PASS information

Title	**Safety Data on Etoricoxib from Swedish Registries of Spondyloarthropathy / Ankylosing Spondylitis Patients**
Version identifier of the final study report	**Version 1.0**
Date of last version of the final study report	30May2013 Note: This is not a "final" report.
EU PAS register number	**Study is not registered**
Active substance	**Etoricoxib** **ATC Code: M01AH05**
Medicinal product	**Etoricoxib (Arcoxia)**
Product reference	**UK/H/0532/01-04**
Procedure number	**EMEA/H/A/31/907 & EMEA/H/A/6(12)/906**
Marketing authorisation holder(s)	**Merck Sharp & Dohme Limited** Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
Joint PASS	***No***
Research question and objectives	**To provide additional post-marketing safety data regarding the use of etoricoxib for the indication of ankylosing spondylitis** **The specific project objectives are to:** • **Describe the characteristics of Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS)** • **Describe the use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS.** • **Estimate and compare the rates of clinical outcomes of special interest (gastrointestinal, renovascular, cardiovascular and cerebrovascular) with use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS.**

Key results and conclusion	**No significantly increased risks were identified in this population of AS and SpA patients for etoricoxib compared to nsNSAIDs and other coxibs. The results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in the treatment of AS and SpA is consistent with the safety profile of the product as labelled and as previously demonstrated during clinical development and through post-marketing pharmacovigilance.**
Country(-ies) of study	**Sweden**

Marketing authorisation holder(s)

Marketing authorisation holder(s)	**Merck Sharp & Dohme Limited** Hertford Road, Hoddesdon Hertfordshire EN11 9BU United Kingdom
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MERCK

Study Report
EP07013.013.13.084

Safety Data on Etoricoxib from Swedish Registries of Spondyloarthropathy / Ankylosing Spondylitis Patients

PPD

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30 May 2013

Table of Contents

1. Abstract

Title

Safety Data on Etoricoxib from Swedish Registries of Spondyloarthropathy / Ankylosing Spondylitis Patients – Annual Report, 30May2013

PPD

Sweden

Keywords

Etoricoxib (MK-0663; ARCOXIA), ankylosing spondylitis, spondyloarthropathy, retrospective analysis, clinical outcomes, safety

Rationale and background

Safety data regarding the usage of etoricoxib in inflammatory spondyloarthropathy (SpA) and ankylosing spondylitis (AS) patients is rather limited. Therefore the rationale for the study is to provide additional post-marketing safety data regarding the use of etoricoxib for these indications.

Research question and objectives

To describe the characteristics of Swedish patients with SpA and AS including the use of etoricoxib, other COX-2 inhibitors, and non-selective NSAIDs (nsNSAIDs). To estimate and compare rates of clinical outcomes of interest (gastrointestinal, renovascular, cardiovascular and cerebrovascular) in patients using various classes of NSAIDs.

Study design

This study is a retrospective analysis of patient level data using linkage of a series of Swedish national health care-related registers. Information on NSAID use was obtained from the prescription register. Clinical outcomes of interest were obtained from the Swedish Patient Register of Hospital Discharges and Outpatient Visits.

Setting

To be included in the cohort, patients had to have a diagnosis of SpA or AS after 01 January 2001. Information about nsNSAID and coxib exposure was extracted from the prescription registry from 01 January 2006 through 31 December 2009.

Subjects and study size, including dropouts

21,108 patients (10275 with AS and 13831 with SpA) were available for follow-up at the end of the study (31 Dec 2009).

Variables and data sources

AS and SpA diagnoses, baseline demographics, medications and comorbidities, exposure, and outcomes were all obtained from the Swedish health care registries. Outcomes included atherosclerotic cardiovascular events, atherosclerotic cerebrovascular events, congestive heart failure, severe hypertension, renovascular events, and gastrointestinal events.

Results

Based on the hospital/outpatient clinic source of the diagnoses and the high frequency of usage of Disease Modifying Anti-Rheumatic Drugs (DMARDs), biologics, and NSAIDs, the cohorts reflect a patient group with moderate to severe AS/SpA. The frequency of comorbidities is generally as expected for AS/SpA patients with a mean age of 46 years. Overall, 7.6% of patients were exposed to etoricoxib, 3.9% were exposed to other coxibs, and 71.2% were exposed to nsNSAIDs. In general, the fraction of patients exposed to etoricoxib, other coxibs and nsNSAIDs were similar for patients with AS and patients with SpA. Exposure in terms of defined daily doses tended to be higher for coxibs than for nsNSAIDs. Patients unexposed to any NSAIDs had slightly higher rates of cardiac and cerebrovascular events and slightly lower rates of gastrointestinal events in some analyses. No major differences were found for the clinical outcomes of interest between the groups of patients receiving etoricoxib, other coxibs, and nsNSAIDs.

Discussion

Overall, the results show no significantly increased risks for etoricoxib compared to nsNSAIDs and other coxibs in this population of AS and SpA patