.2-2.9)	0.24	30.2
Ketorolac	298	4,152	6.1 (5.4-6.9)	6.5 (5.7-7.4)	0.29	9.2
Lornoxicam	37	807	4.5 (3.2-6.4)	4.6 (3.2-6.6)	0.98	0
Mefenamic acid	25	1,320	2.1 (1.4-3.1)	1.9 (1.3-2.9)*	NA	NA
Meloxicam	409	16,402	2.3 (2.1-2.5)	2.7 (1.9-3.7)	<0.001	89.3
Nabumetone	12	1,597	0.7 (0.4-1.2)	NA		
Naproxen	453	18,509	2.3 (2.1-2.5)	2.3 (1.8-3.0)	0.001	77.8
Nimesulide	465	41,909	1.2 (1.1-1.3)	1.2 (1.1-1.3)	0.95	0
Oxaprozin	43	849	5.2 (3.8-7.1)	5.4 (3.9-7.4)	0.84	0
Piroxicam	627	18,030	4.0 (3.7-4.4)	3.9 (3.3-4.6)	0.03	61.5
Rofecoxib	336	20,584	1.6 (1.4-1.8)	1.7 (1.2-2.4)	<0.001	88
Tenoxicam	25	1,052	2.6 (1.8-4.0)	2.9 (1.9-4.4)	0.39	0
Valdecoxib	19	728	2.3 (1.4-3.7)	NA		

ORc, odds ratio of the combined dataset; ORp, pooled odds ratio with random effect.
**only in THIN database measured (i.e. the pooled estimate is from THIN database only).*
[#]only in SISR database measured (i.e. the pooled estimate is from SISR database only).
NA, Not applicable.

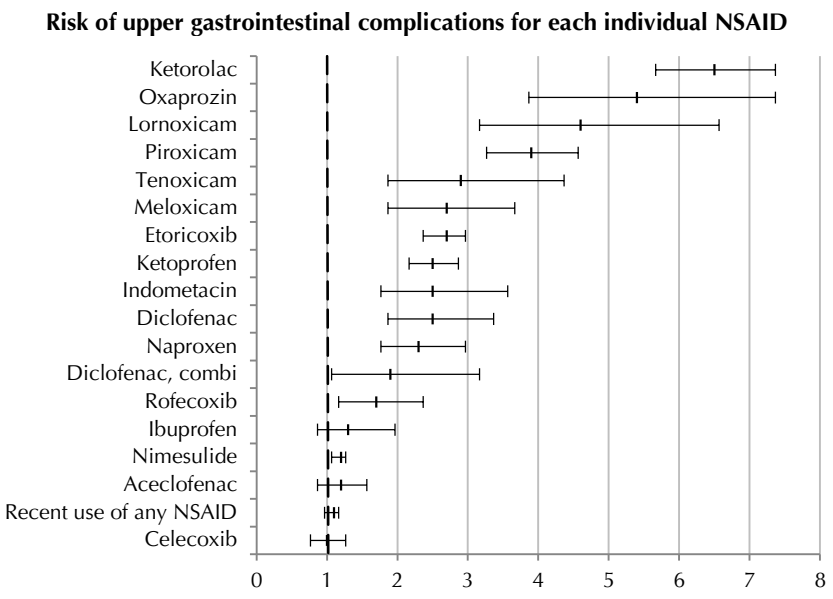

Figure 9.1: Ranked effect of UGIC risk estimates per current use of individual NSAIDs (pooled with random effects)

Discussion

The SOS platform with a population of together 32 million people contributed data on UGI safety related to NSAID use, which is, to the best of our knowledge, the largest study ever conducted on this topic. In total, 8,573,580 adults used an NSAID in the SOS population, of which 28,567 patients developed a UGIC event during follow-up. In this nested case-control study we present the first results comprising six European databases in which we studied the risk of upper gastrointestinal complications associated with the use of individual NSAIDs.

For 20 individual NSAIDs sufficient data was available to estimate an association measure in one of the participating databases. When applying past use of any NSAID as reference category, the risk of UGIC with current use of celecoxib (OR_p: 1.0, 95%CI: 0.8-1.3) was lowest, followed by aceclofenac, nimesulide, ibuprofen, rofecoxib and the fixed combination between diclofenac and misoprostol (pooled OR between 1 and 2). Those results are well in keeping with the results from published meta-analysis[179] and with the meta-analysis on observational studies performed in the SOS project; aceclofenac, celecoxib, ibuprofen and rofecoxib were reported to be the lowest four NSAIDs ranked, but with higher point estimates than in our study.[180] Although nimesulide use was estimated to have a low relative risk in our study, this was in contrast with a relative high risk in the meta-analysis (OR: 3.8, 95%CI: 3.2-4.6). Pooled OR estimates were between 2 and 4 for naproxen, diclofenac, indometacin, ketoprofen, etoricoxib, meloxicam, tenoxicam and piroxicam. In contrast with the previously mentioned meta-analysis, the UGIC risk associated with naproxen use was reported lower in our study (OR_p: 2.3, 95%CI: 1.8-3.0 vs. RR: 4.1; 95% CI, 3.2–5.2). We found an association with the current use of diclofenac on UGIC risk (OR_p: 2.5, 95%CI: 1.9-3.4) which was higher compared with the fixed combination of diclofenac with misoprostol, a prostaglandin analogue which is shown to protect the UGI mucosa (OR_p: 1.9, 95%CI: 1.1-3.2). The highest risks applied to the use of lornoxicam, oxaprozin and ketorolac.

The main strength of this study is the large population of users of NSAIDs included which allowed us to study exposure to individual NSAIDs beyond the class effect (nsNSAIDs vs. coxibs). As result of the large numbers combined with the heterogeneity of NSAID exposure across databases, we were able to estimate relative risks associated with use of less frequently used NSAIDs, such as etodolac, flurbiprofen, lornoxicam, mefenamic acid and oxaprozin of which UGI safety data is currently mostly lacking from observational studies. When we considered the combined dataset, an additional 4 NSAIDs could be studied; acemetacin, dexibuprofen, nabumetone and valdecoxib. Additionally, the common protocol, common event definition and harmonized work-up across databases allowed examining the reasons for varying risk estimates for individual compounds across different characteristics (i.e. type of database or country) other than differences originating from varying study design or exposure definitions.

However, the results should be interpreted with care. First and above all, the relative risk estimates presented derive from an observational study prompting us to discuss issues related to selection bias, information bias, and confounding as this can lead to spurious results. The concern for selection bias is limited as all cases and controls came from the same source population as the case-control study was nested in the cohort. Information bias can relate to misclassification of either exposure or outcome. All data were gathered prospectively for clinical or administrative use and irrespective of the hypothesis studied therefore there is no different work-up for cases than for controls. Some databases capture information on prescription data only (THIN and IPCI) and others on dispensing infor-

mation, but reliable information on actual intake of NSAIDs is not available. In addition, in all countries some NSAIDs were available over-the-counter (OTC) during the study period which is not contained in the databases. Also, information on the prescribed dose and duration of a prescription is not contained in all databases. This may have led to misclassification of NSAID exposure and an attenuation of the association. Some misclassification of endpoints is foreseeable and rely on the hospital administrators or general practitioners when coding an event. For most databases or terminologies validation studies have shown that coding of events is reliable in the databases[181-183], but deaths, particularly before arrival to the hospital, can be an issue. As we have worked with a very stringent outcome classification, we assumed the misclassification to be limited.

Residual confounding is a serious threat for internal validity. As in all observational studies the use of individual NSAIDs is left to the discretion of the responsible physician. As a result of the non-experimental setting of the study, confounding by indication is conceivable as patients with a high-risk profile to develop UGI events are more likely to receive a coxib prescription or a nsNSAID in a lower dose than NSAID users at a lower risk. We have attempted to minimize this type of confounding by matching cases and controls on important covariates and calendar time. Additionally, past use of any type of NSAID was applied as active comparator, instead of no use of NSAIDs. Reassuring was that the recent use of any NSAID was not increased (OR_p: 1.1, 95%CI: 1.0-1.2). This is consistent with the fact that the risk of NSAIDs increases directly after the start of therapy, maintains increased during treatment, and decreases to the background risk after stopping treatment. Also, multivariable adjustment on the most relevant risk factors, comorbidities and concomitant drug use was performed in the analyses. Nevertheless, the matched and the adjusted OR for individual NSAIDs in each database were similar (or practically the same). This can be explained in two manners. The first positive explanation is that confounding is dealt with to a large extent by matching on important factors such as age and calendar time. On the other hand, the availability and level of detail of data might have led to misclassification of confounders. Not all potential confounders (i.e. alcohol abuse or *H. pylori* infection) are contained in (all) databases and not all variables contain the information in desired detail. If this important data lack, it might have hampered the potential for adjusting the models. As example that confounding by indication might still be an issue shows the high estimate for one of the coxibs, namely etoricoxib with a pooled OR of 2.7 (95%CI: 2.4-3.0), whereas this compound has been shown to decrease the risk of peptic ulcer bleeding compared with ibuprofen, diclofenac, or naproxen (pooled relative risk 0.5, 95%CI 0.3-0.7) in clinical trials.[138] In contrast and more in line with the result provided in the current study are two observational studies in which etoricoxib had the highest adjusted RR of the NSAIDs studied.[184, 185] In a third observational study conducted in Italy the adjusted RR for etoricoxib was 3.3 (95%CI: 2.4-4.4).[186]

Also rofecoxib and valdecoxib (two other compounds within the coxib class) might have been deliberately administered to an at-risk group with the intention to reduce UGI complications, and without completely dealing with this confounding, have potentially led to the two-fold increased risk in the current study (rofecoxib; OR_p: 1.7, 95%CI: 1.2-2.4 and valdecoxib; OR_c: 2.3, 95%CI: 1.4-3.7). In the Netherlands, rofecoxib was prescribed in very high dosages and the reimbursement for this drug was initially restricted to patients with rheumatoid arthritis, but that disease is also associated with an increased risk of UGIC. This might have contributed to the observation that the risk estimate for rofecoxib was higher in the Netherlands (PHARMO database) than in the other countries. Currently, valdecoxib and rofecoxib are not available on the European market.[119, 131] Finally, although we have pooled with a random effect approach thereby providing conservative

estimates, we have seen that heterogeneity was very high when pooling the results across databases. Potential explanations for differences in risk estimates for the same type of NSAID across databases are multiple: regional susceptibility, related to local alimentation or to genetic susceptibility, differential drug utilization and differences in health care systems.

In conclusion, in the current study we present the first results from the SOS project on the association between individual NSAID use and the risk of UGIC. Confounding by indication might have distorted the results, especially in the case of coxibs such as etoricoxib, valdecoxib and rofecoxib. A more powerful approach to deal with channeling of coxibs to high-risk patients should be investigated, such as the high dimensional propensity score. Although many more sensitivity analyses are required to test the robustness of the presented estimates, the provided risk estimates for the traditional NSAIDs are within ballpark of what we expect as they are in keeping with pooled results of other observational studies.

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Chapter 10

Risk model for predicting upper gastrointestinal complications in NSAID users: the SOS project

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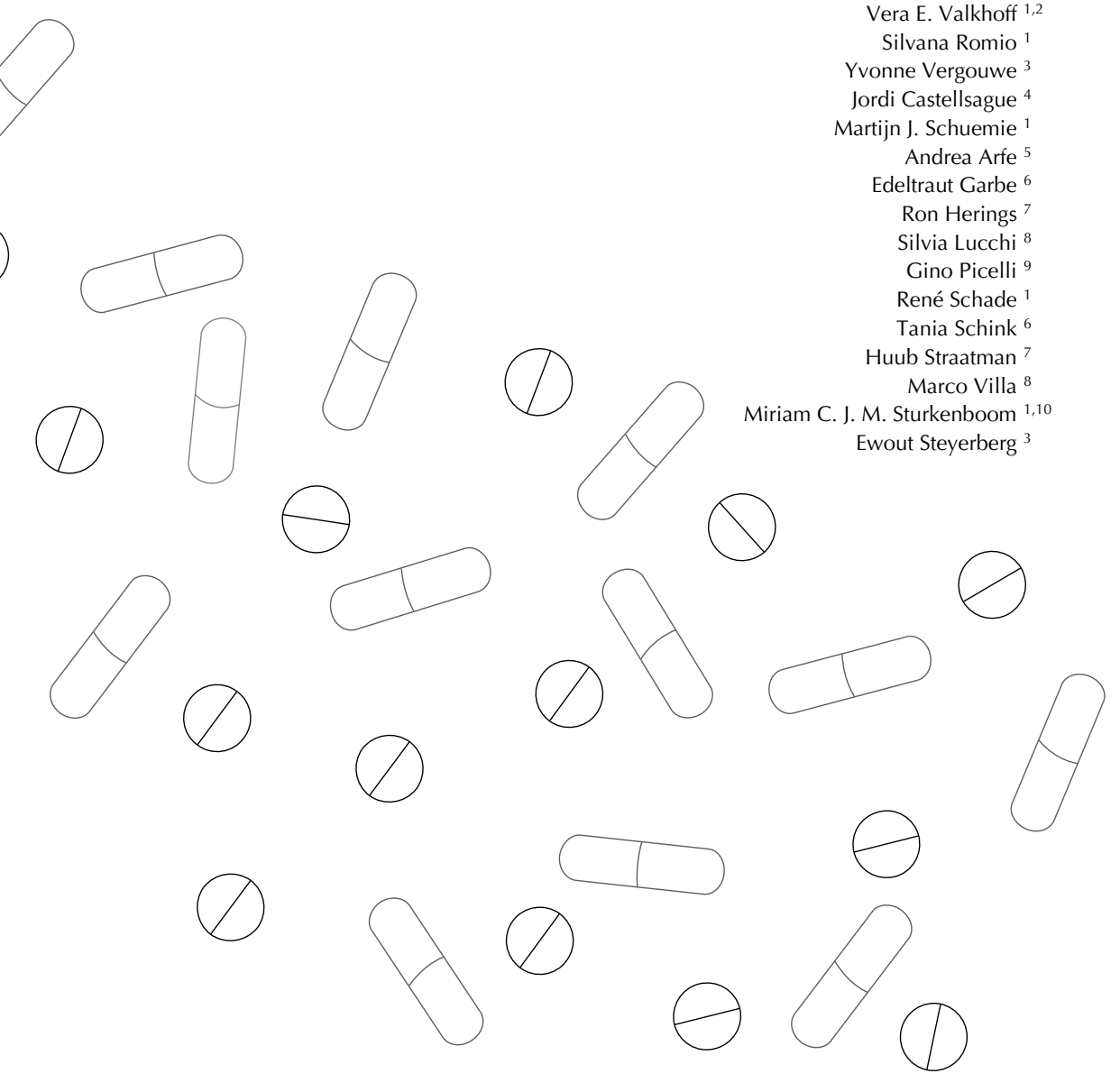


Abstract

Background

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are known to increase the risk of upper gastrointestinal (UGI) complications.

Aim

To develop a risk model for UGI complication in new NSAIDs users.

Methods

Individual patient data were collected from six databases participating in the SOS project: IPCI and PHARMO (Netherlands), SISR and OSSIFF (Italy), GePaRD (Germany) and THIN (United Kingdom). Patients were included from the moment of a first NSAID prescription and followed for a maximum period of five years, until their first UGI complication or transferring out of the database. Two models for the risk of UGI complication were developed with Poisson regression with stratification by database. A simple Core Model included age, sex, and previous UGI complication to estimate risk for different follow up intervals. An Extended Model contained predictors including comorbidities. The models were cross-validated six times by omitting each database once, with the model developed on the remaining databases and discrimination and calibration assessed on the omitted database.

Results

The six databases encompassed almost 9 million new NSAID users, with 23,411 UGI complications. The Core Model showed good discriminative ability in the cross-validation with *c*-statistics ranging from 0.63 to 0.80. The Extended Model had similar discriminative ability. The incidence of UGI complication differed between databases and had to be considered in the model to obtain calibrated predictions.

Conclusions

A simple risk model using age, sex, and previous UGI complication may adequately identify NSAID users at increased risk of UGI complication occurrence. Such a model may support decision making on NSAID prescription in daily clinical practice.

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are pain relievers, commonly used around the world. Since long time it has been known that their use is restricted by the occurrence of upper gastrointestinal (UGI) complications such as peptic ulcer perforations, obstructions, and bleeding.[28] NSAIDs are associated with these disorders as they are blockers of the cyclooxygenase-1 (COX) pathway and hence attenuate the synthesis of gastroprotective prostaglandins. In order to reduce the UGI risk associated with NSAID use, a newer class of drugs was developed, the selective cyclooxygenase (COX)-2 inhibitors (coxibs). By preferentially inhibiting COX-2, and to a lesser extent the house-keeper isoform COX-1, coxibs are effective pain relievers and associated with a lower risk of UGI complication compared with traditional, non-selective (ns)NSAIDs.[38-40] This seemed to bring a solution for patients and their prescribing physicians, but shortly after the coxibs were launched, they came under scrutiny as clinical trials showed that its use increased the risk of serious cardiovascular (CV) events, especially with coxibs.[47, 48] Since then, there is increasing evidence that this risk is also increased by the use of nsNSAIDs, resulting in contra-indications for its use in patients with cardiovascular comorbidity.[49-51, 58]

It is important to identify patients in the population who are at special risk of developing CV and UGI adverse events related to NSAID use. Patients at high risk of NSAID-related UGI adverse events are those with advanced age, a medical history of a UGI complication, serious co-morbidity, and concurrent administration of antiplatelets, anticoagulants or corticosteroids.[53] Directly after the start of NSAID therapy the risk of UGI complications increases, maintains increased during treatment, and decreases to the background risk after stopping treatment.[28]

The combination of a patient's risk-profile and the substantial number of available NSAIDs, both in type and dose, each with a different risk of adverse events results in a complex decision-making process for the prescribing physician. We need decision models that provide insight in the type of NSAID that would yield the lowest UGI and CV risk for an individual patient in clinical practice to substantiate treatment decisions. The SOS (Safety Of Non-steroidal anti-inflammatory drugs) project aims to provide such a decision analytic model for each individual NSAID compound. Key elements for decision support are prediction models for the risk of UGI and CV events. In the present study, we focus on the prediction of UGI complications in NSAID users.

Methods

Data sources

We analyzed individual patient data from six databases containing longitudinal observational data from four European countries with around 32 million patients. Four hospital discharge or administrative databases and two primary care databases provided data from Germany (DE), Italy (IT), Netherlands (NL) and United Kingdom (UK, Table 10.1). In short, the German Pharmacoepidemiological Research Database (GePaRD) is a claims database and covers about 14 million insurants throughout Germany, who represent approximately 17% of the German population. The Health Improvement Network (THIN) is a database of primary care medical records in the UK and the database currently captures 2.7 million active patients. The Integrated Primary Care Information (IPCI) database is also a primary care research database but from NL and covers about 1 million people from

150 active practices. The Dutch PHARMO database is a medical record linkage system of 3.2 million community-dwelling inhabitants from NL. The administrative Italian database called OSSIFF (Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia) accounts for a population of about 3.8 million people. The second Italian database is SISR (Sistema Informativo Sanitario Regionale) that obtain data from the electronic healthcare databases of the Lombardia region, the largest Italian region with about nine million inhabitants (approximately 16% of the national population). Because OSSIFF captures a subset of patients covered by SISR, SISR excluded the common subset of patients to avoid overlap.

All databases contained information on demographics, diagnoses, and drug prescriptions. The clinical information captured by the different databases was recorded using one of four different disease terminologies, i.e. the International Classification of Diseases (ICD) 9th or 10th revision[59], the International Classification for Primary Care (ICPC[61]), and the READ codes.[178] This prompted us to map medical concepts using the Unified Medical Language System (UMLS[71]), which is a biomedical terminology integration system handling more than 150 medical dictionaries. This workflow has been described in more detail elsewhere.[72] Information on drug prescriptions is mapped to or coded following the World Health Organization's (WHO) classification of Anatomical Therapeutic Chemical (ATC[60]) in all databases. Participating databases contained a representative sample of the respective populations based on age and sex, and have been used previously for conducting scientific research.

Only completely de-identified data were shared across databases, in keeping with regulatory and governmental actions. Data were transferred to a data repository in Milan, Italy. This provided a remote environment for shared data analysis. Details on data work-up per database and data sharing have been described previously.[18]

Study cohort

For each database, we identified a cohort of patients of 18 years of age and older who received at least one NSAID prescription during the database-specific study period which started at the first of January 1999 or later. NSAID prescription was defined as ATC codes M01AA - M01AX, excluding ATC codes M01AX05, M01AX12, M01AX14, M01AX21, M01AX24 to M01AX26, which were not considered as NSAID. The date of cohort entry was defined as the date of first NSAID prescription or dispensing. Patients receiving any NSAID prescription during the one year prior to cohort-entry were excluded in order to construct an inception cohort of new NSAID users. At least one year of database history was required before cohort entry to allow uniform assessment of risk factors for each patient. All identified new users of NSAIDs were followed up to a maximum of five years from the start of NSAID therapy, until the date of UGI complication diagnosis, death, last data supply, transferring out of the database, or end of the database-specific study period, whichever came first. If during follow-up a second NSAID was prescribed, this prescription was ignored, regardless of the type of first and second NSAIDs.

Definition and identification of UGI complication as outcome

The study outcome was a first encountered hospitalization for a UGI complication in the hospital discharge or administrative databases (GePaRD, PHARMO, OSSIFF, and SISR) or a first diagnosis of a UGI complication in the primary care databases (THIN and IPCI) during follow-up. A case of UGI complication was defined as a patient with peptic ulcer disease or gastritis complicated by bleeding, perforation or obstruction. Uncomplicated

Table 10.1: Characteristics of participating databases in SOS and incidence rate of upper gastrointestinal complications

						Adult study population (Age 18 years and older)			
Database	Country	Type of Database	Diagnoses	Drugs	Study period	NSAID users	Number of UGIC	PY	IR of UGIC
GePaRD	Germany	Claims database	ICD-10-GM	ATC	2005 – 2008	2,595,738	6,498	6,549,577	9.9
THIN	United Kingdom	GP database	READ	BNF/ Multilex	1999 – 2008	1,587,646	5,488	5,774,448	9.5
IPCI	The Netherlands	GP database	ICPC and free text	ATC	1999 – 2011	190,920	223	377,610	5.9
PHARMO	The Netherlands	Record linkage system	ICD-9-CM	ATC	1999 – 2008	952,345	1,232	3,584,812	3.4
OSSIFF	Italy	NHS registry (claims)	ICD-9-CM	ATC	2000 – 2008	1,165,303	3,713	4,756,106	7.8
SISR	Italy	NHS registry (claims)	ICD-9-CM	ATC	2002 – 2009	2,451,574	6,257	8,609,191	7.3
Total						8,943,526	23,411	29,651,745	7.9

GP, general practitioner; NHS, National Health Service; 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; UGIC, upper gastrointestinal complication; PY, person years of follow-up; IR, incidence rate of UGIC (per 10,000 person years).

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.

Predictors

The selection of candidate predictors of UGI complication was made on the basis of available literature and guidelines on risk stratification in NSAID users.[53] We considered risk factors which were available in all databases ('common risk factors'). Risk factors were measured in the one year before cohort entry in each database and were classified in comorbidities and concomitant drugs. Besides age and gender, we included as comorbidities: (i) history of complicated ulcers; (ii) history of uncomplicated ulcers; (iii) chronic hepatic disorders; (iv) alcohol abuse; (v) smoking; (vi) inflammatory poliarthritis; (vii) osteoarthritis; and (viii) cancer. The following drugs were considered risk factors for UGI complication: (ix) use of systemic glucocorticosteroids; (x) aspirin; (xi) platelet aggregation inhibitors (PAI), excluding aspirin; (xii) anticoagulants; and (xiii) use of gastroprotective agents (GPAs), such as proton pump inhibitors, histamine-2 receptor antagonists and prostaglandin analogues.

Model development

We used Poisson regression to develop a prediction model to estimate the absolute risk of UGI complication, based on the risk profile of a patient. Poisson regression model was preferred over logistic regression since the follow-up time and censoring could readily be taken into account. Poisson regression is computationally much faster than Cox regression, that would be the alternative model to take follow-up time into account. Follow-up time was categorized in 0 to 2 weeks, 3 to 4 weeks, 5 to 52 weeks, 1 to 2 years, 2 to 5 years, assuming constant hazards in these intervals.

Two prediction models were built: a simple 'Core Model', included as risk factors age, sex, and history of complicated ulcer disease; and an 'Extended Model' considered all risk factors from the Core model plus the common risk factors. Age was considered as a categorical variable and classified as follows: 18-30 years, 30-40 years, 40-50 years, 50-60 years, 60-70 years, 70-80 years and 80 years or older. All other predictors were binary, with values 0 for absence and 1 for presence of the condition. We focused on the main effects of predictors in the models, ignoring statistical interactions. For each variable, the association with the risk of UGI complication was expressed as a rate ratio (RR) which can be interpreted as a relative risk with its corresponding 95% confidence interval (95% CI).

Since the prediction models were developed with data from six different databases, we had to account for the clustering of patients within databases. Moreover, the large number of patients hampered directly fitting of one model in the total database. We therefore fitted models in each database and pooled the regression coefficients with a random effects approach. The model intercepts were adjusted per database given the pooled regression coefficients. Analyses were performed with SAS Cary, NC version 9.2 and R software (v 2.12.1, R Foundation for Statistical Computing, Vienna, Austria).[187]

Model performance

Model performance was assessed through calibration and discrimination. Calibration, which assesses the agreement between observed and predicted risks over the full range of predicted risks, was assessed with a calibration slope. The calibration slope was estimated

using a Poisson regression model with UGI complication as outcome variable and the linear predictor as only covariate.[188] The linear predictor was calculated as the sumproduct of the regression coefficients of the model and predictor values.[189, 190] Discrimination is the ability to distinguish patients with and without UGI complication. Discrimination of the model was quantified by a concordance (*c*) statistic.[189] The *c*-statistic of the model ranges from 0.5 (no discriminative power, no better than flipping a coin) to 1.0 (model perfectly predicts which patients will develop UGI complication and who not).

Model validation

If the number of outcomes is high as in our study, overfitting is not an issue and apparent and internal validation show similar results.[188] We therefore applied cross-validation by database as a form of external validation. Each time one database was omitted in the model development process and used for validation of the developed model.[191] In this way, six validations were conducted and model performance (both calibration and discrimination) was quantified. This validation methodology of cross-validation by database is a scientifically stronger test of validity had the database randomly been divided into a development and validation cohort.

Model presentation

The Core model was presented as a score chart, with scores based on rounded multiplications of the Poisson regression coefficients. The sum of scores was then related to the risks of UGI complication occurrence within one month and 2 years.

Results

Study population

The study population comprised 8,943,526 patients in the SOS network who were taking NSAIDs during follow-up between 1999 and 2011 (Table 10.1). The median age of the Italian databases (OSSIFF: 56 years and SISR: 58 years) was higher than the median age in the other databases (median age ranging from 44 years to 47 years). The proportion of males ranged from 42.9% in SISR to 51.3% in GePaRD.

Diclofenac was the most commonly administered NSAID in the entire population with more than 3.2 million prescriptions (38%; OSSIFF/SISR: 21%; PHARMO: 38%; THIN: 44%; GePaRD: 51%; IPCI: 53%), followed by 2 million ibuprofen prescriptions (23%; OSSIFF/SISR: 3-5%; IPCI: 15%; PHARMO: 30%; THIN: 31%; GePaRD: 41%). In Italy, nimesulide attributed for the majority of NSAIDs (OSSIFF: 22%; SISR: 23%). Piroxicam, ketoprofen and naproxen considered around 5% of all first prescribed NSAIDs resulting in cohort inclusion.

Prediction Models

Within the study cohort, 23,411 patients developed an upper gastrointestinal (UGI) complication. The incidence rate of UGI complication in the overall population was 7.9 per 10,000 person years of follow-up with the highest rate for GePaRD and the lowest for PHARMO (Table 10.1). The distribution of the patient characteristics are presented in Table 10.2. The prevalence of alcohol abuse and smoking was higher in the two GP databases THIN and IPCI than in the administrative hospital databases. The prevalence of

comorbidities in PHARMO was very low. The prevalence of comorbidities and use of medication in the Italian databases were well aligned. Age, sex, and history of complicated ulcer disease and the other pre-defined risk factors were independent predictors of UGI complication development in 2 or 4 weeks, 1 year, 2 years and 5 years, except for alcohol abuse and osteoarthritis. Use of gastroprotective agents was also not associated with an increased risk of UGI complications. Age over 80 years showed a very strong association with UGI complications risk (RR: 9.5; 95%CI 6.1-15, Table 10.3).

Table 10.2: Baseline characteristics of study patients by database for the Core and Extended Model

	Germany	United Kingdom	the Netherlands		Italy	
	GePaRD %	THIN %	IPCI %	PHARMO %	OSSIFF %	SISR %
Total (number)	2,595,738	1,587,646	190,920	952,345	1,165,303	2,451,574
Age (years):						
18-30	14.9	14.9	13.3	18.9	7.7	5.8
30-40	19.3	19.3	17.2	20.9	13.8	12.1
40-50	19.9	19.9	22.6	20.2	16.7	15.9
50-60	17.7	17.7	19.8	16.5	19.2	19.3
60-70	14.2	14.2	14.2	11.5	20.5	21.7
70-80	9.4	9.4	8.9	8.1	15.6	17.3
> 80	4.7	4.7	4.1	3.8	6.7	8.0
Gender:						
Male	51.3	44.6	44.2	44.8	44.0	42.9
Female	48.7	55.4	55.8	55.2	56.0	57.1
Comorbidities:						
Prior UGI complication	1.1	0.4	4.6	0.0	0.1	0.1
Prior UGI disease	8.6	1.8	1.8	0.0	0.3	0.2
Chronic hepatic disorders	6.8	0.1	1.8	0.0	0.5	0.6
Alcohol abuse	1.1	11.8	5.2	0.1	0.2	0.2
Smoking	0.0	6.7	15.1	0.0	0.0	0.0
Inflammatory poliarthritis	2.2	0.4	14.7	0.1	0.1	0.2
Osteoarthritis	14.4	5.7	3.0	0.7	0.6	0.7
Cancer	9.7	1.0	8.7	0.1	2.0	2.5
Use of medication:						
Use of glucocorticoids	2.5	0.9	0.8	1.1	2.0	2.3
Use of aspirin	1.8	6.4	5.4	5.6	4.4	6.5
Use of antiplatelets	0.6	0.6	0.7	0.5	0.7	1.2
Use of anticoagulants	2.4	0.4	1.7	1.4	1.7	2.1
Use of gastroprotective agents	8.3	9.5	19.7	9.3	5.6	8.7
Follow-up time (years):						
Median time to event (IQR)	1.4 (0.5-2.5)	2.0 (0.8-3.3)	1.1 (0.5-2.2)	1.8 (0.5-3.2)	2.0 (0.7-3.5)	1.9 (0.7-3.4)

Values are percentages.

Cross-validation

The Core Model demonstrated a reasonable predictive ability for UGI complication risk in each database (*c*-statistics between 0.630 to 0.799, Table 10.4). The Extended Model demonstrated no incremental benefit. The *c*-statistic only modestly changed for GePaRD and IPCI compared with the Core Model (Table 10.4). Calibration showed satisfactory results with calibration slopes close to 1 for most databases, except for IPCI.

Model presentation

The formula for the Core Model is presented in the Supplementary Appendix to estimate a person's absolute risk to develop UGI complication on the short- or long-term after initiating NSAID therapy. The model intercept reflects the risk per week for those patients who have all covariates at the reference category value. We provide country-specific intercepts. For Italy and the Netherlands two databases were available, and the intercept was

derived from the largest database. A simple score chart for the Core Model was based on multiplying regression coefficients by 1.8 and rounding. We illustrate the 1-month and 2-years prediction of cumulative UGI complication occurrence after initiation of NSAID therapy in Table 10.5.

Table 10.3: Univariate and multivariable rate ratios (RR) with 95% confidence interval (95% CI) after pooling across databases by a random effects meta-analysis approach

	Univariate RR (95%CI)	Core Model RR (95%CI)	Extended Model RR (95%CI)
CORE MODEL:			
Age (years):			
40-50	1 (ref)	1 (ref)	1 (ref)
18-30	0.36 (0.3-0.5)	0.38 (0.3-0.5)	0.39 (0.3-0.5)
30-40	0.59 (0.5-0.7)	0.60 (0.5-0.7)	0.61 (0.6-0.7)
50-60	1.72 (1.5-2.0)	1.80 (1.6-2.0)	1.73 (1.6-1.9)
60-70	2.97 (2.5-3.6)	3.13 (2.6-3.8)	2.89 (2.4-3.5)
70-80	5.23 (3.9-7.0)	5.71 (4.2-7.8)	5.06 (3.7-6.9)
> 80	9.30 (6.0-14.4)	10.9 (6.9-17)	9.49 (6.1-15)
Gender:			
Male	1 (ref)	1 (ref)	1 (ref)
Female	0.68 (0.6-0.7)	0.63 (0.5-0.8)	0.65 (0.5-0.8)
Non prior UGI complication	1 (ref)	1 (ref)	1 (ref)
Prior UGI complication	3.81 (2.7-5.4)	2.43 (1.9-3.1)	1.83 (1.5-2.2)
Follow-up time:			
0-2 weeks	1 (ref)	1 (ref)	1 (ref)
2-4 weeks	0.71 (0.6-0.8)	0.69 (0.6-0.8)	0.69 (0.6-0.8)
4 weeks-1 year	0.34 (0.3-0.4)	0.32 (0.2-0.5)	0.32 (0.2-0.5)
1-2 years	0.30 (0.2-0.4)	0.29 (0.2-0.4)	0.29 (0.2-0.4)
2-5 years	0.31 (0.2-0.4)	0.30 (0.2-0.4)	0.30 (0.2-0.4)
Databases:			
SISR	1 (ref)	1 (ref)	1 (ref)
GePaRD	1.34 (1.3-1.4)	1.98 (1.9-2.1)	1.48 (1.4-1.5)
THIN	1.31 (1.3-1.7)	1.86 (1.8-1.9)	1.65 (1.6-1.7)
IPCI	0.78 (0.7-0.9)	1.08 (1.0-1.2)	0.86 (0.8-1.0)
PHARMO	0.48 (0.5-0.5)	0.78 (0.7-0.8)	0.77 (0.7-0.8)
OSSIFF	1.08 (1.0-1.1)	1.19 (1.1-1.2)	1.22 (1.2-1.3)
EXTENDED MODEL:			
Comorbidities:			
Prior UGI disease	2.88 (2.3-3.5)	NA	1.67 (1.4-1.9)
Chronic hepatic disorders	3.93 (2.8-5.5)	NA	2.52 (1.7-3.7)
Alcohol abuse	2.75 (1.2-6.5)	NA	1.71 (0.8-3.5)
Smoking	1.06 (1.0-1.2)	NA	1.19 (1.0-1.4)
Inflammatory poliarthritis	1.88 (1.7-2.2)	NA	1.42 (1.2-1.8)
Osteoarthritis	1.93 (1.8-2.1)	NA	1.06 (0.9-1.2)
Cancer	2.63 (2.5-2.8)	NA	1.45 (1.3-1.7)
Use of medication:			
Use of glucocorticoids	1.70 (1.3-2.3)	NA	1.28 (1.1-1.5)
Use of aspirin	3.40 (2.7-4.2)	NA	1.52 (1.4-1.6)
Use of antiplatelets	3.50 (2.6-4.7)	NA	1.42 (1.2-1.6)
Use of anticoagulants	2.68 (2.0-3.7)	NA	1.55 (1.4-1.8)
Use of gastroprotective agents	1.82 (1.5-2.2)	NA	1.07 (1.0-1.2)

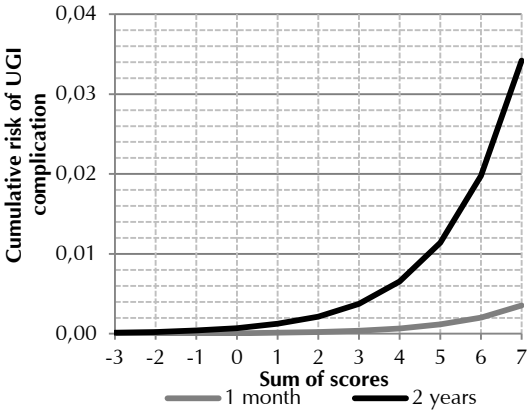
NA: Not applicable.

Table 10.4: Concordance statistic and calibration slope of the Core Model and Extended Model at cross validation. The Core and Extended Models were developed by omitting each of the six database in turn, with cross-validation on the omitted database

	Concordance statistic		Calibration slope	
Database:	Core Model	Extended Model	Core Model (SE)	Extended Model (SE)
GePaRD	0.777	0.789	1.17 (0.01)	0.95 (0.01)
THIN	0.718	0.720	0.76 (0.01)	0.72 (0.01)
IPCI	0.630	0.621	0.44 (0.06)	0.41 (0.06)
PHARMO	0.799	0.802	1.32 (0.03)	1.27 (0.03)
OSSIFF	0.747	0.753	1.13 (0.02)	1.13 (0.02)
SISR	0.746	0.753	1.15 (0.02)	1.12 (0.02)

Table 10.5: Sum of scores can be calculated for the Core Model (age, gender, prior UGI complication, and country)

	Points	Score
Age (years)	see below	
Gender	see below	
Prior UGI complication	see below	
Country	see below	
Sum of scores		



Patient characteristic	Values						
Age (years)	18-30	30-40	40-50	50-60	60-70	70-80	≥80
	-2	-1	0	1	2	3	4
Gender	Female	Male					
	-1	0					
Prior UGI complication	YES	NO					
	2	0					
Country	DE	UK	NL	IT			
	1	1	0	0			

DE, Germany; UK, United Kingdom; NL, the Netherlands; IT, Italy.

Discussion

We developed and validated a model to predict the short-term or long-term risk of UGI complication in new NSAID users. This prediction model was based on six European databases with 9 million patients on NSAID therapy, of which 23,411 developed the outcome-of-interest during follow-up. The large numbers make statistical optimism and internal validation irrelevant, and allowed for reliable external validation on each of the participating databases. Two models were developed with increasing complexity; the Core Model and the Extended Model. The Core Model, composed of characteristics that are very readily available at the time of NSAID prescription, discriminated adequately between patients with and without UGI complication and to the same extent as the more complicated Extended Model, although the latter included more patient characteristics. The main predictor of UGI complication was age. Advanced age has been considered in the risk-stratification of NSAID users in many evidence-based guidelines.[53, 142, 152] In addition, the risk of UGI complications decreased with longer follow-up time. This is probably explained as follow-up time indirectly measures the duration on NSAID therapy. The longer the duration the more likely that the NSAID use was stopped thereby lowering the risk.

As result of large numbers of patients developing the outcome per database and of the limited list of pre-defined risk factors, statistical optimism is not an issue for this analysis. Considering 50 UGI complications per parameter to be estimated as a very safe threshold, the number of outcomes far exceeds this minimum requirement, except for IPCI. Internal validation via bootstrapping was therefore not required.[192] Internal-external cross-validation was performed and showed that good discrimination was seen (*c*-statistic from 0.630 to 0.799).

This proposed prediction model is an important step in constructing an NSAID treatment decision model in which the patients risk profile is considered with respect to both UGI and CV safety. The absolute UGI complication and CV risks per type of NSAID are the input for this decision model. This information will be available when integrating the risk estimates of prediction models with the relative risks of different NSAID relative to each other. The latter are currently studied by case-control studies within the same databases of the SOS project.

Several limitations of this study should be acknowledged. Further validation is necessary, beyond the external cross-validation approach applied here. We anticipate that the Core Model may be transportable to other settings since age, sex and previous history of UGI are reliably determined in any setting. But the average risk of UGI complications may well need updating to local settings.[188, 193]

Although the performance of the presented models was satisfactory, it might have been improved by including additional factors or by including data of higher quality. Not all potential predictors (i.e. *H. pylori* infection) were contained in (all) databases or contain the information in the desired detail. Alcohol abuse or smoking in the administrative databases showed low prevalences. In PHARMO the comorbidities had a low prevalence, but the drugs were captured sufficiently. Some risk factors are very rare in the general population, but contain very high prognostic information. This would not influence the overall performance of the model substantially, but is important for individual risk estimation to consider such risk factors. For example, we lacked information on bleeding disorders, and a patient with this condition is at an increased risk of UGI complication. We focused on risk factors that are easily captured in daily clinical practice. Novel predictors

for UGI complication could therefore not be identified, in line with the aim of the study to obtain a robust and pragmatic prediction model to support decision making.

We have estimated the UGI complication risk on short-term and long-term follow-up, without considering the duration of NSAID therapy. The hypothesis is that a prediction in clinical practice can only be made on baseline risk factors (as we cannot look into the future), although that information is available when doing a retrospective analysis. Since patients entered the cohort upon NSAIDs prescription the short term risks of UGI complication (2 weeks and 1 month) reflect the risk of UGI complications while on NSAID therapy, whereas the longer-term UGI complication risk is a general, background risk during which the NSAID effect is minimal, since most patients in our cohort use NSAIDs only for a very short period of time. This is in line with previous studies in Italy, the Netherlands and the United Kingdom that showed that NSAIDs are used predominantly shorter than 30 days.[122, 153]

In conclusion, the proposed prediction model may assist physicians, regulators or patients in predicting which patients initiating any type of NSAID therapy are at risk to develop UGI complication on the short-term or longer term. The main risk factor in the model was age, followed by sex and a history of complicated ulcer disease. These patient characteristics are all readily available when NSAID therapy is started, and hence may be considered in decision making in the choice of NSAID.

Supplementary Appendix

Details of the Core Model

The cumulative risk of UGI complication in NSAID users is calculated according to the formula:

$$risk = 1 - \exp\left(-\sum_i IR_i * \Delta t_i\right)$$

where

$$IR_i = \exp\left(lp_i\right)$$

and

$$lp = \beta_0 + \sum_i \beta_i * predictor_i + fup - period$$

where $\beta_{0\ country}$ is the intercept (baseline risk) of the model.

$\beta_{0\ country}$ for UGI complication =

Germany:	-10.199
Netherlands:	-11.133
United Kingdom:	-10.262
Italy:	-10.885

lp for UGI complication = $\beta_{0\ country}$ – 0.9560 × (age 18-29 years) – 0.5146 × (age 30-39 years) + 0.5853 × (age 50-59 years) + 1.1409 × (age 60-69 years) + 1.7417 × (age 70-79 years) + 2.3894 × (age 80 and more years) – 0.4691 × (female) + 0.8898 × (prior UGI complication) - 0.3764 × (2-4 weeks) – 1.1460 × (4 weeks-1 year) – 1.2496 × (1-2 years) – 1.2170 × (2-5 years)

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Chapter 11

Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a meta-analysis of randomized clinical trials and observational studies

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Abstract

Background

Low-dose acetylsalicylic acid (LDA, 75–325 mg/day) is recommended for primary and secondary prevention of cardiovascular events, but has been linked to an increased risk of upper gastrointestinal bleeding (UGIB).

Aim

This study aimed to analyze the magnitude of effect of LDA use on UGIB risk.

Methods

PubMed and Embase were searched for randomized controlled trials (RCTs) reporting UGIB rates in individuals receiving LDA, and observational studies of LDA use in patients with UGIB. Studies were pooled for analysis of UGIB rates.

Results

Eighteen studies were included. Seven RCTs reported UGIB rates in individuals randomized to receive LDA (n = 22,901) or placebo (n = 22,923). Ten case–control studies analyzed LDA use in patients with UGIB (n = 10,816) and controls without UGIB (n = 30,519); one cohort study had 207 UGIB cases exposed to LDA only. All studies found LDA use to be associated with an increased risk of UGIB. The average number of extra UGIB cases associated with LDA use in the RCTs was 1.2 per 1000 patients per year (95% confidence interval [CI] 0.7–1.8). The number needed to harm was 816 (95% CI 560–1500) for RCTs and 819 (95% CI 617–1119) for observational studies. Meta-analysis of RCT data showed that LDA use was associated with a 50% increase in UGIB risk (odds ratio [OR] 1.5, 95% CI 1.2–1.8). The risk was most pronounced in observational studies (OR 3.1, 95% CI 2.5–3.7).

Conclusions

LDA use is associated with an increased risk of UGIB.

Introduction

Acetylsalicylic acid (ASA) at doses of 75–325 mg/day (low-dose ASA; LDA) is recommended for secondary prevention of cardiovascular events[194], and it is also commonly used for primary prevention in patients at a markedly increased risk of cardiovascular events. LDA use has been shown to decrease the incidence of cardiovascular events in patients at high cardiovascular risk[195], but its use is associated with an increased risk of upper gastrointestinal bleeding (UGIB).[196-198] Peptic ulcer bleeding (PUB) accounts for most of this increased risk.[199]

It is important to be able to assess the strength of the association between LDA use and UGIB risk because of the widespread use of LDA, both on prescription and as an over-the-counter medication. The overall prevalence of LDA use was 9.6% among adults in the UK in 2006, with a much higher prevalence of 35% in those older than 75 years.[10] Several reviews and meta-analyses have estimated the risk of UGIB with ASA use, but they have used different selection criteria or have been different types of studies.[30-33, 35, 200-206] Many previous reviews have not looked specifically at the risk of UGIB associated with LDA use; they have not separated out UGIB from lower gastrointestinal bleeding or other gastrointestinal complications such as perforation[30, 32, 205-207], have not looked specifically at ASA doses lower than 325 mg/day[33, 35] or have compared the bleeding risk associated with different doses of ASA rather than comparing the risk of bleeding in ASA users with that seen in non-users.[201, 205] In addition, some studies limited inclusion to a single indication for ASA, such as primary cardiovascular prevention[31] or secondary prevention.[203] The majority of reviews included only randomized controlled trials (RCTs).[30, 32, 33, 201-203, 205, 207] However, many of the RCTs included in such reviews exclude patients at high risk of UGIB, and thus can underestimate the risk of bleeding associated with LDA use in real-world practice. One systematic review by García Rodríguez et al.[200] included observational epidemiological studies published from 1990 to 2001, but no RCTs. Another review included only case–control studies conducted before 1989.[35]

The aim of this study was to carry out a meta-analysis of prospective RCTs that compared LDA therapy with placebo in different populations, regardless of indication, duration of follow-up or duration of use, as well as observational studies that evaluated the strength of the association between LDA use and UGIB risk specifically. In addition, the absolute increase in risk of UGIB with use of LDA compared with placebo was determined from the RCTs.

Methods

Study selection

PubMed and Embase were searched (entries from 1989 to 2009) for (i) RCTs reporting UGIB (including hematemesis and/or melena) or PUB involving individuals receiving LDA or placebo, and (ii) observational studies of LDA use in cases with UGIB or PUB, or controls. The references from previous meta-analyses and reviews were also examined. Searches were limited to studies published in English, French, German, Spanish, Italian or Japanese. Search results were combined and any duplicates removed. Microsoft Access (Microsoft Corporation, Redmond, WA, USA) was used to screen the search results in a

structured manner. First, the titles of the studies were screened for relevance, and studies were identified for further screening using the abstract/full text. Studies were excluded if any of the following applied: all studied ASA doses were higher than 325 mg/day; ASA doses were not reported; all patients were taking gastroprotective therapy or receiving *Helicobacter pylori* eradication therapy; patients were taking non-steroidal anti-inflammatory drugs (NSAIDs); or there was no appropriate control group. Studies were also excluded if UGIB or PUB rates were not reported separately from rates of lower gastrointestinal bleeding, rates of upper gastrointestinal complications were reported as a whole rather than UGIB specifically or data were reported only for uncomplicated peptic ulcer disease. Study selection was performed independently by two authors and decisions regarding inclusion of studies were reached by consensus.

Data extraction

Data on study populations, treatments and endpoints were independently extracted from each identified study by two authors and any discrepancies were resolved by consensus. For each treatment arm in the RCTs, the number of trial participants, the follow-up period and the number of patients who developed the primary endpoint of PUB or UGIB were recorded. Two of the RCT publications[5, 208] reported separately on melena and hematemesis. We chose to include only the hematemesis data from these two studies to minimize outcome misclassification and to avoid the possibility of double counting of UGIB events. In a sensitivity analysis, the melena data were included instead.

For the observational studies, the matching criteria, covariates in the model and adjusted odds ratio (OR) with 95% confidence interval (CI) were recorded. For all studies, the mean age at baseline and the percentage of male participants were assessed. For some of the studies[199, 208-210], this involved referring to other published papers on the same study populations.[211-214] For studies in which age was presented in categories we inferred the age of the patients to be the midpoint in the range. For example, for patients aged between 60 and 69 years, we inferred that they were, on average, 64.5 years old.

Data analysis

The rate of UGIB (per 1000 individuals per year) was calculated for each included RCT. The treatment-years weighted average number of extra UGIB cases associated with LDA use (per 1000 individuals per year) was also calculated. The number needed to harm (NNH) based on the inverse of the risk difference in patients using LDA compared with patients receiving placebo was calculated for RCTs. For observational studies, the NNH was calculated[215] with the pooled OR provided by the meta-analyses of the observational studies, given a UGIB event rate of 59/100,000 person-years in subjects not exposed to ASA (derived from the cohort study by Sørensen et al.[216]). The NNH expresses how many patients need to be exposed to LDA to cause UGIB in one patient.

The meta-analyses were based on the OR, which can be interpreted as an estimate of the relative risk (RR). The OR is defined as the odds of LDA exposure among patients with UGIB divided by the odds of exposure to LDA among those without UGIB. For the observational studies, the adjusted ORs or RRs as reported in the original paper were pooled, if possible; in one of the 11 studies[217], raw outcome data were used to calculate unadjusted ORs (which may be susceptible to confounding). None of the RCTs reported an RR, so we calculated the crude OR and the corresponding 95% CI for UGIB comparing exposure to ASA therapy with exposure to placebo for each individual RCT, because we hypothesized that confounding is less of an issue in RCTs than in observational studies. In order to in-

clude the study of Silagy et al.[218], which had four confirmed UGIB cases in the ASA group but no cases in the placebo group, 0.1 events were added to both groups, resulting in 4.1 cases in the ASA group and 0.1 case in the placebo group. This was done in order to avoid an infinite OR due to null events in the placebo group. In a sensitivity analysis, 0.5 events were added to both arms.

In view of the potential diversity of study designs, we performed stratified analyses according to two groups: (i) RCTs; and (ii) observational studies. Within the observational studies, a subgroup analysis was performed of five studies investigating doses of ASA of ≤100 mg and four studies investigating ASA 300–325 mg.

To estimate an overall pooled OR, a fixed-effects model was used for the RCTs (inverse variance model) using Mix version 1.7 (BiostatXL, Sunnyvale, CA, United States 2010).[219] To be as conservative as possible, a random-effects model was also applied. For the observational studies, a random-effects model was used because statistical heterogeneity existed across studies. Publication bias was examined by funnel plot asymmetry and quantified with the Egger regression test.[220] All statistical tests were two sided, and a *P* value lower than 0.05 was considered to be statistically significant.

Statistical heterogeneity

Statistical heterogeneity across studies was tested by using Cochran's Q statistic. For this test, a *P* value of 0.10 (two sided) and below was considered to indicate heterogeneity. To measure the degree of heterogeneity an I^2 value was recorded, with I^2 values less than 30% representing a low level, 30–75% a moderate level and above 75% a high level of heterogeneity.

Results

Search results

PubMed and Embase searches resulted in the identification of 2011 unique studies. The titles of these studies were screened for relevance and 709 studies were identified for further screening using the abstract/full text. A total of 688 studies were subsequently excluded for the reasons listed in Figure 11.1, leaving a total of 21 studies (six RCTs and 15 observational studies) eligible for inclusion. The references from previous meta-analyses and reviews were also examined[30-33, 35, 200-206] and one additional eligible RCT was identified.[208] Thus, a total of 22 studies (seven RCTs and 15 observational studies) were eligible for inclusion (Figure 11.1). Of the 15 observational studies, 14 were case–control studies and one was a cohort study.

Of the 22 studies meeting all the inclusion criteria, three[221-223] were suspected of reporting results from the same study populations as those included in more recently published articles[224, 225] and one[226] presented additional analyses from a sample that overlapped with a previous article.[225] Thus, the final number of studies included in the analyses was 18: seven RCTs[5, 199, 208, 218, 227-229] and 11 observational studies.[209, 210, 216, 217, 224, 225, 230-234]

Study characteristics

The main characteristics of the 18 studies included in the meta-analysis are summarized in Table 11.1 (RCTs) and Table 11.2 (observational studies).

Randomized controlled trials

The seven RCTs reported rates of UGIB or PUB (including hematemesis and/or melena) in 45,824 individuals randomized to receive LDA (average daily dose, 50–300 mg; n = 22,901) or placebo (n = 22,923) (Table 11.1).[5, 199, 208, 218, 227-229] The mean age of patients in the RCTs, weighted for sample size, was 63.3 years (range 53.8–79.0 years), and 70.0% of participants were male (range 21.0–100%). Mean follow-up periods ranged from 35 days to 7 years. None of the RCTs tested more than one dose level of ASA, so it was not possible to assess any potential dose–response relationship.

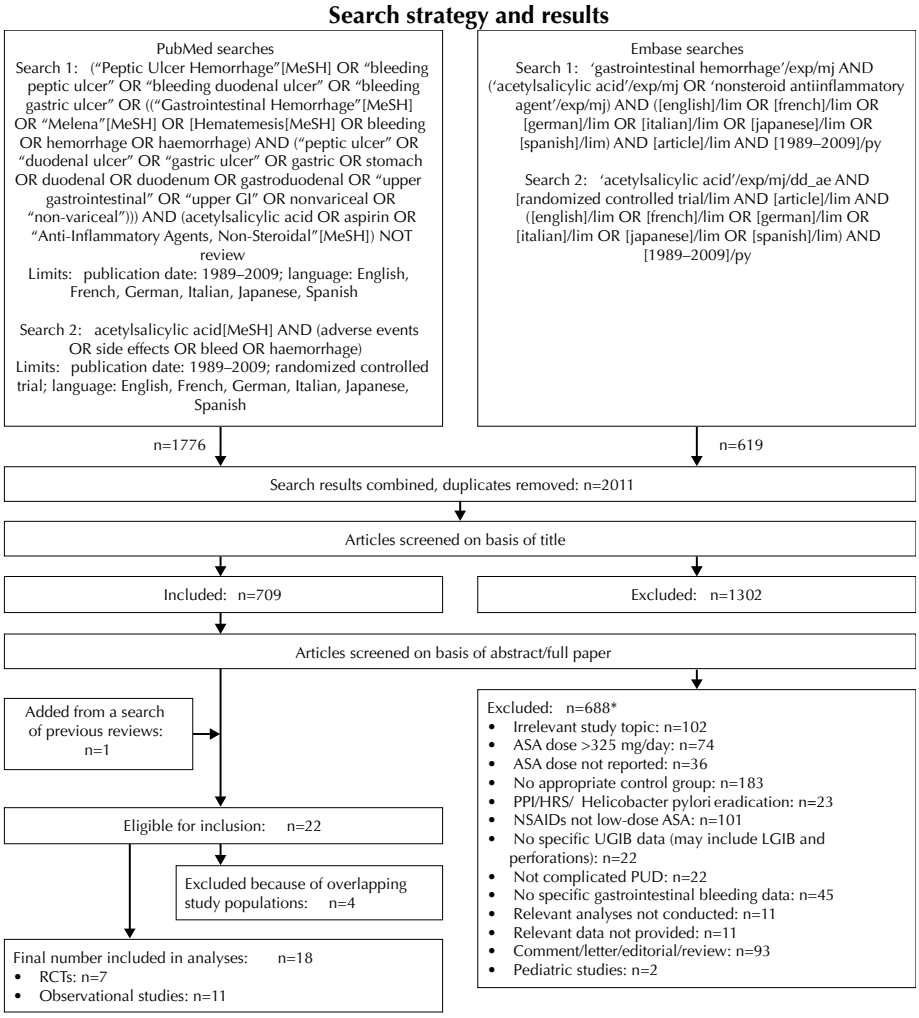

Figure 11.1: Search strategy and results

**Reports may have been excluded for more than one reason.*
ASA, acetylsalicylic acid; H_2RA, histamine-2 receptor antagonist; LGIB, lower gastrointestinal bleeding; NSAID, non-steroidal anti-inflammatory drug; PPI, proton pump inhibitor; PUD, peptic ulcer disease; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.

Observational studies

Eleven observational studies were identified, of which 10 were case–control studies and one was a cohort study. Five of the 10 case–control studies analyzed LDA use in patients presenting with UGIB (rather than PUB specifically) and controls with no UGIB[210, 224, 225, 230, 233], and the other five examined LDA use in patients presenting with PUB and controls with no PUB (Table 11.2).[209, 217, 231, 232, 234] A total of 41,335 patients were observed in the case–control studies, of whom 10,816 were UGIB cases and 30,519 were controls. In the cohort study, there were 207 UGIB cases exposed to LDA only.[216] The mean age in the observational studies, weighted for sample size, was approximately 63.3 years (range 60.1–73.6 years), and 64.0% of participants were male (range 43.7–74.5%).

Table 11.1: Baseline characteristics of study population in seven randomized controlled trials reporting incidence of UGIB in individuals randomized to receive LDA or placebo (n = 45,824)

Reference	Country	Outcome of interest	Patients	Sample size	Male, %	Mean age, years	Average follow-up, months	Average daily ASA dose, mg	UGIB incidence 1000 patients /year
Physicians' Health Study, 1989[5]	USA	Myocardial infarction, stroke, cardiovascular mortality	Male physicians aged 40–84 years randomized to receive ASA or placebo	ASA: 11,037; placebo: 11,034	100	53.8	60.2	162.5	ASA: 0.7; placebo: 0.5
Silagy et al., 1993[218]	Australia	Adverse effects associated with LDA use (part of larger study on cardiovascular and cerebrovascular morbidity and mortality	Individuals aged ≥ 70 years randomized to receive LDA or placebo	ASA: 200; placebo: 200	49.0	73.0	12.0	100	ASA: 20.0; placebo: 0.0
Slattery et al., 1995[199, 214]	UK	Adverse GI events (main UK-TIA study outcomes were stroke, myocardial infarction and death)	Patients with a recent TIA or minor ischemic stroke randomized to receive ASA or placebo	ASA: 806; placebo: 814	72.7	60.0	48.0	300	ASA: 5.0; placebo: 1.5
Diener et al., 1997[208, 211]	13 European countries	Stroke (fatal/non-fatal), death (all cause), stroke and/or all cause -death (allowed first event to be counted for survival analysis but avoided duplicate counting). Secondary outcomes TIA and other vascular events	Patients with a recent TIA or completed ischemic stroke randomized to receive ASA or placebo	ASA: 1649; placebo: 1649	57.8	66.7	24.0	50	ASA: 3.0; placebo: 2.7
Thrombosis prevention trial, 1998[227]	UK	Coronary death and fatal/non-fatal myocardial infarction	Men aged 45–69 years at high risk of ischemic heart disease randomized to receive LDA or placebo	ASA: 1268; placebo: 1272	100	57.5	81.6 (median)	75	ASA: 0.6; placebo: 0.1
Pulmonary Embolism Prevention trial, 2000[228]	Australia, New Zealand, South Africa, Sweden, UK	Pulmonary embolism and deep vein thrombosis	Patients undergoing surgery for hip fracture randomized to receive ASA or placebo	ASA: 6679; placebo: 6677	21.0	79.0	1.2	160 (enteric coated)	ASA: 328.1; placebo: 231.3
Ogawa et al., 2008[229]	Japan	Atherosclerotic events (including ischemic heart disease, stroke, peripheral arterial disease, cardiovascular mortality)	Patients aged 30–85 years with type 2 diabetes mellitus and no history of atherosclerotic disease, randomized to receive ASA or placebo	ASA: 1262; placebo: 1277	54.6	65.0	52.4	90.5	ASA: 0.9; placebo: 0.5

ASA, acetylsalicylic acid; GI, gastrointestinal; LDA, low-dose acetylsalicylic acid; TIA, transient ischemic attack; UGIB, upper gastrointestinal bleeding.

Table 11.2: Baseline characteristics of study population in 11 observational studies (10 case–control, one cohort) of LDA use in patients presenting with PUB or UGIB (n = 41,542)

Reference	Country	Case definition	Control definition	Sample size	Male %	Mean age, years	Definition of LDA	Matching factors	Factors adjusted for
Weil et al., 1995[209, 212]	UK	Patients with gastric or duodenal ulcer bleeding	Hospital patients selected from acute medical admissions (excluding patients with acute myocardial infarction, acute rheumatic diseases and active non-bleeding ulcers); community controls selected from the same primary care practices as cases	Cases: 1121; hospital controls: 1126; community controls: 989	55.7	73.6	75, 150 or 300 mg, 5 days/week for at least the previous month	Age (±5 years) and sex	Other NSAID use, previous ulcer or dyspepsia, smoking and alcohol consumption
Kelly et al., 1996[225]	USA	Patients with major UGIB due to gastric or duodenal ulcer or gastritis	Community controls from general population	Cases: 550; controls: 1202	61.9	60.1*	≤325 mg/day, any use in the 7 days before the index date	Residence, sex and age (±5 years)	Age, sex, marital status, date of interview, years of education, cigarette smoking, coffee consumption, alcohol consumption, use of ASA, paracetamol and NSAIDs
Lanas et al. 2000[224]	Spain	Patients with UGIB caused by ulcers, erosions or acute mucosal lesions of the upper gastrointestinal tract	Hospital patients admitted for reasons that were unlikely to be related to NSAID treatment and community controls from primary care practices (one of each control per case)	Cases: 1122; controls: 2231	69.3	65.2	≤300 mg/day, continuous use per day during the previous 7 days before admission or the day of the interview	Sex and age (±5 years)	Age, sex, hospital, history of UGIB, peptic ulcer disease, cardiovascular disease, cerebrovascular disease and rheumatic disease
Sørensen et al., 2000[216]	Denmark	Cohort study of LDA users with UGIB	UGIB rate in general population	Cases: 207 in 27,694 LDA users; controls: NA	49.9	68.1	100 or 150 mg/day	NA	SIR adjusted for age, sex and calendar time distribution of person-years in cohort
de Abajo and García Rodríguez, 2001[230]	UK	Primary care patients with UGIB whose specific site of bleeding was located in the stomach or duodenum, or in whom the diagnosis was peptic ulcer	Primary care patients with no UGIB	Cases: 1833; controls: 11, 500	62.4	63.4	Various (generally 75–300 mg/day), current use defined as when the supply of a prescription for ASA lasted until the index date or ended within the period of 30 days before the index date	Age (±1 year), sex and calendar year	Antecedents of gastrointestinal disorders, smoking status, alcohol consumption and use of NSAIDs, anticoagulants, steroids, SSRIs and paracetamol
Stack et al., 2002[231]	UK	Patients with PUB admitted to a single hospital	Hospital patients admitted for reasons that would not have had a major effect on use of ASA or NSAIDs	Cases: 203; controls: 203	62.6	66.3	≤300 mg/day, any use within the week prior to admission	Age (±5 years) and sex	Smoking, ulcer history, *Helicobacter pylori* infection, NSAID dose

Reference	Country	Case definition	Control definition	Sample size	Male %	Mean age, years	Definition of LDA	Matching factors	Factors adjusted for
Ibáñez et al., 2006[210, 213]	Spain	Patients with primary diagnosis of acute UGIB from a duodenal or gastric ulcer, acute lesions of the gastric mucosa, erosive duodenitis or mixed lesions	Patients admitted with non-alcohol-related trauma, elective surgery for non-painful disorders, and acute clinical conditions thought to be unrelated to ASA intake	Cases: 2813; controls: 7193	71.6	61.8	Various, any use in the 7 days before the index date	Center, date of admission (within 2 months), sex and age (±5 years)	Clopidogrel, dipyridamole, indobufen, ticlopidine, and triflusal use, history of peptic ulcer, diabetes mellitus, heart failure, acute myocardial infarction, angina, stroke, transient ischemic attack, intermittent claudication, smoking, alcohol consumption, use of antacids, H_2RAs, PPIs, misoprostol, sucralfate, nitrates, systemic NSAIDs, topical NSAIDs, analgesics, calcium-channel blockers, ACE inhibitors, statins, SSRIs, β-blockers
Lanas et al., 2006[232]	Spain	Patients hospitalized due to PUB	Hospital controls presenting for reasons that would not influence NSAID use	Cases: 2777; controls: 5532	59.1	61.0	Various (ranging from 100 to > 1000 mg/day), used within 7 days before the index date	Age (±5 years), hospital and month of admission	Age, sex, calendar semester, ulcer history and use of nitrates, oral anticoagulants, antiplatelet agents, acid-suppressing drugs, NSAIDs, coxibs
Sakamoto et al., 2006[233]	Japan	Patients with bleeding caused by a gastric or duodenal ulcer or gastritis, 93.8% of whom had PUB	Community controls from general population	Cases: 175; controls: 347	74.5	60.9	< 325 mg/day used within 7 days before the index date	Sex, age (±5 years), region	Use of acetaminophen, NSAIDs, consumption of alcohol and caffeine-containing beverages, smoking, history of gastric or duodenal ulcer, *H. pylori* status if available
Udd et al., 2007[234]	Finland	Patients with endoscopically confirmed PUB	Patients undergoing investigation for dyspepsia with no endoscopic evidence of peptic ulcer disease	Cases: 94; controls: 94	62.8	63.8	50–250 mg/day, taken for 2 weeks	Age (±5 years) and sex	Ulcer history, *H. pylori* infection, NSAID use, alcohol consumption, smoking
Uppalapati et al., 2009[217]	USA	Inpatients or outpatients with clinical or endoscopic evidence of bleeding peptic ulcer disease	Inpatients or outpatients with non-bleeding peptic ulcer disease	Cases: 128; controls: 102	43.7	61.8	Various (81–325 mg/day)	None reported	NA: crude OR calculated in the present meta-analysis

**Median age, years.*
ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; H_2RA, histamine-2 receptor antagonist; LDA, low-dose acetylsalicylic acid; NA, not applicable (cohort study); NSAID, non-steroidal anti-inflammatory drug; OR, odds ratio; PPI, proton pump inhibitor; PUB, peptic ulcer bleeding; SIR, standard incidence ratio; SSRI, selective serotonin reuptake inhibitor; UGIB, upper gastrointestinal bleeding.

The control groups used in the 10 case–control studies varied. Three studies used a control group comprising hospital patients[210, 231, 232], three studies included a control group obtained from primary care or the general population[225, 230, 233], and three included a combination of hospital patients and community-based controls.[209, 217, 224] One study used a control group of patients with endoscopically confirmed non-ulcer dyspepsia.[234]

Four of the case–control studies examined the risks of PUB or UGIB associated with specific doses of ASA[209, 217, 230, 232], while the other six grouped ASA doses into one or more dose ranges.[210, 224, 225, 231, 233, 234] The cohort study reported the standard incidence ratios (SIRs) of UGIB for doses of 100 mg/day and 150 mg/day, but it was unclear whether or not these findings were from a group of patients who were also taking other NSAIDs.[216]

Association between LDA use and UGIB

Randomized controlled trials

During follow-up, 1.3% (288/22,901) of participants assigned to the ASA group developed UGIB. During the same period, 0.8% (194/22,923) of participants assigned to the placebo group developed UGIB.

All of the RCT publications reported an increased rate of UGIB or PUB in individuals receiving LDA compared with those receiving placebo, of which two were statistically significant[199, 228] and five[5, 208, 218, 227, 229] were not. Across the various studies, UGIB rates were in the range 0.6–328.1 per 1000 patients per year in the LDA group and 0–231.3 per 1000 patients per year in the placebo group. Based on this analysis, the number of extra UGIB cases associated with LDA use was in the range 0.2–96.8 per 1000 patients per year. The person-years weighted average number of extra UGIB cases associated with LDA use was 1.2 per 1000 patients per year (95% CI 0.7–1.8). The NNH was 816 (95% CI 560–1500), meaning that if 816 individuals received LDA, one would have developed UGIB as a result of treatment.

After pooling the results, the OR of UGIB associated with LDA use was 1.5 (95% CI 1.2–1.8, P< 0.0001) (Figure 11.2). There was no heterogeneity (I^2 0%), and because this was not significant (P = 0.50) we applied a fixed-effects model. The result of the Egger regression test for publication bias was not significant (intercept 0.8, 95% CI –0.3, 1.9, P = 0.12) and no funnel plot asymmetry was observed (Figure 11.3), indicating no evidence of publication bias. The pooled estimate was mostly driven by the Pulmonary Embolism Prevention trial[228] with a relative weight of 75.6%.

As mentioned previously, two of the RCTs[5, 208] reported separately on hematemesis and melena. When the melena data of these studies were included instead of the hematemesis data, the association remained the same as in the primary analysis (OR 1.5, 95% CI 1.3–1.7, P< 0.0001, for heterogeneity P = 0.57, therefore also using a fixed-effects model). In addition, a sensitivity analysis was carried out by adding 0.5 events instead of 0.1 events to the placebo and LDA arms of the Silagy et al. study[218]; this did not influence the result.

Observational studies

All 11 observational studies reported a significant increase in the rate of PUB or UGIB in individuals exposed to LDA compared with those not exposed (Figure 11.4).

The pooled OR of the meta-analysis of the observational studies examining the risk of UGIB associated with ASA use was 3.1 (95% CI 2.5–3.7, P< 0.0001) (Figure 11.4). There was a high degree of heterogeneity (I^2 78%), thus a random-effects model was applied. The result of the Egger regression test for publication bias was not significant (intercept 1.6, 95% CI –1.1, 4.2, P = 0.21), and no funnel plot asymmetry was seen (Figure 11.3), indicating no evidence of publication bias. As mentioned in the Methods section above, in the study by Uppalapati et al.[217], raw outcome data were used to calculate unadjusted crude ORs, regardless of dose (81 mg/day or 325 mg/day). The NNH was 819 (95% CI 617–1119).

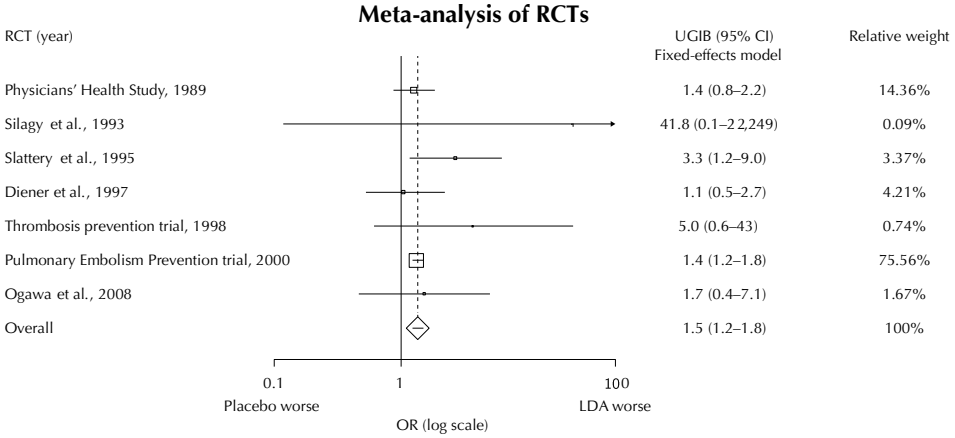

Figure 11.2: Meta-analysis of RCTs showing the association between LDA use and the risk of UGIB

For heterogeneity P = 0.50; I^2 0%.
Fixed-effects model 1.5 (95% CI 1.2–1.8), P< 0.0001.
Random-effects model 1.5 (95% CI 1.2–1.8), P< 0.0001.
CI, confidence interval; LDA, low-dose acetylsalicylic acid; OR, odds ratio; RCT, randomized controlled trial; UGIB, upper gastrointestinal bleeding.

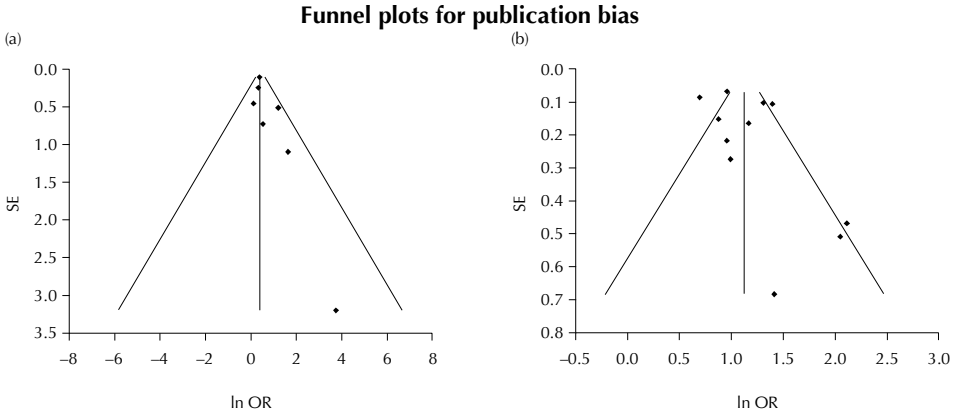

Figure 11.3: Funnel plot for publication bias in (a) seven randomized controlled trials and (b) 11 observational studies

Egger regression P = 0.12 (intercept 0.8, 95% CI –0.3, 1.9).
Egger regression P = 0.21 (intercept 1.6, 95% CI –1.1, 4.2).
CI, confidence interval; OR, odds ratio; SE, standard error.

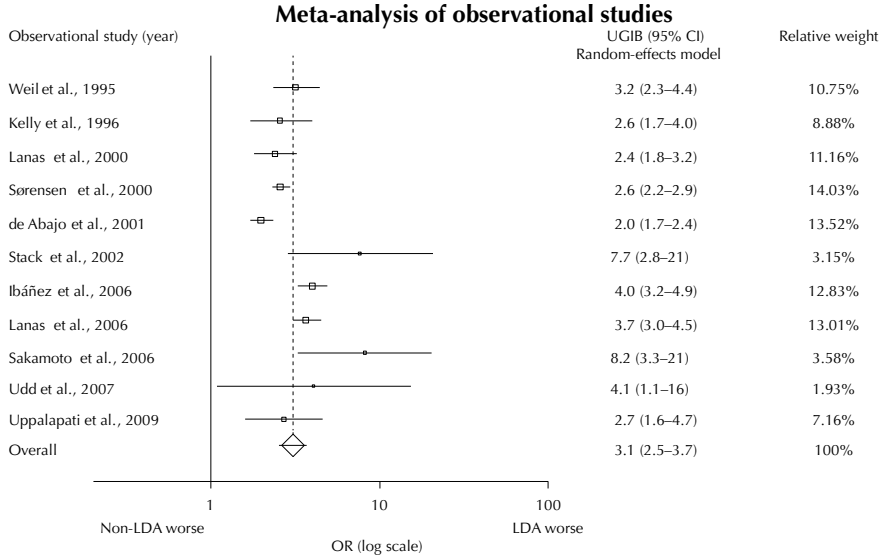

Figure 11.4: Meta-analysis of observational studies showing the association between LDA use and the risk of UGIB

For heterogeneity P< 0.001; I^2 78%.
Random-effects model 3.1 (95% CI 2.5–3.7), P< 0.0001.
CI, confidence interval; LDA, low-dose acetylsalicylic acid; OR, odds ratio; UGIB, upper gastrointestinal bleeding.

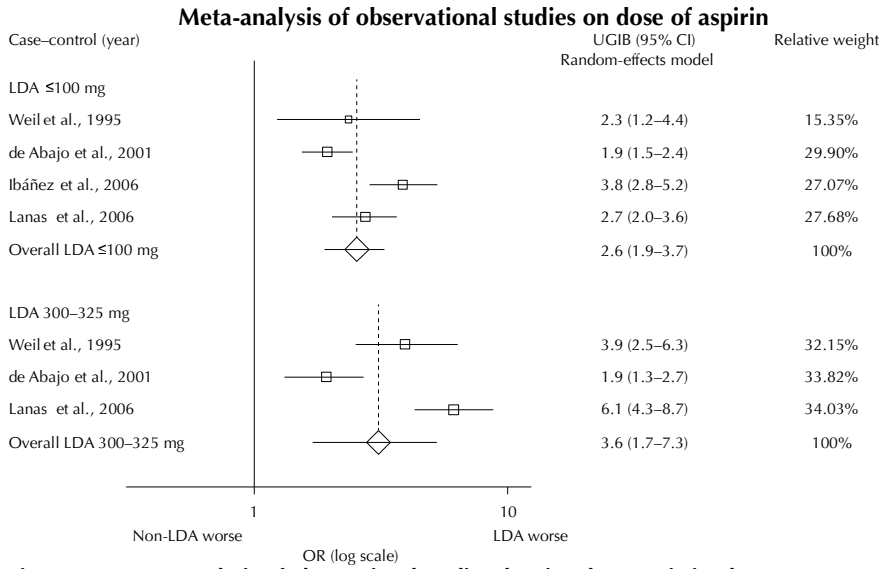

Figure 11.5: Meta-analysis of observational studies showing the association between LDA use and the risk of UGIB, stratified by dose

CI, confidence interval; LDA, low-dose acetylsalicylic acid; OR, odds ratio; UGIB, upper gastrointestinal bleeding

Subgroup analysis within observational studies

Two observational studies showed a trend for a greater risk of UGIB with increasing (but still low) doses of ASA.[209, 232] Another study showed that the risk of UGIB stayed the same.[230] Meta-analysis of the studies examining the risk of UGIB associated with ASA doses ≤100 mg/day found the pooled OR to be 2.6 (95% CI 1.9–3.7, P< 0.001) (Figure 11.5). The OR for doses of 300–325 mg/day was 3.6 (95% CI 1.7–7.3, *P* = 0.001) (Figure 11.5). A random-effects model was applied because there was a high degree of heterogeneity (I^2 76% and 90%, respectively). In the cohort study, the risk was similar for users of ASA 100 mg/day (SIR 2.6, 95% CI 1.8–3.5) and ASA 150 mg/day (SIR 2.6, 95% CI 2.2–3.0), but it is not clear whether ASA was used in combination with other NSAIDs.

Discussion

This meta-analysis demonstrates that use of LDA significantly increases the risk of UGIB compared with non-use. The analysis included data from well-designed RCTs and from observational studies, encompassing a broad range and large number of patients (n = 87,366). The pooled estimate of the RCTs gave an OR of 1.5 (95% CI 1.2–1.8, P< 0.0001) and the observational studies gave an OR of 3.1 (95% CI 2.5–3.7, P< 0.0001).

Although RRs are significantly increased, the absolute increases in UGIB risk are small. RCTs involving more than 22,000 patients taking LDA show that, on average, the number of extra cases of UGIB associated with LDA use are 1.2 per 1000 patients per year. In our analysis, the NNH for the RCTs was 816, meaning that if 816 individuals received LDA rather than placebo for 1 year, one would have developed UGIB as a result of treatment. The observational studies had a very similar NNH of 819.

In spite of different event and/or exposure definitions, several other meta-analyses have examined the risk of gastrointestinal bleeding with LDA use.[30-33, 35, 200-203, 206, 207] In general, our findings are consistent with those of others, who report an absolute rate increase of major gastrointestinal bleeding with LDA use of about 1 per 1000 person-years[32, 202, 206], with a corresponding NNH of 833.[32] The RR of gastrointestinal bleeding due to ASA use has been reported to range from 1.5 to 2.5[30-33, 201-203, 206, 207] for clinical trials, and from 2.6[200] to 3.3[35] for observational studies. A recently published meta-analysis of RCTs reported the risk of major gastrointestinal bleeding (including lower gastrointestinal bleeding) with LDA use as 1.6 (95% CI 1.3–1.9)[207], in line with the findings from our meta-analysis of the risk of upper gastrointestinal bleeding with LDA use in RCTs. Compared with other previously published reviews and meta-analyses, our analyses included fewer studies. This was due to more stringent inclusion and data extraction criteria used in our study – to harmonize the outcome definition across studies we only included studies where UGIB could be clearly separated from other gastrointestinal complications, such as perforation or lower gastrointestinal bleeding. To harmonize the exposure definition we included only studies where LDA dose was clearly reported to be lower than 325 mg/day. Our analysis has extended previous meta-analysis data by looking specifically at low dosages of ASA use only and focusing on the risk of UGIB rather than gastrointestinal bleeding in general, especially from observational data.

A potential limitation of RCTs is that they often recruit highly select populations and therefore may not be representative of patients seen in routine clinical practice. For example, despite some of the RCTs included in this analysis enrolling patients with a history

or a high risk of cardiovascular and cerebrovascular events, all of the RCTs identified excluded certain groups of individuals who would be at an increased risk of bleeding or complications, such as those with a history of peptic ulcer disease[5, 199, 208, 228, 229] or individuals who were also taking NSAIDs, anticoagulants or corticosteroids.[5, 208, 218] The risk of bleeding found in LDA users in these trials may therefore be lower than that in the general population. In addition, the majority of RCTs included in this analysis were post-hoc or subgroup analyses of studies where a cardiovascular or cerebrovascular outcome (and not UGIB) was the original primary outcome measure. Thus, there may be potential under-reporting of UGIB, especially after a cardiovascular event occurred. This is supported by the finding that the risk of UGIB associated with LDA use is higher in the observational studies than in the RCTs, although it is possible that residual confounding could play a role.

None of the RCTs identified in this review tested more than one dose level of LDA. However, several of the observational studies examined the dose–response relationship between LDA and UGIB, although the results were inconsistent. For ASA doses ≤325 mg/day, two studies showed a trend of the risk of UGIB increasing with higher doses of ASA.[209, 232] Another study showed the same risk[230] with increased ASA doses.

There is no evidence of a dose–response relationship in terms of the cardiovascular benefit of LDA, and low doses appear to be as effective as high doses.[196] However, all doses of ASA are associated with an increased risk of UGIB. Therefore, there does not appear to be a 'safe' dose of ASA in terms of its gastrointestinal risks. This suggests that LDA should be prescribed whenever possible not only to ensure cardiovascular benefit but also to reduce the risk of UGIB that is potentially associated with high doses of ASA. This is in line with European and US guidelines, which recommend maintenance treatment with ASA 75–100 mg/day for patients with non-ST-segment elevation myocardial infarctions.[235, 236] US guidelines on reducing the gastrointestinal risks of antiplatelet therapy recommend that doses greater than ASA 81 mg/day should not be used routinely.[237]

Recent studies have highlighted the importance of continuing LDA treatment, even for patients with UGIB.[238, 239] Patients prescribed LDA for secondary prevention of cardiovascular and cerebrovascular events have a 40% increased risk of ischemic stroke or transient ischemic attack for up to 6 months after discontinuation of ASA treatment compared with patients who continue ASA treatment.[240]

US guidelines recommend concomitant gastroprotection for patients taking LDA who are at risk of upper gastrointestinal events (e.g. elderly patients, individuals using other NSAIDs or antithrombotic agents and patients with a history of peptic ulcer disease) rather than treatment with enteric-coated or buffered LDA.[237] To facilitate a more accurate estimation of the risk of UGIB, the current analysis excluded studies that reported that all participants were treated with proton pump inhibitors (PPIs). However, this guideline recommendation is supported by the finding of Ibáñez et al. that the risk of UGIB is lower in patients taking LDA and a PPI than in those taking LDA alone.[210] Furthermore, there is evidence from other RCTs that PPI use decreases the incidence of peptic ulcer disease in patients taking LDA.[241, 242]

This study, in contrast with previous reviews and meta-analyses, systematically evaluated the association between LDA use and UGIB, both in RCTs and in observational studies.

Many previously published meta-analyses have relied on high-quality evidence from RCTs, and although observational studies have some disadvantages, such as the potential

for confounding due to the non-randomized nature of the patient groups, they allow a more representative sample of real-world data to be collected than other study designs.

Despite our efforts to harmonize the outcome definition as much as possible, potential limitations of the included studies are lack of consistency in bleeding definition and ASA dose used, which makes it difficult to compare findings across the studies. In addition, the risk estimates given in the observational studies included in the analysis are influenced by the choice of control group, as in the study by Weil et al.[209] for example, in which cases were compared with hospital controls (OR 2.7, 95% CI 1.9–3.80), community controls (OR 4.2, 95% CI 2.8–6.3) or combined controls (OR 3.2, 95% CI 2.3–4.4). Risk estimates in the observational studies are also dependent on the methods used to analyze the estimates of risk (e.g. variations in matching and adjustment in multivariate analyses).

A potential limitation of the search strategy is that studies published before 1989 were excluded. However, some of the studies published before 1989 that were included in previous reviews would have been excluded from our study owing to other exclusion criteria, such as not separating UGIB from gastrointestinal bleeding as a whole[243] or not reporting on ASA doses lower than 325 mg/day.[244-246] In addition, there were many more case–control studies than cohort studies included in our review; only one cohort study was eligible for inclusion in our analysis.[216] To our knowledge, the only other published systematic review of epidemiological studies of upper gastrointestinal complications and ASA use in this time period also included more case–control studies than cohort studies.[200] This may have led to an underestimation of some of the results. However, it does ensure that the focus is on recent data and that the results are likely to be as representative as possible of current clinical practice.

Another potential limitation is that it was not possible to assess precisely how many individuals in the included studies were taking gastroprotective medication. This may have resulted in the incidence of UGIB being underestimated.

All of the observational studies and all of the RCTs included in these analyses show that LDA use is associated with an increased risk of UGIB. Gastroprotective prophylaxis should be considered in patients receiving long-term LDA therapy, particularly in those who have additional risk factors such as concomitant NSAID use or a history of peptic ulcer complications.

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Chapter 12

Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors.

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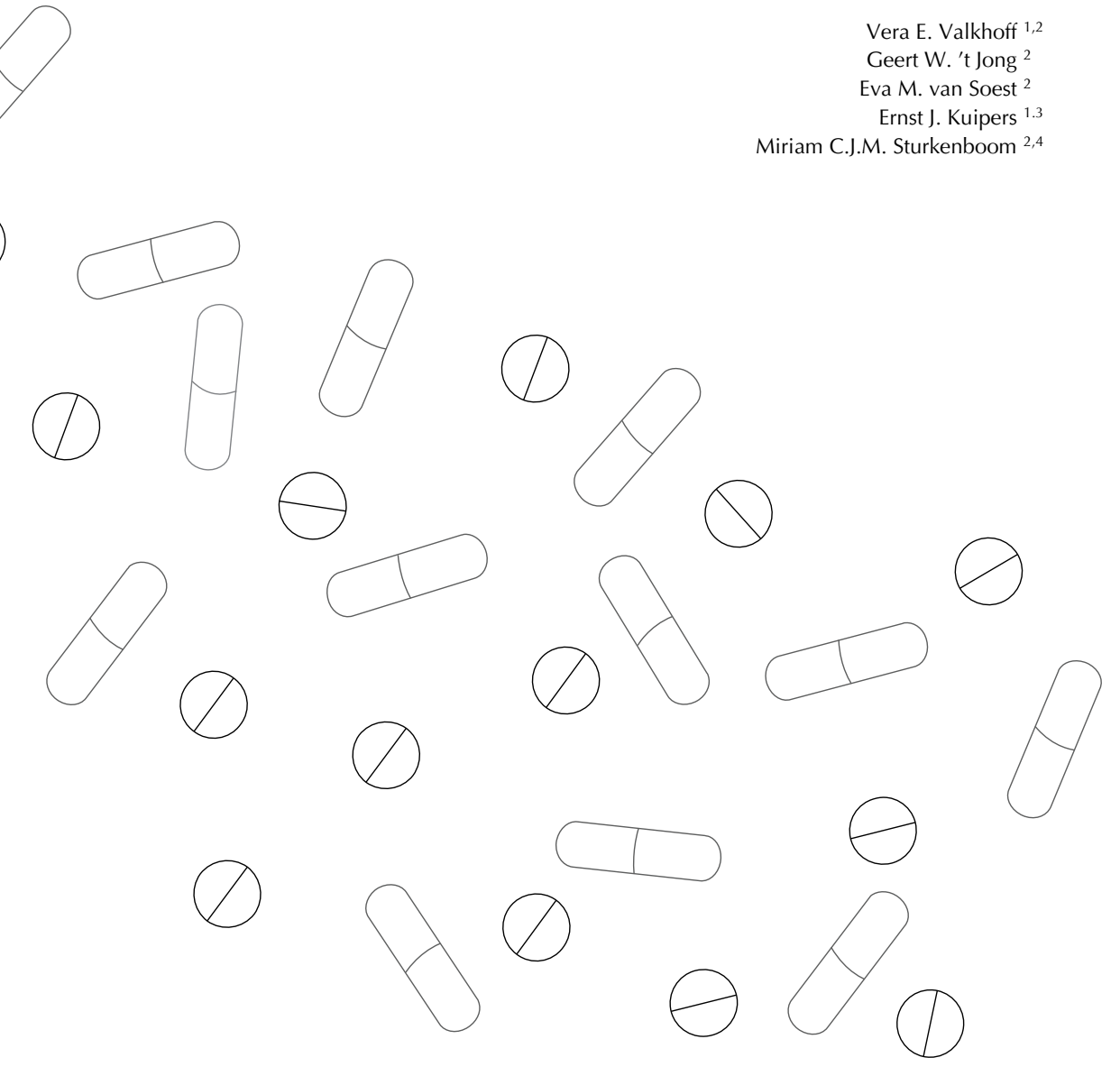

Abstract

Background

The association between myocardial infarction (MI) and co-administration of proton pump inhibitors (PPIs) and clopidogrel remains controversial.

Aim

To quantify the association between concomitant use of PPIs and clopidogrel and occurrence of recurrent MI.

Methods

We conducted a case-control study within a cohort of acute MI patients in PHARMO Record Linkage System (1999-2008). Cases were patients readmitted for MI. PPI exposure was categorized as current (3-1 days before MI), past (30-3 days before MI), or no use (> 30 days before MI). We used conditional logistic regression analyses.

Results

Among 23,655 patients hospitalized following MI, we identified 1,247 patients readmitted for MI. Among clopidogrel users, current PPI use was associated with an increased risk of recurrent MI (OR:1.62, 95%CI:1.15-2.27) when compared with no PPI use, but not when compared with past PPI use (OR:0.95, 95%CI:0.38-2.41). Among clopidogrel-non-users, current PPI use was associated with an increased risk of recurrent MI (OR:1.38, 95%CI:1.18-1.61) when compared with no PPI use

Conclusions

The apparent association between recurrent MI and use of PPIs with clopidogrel depends on the design and is affected by confounding by indication. The association is not present when (un)measured confounding is addressed by design.

Introduction

Clopidogrel is an oral antiplatelet agent commonly used in addition to aspirin to reduce cardiovascular (CV) events. Clopidogrel is converted in the liver from an inactive pro-drug to its active metabolite, that binds irreversible to $P2RY_{12}$ adenosine diphosphate (ADP) receptors on the platelet surface, thereby preventing platelet aggregation.[247]

Clopidogrel conversion is catalyzed by several cytochrome P450 (CYP) enzymes, of which CYP2C19 is the most important. Patients with loss-of-function polymorphisms in the gene encoding for CYP2C19 have lower levels of the active metabolite and have reduced platelet inhibition during clopidogrel treatment. This results in higher rates of acute myocardial infarction (MI).[248, 249] In contrast, rapid metabolizers of clopidogrel (with CYP2C19 variants leading to increased enzyme activity) have a higher rate of clopidogrel activation and more efficient platelet inhibition.[250]

Proton pump inhibitors (PPIs) are routinely co-administered with clopidogrel to prevent upper gastrointestinal (UGI) bleeding[251-253], which is in line with expert consensus guidelines.[237] PPIs are also metabolized by CYP2C19, and can competitively bind to its catalytic site. Therefore, PPIs are potentially hindering the conversion of clopidogrel to its active metabolite. Both the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) recently advised against the concurrent use of PPIs and clopidogrel in the absence of a strong indication[254, 255], because several pharmacodynamic[256-259] and clinical outcome studies[260-265] suggest a detrimental interaction between clopidogrel and PPIs.

Evidence on the association between cardiovascular events and co-administration of PPIs with clopidogrel remains inconclusive. Observational studies show a small increased risk of recurrent MI in patients using PPI – clopidogrel combination therapy compared with those using clopidogrel alone. Estimated relative risks vary from 0.92 to 1.93.[248, 253, 258, 260-265] These results are likely influenced by confounding by indication. Confounding by indication is introduced when more severely ill patients with a worse prognosis are more likely to receive PPIs than healthier patients. Furthermore, some published observational studies may have suffered from immortal time bias.[260,266] Both biases could distort the studied association in either direction.

Other studies failed to show an interaction between the use of PPIs and clopidogrel.[248, 252, 253, 258, 264, 267, 268] Recently, results of a *post hoc* analysis of a randomized trial revealed no association between PPI use and the risk of the primary CV endpoint for patients treated with clopidogrel or the novel thienopyridine prasugrel (a prodrug also requiring metabolization through CYP enzymes).[258] The main limitation of this randomized trial was that use of a PPI was not randomized. Preliminary analysis (pre-specified sample size and follow-up time not reached) of the unpublished Clopidogrel and the Optimization of Gastrointestinal Events (COGENT) trial, a randomized double-blind trial of omeprazole 20 milligram (mg) vs. placebo in patients taking dual therapy (clopidogrel and aspirin) demonstrated no significant difference in CV events between both study arms (hazard ratio = 1.02, 95% CI: 0.70-1.51).[252]

As a result of the potential clinical consequences for a large patient group at risk for both recurrent CV as well as UGI events, residual uncertainty about this potential drug-drug interaction should be minimized. Therefore, we conducted a nested case-control study using data from the PHARMO Record Linkage System (RLS) (1999-2008) to quantify the

association between use of PPIs and recurrent MI in the absence or presence of clopidogrel, while addressing the issues of both study design (avoidance of immortal time bias) and residual confounding (using past exposure to PPIs as the reference category and propensity score-based adjustments).

Methods

Study design

A population-based nested case-control study (1999-2008) was conducted within a cohort of patients admitted for acute MI during the study period.

Setting

The study was conducted using data from the PHARMO RLS. This system comprises drug-dispensing records mostly from community pharmacies and hospital discharge records of more than three million inhabitants of 50 demographically defined areas in the Netherlands. For all participants, the computerized drug-dispensing histories contain data concerning the name of the dispensed drug, dispensing date, dispensed amount, prescribed dosing regimens, and the legend duration of use (prescription length). All drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification.[60] The hospital records include detailed information concerning discharge diagnosis, procedures, dates of hospital admission and discharge, discharge destination (or death in the hospital before discharge). Diagnoses are consistently classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) during the entire study period. For a detailed description of the database we refer to a previous publication.[269]

Study cohort

The study cohort included all patients in the PHARMO RLS who were hospitalized between January 1st, 1999 and December 31st, 2008 for a primary diagnosis of acute MI. Cohort entry was date of discharge from hospital of an acute MI, registered as a primary discharge diagnosis code 410 according to ICD-9-CM. Secondary diagnoses were not queried, because it is likely that prevalent MI events (comorbidity) are recorded as secondary diagnosis. For reasons of the dynamic study population, patients were required to have had one prescription filled at least one year preceding the date of cohort entry (i.e. one year of valid database history) to allow uniform assessment of the presence of comorbidity and confounding factors. Patients were followed from cohort entry until diagnosis of recurrent MI, last filled prescription, or the end of the study period (31st December 2008), whichever came first.

Case selection

The study outcome was hospitalization for a subsequent acute MI, registered as primary diagnosis ICD-9-CM code 410. Only the first encountered recurrent acute MI during follow-up was included in the analysis. The date of rehospitalization for the MI was used as index date. To avoid misclassification of the exposure, we required a 30-day period between discharge from baseline MI and recurrent MI as outpatient time was needed to observe filling of outpatient prescriptions. In a sensitivity analysis, we used the requirement of a 90-day period between discharge from baseline MI and recurrent MI.

Control selection

For each patient readmitted for acute MI, controls were randomly selected from the cohort, matched on gender, age (same year of birth), being at risk of a recurrent MI, and calendar time by means of incidence density sampling.[270] Only those controls were considered to be at risk of developing a recurrent MI when they had a baseline acute MI ≥ 30 days prior to the index date.

Definition of exposure

Drug exposure data were obtained from outpatient drug dispensing files of community pharmacies, as recorded in the PHARMO RLS. The exposures of interest were clopidogrel and PPIs. PPIs included in the analyses were omeprazole, pantoprazole, lansoprazole, rabeprazole, and esomeprazole. Duration of use was obtained by dividing the total amount of dispensed units by the prescribed amount per day. We calculated the end of each prescription by adding the duration to the dispensing date.

Clopidogrel use was classified at the index date as either 'no' use (no use or use at least 30 days before index date), 'past' use (end of prescription between seven and 30 days before the index date), or 'current' use (use at index date, or end of prescription less than seven days before index date). As half-time values of PPIs are short (a few hours), the current, past, and no use of PPIs was defined differently: 'no' use (no use or use at least 30 days before index date), 'past' use (end of prescription between three and 30 days before index date), and 'current' use (use at index date, or end of prescription less than three days before index date). To avoid protophatic bias, only prescriptions dispensed at least one day before index date were considered 'current' use. In sensitivity analyses, the definition of past PPI use (which was the reference) was adjusted to use between 3 and 90 days or between 14 and 90 days preceding the index date. In the latter case the definition of 'current' PPI switched to use at index date, or end of prescription less than 14 days before index date. The study is not subject to immortal time bias as the outcome under study could be assessed equally for cases and controls after the 30- or 90-day period.

Covariates

At baseline, we considered the following factors as potential covariates: percutaneous transluminal coronary artery angiography (PTCA) within 30 days of baseline MI, prior hospitalization for cardiogenic shock, congestive heart failure, cancer, cerebrovascular disease, acute renal failure, chronic renal failure, cardiac dysrhythmia (including atrial fibrillation), or UGI ulcer. The covariate diabetes mellitus was a combination of prior hospitalization for diabetes mellitus and antidiabetic drug use. As a proxy for (the degree of) comorbidity, we aggregated all prescriptions per ATC-code in the one year preceding cohort entry and we refer to this 'score' as the number of different prescriptions. In addition, we considered use of commonly prescribed CV medications (anti-hypertensive drugs, low-dose acetylsalicylic acid, β-adrenergic antagonists, digoxin, and lipid lowering drugs) or NSAIDs at baseline. We defined comorbidity and medication at baseline rather than at recurrent MI to avoid adjustment on intermediates in the pathway from exposure to outcome. Medications inducing or inhibiting cytochrome P450 2C19 or cytochrome P450 3A4 (directly affecting levels of clopidogrel and PPIs)[271], as well as standard secondary prevention medications such as lipid lowering drugs and anti-hypertensive agents were assessed at the index date. Furthermore, days of follow-up (number of days between date of discharge of baseline MI and index date) and length of hospital stay for the baseline MI were also considered as covariates.

Statistical analysis

Descriptive analyses were performed to describe the cohort with regard to baseline characteristics. Prescription rates for PPIs and clopidogrel for the cohort were calculated per calendar month to assess prescription time-trends. Survival rates were estimated using the Kaplan-Meier method and evaluated the probability of recurrent MI free survival during follow-up.

Baseline characteristics were compared between cases with a recurrent MI and controls without recurrent MI in patients unexposed to PPIs, and between all PPI users and PPI non-users in patients without recurrent MI using univariate conditional logistic regression analyses. We applied conditional logistic regression analysis to estimate matched and adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for the association between recurrent MI and exposure to PPI. The analyses were performed in two subgroups: (i) current clopidogrel users, and (ii) clopidogrel non-users to examine whether there was a true drug-drug interaction between clopidogrel and PPIs. The reference group included patients with no prescription of PPIs in the previous month (non-PPI users). A second analysis that more effectively deals with confounding by indication was performed applying past PPI users as the reference category. In the adjusted model we included all factors that changed the unadjusted odds ratio with more than 10%. To test the robustness of our finding, we examined the effect of extension of the past PPI exposure window on the observed associations as a sensitivity analysis. Finally, we estimated the OR for current use of omeprazole and esomeprazole, using current pantoprazole as the reference group.

As the use of PPIs was not randomly assigned, we developed a propensity score (summary exposure risk score). The propensity score represents the likelihood of exposure to a PPI for each individual patient.[272] The propensity score for use of PPI was developed using logistic regression modeling. The log odds of the probability that a patient received a PPI at any point of time during follow-up was modeled as a function of all previously described baseline covariates and was included in our dataset as a separate confounder. The PPI propensity score was only included in the adjusted analysis when it changed the odds ratio with more than 10%, unless we adjusted for individual covariates, to avoid double adjustment for the same covariate.

Statistical significance was assumed for two-sided P-values < 0.05. All statistical analyses were performed using SPSS software version 15.0 (SPSS Inc, Chicago, Il, USA).

Results

The initial study population comprised 27,513 patients who were admitted to the hospital with an acute MI during follow-up. After exclusion of patients of whom not one year of valid data before baseline MI was available, the final cohort comprised 23,655 patients. The mean age was 64.7 (± standard deviation (s.d.) 13.2) years and 15,897 (67.2%) were men. The median follow-up time after discharge was 42.6 months (interquartile range (IQR) 16.8-71.7 months). Comorbidity at baseline was substantial: 4.4% of patients had been hospitalized for cancer, 3.3% for cardiac dysrhythmia, and 2.8% for cerebrovascular disease. Prevalence of diabetes mellitus was 21.6%. The median number of distinct prescribed drugs in the one year before cohort entry was 5 (IQR 2-9 prescriptions) (Table 12.1; column 2). At baseline, 10.5% of the patients used PPIs and 315 patients (1.3%) used clopidogrel.

Table 12.1: Characteristics of cohort patients (column 2), of those readmitted to the hospital with MI (cases) vs. their controls (column 3 and 4), and of PPI users vs. non-PPI users in the case-control setting (column 5 and 6)

	Total	Cases with recurrent MI	Controls without recurrent MI	PPI users	Non-PPI users
	n (%)	n (%)	n (%)	n (%)	n (%)
		In patients unexposed to PPIs		*In controls without recurrent MI*	
Total	23,655 (100)	616 (100)	126,817 (100)	69,313 (100)	126,817 (100)
Mean age (SD)	64.7 (13.2)	66.1 (13.2)	66.3 (10.4)	68.1 (10.3)	66.3 (10.4)
Median follow-up time in months (IQR)	42.6 (17-72)	11.4 (4-29)*	29.5 (13-52)*	34.5 (16-58)*	29.5 (13-52)*
Median number of different prescriptions (IQR)**	5 (2-9)	5 (2-8)*	3 (1-6)*	6 (3-10)*	3 (1-6)*
Median length of stay baseline MI in days (IQR)	7 (4-10)	7 (5-9)	7 (5-10)	7 (5-10)*	7 (5-10)*
Male sex	15,897 (67.2)	436 (70.8)	72,020 (85.1)	55,377 (79.9)	72,020 (85.1)
PTCA during or within 30 days of baseline MI	7,889 (33.4)	126 (20.5)	23,808 (28.1)	21,851 (31.5)*	23,808 (28.1)*
Presence of diabetes mellitus	5,100 (21.6)	125 (20.3)*	13,774 (16.3)*	14,022 (20.2)*	13,774 (16.3)*
Hospitalizations before baseline MI:					
Cardiogenic shock	12 (0.1)	1 (0.2)	31 (0.0)	37 (0.1)	31 (0.0)
Congestive heart failure	551 (2.3)	14 (2.3)*	858 (1.0)*	961 (1.4)*	858 (1.0)*
Cancer	1,045 (4.4)	13 (2.1)	2,380 (2.8)	2,710 (3.9)*	2,380 (2.8)*
Cerebrovascular disease	651 (2.8)	11 (1.8)	1,378 (1.6)	1,836 (2.6)*	1,378 (1.6)*
Acute renal failure	32 (0.1)	0 (0.0)	49 (0.1)	84 (0.1)*	49 (0.1)*
Chronic renal failure	210 (0.9)	4 (0.6)	449 (0.5)	667 (1.0)*	449 (0.5)*
Cardiac dysrhythmia	775 (3.3)	18 (2.9)	1,898 (2.2)	1,960 (2.8)*	1,898 (2.2)*
UGI ulcer and gastritis	153 (0.6)	1 (0.2)	101 (0.1)	630 (0.9)*	101 (0.1)*
Medication use at the time of baseline MI:					
Angiotensin-converting-enzyme inhibitor	3,141 (13.3)	84 (13.6)*	9,122 (10.8)*	8,601 (12.4)*	9,122 (10.8)*
Angiotensin-receptor antagonist	1,787 (7.6)	38 (6.2)*	4,200 (5.0)*	5,034 (7.3)*	4,200 (5.0)*
Acetylsalicylic acid	5,364 (22.7)	153 (24.8)*	16,181 (19.1)*	17,120 (24.7)*	16,181 (19.1)*
β-Adrenergic antagonist	5,531 (23.4)	148 (24.0)*	16,915 (20.0)*	16,891 (24.4)*	16,915 (20.0)*
Calcium-channel antagonist	3,150 (13.3)	92 (14.9)*	9,257 (10.9)*	10,031 (14.5)*	9,257 (10.9)*
Digoxin	592 (2.5)	14 (2.3)	1,204 (1.4)	1,311 (1.9)*	1,204 (1.4)*
Spironolactone	336 (1.4)	5 (0.8)	455 (0.5)	559 (0.8)*	455 (0.5)*
Lipid lowering drugs	4,144 (17.5)	113 (18.3)*	13,034 (15.4)*	13,307 (19.2)*	13,034 (15.4)*
Thiazide diuretic	806 (3.4)	16 (2.6)	2,080 (2.5)	1,958 (2.8)	2,080 (2.5)
Other diuretic, excluding thiazide	2,713 (11.5)	63 (10.2)	5,299 (6.3)	6,094 (8.8)*	5,299 (6.3)*
Non-steroidal anti-inflammatory drug	1,720 (7.3)	30 (4.9)	3,910 (4.6)	6,384 (9.2)*	3,910 (4.6)*
Medication use at recurrent MI					
Angiotensin-converting-enzyme inhibitor		213 (34.6)	29,328 (34.6)	24,817 (35.8)	29,328 (34.6)
Angiotensin-receptor antagonist		50 (8.1)	9,301 (11.0)	9,535 (13.8)*	9,301 (11.0)*
Acetylsalicylic acid		408 (66.2)	56,621 (66.9)	45,511 (65.7)	56,621 (66.9)
β-Adrenergic antagonist		377 (61.2)	52,200 (61.7)	43,575 (62.9)	52,200 (61.7)
Calcium-channel antagonist		116 (18.8)	14,252 (16.8)	13,727 (19.8)*	14,252 (16.8)*
Lipid lowering drugs		356 (57.8)	54,475 (64.4)	45,776 (66.0)*	54,475 (64.4)*
Thiazide diuretic		24 (3.9)	2,690 (3.2)	2,672 (3.9)	2,690 (3.2)
Other diuretic, excluding thiazide		130 (21.1)*	12,606 (14.9)*	14,510 (20.9)*	12,606 (14.9)*
Cytochrome P450 2C19 inhibitor(s)		7 (1.1)	679 (0.8)	676 (1.0)*	679 (0.8)*
Cytochrome P450 2C19 inducer(s)		13 (2.1)	1,043 (1.2)	2,973 (4.3)*	1,043 (1.2)*
Cytochrome P450 3A4 inhibitor(s)		56 (9.1)	5,725 (6.8)	5,854 (8.4)*	5,725 (6.8)*
Cytochrome P450 3A4 inducer(s)		8 (1.3)	823 (1.0)	724 (1.0)	823 (1.0)

PPI, proton pump inhibitor; MI, myocardial infarction.
The numbers in columns three to six (reflecting the case-control setting) can be larger than the total number in column two (reflecting the cohort setting) due to the control sampling method.
** Median number of different prescriptions on full ATC-level one year prior to cohort entry.*
*** Index date: date of recurrent MI. Only available for the case-control set.*

Figure 12.1 shows that prescription rates of both PPIs and clopidogrel changed over time between 1st January 1999 and 31st December 2008, illustrating the increased use of the study drugs over a decade. Within the study cohort, 1,247 patients were readmitted to the hospital with an acute MI. The risk of a recurrent MI at least 30 days after discharge was 2.8% (95% CI: 2.6% - 3.0%) in the first year, and 10.3% (95% CI: 9.1% - 11.5%) in 10 years. Of the cases with a recurrent MI, 1,224 (98.2%) could be matched to at least one control without a recurrent MI. Characteristics of cases and controls (in the unexposed group to PPIs) are depicted in Table 12.1 (columns 3 and 4). As expected, cases were more likely to have been hospitalized for co-morbidities associated with an increased risk of recurrent MI, such as congestive heart failure and diabetes mellitus. At baseline, cases used several types of CV drugs more frequently, for instance angiotensin-converting-

enzyme (ACE) inhibitors and lipid lowering drugs. To understand whether selective prescribing (channeling) of PPIs to persons at increased risk of recurrent MI occurred, we assessed the presence of risk factors in PPI users and PPI non-users (in patients who did not develop a recurrent MI) (Table 12.1; columns 5 and 6). Patients using PPIs were older, were more frequently men, had been hospitalized more frequently prior to cohort entry for several co-morbid conditions, and more frequently used CV medications at baseline.

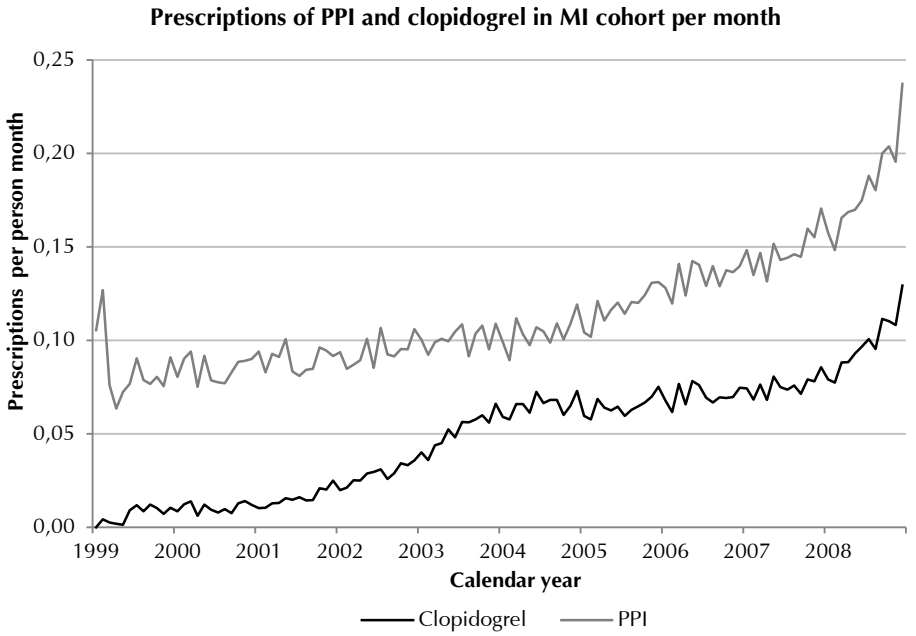

Figure 12.1: Prescriptions of proton pump inhibitor (PPI) and clopidogrel in myocardial infarction (MI) cohort per month.

Number of prescriptions per person month for PPIs and clopidogrel calculated per calendar month during study period in cohort of acute MI patients (N = 23,655).

Among current clopidogrel users, a significant association was observed between current PPI use and recurrent MI when compared with PPI non-use (OR: 1.62, 95% CI: 1.15-2.27). When applying past PPI use as the reference category rather than PPI non-use, we found no association between recurrent MI and current use of PPI (OR: 0.95, 95% CI: 0.38-2.41) (Table 12.2). Repeated analyses with variations in the definition of past PPI use (3-90 days or 14-90 days) did not affect the study findings appreciably; OR: 1.15, 95% CI: 0.51-2.61, and OR: 1.34, 95% CI: 0.50-3.62, respectively.

Among clopidogrel non-users, current use of PPI was associated with recurrent MI when compared with PPI non-use (OR:1.38, 95% CI: 1.18-1.61). When applying past PPI users as the reference category, a weak association between recurrent MI and current use of PPI was found (OR: 1.22, 95% CI: 0.79-1.88), although the latter's confidence interval cross the null, which was likely due to insufficient power (Table 12.3).

The analysis by type of PPI among current clopidogrel users showed that pantoprazole was most frequently used, followed by omeprazole and esomeprazole. Lansoprazole and rabeprazole were rarely used. Using current pantoprazole as the reference category, current use of omeprazole and of esomeprazole were not associated with an increased risk of recurrent MI (respectively, OR: 1.07, 95 % CI: 0.58-1.99 and OR: 0.83, 95 % CI: 0.40-1.69, respectively) (Table 12.4).

Table 12.2: Association between current clopidogrel plus current PPI and recurrent MI compared with current clopidogrel without PPI and to current clopidogrel with past PPI

	Cases n	Controls n	$OR_{matched}$ (95% CI)	$OR_{adjusted}$ (95% CI)
Total	1,224	153,967		
Current clopidogrel / No PPI	90	11,147	1 (ref)	1 (ref)
Current clopidogrel / Current PPI	78	4,715	1.89 (1.37-2.63)	1.62 (1.15-2.27)#
Other*	1,056	138,105		
Current clopidogrel / Past PPI	6	436	1 (ref)	1 (ref)
Current clopidogrel / Current PPI	78	4,715	1.15 (0.46-2.86)	0.95 (0.38-2.41)±
Other**	1,140	148,816		

PPI, proton pump inhibitor; MI, myocardial infarction.
**No or past clopidogrel, or past PPI use.*
***No or past clopidogrel, or no PPI use.*
 # Adjusted for follow-up time in days and total number of prescriptions one year prior to baseline MI.
± Adjusted for follow-up time in days.

Table 12.3: Association between current PPI use and recurrent MI compared with no PPI and to past PPI use in the absence of clopidogrel

	Cases n	Controls n	$OR_{matched}$ (95% CI)	$OR_{adjusted}$ (95% CI)
Total	1,224	153,967		
No clopidogrel / No PPI	766	110,002	1 (ref)	1 (ref)
No clopidogrel / Current PPI	237	23,335	1.56 (1.34-1.81)	1.38 (1.18-1.61)#
Other*	221	20,630		
No clopidogrel / Past PPI	25	2,941	1 (ref)	1 (ref)
No clopidogrel / Current PPI	237	23,335	1.22 (0.79-1.88)	1.22 (0.79-1.88)χ
Other**	962	127,691		

PPI, proton pump inhibitor; MI, myocardial infarction.
**Current or past clopidogrel, or past PPI use.*
***Current or past clopidogrel, or no PPI use.*
 # Adjusted for total number of prescriptions one year prior to baseline MI.
χ No adjustments.

Table 12.4: Association between current clopidogrel plus specific current PPI use and recurrent MI compared with current clopidogrel plus current pantoprazole

	Cases n	Controls n	$OR_{matched}$ (95% CI)	$OR_{adjusted}$** (95% CI)
Total	1,224	153,967		
Current clopidogrel + pantoprazole	36	2,271	1 (ref)	1 (ref)
Current clopidogrel + omeprazole	26	1,339	1.03 (0.57-1.84)	1.07 (0.58-1.99)
Current clopidogrel + esomeprazole	13	827	0.96 (0.48-1.92)	0.83 (0.40-1.69)
Current clopidogrel + lansoprosole or rabeprazole	2	186	-	-
Other*	1,147	149,344		

Combinations of PPIs were excluded.
PPI, proton pump inhibitor; MI, myocardial infarction.
**No or past clopidogrel, or no or past PPI use.*
***Adjusted for follow-up time in days and propensity score.*

Discussion

This population-based cohort study showed that the association between clopidogrel –PPI co-therapy and risk of recurrent MI is highly affected by confounding by indication[273], which may explain the contrasting results in the literature. To illustrate the problem of confounding we compared current PPI users to none or past PPI users in the absence of clopidogrel. To deal with the problem of confounding by indication, we compared current use of clopidogrel plus current use of PPI not only to current clopidogrel without PPIs, but also to current clopidogrel use plus past use of PPIs, which reduces confounding by indication. When current PPI use was compared with past PPI use the association disappeared, suggesting that the observed association between current PPI use and recurrent MI when PPI non-use was the reference, may have been the result of residual confounding.

Our findings are in line both with other observational studies showing an increased risk among PPI users when compared with PPI non-users[260-265], and those that did not find such an association if better control of confounding was applied.[252, 258, 264, 274] In observational studies or *post hoc* analyses in randomized controlled trials, the use of PPI is by definition not randomly assigned, most likely leading to confounding by indication. It is arguable whether adequate adjustment for this harmful type of confounding is possible since much of the confounding will be subtle and unmeasurable. Design choices and progressive adjustment techniques can be used to avoid residual confounding, as we have shown. By careful selection of the study design one can match cases and controls on important covariates, including calendar time. We illustrated the increased use of the study drugs over a decade (Figure 12.1), and thereby the importance of matching on index date (thus calendar time) as potential confounder. In addition, one can use a so-called 'active comparator' as reference, such as past users of PPIs instead of none users. For adjustment, high-dimensional propensity scores[264], summary disease risk scores (probability of short term mortality)[261], or conventional propensity scores[258, 265] can be applied. Table 12.5 provides an overview of techniques used in other observational studies on this topic to deal with confounding by indication.

Our study further confirms the relevance of confounding, illustrated by the fact that PPI users had more comorbidity and used more co-medication than PPI non-users at baseline and also by the results of the analysis in clopidogrel non-users. The increased risk for recurrent MI with current PPI use (OR 1.38, 95% CI: 1.18-1.61) compared with no PPI use in the absence of clopidogrel therapy provides further support for this. Another explanation would be that PPIs have a harmful effect irrespective of clopidogrel status. We are aware of two studies that conducted similar analysis in clopidogrel non-users that also showed significantly elevated risks with PPI use (adjusted OR 1.29 and 1.55) compared with PPI non-use.[268, 275] In two other observational studies, however, no significant increase in CV events was shown in patients prescribed PPIs without clopidogrel.[260, 276]

We addressed the confounding issue by all possible design and adjustments measures, but still the comparison against non-use of PPI seemed confounded. Applying past PPI use as active comparator changed the association from increased to no effect and was the most powerful approach to deal with channeling of PPIs, more than adjustment for the propensity score. The propensity score did not have large explanatory power in this study due to the fact that relatively little clinical information was available to construct the score.

Our study is internally valid as we used a population-based design, so selection bias was unlikely as all cases and controls came from the same source population. The same pertains to information bias because data were gathered prospectively without knowledge of the hypothesis studied. The method to control for confounding was discussed previously. The database is proven valid for research as the diagnoses are labeled with ICD-9-CM codes in each hospital by official coding personnel from the national registry of hospitalization discharge records and linked to pharmacies with complete information on outpatient dispensing. In the Netherlands, patients usually go to one pharmacy because of billing purposes (invoices being directly sent to insurance without the need to prepay by patient) and medication surveillance. The exposure drugs, clopidogrel and PPIs, are dispensed through regular pharmacies. With regard to external validity, the individuals captured in the database are representative for the entire population of the Netherlands in terms of age, gender, socio-economic background, morbidity and mortality, drug use, and geographic distribution.

This study adds to the existing literature because we revealed the difficulties to deal with confounding by indication in observational studies and we adjusted for confounding in the most optimal way by applying past PPI use as the reference category. Furthermore, few other studies could account for the use of low-dose aspirin as important risk factor for recurrent MI.[264, 265] We avoided immortal time bias by assigning exposure to the category it belongs to and not using follow-up time to define exposure. Immortal time bias alludes to the fact that the outcome under study cannot be assessed when follow-up time is used to define the exposure status. We used a time varying exposure assessment, whereas some other cohort studies applied a fixed exposure status[258, 265], which leads to misclassification of exposure at the index date (e.g. patients were defined at baseline as PPI non-users irrespective of changes in PPI use during follow-up). In addition, we used an European database whereas many published studies so far were conducted in North-America. None of the PPIs were available over the counter during the study period, and we have illustrated that there was no difference in the risk of recurrent MI between esomeprazole, omeprazole, and pantoprazole.

There are several important limitations to this analysis. First, we were unable to study actual drug utilization and adherence to dispensed drugs, because only dispensing data were available in the database instead of more reliable proxies for drug use. Second, using the past PPI group as reference, we may compare current PPI users to past PPI users who had not been fully adherent to the prescribed PPI and therefore still had medication available and were actually also current PPI users at the time of the recurrent MI. To address this point, we conducted several sensitivity analyses varying the time window to define past PPI use and this did not affect the estimates. In addition, although the internal validity may be jeopardized by noncompliance of the patient, this is unlikely to have affected the comparison between active compounds (e.g. omeprazole/esomeprazole compared with pantoprazole). Third, as most persons continue PPIs once started, applying past PPI use as reference reduces study power substantially (resulting in wide confidence intervals). Finally, residual confounding remained due to lack of data on important cardiac risk factors, such as smoking status, lipoproteins, or type of coronary stents, which was likely providing an overestimation of the effect measure and this was illustrated when applying PPI non-use as the reference.

In conclusion, this study provides a unique angle on the association between clopidogrel –PPI co-therapy and risk of recurrent MI by using several techniques to deal with confounding by indication and other methodological issues. Among clopidogrel users, current use of PPIs was associated with an increased risk of recurrent MI when compared

with PPI non-use, but not when compared with past PPI use, which shows the magnitude of the confounding by indication that is present. In clopidogrel non-users, current PPI use was also associated with an increased risk of recurrent MI when compared with PPI non-use. This study thus demonstrates that previously reported associations between PPI-clopidogrel co-therapy and risks of recurrent MI are influenced by confounding. It further demonstrates that such confounding can be (at least partly) circumvented by careful selection of study design and conventional adjustments techniques. Further work should concentrate on well-conducted prospective randomized trials to dissolve the confusion around this controversial drug-drug interaction.

Table 12.5: Summary of used methods to deal with confounding in observational studies assessing the effect of PPI on CV events in clopidogrel users, excluding restrictions in study design

Authors	Study type	Study population	Outcome	Methods to deal with confounding
Simon et al.[248]	Prospective cohort	Patients with acute MI	Death, MI, stroke	- Multivariable adjustments - Propensity analysis for CYP2C19 loss-of-function-alleles which was used to match 5 controls for each patient with 2 variant alleles
Bhatt et al.[252]	Double-blind randomized trial	Patients with ACS undergoing coronary stent placement	MI, stroke, CABG, PCI, CV death	- Randomization
Ray et al.[277]	Retrospective cohort study	Patients hospitalized for MI, coronary artery revascularization, or unstable AP on clopidogrel	serious CV disease ((non)fatal MI, stroke, other CV death).	- Multivariable adjustments - Propensity score for the use of PPI was converted in deciles and included as variable in model
O'Donoghue et al.[258]	Retrospective cohort within RCT	Patients with ACS undergoing PCI	CV death, MI, stroke	- Multivariable adjustments - Propensity score for the use of PPI and strata matched on this score
Ho et al.[260]	Retrospective cohort study + case-control study	Patients with ACS on clopidogrel	All-cause mortality, rehospitalization for ACS	- Multivariable adjustments - matched on duration of follow-up
Juurlink et al.[278]	Nested case-control	Patients with acute MI on clopidogrel	Recurrent MI, death	- Multivariable adjustments - Matched on age, PCI, date of hospital discharge, predicted probability of short-term mortality
Pezalla et al.[262]	Retrospective cohort study	Patients adherent to clopidogrel	Acute MI	- Subgroup analysis; restriction to patients who all had diagnosis of ischemic heart disease, congestive heart failure, hypertension, hyperlipidemia, and diabetes before the start of clopidogrel therapy.
Stanek et al.[263]	Retrospective cohort study	Patients adherent to clopidogrel following coronary stenting	CV events (MI, unstable AP, TIA / stroke, coronary vascularization, CV death)	- Multivariable adjustments
Rassen et al.[264]	Retrospective cohort study	Patients undergoing PCI or hospitalized for ACS on clopidogrel	MI, revascularization, all-cause mortality	- Multivariable adjustments - High-dimensional propensity score and strata matched on this score (1:1)
Stockl et al.[279]	Retrospective cohort study	Patients with MI or coronary stent on clopidogrel	Acute MI	- Propensity score and strata matched on this score (1:1)
Collet et al.[267]	Prospective cohort	Survivors of MI (< 45 years)	CV death, non-fatal MI, urgent revascularization	- Multivariable adjustments
Dunn et al.[268]	Retrospective cohort within RCT	Patients undergoing PCI	Death, MI, Stroke (1 year)	- No information on adjustment to covariates

MI, Myocardial infarction; ACS, Acute Coronary Syndrome; CABG, Coronary artery bypass graft; PCI, Percutaneous coronary intervention; CV, Cardiovascular; AP, Angina pectoris; PPI, Proton pump inhibitor; RCT, Randomized controlled trial; TIA, Transient ischemic attack.

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Submitted

Chapter 13

Has outcome misclassification of upper gastrointestinal bleeding an impact on risk estimates? A validation study in four European electronic healthcare databases

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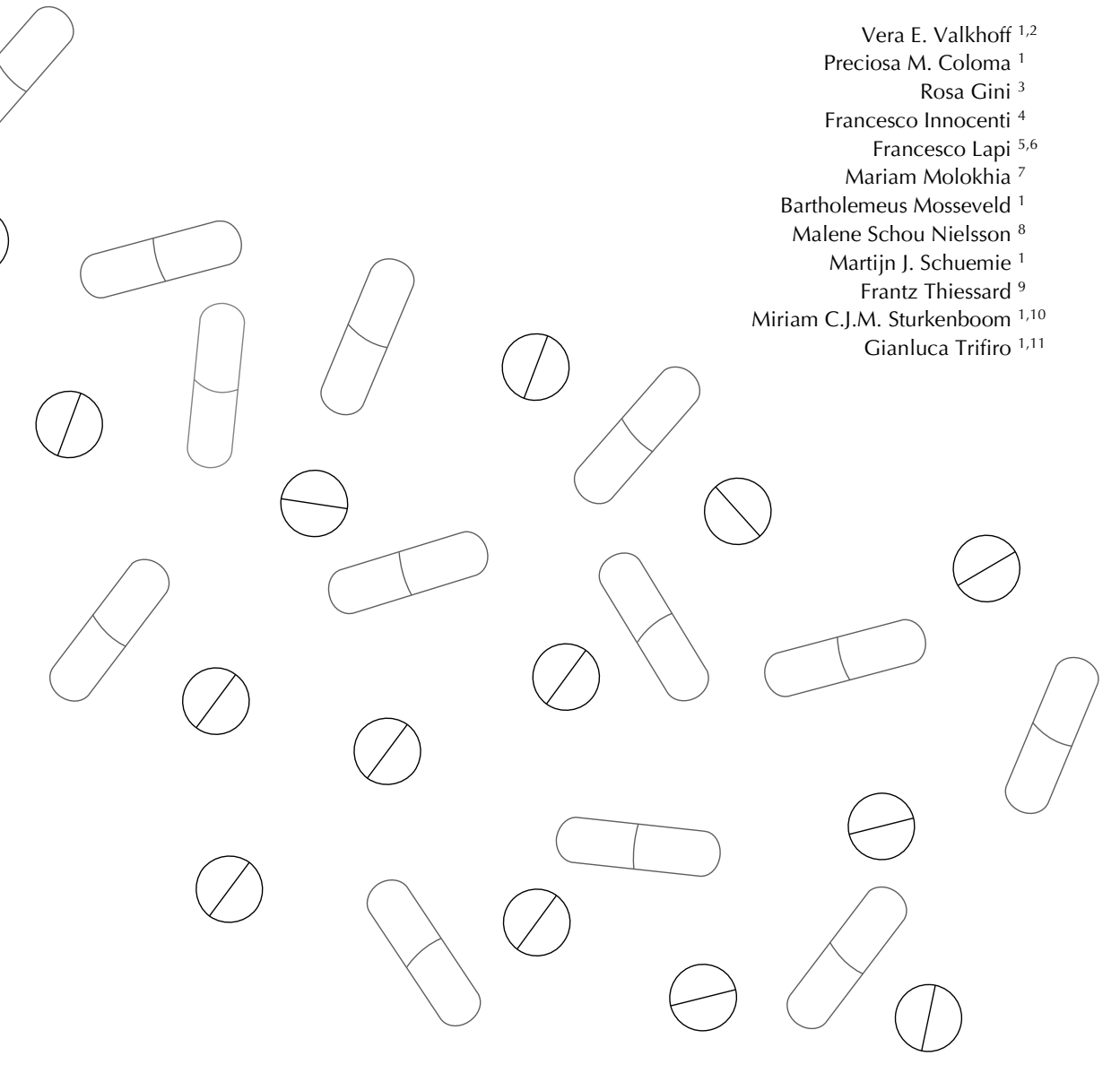


Abstract

Background

Validation of upper gastrointestinal bleeding (UGIB) is warranted when using electronic healthcare databases (DB).

Aim

We evaluated the accuracy of various disease coding systems and unstructured clinical information (free text) for identifying patients with UGIB from electronic healthcare data and the implication of misclassification on estimation of risk of UGIB during drug use.

Methods

A validation study was conducted in the following DBs: (i) IPCI (Netherlands); (ii) HSD (Italy); (iii) ARS Tuscany (Italy); and (iv) Aarhus (Denmark). The first two are primary care DBs, the latter are administrative DBs. Three diagnosis coding systems were used: (i) International Classification of Diseases (ICD) 9th revision (HSD, ARS); (ii) ICD-10th revision (Aarhus); and (iii) International Classification of Primary Care (ICPC) (IPCI). In addition, UGIB-related key words were used in IPCI and HSD. A random sample of 200 potential UGIB cases was selected from each DB (400 for IPCI) and reviewed manually by medically trained assessors. Positive predictive values (PPV) for UGIB were calculated. Incidence rate ratios (IRR) were estimated for a set of drugs known to be associated, and not known to be associated, with UGIB and the effect of misclassification evaluated using varying thresholds for PPV.

Results

The PPV was 23% (95% CI: 17%-30%) and 25% (95% CI: 18%-31%) in IPCI for free text and ICPC codes, respectively. The PPV was 92% (95% CI: 88%-97%) for codes and 50% (95% CI: 37%-63%) for free text only in HSD. The overall PPV for the ICD-9 based system in ARS was 77% (95% CI: 71%-83%) and 84% for the ICD-10 based coding system (95% CI: 78%-89%) in Aarhus. In general, the impact of codes with low PPVs on estimation of IRR was small, but when considering the most specific outcome definition the precision was lower.

Conclusions

There are differences in the accuracy of automated case identification when using various healthcare databases (hospitalization claims vs. medical records) that stem from differences in the coding systems and in the type of data collected. Use of codes with lower PPV resulted in only small changes in the estimated relative risks of drugs known to be associated with UGIB.

Introduction

Electronic healthcare databases (DB) are frequently used data sources for investigating adverse clinical outcomes that occur during use of certain drugs.[280] The advantages of using DB rely on the fact that real-world data are captured on a large scale, allowing for cost-efficiency and flexibility in study design to analyze the risk of adverse events associated with a wide range of drugs. Both medical record databases and administrative/claims databases have been used to characterize healthcare utilization patterns as well as monitor patient outcomes.[281, 282] The use of such databases for proactive drug safety surveillance is gaining worldwide interest.[18, 283, 284]

One of the most important drug-induced adverse events is upper gastrointestinal bleeding (UGIB), which accounts for many adverse drug reaction (ADR)-related hospitalizations (e.g. non-steroidal anti-inflammatory drugs-related UGIB).[285] The accuracy of the diagnosis codes for the identification of UGIB has been previously assessed in several studies,[181-183, 286-288] but only for two disease coding terminologies: International Classification of Diseases (ICD) - 9th revision and READ codes. To our knowledge, no validation studies have been conducted so far to evaluate the accuracy of International Classification of Primary Care (ICPC) and ICD-10th revision codes for ascertainment of UGIB.

In this study, we determined the accuracy of several terminology-specific codes and unstructured clinical information (i.e. free text) in the identification of UGIB cases from electronic healthcare data. In addition, we investigated the impact of outcome misclassification on the estimation of risk of UGIB during use of five drugs known to be associated with, and five drugs known to be not associated with UGIB.[289] This validation study was conducted within the context of the European Commission-funded EU-ADR Project (*Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge*; http://www.euadr-project.org), a computerized integrated system of European databases geared towards the early detection of drug safety.[18]

Methods

Data sources

The EU-ADR platform comprises anonymized healthcare data from eight European DBs. Four DBs participated in this validation study and conducted review of hospitalization charts or general practitioner (GP) records. These four DBs are located in three European countries: two GP DBs (Integrated Primary Care Information (IPCI), Netherlands,[102] and Health Search/CSD Patient DB (HSD), Italy[146]), and two administrative claims DBs (ARS Tuscany, Italy[290] and Aarhus University Hospital Database, Denmark[291]). In these countries, all citizens are registered with a primary care practice, which maintains computerized records of all relevant medical information and drug prescriptions. In Tuscany, all hospitalizations reimbursed by the Regional Health Service are recorded in a centralized DB with a main diagnosis coded at discharge and all reimbursed drugs are recorded at dispensing. In Aarhus, data are obtained from the following two DBs; the Danish National Patient Registry (DNPR), which records all discharges from all non-psychiatric hospitals (since 1977) and emergency room and outpatient clinic visits (since 1995) in Denmark, and the Aarhus University Prescription Database, which records all reimbursed medications dispensed at all community pharmacies of the North Denmark Region and the Cen-

tral Denmark Region. The Italian databases (HSD and ARS) record medical events using the ICD-9th Revision, Clinical Modification (ICD-9-CM), Aarhus DB uses the ICD-10th revision,[59] and IPCI, the International Classification for Primary Care (ICPC).[61] The primary care DBs HSD and IPCI also register clinical notes from general practitioners or medical specialists as narratives, which may include records of referrals to medical specialists. All DBs use the Anatomical Therapeutic Chemical (ATC) classification system to register prescriptions (IPCI and HSD) or dispensings (ARS and Aarhus).[60] These four DBs cover in total a population of 8 million European inhabitants during the study period ranging from 1995 to 2009. All DBs have been extensively used for epidemiological research.[18]

UGIB case identification

Patients registered as having UGIB were identified through automated retrieval using diagnosis codes (listed in Table 13.1) and free text search. The process of terminology mapping and harmonization of event data extraction from different DBs in the EU-ADR project has been described in more detail in previous publications.[18, 292]

UGIB case validation

For each DB a random sample of 200 potential UGIB cases was obtained. Since the use of free text search was known to be extensive in IPCI, an additional 200 potential cases, identified via free text, were randomly selected to better explore the accuracy of free text search.

The medical records in primary care DBs (IPCI and HSD) or hospitalization charts in claims DBs (ARS and Aarhus) of the randomly selected UGIB cases were retrieved and abstracted. A standardized electronic questionnaire containing all pertinent questions, pilot-tested in the DBs and reviewed by a panel of experts, was employed in the case validation. The DBs were provided with custom-built electronic data entry software, Chameleon©, that implemented the standardized questionnaire. Medically trained assessors filled in the required data for the validation of each of the randomly selected cases according to the questionnaire. In particular, clinically relevant information was captured regarding signs/symptoms (i.e. hematemesis, melena, peptic ulcer disease), bleeding site, endoscopy findings, and potential alternative explanations, such as black stools due to ingestion of iron/ferrous-containing medications. The etiology of UGIB, if known, was likewise noted (e.g. peptic ulcer bleeding, Mallory-Weiss (MW) syndrome, angiodysplasia, Dieulafoy lesion, iatrogenic UGIB, variceal bleeding, or due to a GI malignancy).

Additionally, the date of onset of bleeding (i.e. date of first symptom/occurrence of UGIB), if documented, was retrieved ('reviewed date') to compare it with the date that was automatically detected using the coding algorithm such as date of hospitalization ('coded date'). For GP databases (IPCI and HSD) it was also indicated whether the diagnosis of UGIB was made directly by the GP alone or with additional report by a medical specialist.

Two types of validation were performed: based on judgment of a medically trained assessor in response to the questionnaire ('assessor') and based on an algorithm automatically generated from the filled questionnaire ('algorithm broad and narrow'). The potential UGIB cases were classified as: (i) definite case; (ii) non-case; or (iii) non-assessable case, if the available information was deemed insufficient to enable proper case validation (e.g. a diagnosis of gastrointestinal bleeding from unspecified location without further clinical or endoscopic information). A patient with UGIB was defined as a confirmed case if: (i)

melena or hematemesis was described and bleeding site was located in esophagus/stomach/duodenum; or (ii) gastrointestinal bleeding was mentioned in the records as being consistent with peptic ulcer disease, gastric erosions or gastritis and no source of bleeding outside the UGI tract ('algorithm broad').

Table 13.1: List of diagnostic codes (plus related label) for upper gastrointestinal bleeding case identification in electronic medical records stratified by coding system

ICD-9 (ARS, HSD)		ICD-10 (Aarhus)		ICPC (IPCI)	
530.21	Ulcer of esophagus with bleeding				
530.82	Esophageal hemorrhage				
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		

Because drug safety surveillance is the primary concern in the EU-ADR project, we focused on potentially drug-induced UGIB. Therefore, in one of the two algorithms for case validation, we have excluded the following conditions as case: MW syndrome, angiodysplasia, Dieulafoy lesion, iatrogenic UGI bleeding, variceal bleeding, or bleeding caused by a gastrointestinal malignancy ('algorithm narrow'). As primary outcome of the study,

we used the PPV derived via the algorithm for UGIB definition in general ('algorithm broad') to ensure uniformity across DBs in the case definition.

Assessment of UGIB misclassification on risk estimates

To investigate the impact of outcome misclassification on estimation of risk of drug-related UGIB, we evaluated the association between selected drugs and risk of UGIB in the entire population covered by the four DBs. Ten pre-specified drugs were studied; five of them are well-known from literature to be positively associated with UGIB (viz., heparin, acetylsalicylic acid, prednisolone, indometacin, and ibuprofen) and the other five are unlikely to be associated with UGIB, based on currently available literature (viz., simvastatin, goserelin, zopiclone, fexofenadine, and dorzolamide).[289] We employed case definitions of UGIB taking into account codes and free text with varying values of PPV: (i) 'UGIB' included all eligible codes and free text to identify patients with UGIB; (ii) 'UGIB25' included codes and free text having PPV $\geq$ 25%; (iii) 'UGIB50' included codes and free text having PPV $\geq$ 50%, and (iv) 'UGIB75' included codes and free text having PPV of $\geq$ 75%.

Statistical Analysis

For the primary analysis, we calculated the overall and code or free text-specific PPVs based on both automatic ('broad' and 'narrow' algorithm) and assessor-based validation. The overall PPV was calculated as the proportion of the number of UGIB confirmed cases out of the total number of randomly selected potential cases, together with 95% confidence intervals (95% CIs). Non-assessable cases were not included in either the numerator or the denominator for the PPV calculation.

Secondly, we calculated the difference in days between the date of UGIB as registered in the DB ('coded date') and the date of onset of UGIB based on first symptoms ('reviewed date'). This was done for the confirmed UGIB cases only.

Thirdly, a cohort design was employed to estimate incidence rate ratios (IRR) of UGIB during drug exposure to that of UGIB during non-exposure to the same drug.[293] A Mantel-Haenszel test was used to assess the differences between the incidence rates, correcting for age and sex. Data from different DBs were pooled on patient level.

Results

Overall, the four databases covered a population of 8 044 637 European inhabitants with 41,086,273 person-years of follow-up in the period 1995-2011 (distribution of follow-up time as follows: ARS 46%; HSD 15%; Aarhus 35%; IPCI 4.1%). Within this population, a total of 39 870 potential cases of UGIB were identified. The medical/hospitalization charts for 943 of the 1 000 randomly selected potential cases could be retrieved for validation: ARS: 185; HSD: 200; Aarhus: 158; IPCI: 400, subdivided in 200 records for free text and 200 records for codes. The hospitalization charts for 15 and 42 UGIB potential cases in ARS and Aarhus, respectively, were not available. Patient demographics and other characteristics of the randomly selected cases are described in Table 13.2.

Of the 943 potential UGIB cases, which were reviewed for validation, 517 (54.8%) were confirmed cases. The positive predictive value (PPV) for the coding algorithms used in ARS and Aarhus was moderate to high, with PPVs of 77% (95% CI: 71%-83%) and 84%

(95% CI: 78%-89%), respectively. For IPCI, the PPV (for both ICPC coding and text) was 24% (95% CI: 20%-29%) and for HSD (ICD-9 coding and text) it was 80% (95% CI: 74%-85%) (see Table 13.3, PPV values as calculated using broad algorithm).

Among the 18 ICD-9 codes used for UGIB identification in ARS, code 532.00 (22%) was the most frequently used code, followed by 578.9 (19%) and 531.00 (16%) with respective PPVs equal to 95%, 67%, and 83%. For HSD, UGIB cases were more frequently identified using 578.1 code (melena) (38%) and free text (30%). Aside from code 531.10 (n = 3) and code 533.00 (n = 3), the PPVs for all codes were above 93%, while the PPV for free text was much lower: 50% (95% CI: 37%-63%).

As for the extraction of UGIB events in Aarhus, the following codes had the greatest contribution: K26.0 (27%), K25.0 (24%), and K92.0 (18%), with corresponding PPVs of 98%, 92%, and 93%. Only in Aarhus was the code for hematemesis more frequently reported than the code for melena (28 vs. 13 case patients). When comparing the PPVs for the ICD-9 based systems with the ICD10-based system, code 578.9 for ICD-9 (unspecified hemorrhage of gastrointestinal tract) had a higher PPV for Italian DBs (ARS: 67%; HSD: 100%) compared with the PPV for its corresponding code for ICD-10 in Aarhus (K92.2; 60%).

Table 13.2: Characteristics of randomly selected potential UGIB case patients

	ARS		HSD		Aarhus		IPCI	
	Total n (%)	Confirmed cases n (%)	Total n (%)	Confirmed cases n (%)	Total n (%)	Confirmed cases n (%)	Total n (%)	Confirmed cases n (%)
Total	185	142	200	159	158	132	400	84
Male sex	101 (55)	84 (59)	105 (53)	84 (53)	95 (60)	80 (61)	172 (43)	44 (52)
Female sex	84 (45)	58 (41)	95 (48)	75 (47)	63 (40)	52 (40)	228 (57)	40 (48)
Mean age (years)	67.4	69.3	65.1	65.2	69.4	70.4	52.5	57.4
Age categories: (years):								
0 - 20	14 (8)	8 (6)	2 (1)	2 (1)	2 (1)	1 (1)	48 (12)	8 (10)
20 - 40	8 (4)	7 (5)	20 (10)	17 (11)	8 (5)	6 (5)	69 (17)	8 (10)
40 - 60	26 (14)	18 (10)	51 (26)	38 (24)	31 (20)	26 (20)	120 (30)	24 (29)
60 - 80	82 (44)	61 (33)	86 (43)	68 (43)	69 (44)	55 (42)	101 (25)	28 (33)
> 80	55 (30)	48 (34)	41 (21)	34 (21)	48 (30)	44 (33)	62 (16)	16 (19)
Sign of UGIB:*								
Melena	98 (53)	93 (65)	92 (46)	87 (55)	94 (59)	92 (70)	83 (21)	40 (48)
Hematemesis	42 (23)	38 (27)	24 (12)	24 (16)	78 (49)	76 (58)	60 (15)	42 (50)
Etiology of UGIB:								
MW syndrome	1 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	11 (3)	6 (7)
Angiodysplasia	3 (2)	3 (2)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0)	1 (1)
Dieulafoy lesion	1 (1)	1 (1)	0 (0)	0 (0)	5 (3)	5 (4)	0 (0)	0 (0)
Iatrogenic	2 (1)	1 (1)	0 (0)	0 (0)	1 (1)	1 (1)	1 (0)	1 (1)
Varices	3 (2)	3 (2)	3 (2)	1 (1)	2 (1)	2 (2)	2 (1)	2 (2)
Cancer	10 (5)	7 (5)	1 (1)	1 (1)	6 (4)	6 (4)	12 (3)	4 (5)
Peptic ulcer	83 (45)	72 (51)	44 (22)	38 (24)	78 (49)	78 (59)	24 (6)	20 (24)
Erosion	14 (8)	12 (8)	0 (0)	0 (0)	6 (4)	6 (4)	4 (1)	4 (5)
Esophagitis/ Gastritis	16 (9)	13 (9)	12 (6)	11 (7)	13 (8)	12 (9)	16 (4)	13 (15)
Undocumented	52 (28)	29 (20)	140 (70)	108 (68)	46 (29)	20 (15)	329 (82)	33 (39)
Diagnosis made by:**								
GP	NA	NA	197 (99)	156 (98)	NA	NA	75 (19)	27 (32)
Specialist	100%	100%	3 (2)	3 (2)	100%	100%	79 (20)	55 (65)

MW, Mallory-Weiss; NA, not applicable; GP, general practitioner.
** Can sum up to more than 100%.*
*** Only relevant for GP databases (HSD and IPCI).*

The overall PPV in IPCI was 24% (95% CI: 20%-29%). When stratified according to free text or ICPC codes, the PPV was 23% (95% CI: 17%-30%) and 25% (95% CI: 19%-31%), respectively. All four recommended ICPC codes (Table 13.1), were retrieved in the random sample of 200 patients, with the code for melena being the most frequent and the code for hematemesis being the least frequent. Table 13.3 shows the PPV for each of the codes and free text used in each DB.

Validation of date of upper gastrointestinal bleeding occurrence

The actual date of onset of UGIB ('reviewed date') was earlier than, or consistent with, the automatically detected date of UGIB ('coded date') for majority of the confirmed cases across all databases (see Figure 13.1). In ARS, for 116 out of 142 confirmed cases (82%), the date of onset upon review was earlier than the recorded diagnosis date while in 39 (27%) confirmed cases the 'reviewed date' was much later than the 'coded date' (range -29 day to +19 day). For only three cases was the reviewed date occurring before the coded date in HSD (range -9 to -3 days). In Aarhus, 27 out of 132 (20%) of confirmed cases had a different reviewed date of event as recorded (range -2 days to +364 days). In IPCI, 25 (30% of confirmed cases) had a reviewed date earlier than the coded event date and one had a reviewed date later than coded date (range -1200 days to + 1096 days).

Impact of accuracy of upper gastrointestinal bleeding events on the estimation of relative risk

Figure 13.2 shows the incidence rate ratio (IRRs), adjusted for age and sex for different drugs across different PPV categories (UGIB, UGIB25, UGIB50 and UGIB75). Taking the drug simvastatin as an example of a drug not known to be associated with UGIB, the number of identified UGIB cases decreased from 1 903 to 774 when the case definitions were changed from using all codes ('UGIB' category) to include only codes and free text having PPV of $\geq$ 75% ('UGIB75' category). The corresponding IRRs changed from 1.3 (95% CI: 1.2-1.3) for 'UGIB' to 1.4 (95% CI: 1.3 – 1.5) for 'UGIB75.' The changes in risk estimation with changes in outcome definition for the other drugs not known to be associated with UGIB (zopiclone, goserelin, fexofenadine, and dorzolamide) are also shown in Figure 13.2 With respect to the drugs known to be associated with UGIB, there was no trend with increasing accuracy of outcome definition for heparin and acetylsalicylic acid use. The use of indometacin and ibuprofen was associated with the highest risk for the UGIB definition with the highest accuracy [indometacin; UGIB: 3.7 (95% CI: 2.8 – 4.8) and UGIB75: 5.3 (95% CI: 3.6 – 7.9) and ibuprofen; UGIB: 2.6 (95% CI: 2.4 – 2.8) and UGIB75: 3.2 (95% CI: 2.8 – 3.5)]. The higher accuracy of UGIB as event definition, the lower the risk estimate for prednisolone use with IRR from 3.2 (95% CI: 2.9 – 3.4) for UGIB, followed by 3.0 (95% CI: 2.7 – 3.3) for UGIB25, 2.9 (95% CI: 2.6 – 3.3) for UGIB50 to 2.7 (95% CI: 2.3 -3.1) for UGIB75.

Table 13.3: Positive predictive value of diagnostic codes for upper gastrointestinal bleeding, stratified by coding system and database

Codes	Charts reviewed *n (%)*	PPV broad Algorithm (95%-CI)	PPV Assessor (95%-CI)	PPV Narrow Algorithm (95%-CI)
ICD-9 ARS:	185 (100)	77 (71-83)	72 (66-79)	72 (65-78)
530.82 Esophageal hemorrhage	1 (1)	100 (100-100)	100 (100-100)	100 (100-100)
531.00 Gastric ulcer, Acute with hemorrhage	29 (16)	83 (69-97)	79 (65-94)	79 (65-94)
531.01 Gastric ulcer, Acute with hemorrhage, with obstruction	1 (1)	100 (100-100)	100 (100-100)	0 (0-0)
531.10 Gastric ulcer, Acute with perforation	1 (1)	0 (0-0)	0 (0-0)	0 (0-0)
532.00 Duodenal ulcer, Acute with hemorrhage	40 (22)	95 (88-102)	93 (84-101)	95 (88-102)
532.01 Duodenal ulcer, Acute with hemorrhage, with obstruction	2 (1)	100 (100-100)	100 (100-100)	100 (100-100)
532.10 Duodenal ulcer, Acute with perforation	9 (5)	44 (12-77)	50 (15-85)	44 (12-77)
533.00 Peptic ulcer, site unspecified, Acute with hemorrhage	5 (3)	100 (100-100)	100 (100-100)	80 (45-115)
533.20 Peptic ulcer, site unspecified, Acute with hemorrhage and perforation	1 (1)	100 (100-100)	100 (100-100)	100 (100-100)
534.00 Gastrojejunal ulcer, Acute with hemorrhage	4 (2)	100 (100-100)	100 (100-100)	100 (100-100)
534.01 Gastrojejunal ulcer, Acute with hemorrhage, with obstruction	1 (1)	100 (100-100)	100 (100-100)	100 (100-100)
534.21 Gastrojejunal ulcer, Acute with hemorrhage and perforation	1 (1)	100 (100-100)	100 (100-100)	100 (100-100)
535.01 Acute gastritis with hemorrhage	17 (9)	65 (42-87)	65 (42-87)	65 (42-87)
535.11 Atrophic gastritis with hemorrhage	1 (1)	0 (0-0)	0 (0-0)	0 (0-0)
535.41 Other specified gastritis with hemorrhage	3 (2)	33 (0-20)	33 (0-20)	33 (20-87)
578.0 Hematemesis	12 (6)	83 (62-104)	83 (62-104)	67 (40-93)
578.1 Melena	21 (11)	67 (47-87)	57 (36-78)	62 (41-83)
578.9 Hemorrhage of gastrointestinal tract, unspecified	36 (19)	67 (51-82)	53 (37-69)	58 (42-74)
ICD-9 HSD:	200 (100)	80 (74-85)	82 (76-88)	78 (72-84)
All codes:	140 (70)	92 (88-97)	91 (86-96)	91 (87-96)
531.10 Gastric ulcer, Acute with perforation	3 (2)	0 (0-0)	0 (0-0)	0 (0-0)
531.00 Gastric ulcer, Acute with hemorrhage	17 (9)	100 (100-100)	94 (83-105)	100 (100-100)
532.00 Duodenal ulcer, Acute with hemorrhage	4 (2)	100 (100-100)	100 (100-100)	100 (100-100)
533.00 Peptic ulcer, site unspecified, Acute with hemorrhage	3 (2)	0 (0-0)	0 (0-0)	0 (0-0)
535.01 Acute gastritis with hemorrhage	2 (1)	100 (100-100)	0 (0-0)	100 (100-100)
535.41 Other specified gastritis with hemorrhage	3 (2)	100 (100-100)	0 (0-0)	100 (100-100)
535.51 Unspecified gastritis and gastroduodenitis with hemorrhage	2 (1)	100 (100-100)	50 (0-19)	100 (100-100)
578.0 Hematemesis	16 (8)	100 (100-100)	100 (100-100)	100 (100-100)
578.1 Melena	75 (38)	93 (88-99)	89 (82-96)	92 (86-98)
578.9 Hemorrhage of gastrointestinal tract, unspecified	15 (8)	100 (100-100)	100 (100-100)	100 (100-100)
Text	60 (30)	50 (37-63)	57 (42-72)	47 (34-59)
ICD-10 Aarhus:	158 (100)	84 (78-89)	73 (66-80)	77 (70-83)
K25.0 Gastric ulcer, Acute with hemorrhage	38 (24)	92 (84-101)	84 (73-96)	84 (73-96)
K25.1 Gastric ulcer, Acute with perforation	6 (4)	17 (0-13)	0 (0-0)	17 (13-47)
K25.2 Gastric ulcer, Acute with both hemorrhage and perforation	2 (1)	100 (100-100)	100 (100-100)	100 (100-100)
K26.0 Duodenal ulcer, Acute with hemorrhage	42 (27)	98 (93-102)	93 (85-101)	98 (93-102)
K26.1 Duodenal ulcer, Acute with perforation	4 (3)	0 (0-0)	0 (0-0)	0 (0-0)
K26.2 Duodenal ulcer, Acute with both hemorrhage and perforation	2 (1)	100 (100-100)	100 (100-100)	100 (100-100)
K27.0 Peptic ulcer, site unspecified, Acute with hemorrhage	1 (1)	100 (100-100)	100 (100-100)	100 (100-100)
K28.0 Gastrojejunal ulcer, Acute with hemorrhage	2 (1)	50 (0-19)	50 (0-19)	50 (19-119)
K29.0 Acute hemorrhagic gastritis	5 (3)	100 (100-100)	80 (45-115)	100 (100-100)
K92.0 Hematemesis	28 (18)	93 (83-102)	70 (53-88)	75 (59-91)
K92.1 Melena	13 (8)	69 (44-94)	58 (30-86)	62 (35-88)
K92.2 Gastrointestinal hemorrhage, unspecified	15 (9)	60 (35-85)	43 (17-69)	47 (21-72)
ICPC IPCI:	400 (100)	24 (20-29)	16 (13-20)	22 (17-26)
All codes:	200 (50)	25 (19-31)	16 (11-21)	22 (15-28)
D14 Hematemesis/ vomiting blood	40 (10)	71 (55-87)	33 (18-47)	58 (41-75)
D15 Melena	62 (16)	39 (25-52)	25 (14-35)	35 (21-48)
D85 Duodenal ulcer	49 (12)	2 (0-2)	2 (0-2)	2 (2-6)
D86 Peptic ulcer other	49 (12)	4 (0-2)	4 (0-2)	4 (2-10)
Free text	200 (50)	23 (17-30)	17 (12-22)	22 (15-28)

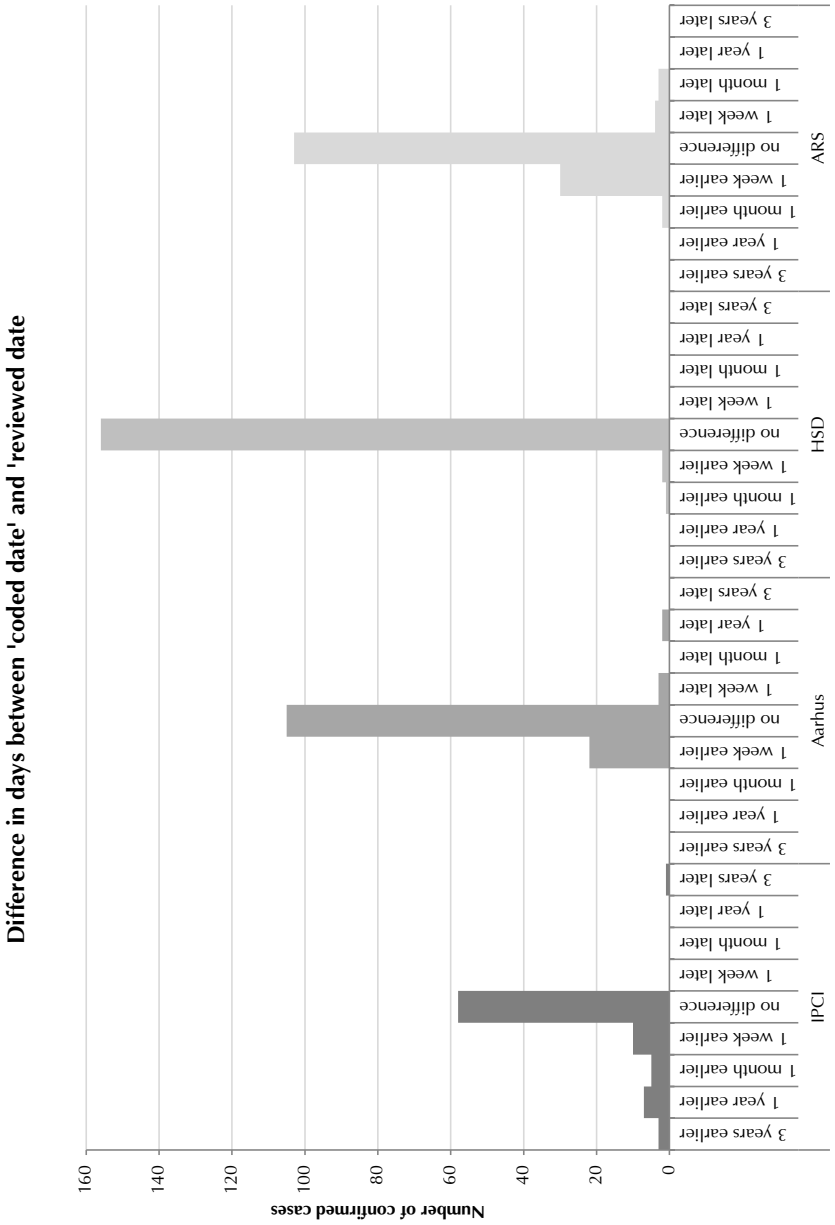


Figure 13.1: Distribution of difference in days between coded date and reviewed date of event in confirmed UGIB cases only per database.

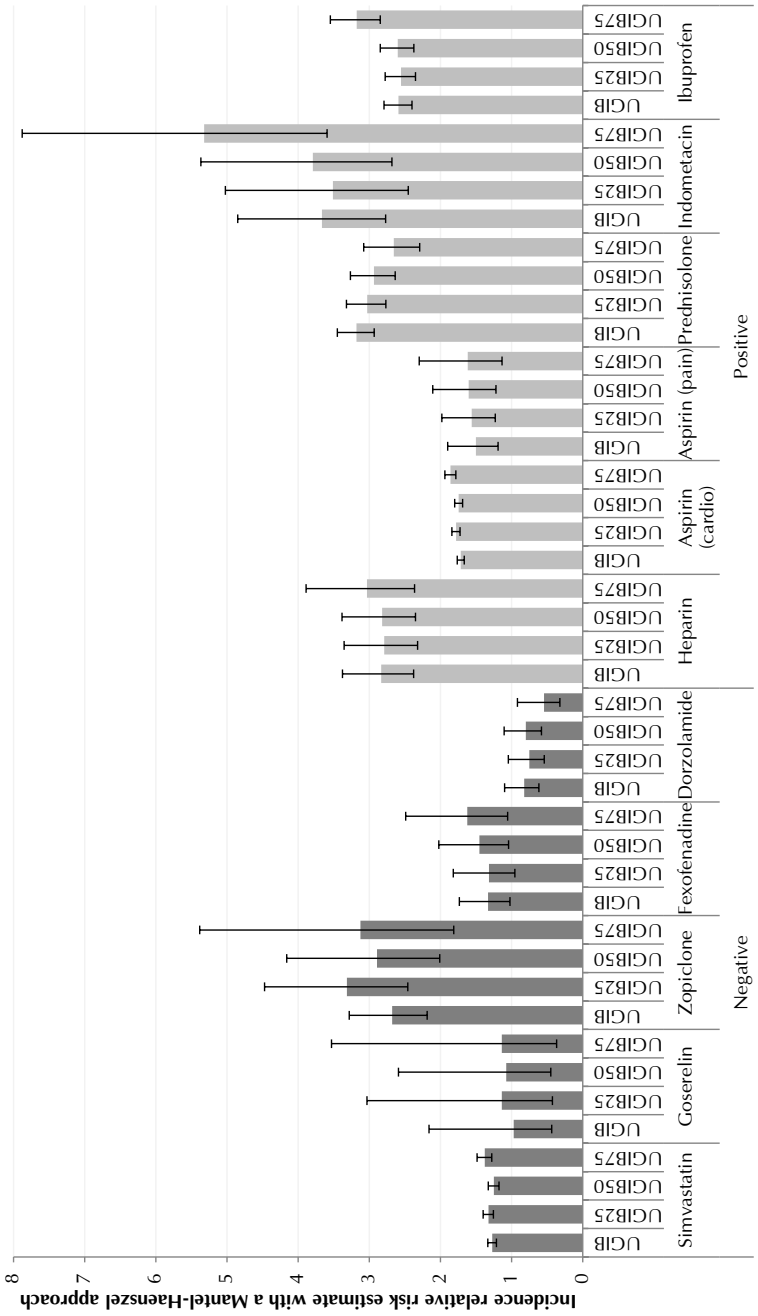


Figure 13.2: Impact of codes and free text with different positive predictive values (PPV) on estimation of age- and sex-adjusted relative risk estimates for UGIB in a cohort study

UGIB: all eligible codes to identify patients with UGIB; UGIB25: only codes with PPV of more than 25%; UGIB50: only codes with PPV of more than 50%; UGIB75: only codes with PPV of more than 75%.

Discussion

In this validation study we determined the positive predictive value (PPV) of diagnostic codes and free text for the identification of patients with UGIB in different European electronic healthcare databases. We analyzed the accuracy of three widely used disease coding systems (ICD-9th and 10th revision and ICPC), free text vs. code search, in databases originating from three different countries (Denmark, Italy, and the Netherlands). In addition, we explored the difference in PPV for the same codes used in a primary care (HSD) vs. hospital setting (ARS) from Italy, which adopted the same coding system (ICD-9-CM). Finally, we studied the impact on relative risk estimates of the accuracy of UGIB case identification in the context of a cohort study. This is a strength and novelty of our study.

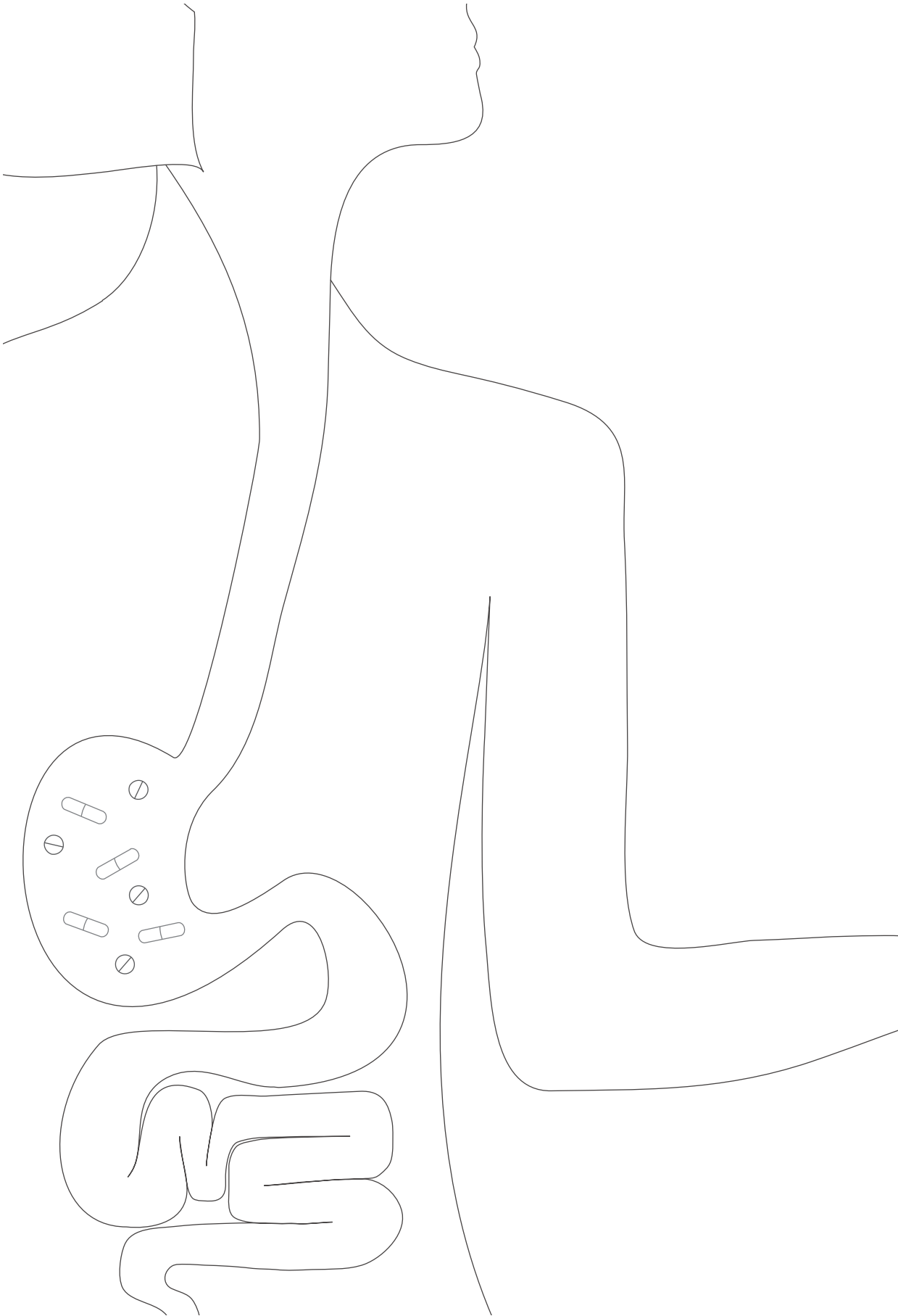
In general, the PPV of the more extensive coding system of ICD-9 and ICD-10 outperformed the less granular coding system of ICPC. This is probably explained by the fact that none of the four available ICPC codes refers specifically to UGIB, but rather to uncomplicated peptic ulcers or signs of UGIB only. For two databases we had the opportunity to explore the PPV of free text for the identification of UGIB events. For HSD, 30% of cases were identified via free text with a PPV of 50%, indicating that the PPV for free text search was significantly lower than for diagnosis codes. In IPCI, up to 70% of the cases were identified by free text search alone. The PPV for free text was very low (23%) but, surprisingly, equal to PPV for codes alone (25%). This shows that for complete information regarding the cases, the free text search is valuable, but it should not be used in an automatic search without manual case validation. In the IPCI database manual review is always conducted and advanced text mining techniques are currently being implemented to reduce the burden of manual inspection of medical records.[294] Our findings of the PPVs originating from the ICD-9 diagnoses codes (ARS, HSD) can be compared with other studies. One study, also originating from Italy, studied UGIB (including perforation) and the PPVs are in line with the PPVs we obtained.[181] The reported PPV for hematemesis (ICD-9: 578.0) was lower (59% vs. ARS 83% and HSD 100%), but our results on the PPV concerning code 578 were similar to the study by Raiford *et al.*[183] Two other studies with ulcer disease and UGIB as endpoint had lower PPVs (around 60%) as reported in the current study,[286, 287] especially the PPV for non-specific codes (578) was reported low (9% only) in a study with eight Health Maintenance Organizations.[286] To our knowledge, no studies to date have been conducted that analyze the PPV of ICPC or ICD-10 codes in identification of UGIB from electronic healthcare data. However, a related study reported a PPV of 98% specifically for ulcer disease (both uncomplicated and complicated) for ICD-10 codes in Aarhus.[295]

We have also investigated the impact of misclassification of the outcome definition on the association measure. As an example we used drugs known to be associated with UGIB and drugs unlikely to be associated with UGIB to determine the association between drug exposure and risk of UGIB, while using different scenarios (excluding codes with low PPV). Some of the drugs presumed to be not associated with UGIB showed increased risk estimates and this demands further investigation. We have shown that, despite loss of precision, the use of codes with lower PPV did not result in significant changes in the estimated relative risks. Non-differential misclassification biases the risk estimates towards the null; indeed, the IRRs tend to increase with higher accuracy of outcome definitions for indometacin and ibuprofen, and to a lesser degree for heparin and acetylsalicylic acid. However, for prednisolone the IRRs decrease with higher accuracy. In general, the use of codes with lower PPV resulted in only small changes in the estimated relative risks probably due to the fact that the codes and free text with low accuracy still identify patients

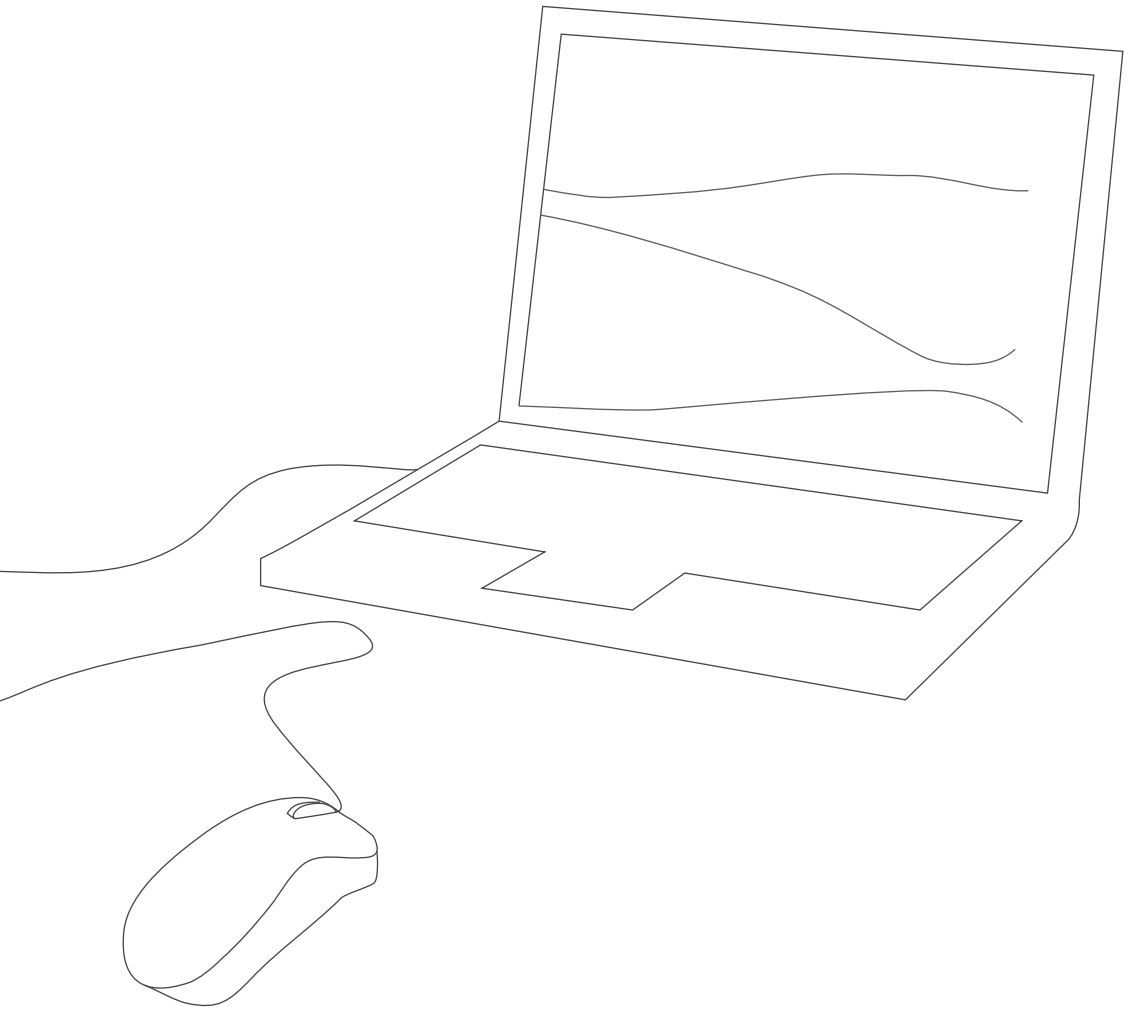
with a event in a similar pathophysiological pathway, such as uncomplicated ulcer disease or ulcer perforation.

There are several limitations to our study. First, despite a standardized event definition for UGIB provided and a common tool (Chameleon©) with which to enter the available information in a structured manner, the UGIB case ascertainment process relied, to some degree, on the assessor's judgment. Therefore, apart from the judgment of the assessor, an automated algorithm was developed to allocate UGIB cases to avoid subjectivity in the case definition across databases. The PPVs derived from the automated algorithm and from the assessor were similar, except for hematemesis in IPCI, which might be explained by a conservative validation approach by the medical assessor in IPCI. Moreover, in this study we have limited the event definition to UGIB, with a special focus on potentially drug-related UGIB, whereas other studies included perforation or uncomplicated ulcer disease in general. The reason that the PPVs for the narrow concept of UGIB were not much lower than the PPVs for the broad concept of UGIB is understandable as peptic ulcer bleeding and erosive disease are responsible for the great majority of UGIB cases as reported in literature,[25] and similar to our results. Another limitation is that we adjusted only for sex and age in the cohort study, but not for other potential confounders potentially resulting in spurious associations.

In conclusion, databases present a potentially good source of identifying patients with UGIB. However, there are differences in the accuracy of case identification between databases that stem from differences in the coding systems used, the use of free text search, and the type of data collected (hospitalization claims vs. medical records). Using the most specific codes for UGIB does not significantly change the risk estimate, but reduces the precision of such risk estimates.



Summary and Discussion



Chapter 14

Summary and General Discussion

Summary

Non-steroidal anti-inflammatory drugs (NSAIDs) are one of the most important therapies for pain relief. This thesis dealt with the use and safety of both NSAIDs and NSAID-use-related gastroprotection and was divided in four sections. The first section (Chapter 1) provided an introductory summary on NSAIDs, followed by the aim and outline of this thesis.

In the second section we have provided more insight in the utilization patterns of NSAIDs and gastroprotection to understand the public health impact of NSAID use. We have studied the use of NSAIDs in specific subgroups such as West-European children (Chapter 2) and patients with musculoskeletal complaints (Chapter 5). We assessed whether NSAID users were at risk for either upper gastrointestinal (UGI) events or cardiovascular (CV) events and whether appropriate measures were being taken to reduce that risk (Chapter 3-5). The chapters in this part of the thesis were descriptive of nature.

In the third section we have assessed and predicted the risk of UGI complications related to NSAID use, with or without gastroprotection. We demonstrated that full adherence to gastroprotective agents (GPA) is of importance in reducing the risk of NSAID-related UGI complications, both in traditional, non-selective NSAID users (Chapter 6) and in coxib (COX-2 selective inhibitors) users (Chapter 7). Use of non-selective NSAIDs plus gastroprotective agents was an equally safe strategy as use of coxibs regarding UGI complications (Chapter 8). When we focused on the magnitude of each individual NSAID on the risk of UGI complications a wide variety of risk estimates was shown, from no increased risk with the use of celecoxib to a seven-fold increased risk with the use of ketorolac (Chapter 9). Age, sex and a history of UGI events were confirmed to be risk factors in predicting UGI complications in NSAID users (Chapter 10). Low-dose aspirin, by a lay public generally accepted as a safe and innocent drug, had a two to three fold increased risk of UGI bleeding (Chapter 11). We showed that proton pump inhibitors are probably safe to use in combination with clopidogrel as this will not subsequently lead to an increased risk of CV events (Chapter 11). Finally, we have shown that misclassification of UGI bleeding as outcome does not impact risk estimates substantially (Chapter 13). We finished with the main findings, summarized and discussed in the fourth section (Chapter 14).

Main findings

Use of NSAIDs in children

In **Chapter 2** we describe the results of a drug utilization study in the SOS (Safety of Non-steroidal Anti-inflammatory Drugs) project. The SOS project is a research and development project requested by the European Medicines Agency and funded by the Health Area of the European Commission under the Seventh Framework Programme, with the aim of assessing the CV and UGI safety of NSAIDs in adults and children. In a West-European study population consisting of 7.7 million children from the Netherlands, the United Kingdom, Germany, and Italy, 56 out of 1,000 children or adolescents received an NSAID prescription each year. This prevalence varied greatly between countries, with the lowest prevalence in Italy and the highest in Germany. A remarkably high consumption of NSAIDs was found in very young German children. This surprising result might be explained by the fact that ibuprofen (one of the NSAIDs) is recommended in German guidelines for the treatment of fever in children besides paracetamol (acetaminophen).[76] In Italy and UK, the same advise applies; either paracetamol or ibuprofen are the recommended antipyretic drugs in children with fever.[77, 78] The prescription/dispensing rates within Italy differed between the studied databases. In the Italian Pedianet databases, to which family pediatricians provide data, a higher utilization of NSAIDs was seen in the young children, which is in contrast to the other two Italian administrative databases. Conversely, the Dutch general practice guideline recommends paracetamol as first choice medication in case of discomfort in a feverish child.[79, 296] Although ibuprofen reduces a child's body temperature faster than paracetamol, the Dutch advice is based on the observation that severe adverse events, like hepatic failure, are rare with the use of paracetamol, and are thought to occur less frequently than with ibuprofen.

By combining seven European databases the SOS platform contained data on 1.3 million children with prescriptions for NSAIDs, which made this a potential source for studying the safety of NSAIDs in children. However, only for ibuprofen the drug exposure captured in the databases will be sufficient to investigate asthma exacerbation -the most common event in the pediatric population- for an expected weak association (relative risk of 2).

Use of gastroprotective strategies with NSAIDs in the Netherlands

The use of NSAIDs is related to an increased risk of UGI ulcers and its accompanying complications. The most common complication of peptic ulcer disease is bleeding from the UGI tract. Although therapeutic and endoscopic treatment options improved in recent decades, the mortality of this serious condition still ranges from 5% to 14%.[20, 25, 27] Therefore, it is best to reduce the risk of such serious adverse events with NSAID therapy. The most commonly employed gastroprotective strategy to reduce the gastrointestinal risk associated with NSAIDs is to co-prescribe acid suppressive therapy in the form of proton pump inhibitors (PPIs), histamine-2 receptor antagonists (H_2RAs) or misoprostol. In this thesis these drugs were defined as gastroprotective agents (GPAs). Alternatively, the traditional non-selective (ns)NSAID can be replaced by the newly developed coxib, which is generally believed to be a safer alternative than nsNSAIDs.[38-41] This advice is reflected in many international evidence-based guidelines.[53, 88, 142, 152]

In **Chapter 3** a study population comprising 50,126 Dutch NSAID users of 50 years and older originating from the Integrated Primary Care Information (IPCI) database were studied with respect to gastroprotective strategies employed. In NSAID users with an increased risk of developing UGI complications while on NSAID therapy, under-

prescription of preventive strategies steadily decreased between 1996 and 2006. However, 60% of NSAID users at increased risk of NSAID complications still did not receive adequate protection in 2006, despite treatment recommendations. As a history of UGI complications is generally acknowledged to be the most important risk factor for UGI complications, we restricted the cohort to 661 subjects (1.3%) who experienced such an event in the past in an additional analysis. Even in this high risk group, under-prescription was still unacceptably high in 2006 as over half of them (51.5%) did not receive a gastroprotective measure. Comorbidity factors increasing the likelihood of receiving a gastroprotective strategy were a history of UGI complications, age of 65 years or older, and concomitant use of antiplatelets, systemic steroids or vitamin K antagonists. The likelihood of receiving a preventive strategy was the highest for prescriptions of indometacin (Odds ratio (OR) 3.1; 95%CI 1.9-5.2) and ketoprofen (OR 2.5; 95%CI 1.2-5.5) compared with ibuprofen (the reference category). In literature, ketoprofen and indometacin are found to increase the risk of UGI complications to a higher degree than ibuprofen.[179, 180, 297] General practitioners (GPs) might be aware of this elevated risk and are therefore more accurate in prescribing a gastroprotective strategy. However, piroxicam is one of the compounds associated with the highest risk of UGI complications (seven to eight times), but in the current study the likelihood of receiving a preventive strategy was only moderately increased (OR 1.5; 95%CI 1.0-2.3).[179, 180, 297]

Use of gastroprotective strategies with NSAIDs in United Kingdom, the Netherlands, and Italy

As the previous study (Chapter 3) received substantial media attention both nationally and internationally[298], we were interested to evaluate whether the unfavorable Dutch situation in the single primary care database could be extrapolated to other countries. Although data concerning gastroprotective strategies in NSAID users of other countries were published and were in concordance with ours[99, 111-114], many studies used different outcome measures, study populations, and definitions for at risk NSAID users. In **Chapter 4** a population-based cohort study is described that was conducted in three European primary care research databases; the GPRD (General Practice Research Database from the UK: 1998-2008), the IPCI database (from the Netherlands: 1996-2007) and the HSD (Health Search/CSD Longitudinal Patient Database from Italy: 2000-2007). The study populations consisted of 384,649 British, 55,004 Dutch, and 177,747 Italian NSAID users and revealed a similar pattern of gastroprotective strategies in NSAID users across countries. Again, improvement was seen over a 7 to 10-year time period. Yet, in all three countries a significant number of NSAID users at risk of UGI events were not receiving appropriate gastroprotective strategies (71% in the UK, 58% in the Netherlands, and 76% in Italy). In line with other studies and with the study in Chapter 3, a history of UGI complications and concomitant systemic steroid use were the strongest predictors of receiving a gastroprotective strategy in at-risk NSAID users across countries.[108, 110, 115] Although advanced age is a generally accepted risk factor for UGI complications attributable to NSAIDs, age of 65 years and older did not increase the likelihood of receiving gastroprotective strategies in the Netherlands (OR 1.1; 95%CI 0.8-1.4), which was in contrast with the result of the previous study (adjusted OR 1.7; 95%CI 1.3-2.2). One explanation could be that in the study, as described in Chapter 4, residual confounding could have been introduced as factors such as diabetes mellitus or heart failure were not adjusted for in this study but were adjusted for in the study described in Chapter 3.

In the before-mentioned study from the Netherlands (Chapter 3), we also observed a significant, but temporary, decrease in use of gastroprotection in at-risk NSAID-users after

2004. This observation was probably attributable to the CV safety concerns for coxibs that eventually lead to rofecoxib withdrawal in September 2004.[47, 94] This hypothesis was explored by comparing under-prescription rates in three successive study periods using a χ^2-test. In the latter study (Chapter 4), interrupted time-series analysis was performed as a substitute for the χ^2-test to assess the impact of rofecoxib withdrawal on gastroprotective strategies.[123] This auto-regressive, integrated, moving average (ARIMA) model analysis is an established method in economics that is gaining popularity in pharmaco-epidemiology in recent years. An ARIMA model can be used to understand whether a significant change in frequency of an event is measurable after an intervention like a drug safety warning from regulatory agencies or drug withdrawal.[299] In our study rofecoxib withdrawal was the intervention. Using the ARIMA model the intervention can be modeled as abrupt or gradual and as permanent or temporary effect. One disadvantage is that enough data observation points are necessary, both before and after the intervention.

In the UK and the Netherlands, rofecoxib withdrawal resulted in a significant increase in under-use of gastroprotective strategies (p-value = 0.038 and p-value = 0.027, respectively). In Italy a similar trend was observed, although not significant (p-value = 0.057). Although general practitioners did not immediately prescribe appropriate gastroprotective strategies when replacing rofecoxib they did in the year after rofecoxib withdrawal.

Use of NSAIDs in patients with cardiovascular comorbidity

After a two-fold increased risk of ischemic CV events attributable to rofecoxib use was observed,[47] other studies and meta-analyses were published with respect to the cardiovascular safety of other coxibs and traditional nsNSAIDs. These studies showed that the risk of CV events was not limited to coxibs.[48, 49, 51] Based on guidelines and consensus the prescription of NSAIDs in patients at high CV risk, defined as a history of myocardial infarction, angina pectoris, stroke, transient ischemic attack or peripheral arterial disease, is contraindicated.[52-54] It has been suggested that the use of NSAIDs should also be avoided in patients with a moderately increased risk of CV events (related to diabetes mellitus, hypertension or hyperlipidemia).[54] It is not clear whether general practitioners (GPs) consider this cardiovascular risk profile when prescribing NSAIDs. Therefore in **Chapter 5**, we examined the influence of the patients' cardiovascular risk profile on the prescription of NSAIDs in patients with musculoskeletal (MSK) complaints, the most commonly presented complaint in the primary care population in the Netherlands.[130]

We included 474,201 patients presenting with a MSK complaint between 2000 and 2010, of which 67,184 (14.2%) had a moderate CV risk and 41,483 (8.8%) had a high CV risk. Patients with CV risk factors were more likely to be at high UGI risk: 60.3% of patients at a high CV risk were also at a high UGI risk, vs. 35.9% of patients at a moderate CV risk and only 7.0% of patients at a low CV risk (p-value < 0.001). Of all patients presenting with a MSK complaint, 25.8% were treated with a nsNSAID or a coxib. Patients at high CV risk were more likely to be treated with a coxib than patients with a low risk of developing CV events (OR 1.9; 95%CI 1.8-2.0). Conversely, they were less likely to be treated with nsNSAIDs (OR 0.8; 95%CI 0.7-0.8). This difference in nsNSAID prescription between high and low CV risk patients was already present over the first part of the decade, before evidence of an association between nsNSAID use and cardiovascular events first emerged. The observed differences in coxib and nsNSAID prescription in patients with a high CV risk vs. patients with a low CV risk are probably explained by the strong overlap between CV risk factors and UGI risk factors. These data suggest that GPs base their choice of NSAID therapy on the patient's UGI risk profile, rather than taking their

CV risk profile into account. This does not come as a surprise as the concern of ischemic cardiovascular adverse events related to NSAID use is of a more recent date than the UGI complications. In addition, although recommendations and warnings regarding the cardiovascular risks of NSAIDs have been issued in general Dutch prescription guidelines[54, 137], no national Dutch guideline for GPs has been published on this topic specifically.

Impact of adherence to gastroprotective agents with NSAIDs

Non-selective NSAIDs

Gastro-protective agents (GPAs) are co-prescribed with NSAIDs, but to what extent therapy adherence influences the protective effect is uncertain. Non-adherence to concomitant GPAs was associated with an increased risk of non-selective NSAID-related UGI events, but the concerned studies encompassed only few events.[118, 144] To extend these data and to investigate the risk of UGI events with suboptimal GPA adherence during nsNSAID use, a case-control study nested within a cohort of nsNSAID+GPA users aged ≥ 50 years was conducted. The results are described in **Chapter 6**. The same three European primary care research databases were used as in Chapter 4; GPRD from the UK, IPCI from the Netherlands, and HSD from Italy. Adherence to GPAs was calculated as the proportion of nsNSAID treatment days covered by a GPA prescription (PDC). In other words, each particular nsNSAID day was classified as being covered with a GPA prescription or not. A schematic illustration is depicted in Figure 14.1. The cohort consisted of 91,282 nsNSAID users, generating 117,307 nsNSAID episodes that were (partly) covered by prescription of a GPA. Of these episodes, 4.9% had a PDC lower than 20% (non-adherence), and 68.1% had a PDC over 80% (full adherence). We identified 339 patients who experienced a UGI event, and they were matched to 71,380 controls. Users of a nsNSAID who were non-adherent to GPAs had a 2.4-fold increased risk of UGI events (95%CI: 1.7-3.4) as compared with patients who were fully adherent. With every 10% decline in PDC, the risk of a UGI event increased by 9% (95%CI: 5-13%). In other words, with every three-day reduction of GPA coverage per 30 days of nsNSAID use, the risk of UGI events increased by 9%.

Definition of NSAID exposure and coverage with gastroprotective agents

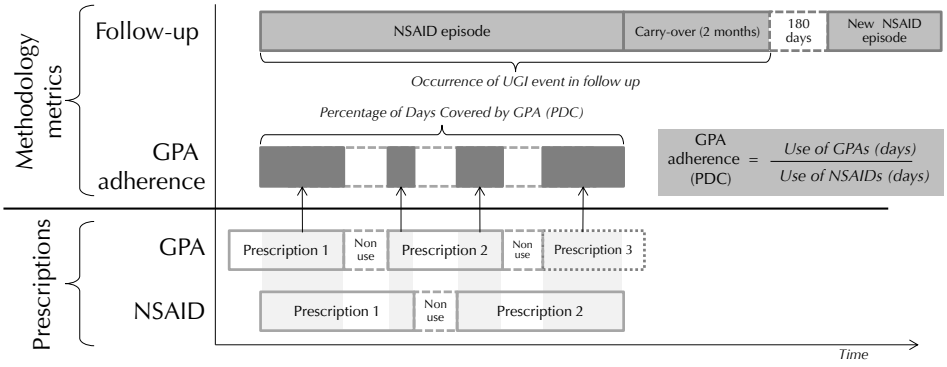


Figure 14.1: Schematic illustration of NSAID exposure and GPA adherence calculation

Coxib users

In **Chapter 7** a similar study was conducted as in Chapter 6 and within the same databases, but with the specific aim to estimate the magnitude of non-adherence to GPAs during coxib use. The combination of a coxib plus GPA is currently advised for NSAID users with a very high risk of developing UGI events, such as patients with a prior history of a UGI event or multiple UGI risk factors.[53, 152] Two clinical studies highlighted the importance of co-prescription of GPAs to high-risk coxib users,[104, 105] which were supported by two large database studies investigating high-risk and low-risk coxib users.[95, 151] Those studies consistently showed that the incidence of coxib-related UGI events is further reduced when PPIs are provided to coxib users. In this study we investigated whether decreased adherence to GPAs increased the risk of coxib-related UGI events in patients treated with the combination of coxibs and GPAs.

The cohort consisted of 14,416 coxib users, generating 16,442 coxib episodes that were (partly) covered by prescription of a GPA (Figure 14.1). Non-adherence (PDC lower than 20%) was present in 7.2% of episodes and full adherence (PDC > 80%) in 59.7%. Seventy-four patients had a UGI event during or shortly after these episodes. The relative risk of UGI events was 1.97 (95%CI 0.84-4.60) for low GPA adherers (PDC< 20%) compared with full adherers (PDC > 80%). For every 10% decrease in GPA adherence, the risk of UGI events increased by 9% (95%CI: 0-18%).

In our study we stratified by low-dose aspirin use in an exploratory analysis. It is believed that the beneficial effect of coxibs compared with nsNSAIDs is negated when patients concomitantly use low-dose aspirin.[40, 176] In patients without low-dose aspirin a decrease of 10% in GPA adherence resulted in an 8% increased risk of a UGI event (95%CI: -3% to 19%); in patients who did use low-dose aspirin the risk increased by 15% (95%CI: -2% to 36%). This would suggest that adequate gastroprotection during coxib use is important in those on aspirin therapy.

It is worth noting that GPAs were more frequently prescribed in combination with coxibs (Chapter 7) than in combination with nsNSAIDs (Chapter 6), which is remarkable as Dutch and Italian national guidelines advise GPA co-prescription with nsNSAIDs, but not with coxibs.[88, 128] Our studies showed that the percentage of GPA co-prescription was 16.6% with coxibs and 10.6% with nsNSAIDs. It is conceivable that GPs in clinical practice already incorporated the co-prescription of GPAs in coxib users well before this recommendation was captured by national guidelines. The British national guideline was updated with the recommendation to prescribe GPAs with coxibs (in high risk users) around 2007, which was within our study period, resulting in higher GPA co-prescription with coxibs in the UK (21.2%) than in the Netherlands (13.4%) or Italy (11.0%).[152] Although the percentage of coxib users that received a GPA prescription was higher when compared with nsNSAIDs, adherence was lower among coxib users (coxib: mean PDC: 76% vs. nsNSAID: mean PDC: 81%).

To summarize Chapter 6 and Chapter 7, GPA adherence is a major aspect in reducing the risk of UGI tract events in coxib and nsNSAID-treated patients. This is clinically relevant since non-adherence to GPAs is a modifiable risk factor. GPA adherence should be underlined by prescribers of NSAIDs and by pharmacists, especially in the wake of the retrenchment of the Dutch basic health insurance package. As of 1 January 2012, GPAs are currently only reimbursed or partly reimbursed in chronic use. This measure has influenced the willingness of patients to faithfully adhere to GPAs while on NSAID therapy. In a Dutch pharmacy database, a very recent publication showed that the dispensing rate of

GPAs in patients aged 70 years and above who initiated NSAID therapy decreased (last quarter of 2011: 83% and first quarter of 2012: 78%). This decrease of 5 percentage points reflected an absolute increase of 700 new users of NSAIDs with advanced age who were unprotected with GPAs (Figure 14.2).[300]

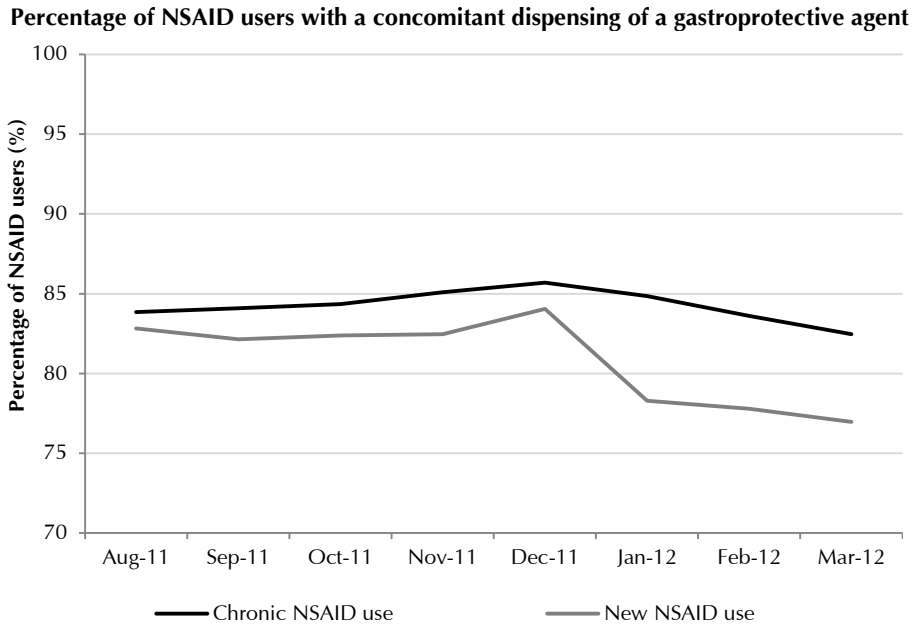


Figure 14.2: Time trend of the percentage of patients with a dispensed NSAID of 70 years and older that is protected by the concomitant dispensing of a GPA, stratified by new users and prevalent users of NSAIDs (source and adapted from: Stichting Farmaceutische Kengetallen).[300]

The budget cut measure of GPAs has come as a surprise. Two Dutch studies published in 2006 showed that medication-related hospital admissions are a substantial problem in the Netherlands, and more over almost half of the hospital admissions related to medicines (HARMs) are potentially preventable.[301, 302] One remarkable finding was that bleeding in general, including gastrointestinal bleeding, is the most common type of potentially avoidable adverse drug event leading to hospitalization. After oral anticoagulants, the two drugs most commonly associated with these bleedings were found to be aspirin and NSAIDs.[36] This dubious honor of being in the top-3 of medications causing avoidable hospitalizations was also confirmed in international studies.[303] In response to these developments the Dutch Ministry of Health issued recommendations in 2008 with the aim of realizing a significant reduction of preventable deaths and other types of inadvertent patient harm within five years' time in a quick win way. The reimbursement stop for GPAs in new aspirin or NSAID users since the beginning of 2012 contravene the ministerial ambition as postulated in 2008.

Relative safety of coxibs and nsNSAIDs plus gastroprotection

The previous two chapters (Chapters 6 and 7) raise the question which of the two gastroprotective strategies is preferred for UGI safety; concomitant use of GPAs and nsNSAIDs or the sole use of coxibs? Randomized clinical trials on this topic have been conducted and showed no superiority for one over the other.[43-45, 157, 304] However, the generalizability of these findings is limited as either a selected group of high-risk patients (i.e. those with a UGI event history) was included or a selected group of patients at lower risk of UGI events (i.e. by excluding certain comorbidities and concomitant drug use). In **Chapter 8** we attempted to determine which group of patients would benefit from which gastroprotective strategy in daily clinical practice. In the same study cohort as described in Chapter 6 and Chapter 7, a nested case-control study was conducted including all patients newly starting on nsNSAID therapy that was fully covered by a GPA (≥ 80% GPA adherence) and coxib users (without GPA use), aged 50 years and older. We identified 398 cases with a UGI event that were matched to cohort members without a UGI event. The risk of UGI events was equivalent for both groups (OR 1.0; 95%CI: 0.8-1.4). In a subgroup-analysis we confirmed that in patients on aspirin therapy the combination of nsNSAID plus GPA is safer compared with coxib. Interestingly, in patients who were using glucocorticoids, the risk of UGI events was significantly elevated for nsNSAID+GPA (≥ 80% adherence) users as compared with coxib users (OR 9.0; 95%CI: 1.6-51). Although the latter observation was based on a small sample size, it warrants further investigation.

The terminology used to refer to adherence to GPAs in Chapters 6 to 8 may be perceived as misused. Medication adherence or medication compliance is defined as the degree to which a patient correctly follows the recommended drug regimen. In our studies, we in fact estimate the coverage of NSAID prescriptions by GPA prescriptions only. In future studies we might consider to change the terminology to 'prescription coverage' instead of 'adherence' to better reflect what we truly measure. We studied a pattern of GPA prescriptions as a proxy for actual GPA adherence. The actual adherence pattern may be different from the prescription pattern, which may have led to misclassification of exposure. However, the term adherence has been used in previous publications by us[118] and by others.[107, 144] Although misclassification of exposure is conceivable, there is no reason to believe that this misclassification would be differentially distributed among cases and controls. The presented risk estimates will therefore be a conservative estimate. That we are able to find a two-fold increased risk on UGI events with non-adherence to GPAs on prescription level only, is an indication that adherence is an important factor in real life circumstances. The interpretation of the results are further complicated by the fact that we were unable to disentangle the GP-related or patient-related adherence to GPA prescriptions. Is the patient requesting a refill for GPA prescriptions when he or she has finished the first prescription or is the GP not prescribing the GPA directly at start of NSAID therapy, or not at all? Therefore the adherence as discussed in these papers reflect a combination of GP and patient adherence.

Variability in risk of UGI complications with different NSAIDs

It is well-known that the risk of complications of the UGI tract varies between individual NSAIDs.[179, 180] The degree of variability between the approximately 70 compounds is still under debate. In the SOS project, introduced in Chapter 2, one of the specific aims was to compare the UGI risk between individual NSAIDs in daily clinical practice. In particular, the objective was to assess whether all individual coxibs were as safe as was shown in the randomized clinical trials, and in addition whether some traditional, non-selective NSAIDs were equally safe compared with coxibs regarding UGI complications. To answer such questions, a large population exposed to a variety of NSAIDs is required, especially as the outcome under investigation (i.e. UGI complications) is relatively rare. In **Chapter 9** we are proud to present the preliminary results of a nested case-control study on this topic, which is the largest in size ever conducted. During follow-up, 28,567 patients developed a first or recurrent UGI complication. For 20 individual NSAIDs sufficient data was available to estimate their risk of UGI complications. All NSAIDs were ranked according to their relative risk of UGI complication. The ranking of the individual NSAIDs was well in line with the results from the meta-analysis on observational studies performed within the SOS project, albeit the risk estimates were lower in the presented study.[180] The lower estimates may be related to the fact that the current SOS data did not exclude patients with a recurrent event. Since NSAIDs should not be used in patients with a recent UGIC, at least not without gastroprotection, the chance of NSAID exposure with a recurrent event is lower than with a first event. Therefore the estimates may be lower than reported in the literature. In a participating British GP database (THIN), outcome misclassification might have occurred for recurrent events (recurrent codings for UGI complication may be related to a prior event rather than true recurrent events), which may bias the estimates towards the one. For this database the risk estimates per individual NSAID were lower than those estimates derived from the other databases. Future sensitivity analysis of first events only will lead to a reduction of the number of cases, a reduction in the potential to study infrequently used NSAIDs, and will potentially lead to an increase in the relative risk estimates.

Prediction of upper gastrointestinal complications in NSAID users

The life of the NSAID prescriber or regulator has not become easier in present times. The many types of NSAIDs that can be chosen (and all with their individual UGI or CV safety issues), combined with the patient's individual risk-profile has resulted in a complex decision-making process. Decision models that provide insight in the type of NSAID that would yield the lowest UGI and CV risk for an individual patient are needed in clinical practice to substantiate and support treatment decisions. The SOS project aims to provide such a decision analytic model for each individual NSAID compound. A prediction model, as described in **Chapter 10**, is the first step in constructing an NSAID treatment decision model in which the patient's risk profile is considered with respect to UGI safety. Within the SOS participating databases, 9 million new NSAID users were captured with 23,411 developing a first event of UGI complication during follow-up time. Two models for the risk of UGI complication were developed with Poisson regression. The Core Model included age, sex, and previous UGI complication as predictors. The Extended Model contained a common set of predictors including comorbidities. The Core Model showed good discriminative ability in the cross validation with c-statistics ranging from 0.63 to 0.80. The Extended Model had similar discriminative ability. A simple risk model using age, sex, and previous UGI complication and follow-up interval may provide adequate discrimination between NSAID users with and NSAID users without UGI complication occurrence.

Use of low-dose aspirin and risk of UGI bleeding

Not only NSAIDs, but also aspirin in a low dose (75-325 mg/day) can increase the risk of UGI bleeding.[207] Low-dose aspirin (LDA) is recommended for the secondary prevention of cardiovascular events.[8] Although a substantial number of meta-analyses have been published on this topic, the majority of reviews included only randomized controlled trials (RCTs).[30-33, 202, 203, 207] However, many of the RCTs exclude patients at high risk of UGI bleeding, and thus can underestimate the risk of bleeding associated with LDA use in real-world practice. One systematic review by García Rodríguez et al. included observational epidemiological studies published from 1990 to 2001, but no RCTs.[34] Therefore the study in **Chapter 11** aimed to analyze the magnitude of UGI bleeding risk with LDA use in an up-to-date meta-analysis of both prospective RCTs and observational studies. Eighteen studies were included; 7 RCTs, 10 case-control studies, and 1 cohort study. All studies found LDA use to be associated with an increased risk of UGI bleeding. Meta-analysis of RCT data showed that LDA use was associated with a 50% increase in UGI bleeding risk (OR 1.5; 95%CI: 1.2-1.8). The risk was more pronounced in observational studies (OR 3.1; 95%CI: 2.5-3.7). Further research is needed to identify patients at risk of UGI bleeding related to aspirin use as those should be targeted with GPAs. One Dutch prescription guideline currently provides recommendations to which aspirin users GPAs should be prescribed.[54, 55]

Risk of recurrent MI with concurrent use of clopidogrel and PPI

In this thesis we have elaborated on the use of gastroprotective agents, such as PPIs. The use of PPIs was strongly encouraged in patients at risk of NSAID attributable UGI tract damage. Although PPIs are considered to be relatively safe drugs with few adverse events, no drugs are completely without risk. The question is whether it would it be advisable for all NSAID users to use PPIs as a preventive strategy. One part of the answer lies within the safety assessment of the PPI itself. The widespread and often chronic use of PPIs (Figure 12.1) has raised concerns about the consequences of profound acid suppression. Although generally accepted as being safe, PPI safety issues have been evaluated by other investigators and were found to be associated with an increased risk of community-acquired pneumonia, bone fractures, *Clostridium difficile*-associated diarrhea and bacterial overgrowth, although some of these associations are still under debate.[305-308]

In **Chapter 12** we investigated a safety concern of more recent date related to PPI use in combination with clopidogrel and the occurrence of recurrent myocardial infarction (MI). Clopidogrel is an oral antiplatelet agent commonly used in addition to aspirin to reduce the risk of CV events. The conversion of clopidogrel to its active compound is catalyzed by several cytochrome P450 (CYP) enzymes, of which CYP2C19 is the most important.[247] PPIs, routinely co-administered with clopidogrel to lower UGI bleeding risk, are also metabolized by CYP2C19, and can competitively bind to its catalytic site. Therefore, PPIs are potentially hindering the conversion of clopidogrel to its active metabolite. RCTs that used ex vivo platelet function tests as surrogate markers for clinical endpoints, demonstrated that patients treated with omeprazole had an impaired clopidogrel response,[256, 309] but whether these changes translate into clinically meaningful differences had to be established.

To quantify the association between the concomitant use of PPIs and clopidogrel and the occurrence of recurrent MI a case-control study was conducted within a cohort of acute MI patients in the PHARMO Record Linkage System between 1999 and 2008. Cases were patients readmitted for MI. Among 23,655 patients hospitalized following MI, we identi-

fied 1,247 patients readmitted for a new ischemic event. Among clopidogrel users, current PPI use was associated with an increased risk of recurrent MI (OR 1.6; 95%CI: 1.2-2.3) when compared with no PPI use, but not when compared with past PPI use (OR 1.0; 95%CI: 0.4-2.4). The apparent association between recurrent MI and use of PPIs with clopidogrel could have resulted from confounding by indication. Observational studies on this topic, including ours, might lead to spurious results as they are unable to deal with unmeasured confounding. Study design that can partially overcome the risk of unmeasured confounders are case-only designs, for example a case-crossover study.[81] This is an elegant and efficient design in which only information is used from cases. As cases serve as their own control it deals efficiently with confounding factors that remain stable over the time within a person. This design would have been appropriately used as the outcome-of-interest, i.e. acute myocardial infarction, is an acute onset disease and PPI use can be thought of as having a short-term effect. However, the systematic increase of PPI utilization as was shown in this chapter (Figure 12.1) would potentially bias the results. Very recently a self-controlled-case series, another example of a case-only study, was published on this topic and showed no increased risk of CV events with the combined intake of clopidogrel and PPIs.[310] One randomized double-blind trial (which was prematurely terminated when the sponsor lost financing) of omeprazole vs. placebo in 3,761 patients taking dual therapy (clopidogrel and aspirin) demonstrated no significant difference in CV events between both study arms (hazard ratio 0.99; 95%CI: 0.68-1.44).[311] A second much smaller trial showed that PPI co-treatment (esomeprazole) significantly reduced the incidence of endoscopic ulcers in 165 patients at high risk of CV and UGI events, but did not find a significant difference in CV events and mortality.[312] Pharmacodynamic data consistently indicate that omeprazole diminishes the effect of clopidogrel on platelets, but this might not translate into clinical relevant endpoints. Although the only larger and well-designed RCT on this topic investigated omeprazole and revealed no significant difference in a composite CV endpoint, until this date a precaution is still in force to avoid omeprazole and esomeprazole in patients on clopidogrel therapy in Europe. Pantoprazole is suggested as a safe alternative. However, PPI co-therapy should not be withheld from patients on clopidogrel and aspirin if they have additional risk factors for UGI complications to provide the optimal balance of risks and benefits.

Validity of coding for upper gastrointestinal bleeding

All studies described in this thesis are based on various disease coding systems to identify patients with UGI bleeding or MI from the participating databases. To perform valid research the quality of the data should be trustworthy. In **Chapter 13** a validation study was conducted in four databases: (i) IPCI (Netherlands); (ii) HSD (Italy); (iii) ARS Tuscany (Italy); and (iv) Aarhus (Denmark). Three diagnosis coding systems were used: (i) International Classification of Diseases (ICD-) 9th revision (HSD, ARS[59]); (ii) ICD-10th revision (Aarhus); and (iii) International Classification of Primary Care (ICPC[61]) (IPCI). A random sample of 200 potential UGI bleeding cases was selected from each database (400 for IPCI) and reviewed manually by medically trained assessors. Positive predictive values (PPV) for UGI bleeding were calculated. The PPV was 23% (95%CI: 17%-30%) and 25% (95%CI: 18%-31%) in IPCI for free text and ICPC codes, respectively. The PPV was 92% (95%CI: 88%-97%) for codes and 50% (95%CI: 37%-63%) for free text only in HSD. The overall PPV for the ICD-9-based system in ARS was 77% (95%CI: 71%-83%) and 84% for the ICD-10-based coding system (95%CI: 78%-89%) in Aarhus. This showed that there were substantial differences in the accuracy of automated case identification using various databases with differences in the coding systems and in the type of data collected.

To evaluate whether coding misclassification impacted risk estimation of drug-related UGI bleeding, a cohort study was performed in the four databases. Relative risks were estimated for a set of drugs known to be associated with UGI bleeding and the effect of misclassification was evaluated using varying thresholds for PPV. In general, the use of codes having lower PPV resulted in only small changes in the estimated RRs of drugs known to be associated with UGI bleeding. This validation study was conducted within the context of the European Commission-funded EU-ADR Project (Exploring and Understanding Adverse Drug Reactions by integrative mining of clinical records and biomedical knowledge). This is a computerized integrated system of European databases aiming for early detection of drug safety signals.

Methodological considerations

Setting

All studies, except for the meta-analyses described in Chapter 11, were conducted in electronic health care databases. The IPCI database is one of them and is used in all studies, except for Chapter 12. The IPCI Project was started in 1992 by the Department of Medical Informatics of the Erasmus University Medical Center.[102] IPCI is a longitudinal observational database that contains data from computer-based patient medical records of a selected group of general practitioners (GPs) throughout the Netherlands, who voluntarily choose to supply data to the database. GPs receive a minimal reimbursement for their data and control usage of their data through a steering committee. GPs are permitted to withdraw data for specific studies. Collaborating practices are located throughout the Netherlands and the collaborating GPs are comparable with other GPs in the country according to age and gender. The database contains information on over 1 million patients. This is the cumulative number of patients who have ever been part of the dynamic cohort of patients registered in the database. The database is updated approximately every 6 months when a data draw down is made for research purposes. The database contains identification information (age, sex, patient identification, GP registration information), notes on symptoms and diagnoses, prescriptions, physical findings, and laboratory values (e.g. potassium, sodium, creatinine). Prescription data such as product name, quantity dispensed, dosage regimens, strength and indication are entered and are coded following the Anatomical Therapeutic Chemical (ATC) classification scheme recommended by the WHO.[60] ICPC is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. This is one of the unique features of the database as the information recorded in narratives can be considered as a very rich source on specialists discharge letters and on symptoms, but this is also its Achilles heel. As a result of the unstructured way that free text is entered in the medical record (including spelling and typing errors) by the GPs, an automated search in free text unavoidably leads to the inclusion of false positives. As a result the accuracy of identifying patients with a certain disease is low for free text as was shown in Chapter 13. However, in the case of UGI bleeding, the ICPC codes related to UGI bleeding also poorly identify patients with UGI bleeding as the ICPC coding terminology is very restrictive. None of the four available ICPC codes refers specifically to UGI bleeding, but rather to uncomplicated peptic ulcers or signs of UGI bleeding only. In the case of other events, such as acute myocardial infarction or colorectal cancer, the ICPC codes correspond to a higher positive predictive value in IPCI; 75% and 90%, respectively.[313] This shows that for complete information regarding the cases, the free text search is of importance as not all events are

recorded according to an ICPC code, but free text should not be included without manual validation. In the included studies UGI events in the IPCI database were always manually reviewed, except for Chapter 9. Currently advanced text mining activities are being implemented to reduce the burden of manual inspection of medical records.[294]

A variety of other electronic healthcare databases have been used in the context of the gastroprotection studies (Chapters 4, 6-8), the SOS study (Chapter 2, 9 and 10) and the validation study (Chapter 13). They can be classified as medical record databases such as IPCI, GPRD, THIN, HSD, and Pedianet, or as administrative hospital databases such as PHARMO, GePaRD, OSSIFF, SISR, Tuscany and Aarhus. The databases originated from the Netherlands, UK, Germany, Denmark, and Italy. All of the databases have been described in more depth in the individual studies. Each database has specific limitations and strengths with regard to size, follow-up time, richness or detail in which the data is captured, representativeness of the underlying cohort and the possibility to capture over-the-counter (OTC) drug use. When initiating a research project it is important to reflect which database, or which combination of databases, can serve as a valid data source.

General limitations related to observational research

All databases are of an observational nature, which means that associations are examined in their natural setting without an experimental intervention. This has some advantages over high-quality evidence from RCTs (the counterpart of observational studies) as observational data allow a more representative sample of real-world data to be collected. This helps in translating and extrapolating the study findings to a more general public. In addition, observational studies are often the only practical method to overcome problems as RCTs might be unethical in certain circumstances (for example to study the association between smoking and lung cancer, and to a lesser extent in the study on adherence to GPAs as described in Chapters 6 and 7. Observational data is known to include a larger study population with a longer follow-up period and thereby can provide more stable risk estimates. The study costs are generally lower than for RCTs. In addition, results can be obtained relatively quickly when working with retrospective data compared with prospective data. However, poor conduct of observational studies, and in particular of case-control studies, has led to a bad reputation of this study design. Indeed, observational studies also have substantial drawbacks, such as the potential for confounding due to the non-randomized nature of the patient groups. Results from observational data should therefore be interpreted with care as they are susceptible to bias (selection and information) and confounding.[314] These issues have been discussed in the individual discussion sections of the chapters. In short, selection bias occurs at the stage of recruitment of participants when selection probabilities are influenced by exposure or disease status. The best example is nonresponse bias; people who respond to participate in a study tend to have a healthier lifestyle than the non-responders. The risk of selection bias is limited in database research, as the cases and controls derive from the same population and the same in- and exclusion criteria apply.

Information bias may occur when the information obtained from subjects is inaccurate regarding the outcome or the exposure. If the information on drug exposure is obtained differently in cases and controls, a differential information bias is the result. In database studies the risk for differential misclassification is reduced because the data is gathered prospectively and independently of a specific hypothesis. However, in the case of NSAID use and risk of UGI complications, misclassification of outcome is possible. Individuals using NSAIDs may be more likely to consult their physician when experiencing gastrointestinal complaints, as they may have been advised to do so by the prescriber. In addition,

knowledge of an individual's exposure status to NSAIDs may affect the likelihood of GPs or specialists diagnosing a UGI complication, as this is a well-known NSAID-related drug reaction. In this specific case that would lead to an overestimation of the true estimate. Apart from the differential misclassification, which could result in an over- or underestimate of the real association, non-differential misclassification may occur when the exposure or outcome is not completely accurately captured, but for both cases and controls equally. This will drive the risk estimates towards the null (towards an OR of 1). In our studies over-the-counter (OTC) use of NSAIDs and GPAs is not captured. We might have assessed patients as not taking NSAID therapy while they were purchasing NSAIDs OTC. This might have resulted in an underestimation of the true effect.

Confounding, and in our studies especially confounding-by-indication, can lead to spurious results. A confounder may explain (partially) the observed association between the exposure and outcome when it is associated with the exposure and is a risk factor for the outcome, but not an intermediate factor in the causal pathway. Confounding-by-indication is introduced when more severely ill patients with a worse prognosis are more likely to receive a treatment than healthier patients. One example from Chapter 12 of the thesis is that PPI use in combination with clopidogrel increases the risk of developing acute myocardial infarction (MI). However, patients with comorbidities more frequently use PPI and comorbidities increase the risk of acute MI. Comorbidity (i.e. measured through the number of different prescriptions in the one year preceding cohort entry) is the confounder in this example. Confounding can be dealt with through restriction to patients with, in this example, no comorbidity or by matching on comorbidity status. Matching was performed in all the described case-control studies on factors which were conceived as major risk factors for the disease, such as age or sex. In the analysis phase, adjustment for multiple potential confounders or stratification can be applied. Sometimes information is not available on all confounders in our datasets. As a result confounding adjustment is impaired and residual confounding (both from unmeasured confounders or confounders not properly captured) may have occurred. In order to minimize the risk of confounding by indication we chose to use an active comparator reference category in Chapter 9 (past use of any NSAIDs) and in Chapter 12 (past use of PPIs). In Chapter 12, a propensity score was developed to balance the exposed group with the unexposed group to PPIs.

Future directions

Extensive research has been performed on the occurrence of UGI complications in patients receiving NSAID therapy. In recent studies, the focus has shifted from events of the upper GI tract to events of the lower GI tract, especially bleeding from the small intestine. Coxibs are thought to be potentially safer to the entire gastrointestinal tract than the combination of nsNSAID plus GPAs. Unfortunately, the identification of small intestinal bleeding is difficult and this outcome is not easily obtained in database studies.

However, how safe are the coxibs compared with nsNSAIDs with respect to CV safety? In studies such as the SOS project, multiple outcomes are considered. A more holistic approach should be considered when dealing with adverse events related to NSAID use. The risk of CV events and UGI events should be weighed for each individual patient so an informed decision can be made on whether a patient is a suitable candidate for NSAID therapy and, if so, which type of NSAID would be the safest option. The effectiveness of NSAID-therapy in the condition with which the patient presents should also be taken into

account. The decision-making model for the prescription of NSAIDs should thus include not only the patients' risk profile but also clear indications for which prescription is warranted. We should aim for personalized medicine and provide tailor-made recommendations. With all the overwhelming evidence now available, clear guidance should be provided to prescribers and patients concerning efficacy and safety. This could be achieved not only in the form of guidelines and recommendations, but with easily accessible smart phone-applications or web-based tools integrated into the electronic medical record, to help assist in the safe prescription of NSAIDs.

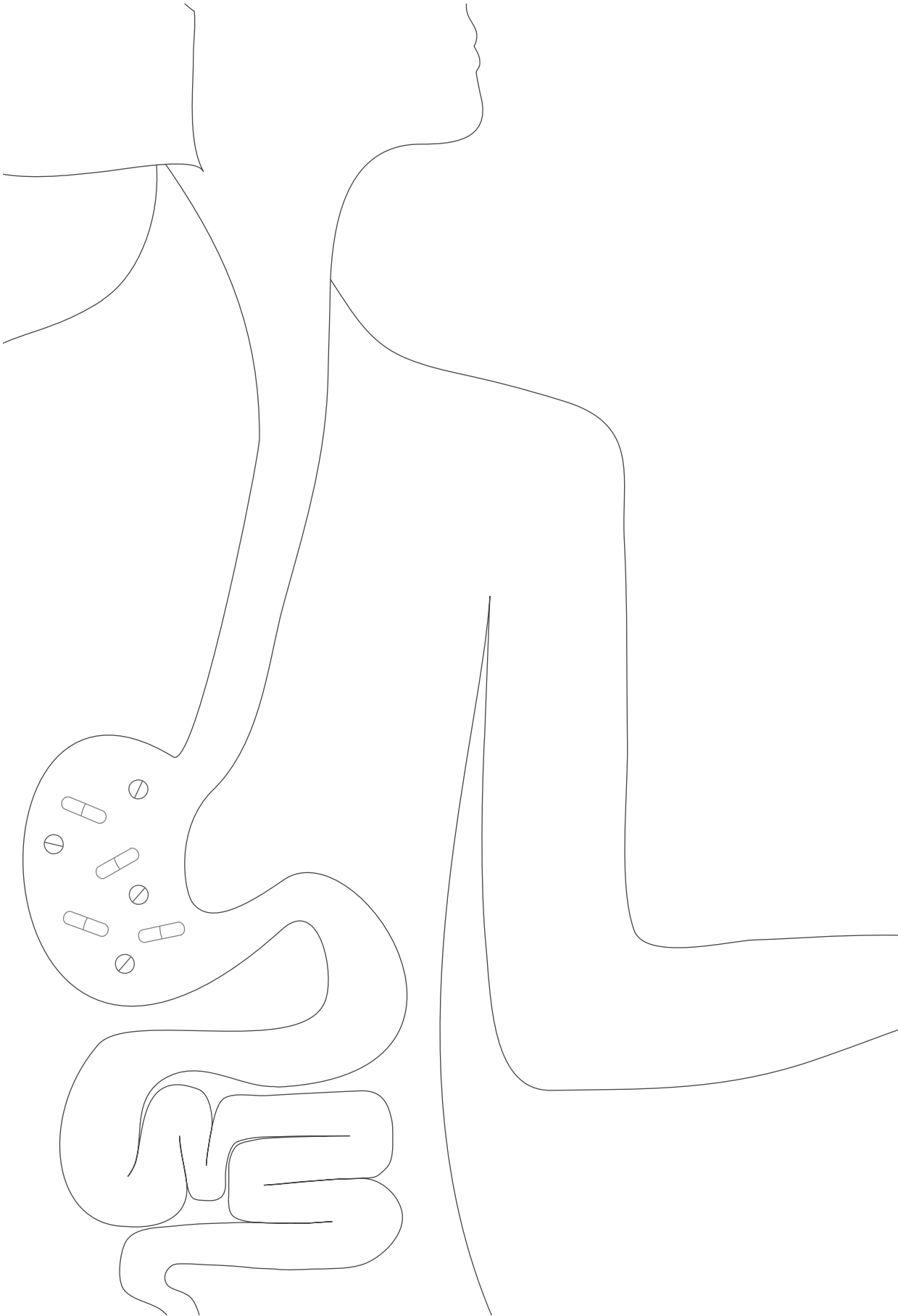
The collaboration between multiple electronic healthcare databases results in a large amount of combined data. This provides the opportunity to investigate relatively rare adverse events in commonly used drugs, such as UGI bleeding in all NSAID users, and rare drug exposure. However, despite the large numbers, rare outcomes related to less commonly used drugs cannot be studied. Creating larger data platforms by forming further international collaborations would increase the potential to study infrequently used NSAIDs and their UGI and CV risk. Apart from the UGI and CV risks associated with NSAID therapy, they are known to cause a deterioration in renal function and liver enzyme disorders. Other, yet unknown, adverse events also deserve further exploration. Although these may seem unlikely as NSAIDs have been marketed for a long time, events with a high background incidence rate and with a multifactorial causal pathway may as yet have gone unrecognized, as this makes it more difficult to identify NSAIDs as one of the contributing risk factors. In addition, adverse events with a limited increased relative risk may have major implications for public health as NSAID use is highly prevalent. Hypothesis-generating studies on other risks related to NSAID or aspirin therapy can be generated by projects such as EU-ADR and its equivalents. Besides single drug adverse events, drug-drug interactions can also be investigated in larger platforms. Concomitant use of NSAIDs, aspirin and other drugs believed to increase the risk of UGI bleeding can only be studied in large datasets. This data is mostly lacking at present. Further investigations should focus on the safety of concomitant use of nsNSAIDs, PPIs, and glucocorticoids.

The safety of PPIs should be monitored closely. PPIs are extensively used in the general population and are often used over a long time period. As PPIs have only been available for three decades, long-term adverse drug events may still emerge as a result of profound acid suppression. Future studies should evaluate the possible safety issues of PPIs, and potential undesired drug-drug interactions as PPIs are metabolized via the cytochrome P450 (CYP) enzymes. Initiatives such as EU-ADR can contribute to pro-active safety monitoring of PPIs over time.

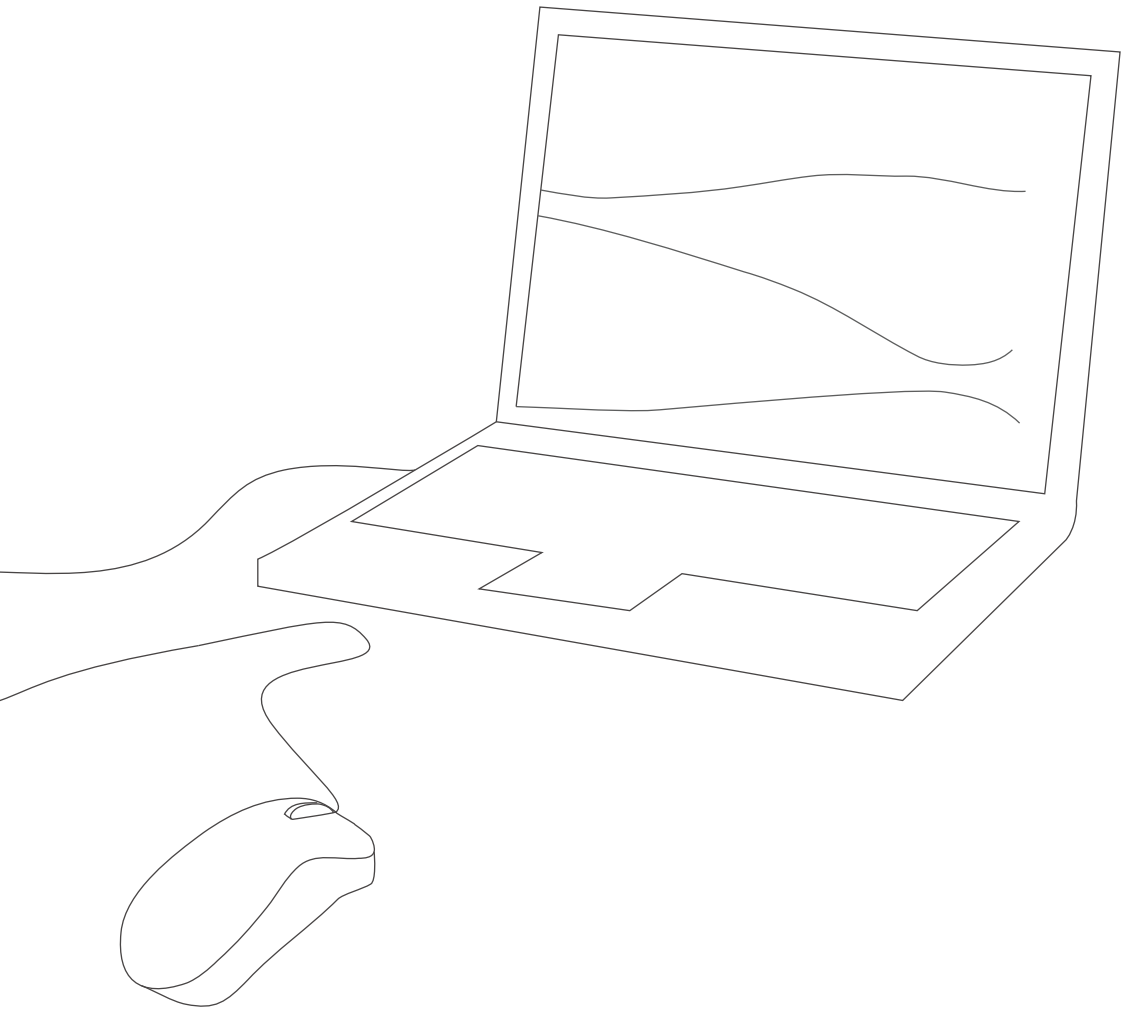
Additionally, the impact of the retrenchment of the Dutch basic health insurance package on GPA reimbursement should be investigated to understand whether these measures have led to an increased hospitalization rate as result of aspirin or NSAID intake, unprotected by GPAs.

The risk of UGI bleeding associated with aspirin use is not always recognized, neither in the general population nor by physicians. Prescribers of aspirin are often not fully aware which comorbidities are associated with an increased risk of aspirin related UGI bleeding and whether GPAs are recommended to lower that risk. It is generally assumed that the risk factors for NSAID-related UGI bleeding risk apply to low dose aspirin users as well. Risk profiling of aspirin users needs to be investigated in more depth in the future.

To end, there is also positive news on the frontline of research on aspirin and NSAID therapy. Aspirin and NSAIDs are suggested to have a protective effect against colorectal carcinoma. In addition they may play a role in the prevention of adenocarcinoma of the esophagus in patients with Barrett's esophagus. Further studies into these topics are appropriate and should focus on the lowest effective dose and optimum treatment duration.



Appendix



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List of abbreviations

Abbreviation	Explanation
ADP	Adenosine diphosphate
AP	Angina pectoris
ARIMA	Auto-*r*egressive, *i*ntegrated, *m*oving *a*verage
ASA	Acetylsalicylic acid
ATC	Anatomical Therapeutic Chemical Classification System
BC	Before Christ
BNF	British National Formulary
CI	Confidence Interval
COGENT	Clopidogrel and the Optimization of Gastrointestinal Events
COX	Cyclo-oxygenase
Coxib	Cyclooxygenase-2 inhibitor
CV	Cardiovascular
CYP	Cytochrome P450 enzymes
DDD	Defined daily dose
DE	Germany
DW	Data warehouse
EC	European Commission
EMA	European Medicines Agency
EU	European Union
FDA	Federal Drug Agency
FP7	Seventh Framework Programme for Research and Technological Development of the European Union
GePaRD	German Pharmacoepidemiological Research Database
GP	General practitioner / family physician
GPA	Gastroprotective Agent
GPRD	General Practitioner Research Database
H_2RA	Histamine-2-receptor Antagonist
HES	Hospital Episode Statistics
HSD	Health Search/CSD Longitudinal Patient Database
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICH	International Conference of Harmonization
IPCI	Integrated Primary Care Information database
IT	Italy
LDA	Low-dose acetylsalicylic acid

Abbreviation	Explanation
MI	Myocardial infarction
MSK	Musculoskeletal
NA	Not applicable
NL	The Netherlands
NNH	Number Needed to Harm
NNT	Number Needed to Treat
NSAID	Non-Steroidal Anti-inflammatory Drug
nsNSAID	Non-selective Non-Steroidal Anti-inflammatory Drug
OPCS-4	Office of Population, Censuses and Surveys: Classification of Interventions and Procedures, 4th Revision
OR	Odds Ratio
OSSIFF	Osservatorio Interaziendale per la Farmacoepidemiologia e la Farmacoeconomia
OTC	Over-the-counter
PAD	Peripheral arterial disease
PAI	Platelet aggregation inhibitors
PDC	Percentage of Days Covered
PPI	Proton Pump Inhibitor
PY	Person years (a commonly used denominator correcting for incomplete participation of individual patients)
RLS	Record Linkage System
RR	(incidence) rate ratio – relative risk
SAE	Serious adverse event
SISR	Sistema Informativo Sanitario Regionale (Regional Health Information System)
SSRI	Selective Serotonin Reuptake Inhibitor
THIN	The Health Improvement Network
TIA	Transient ischemic attack
UGI	Upper Gastrointestinal
UGIB	Upper gastrointestinal bleeding
UGIC	Upper gastrointestinal complication
UK	United Kingdom
WHO	World Health Organization of the United Nations

Nederlandse samenvatting

Introductie

Dit proefschrift beschrijft studies over de risico's van pijnstillers, zoals ibuprofen, diclofenac en naproxen. Dit zijn pijnstillers die bijna iedere Nederlander wel een keer heeft gebruikt voor hoofdpijn of voor buikpijn. In Nederland worden deze pijnstillers, ook wel NSAID's (Non-Steroidal Anti-Inflammatory Drugs) genoemd, door ruim 3 miljoen mensen per jaar gebruikt. De pijnstillers zijn te koop bij de drogist of de supermarkt zonder recept van de huisarts. Echter het gebruik van geen enkel medicijn is volledig zonder risico's. Deze NSAID's kunnen namelijk complicaties op het maagdarmstelsel geven. Mensen die deze pijnstillers gebruiken, hebben een drie tot vier keer zo hoog risico op het ontstaan van maag complicaties in vergelijking met niet-gebruikers van NSAID's. Het gebruik van NSAID's kan namelijk leiden tot beschadiging van het slijmvlies van de maag en darmen. Bij een klein deel van de mensen kan dit tot ernstige gevolgen leiden, zoals een maagbloeding. Ondanks dat de behandelmogelijkheden sterk verbeterd zijn in de afgelopen decennia, gaat een maagbloeding nog steeds gepaard met sterfte. Ongeveer tien procent van de mensen met een maagbloeding komt hieraan te overlijden.

Onder het mom van 'voorkomen is beter dan genezen' zijn er maagbeschermers beschikbaar, welke gelijktijdig kunnen worden ingenomen met de NSAID's om het risico op ernstige maag complicaties te verkleinen. Deze beschermende tabletten zijn met name bestemd voor patiënten met een hoger risico op maagbloedingen. Risico patiënten zijn onder andere oudere mensen, mensen die al eerder ernstige maag complicaties hebben gehad, en mensen die gelijktijdig andere medicatie gebruiken zoals bloedverdunners.

Er zijn landelijke richtlijnen voor huisartsen en medisch specialisten opgesteld die dienen als leidraad in het voorschrijven van NSAID's. Hierin wordt uitgelegd welke risico patiënten in aanmerking komen voor een beschermend maagtablet ten tijde van het gebruik van een NSAID. Als alternatief is er ook de mogelijkheid om de traditionele NSAID in te wisselen voor een nieuw ontwikkelde NSAID, namelijk Cox2-remmers (coxibs). Deze coxibs worden veiliger geacht dan de traditionele NSAID's met betrekking tot complicaties van het maagdarmstelsel. Soms worden er ook nog extra maagbeschermers voorgeschreven aan mensen die coxibs gebruiken als additionele voorzorgsmaatregel. Helaas veroorzaken NSAID's ook nog bijwerkingen buiten het maagdarmstelsel. Het gebruik van NSAID's, in het bijzonder de coxibs, wordt namelijk geassocieerd met een hoger risico op een hartaanval of een beroerte. Deze verontrustende berichten zijn sinds 2004 aan het licht gekomen. Deze achtergrond wordt in **hoofdstuk 1** beschreven.

Belangrijkste resultaten

Het gebruik van NSAID's en maagbeschermers

In **hoofdstuk 2** beschrijven we dat het gebruik van NSAID's erg laag is bij kinderen in Nederland en Italië, maar toeneemt onder adolescenten. In Duitsland en Engeland daarentegen worden NSAID's veelvuldig voorgeschreven aan kinderen onder de drie jaar. De verklaring ligt waarschijnlijk in het feit dat ibuprofen ook gebruikt wordt als behandeling van koorts. In **hoofdstukken 3 en 4** tonen we aan dat ruim de helft van de volwassen patiënten die een hoog risico lopen om maag complicaties te ontwikkelen bij het gebruik

van NSAID's daarbij niet de gewenste beschermende middelen ontvangen. Deze ongewenste situatie is vergelijkbaar in Engeland, Nederland en Italië. Gelukkig is er een sterke verbetering ten opzichte van tien jaar geleden zichtbaar. In **hoofdstuk 5** ligt de focus op patiënten die een verhoogd risico hebben op hartklachten ten tijde van NSAID gebruik. Hieruit blijkt dat er bij een kwart van de mensen die bij de huisarts komen met een spier- of gewrichtsklacht een NSAID wordt voorgeschreven. Tevens blijkt dat er onvoldoende rekening gehouden wordt met het risico van sommige van deze patiënten op hart- en vaatziekten.

Beoordeling van de veiligheid van NSAID's en maagbeschermers

Uit de studies beschreven in **hoofdstukken 6 en 7** blijkt dat als een patiënt die NSAID's gebruikt niet zorgvuldig genoeg omgaat met maagbeschermers, deze een verhoogd risico loopt op maagbloedingen. Patiënten met slechte therapietrouw voor de maagbeschermer tijdens het gebruik van NSAID's hadden een verdubbeling van de kans op een maagbloeding. Dit verhoogde risico op complicaties is vermijdbaar door de maagbeschermers trouw te gebruiken. Verder toont de studie in **hoofdstuk 8** aan dat er geen verschil is in het risico op ernstige maagklachten tussen het gebruik van de traditionele NSAID's met zorgvuldig gebruik van de maagbeschermer of de nieuwere coxib. In **hoofdstuk 9** onderzoeken we of het risico op maagbloedingen en andere complicaties van het maagdarmstelsel, zoals een maagperforatie of obstructie, verschilt per individueel NSAID. Sommige van de in totaal 20 onderzochte individuele NSAID's hebben nagenoeg geen verhoogd risico op maagproblemen. Anderzijds gaven andere individuele NSAID's een zeven keer verhoogd risico op maagklachten. Deze studie is verricht in een zeer grote West-Europese populatie waarin we 8,5 miljoen gebruikers van NSAID's volgden. Dit is daarmee dan ook de grootste studie welke verricht is op dit gebied. Uit de resultaten gepresenteerd in **hoofdstuk 10** blijkt dat voorspellers voor de ontwikkeling van een maagbloeding tijdens NSAID gebruik een hogere leeftijd, het mannelijk geslacht en een voorgeschiedenis van een eerdere maagcomplicatie zijn. In de literatuurstudie verricht in **hoofdstuk 11** onderschrijven we dat niet alleen NSAID's maar ook de nauw verwante aspirine een anderhalf tot drie keer verhoogd risico geeft op maagbloedingen. Aspirine is een bloedverdunner en wordt vaak voorgeschreven ter preventie van hart- en vaatziekten aan mensen die al eerder een hartaanval of een beroerte gehad hebben. In **hoofdstuk 12** onderzoeken we of de maagbeschermer zelf veilig is, of dat deze een negatieve interactie aangaat met een andere bloedverdunner, genaamd clopidogrel. De interactie tussen deze twee medicijnen zou ertoe kunnen leiden dat de bloedverdunner onvoldoende werkzaam is. We komen tot de conclusie dat de vermeende interactie welke gevonden is in andere database onderzoeken ook het gevolg kan zijn geweest van 'verstorende factoren', ook wel 'bias' genoemd. Als laatste bekijken we in een validatie studie of we mensen met een maagbloeding goed kunnen identificeren via bepaalde coderingssystemen (**hoofdstuk 13**). Het blijkt dat de toegekende codes voor maagbloedingen door huisartsen of ziekenhuismedewerkers vaak terecht zijn. Voor een van de deelnemende databases is het noodzakelijk om per patiënt het volledige medisch dossier na te kijken of deze daadwerkelijk een maagbloeding gehad heeft.

In het afsluitende hoofdstuk (**hoofdstuk 14**) worden de belangrijkste bevindingen van de voorgaande hoofdstukken samengevat en in een breder context geplaatst. Daarnaast worden de databases met hun methodologische tekortkomingen en de mogelijkheden voor vervolgonderzoek besproken.

PhD Portfolio

Research skills

2008 – 2010	Master of Science in Clinical Epidemiology, Netherlands Institute for Health Sciences, Rotterdam
2009	Scientific English writing course, Erasmus University, Rotterdam

Oral Presentations

Influence of naïve period on incidence of NSAID use
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, USA 2011

Adherence to gastroprotective agents and the risk of upper gastrointestinal complications in NSAID users
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, UK 2010
- Digestive Disease Week, Chicago, USA 2011

Adherence to proton pump inhibitors and the risk of upper gastrointestinal complications in coxib users
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, UK 2010
- Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2011

Concomitant use of a proton pump inhibitor does not increase the risk of recurrent myocardial infarction among clopidogrel users
- Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2010
- Digestive Disease Week, New Orleans, USA 2010

Changes in use of prophylactic strategies with NSAID treatment over the past decade
- Dutch Society of Gastroenterology, Veldhoven, the Netherlands 2009
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Rhode Island, USA 2009

Poster Presentations

Validation of the diagnosis for upper gastrointestinal bleeding
- Digestive Disease Week, San Diego, USA 2012
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Barcelona, Spanje 2012

NSAID use among children in Europe in the SOS project
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Chicago, USA 2011
- Digestive Disease Week, San Diego, USA 2012

Risk factors for upper gastrointestinal bleeding in patients using low-dose acetylsalicylic acid: a systematic literature review
- United European Gastroenterology Week, Stockholm, Sweden 2011

Trends in use of gastroprotective strategies with NSAID treatment in the UK, Italy, and the Netherlands
- International Conference on Pharmacoepidemiology & Therapeutic Risk Management, Brighton, UK 2010
- Digestive Disease Week, Chicago, USA 2011

Adherence to proton pump inhibitors and the risk of upper gastrointestinal complications in coxib users
- Digestive Disease Week, Chicago, USA 2011

Changes in use of prophylactic strategies with NSAID treatment over the past decade
- Digestive Disease Week, Chicago, USA 2009

Memberships

2009	Dutch Society of Gastroenterology
2009	International Society for Pharmacoepidemiology

Peer reviews

- Gut
- Aliment Pharmacology and Therapeutics
- Pharmacoepidemiology and Drug Safety
- Drugs & Aging
- BMC Family Practice

Tutoring

Supervising projects for PhD-students

- **Lisanne Holster**, "Gastrointestinal bleeding risk of the new oral anticoagulants – a systematic review of randomised controlled trials and meta-analysis", Department of Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, the Netherlands.

- **Aafke R. Koffeman**, "Prescription of NSAIDs in a primary care population with musculoskeletal complaints and ischemic cardiovascular risk", Department of General Practice, Erasmus University Medical Center, Rotterdam, the Netherlands.

- **Gwen M.C. Masclee**, "Cyclo-oxygenase-2 inhibitors or nonselective NSAIDs plus gastroprotective agents: what to prescribe in daily practice?", Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, the Netherlands.

- **Airin C.R. Simon**, "Use of Glucose Lowering Drugs and the Risk of Cancer Among Patients With Type 2 Diabetes: A Case-Control Study in The Netherlands", Department of Internal Medicine, Academic Medical Center, Amsterdam, the Netherlands.

- **Margreet F. Warlé-van Herwaarden**, "Development and application of quality indicators concerning the prevention of potentially avoidable hospital admissions related to medication (HARMs)", IQ Healthcare, Radboud University Medical Center, Nijmegen, the Netherlands.

Others

2010 - 2011	Student council International Society for Pharmacoepidemiology
2011 - 2012	Contributing to a report on the prevalence of hospital admissions related to medicines commissioned by the Dutch ministry of Health, Welfare and Sport

International and national press releases:

June 2010	More action needed to prevent stomach problems in NSAID users, despite recent progress
	Patiënten onvoldoende beschermd tegen bijwerking pijnstillers
April 2012	Not Taking Gastroprotective Drugs Prescribed with Anti-inflammatory Medicines Increases Risk of Upper GI Complications
	Maagbeschermers bewezen effectief bij pijnbestrijding

Publications

Publications based on studies described in this thesis

1. **Valkhoff VE**, Sturkenboom MC, Hill C, Veldhuyzen van Zanten S, Kuipers EJ.
   Low-dose acetylsalicylic acid use and the risk of upper gastrointestinal bleeding: a meta-analysis of randomized clinical trials and observational studies
   Canadian Journal of Gastroenterology, 2012.

2. **Valkhoff VE**, van Soest EM, Masclee GM, de Bie S, Mazzaglia G, Molokhia M, Kuipers EJ, Sturkenboom MC.
   Prescription of non-selective NSAIDs, coxibs and gastroprotective agents in the era of rofecoxib withdrawal – a 617,400-patient study
   Aliment Pharmacology and Therapeutics, 2012 Oct;36(8):790-9.

3. **Valkhoff VE**, van Soest EM, Mazzaglia G, Molokhia M, Schade R, Trifirò G, Goldstein JL, Hernandez-Diaz S, Kuipers EJ, Sturkenboom MC.
   Adherence to gastroprotection during cyclooxygenase-2 inhibitor use and the risk of upper gastrointestinal events: a population-based study
   Arthritis & Rheumatism, 2012 Aug;64(8):2792-2802.

4. van Soest EM, **Valkhoff VE**, Mazzaglia G, Schade R, Molokhia M, Goldstein JL, Hernandez-Diaz S, Trifirò G, Dieleman JP, Kuipers EJ, Sturkenboom MC.
   Suboptimal gastroprotective coverage of NSAID use and the risk of upper gastrointestinal bleeding and ulcers: an observational study using three European databases
   Gut, 2011 Dec;60(12):1650-59.

5. **Valkhoff VE**, 't Jong G, van Soest EM, Kuipers EJ, Sturkenboom MC.
   Risk of recurrent myocardial infarction with the concomitant use of clopidogrel and proton pump inhibitors
   Aliment Pharmacology and Therapeutics, 2011 Jan;33(1):77-88.

6. **Valkhoff VE**, van Soest EM, Sturkenboom MC, Kuipers EJ.
   Time-trends in gastroprotection with non-steroidal anti-inflammatory drugs (NSAIDs)
   Aliment Pharmacology and Therapeutics, 2010 Jun;31(11):1218-28.

Other publications

7. **Valkhoff VE**, Sturkenboom MC, Kuipers EJ.
   Risk factors for gastrointestinal bleeding associated with low-dose aspirin
   Best Practice & Research: Clinical Gastroenterology, 2012 Apr;26(2):125-40.

8. Hunfeld NG, **Valkhoff VE**, Touw DJ, Sturkenboom MC, Kuipers EJ.
   Clopidogrel and proton pump inhibitors: insufficient evidence of interaction
   Nederlands Tijdschrift Geneeskunde, 2011;155(28):A2404.

9. Sarker R, **Valkhoff VE**, Zachos NC, Lin R, Cha B, Chen TE, Guggino S, Zizak M, de Jonge H, Hogema B, Donowitz M.
   NHERF1 and NHERF2 are necessary for multiple but usually separate aspects of basal and acute regulation of NHE3 activity
   American Journal of Physiology-Cell Physiology, 2011 Apr;300(4):C771-82.

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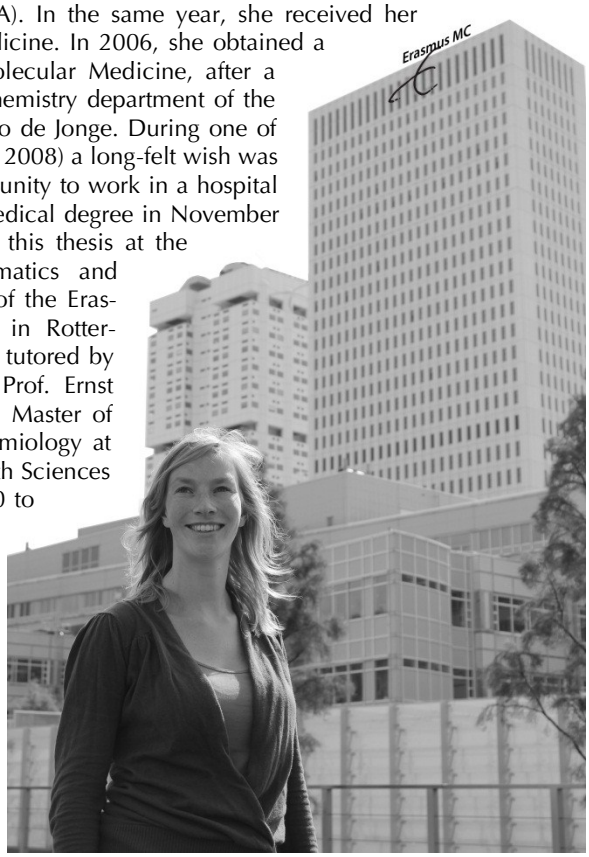
Vera

About the Author

Vera Esther Valkhoff was born on July 27th, 1983 in Delft, the Netherlands. In 2001 she graduated from Sint Stanislas college in Delft. She started medical school at Erasmus University in Rotterdam in 2001 and received her first-year diploma with cum laude honors. During her medical study she developed a special interest in basic science. Through a scholarship Vera had the opportunity to complete a research period of five months in 2005 at the Gastroenterology department of the John Hopkins University in Baltimore under supervision of Prof. Mark Donowitz, former chairman of the American Gastroenterological Association (AGA). In the same year, she received her Master of Science degree in Medicine. In 2006, she obtained a Master of Science degree in Molecular Medicine, after a year-long placement at the Biochemistry department of the Erasmus University with Dr. Hugo de Jonge. During one of her last clinical rotations (2006 to 2008) a long-felt wish was fulfilled when she had the opportunity to work in a hospital in Malawi. After receiving her medical degree in November 2008, Vera started her work on this thesis at the Departments of Medical Informatics and Gastroenterology & Hepatology of the Erasmus University Medical Center in Rotterdam. During this period she was tutored by Prof. Miriam Sturkenboom and Prof. Ernst Kuipers. In 2010 she obtained a Master of Science degree in Clinical Epidemiology at the Netherlands Institute for Health Sciences (NIHES) in Rotterdam. From 2010 to 2011 Vera was active as chair in the student council of the International Society for Pharmacoepidemiology. As of September 2012 she started her two-year internal medicine residency at Sint Franciscus Hospital in Rotterdam, after which she will start her training in Gastroenterology and Hepatology at Erasmus University Medical Center in Rotterdam.



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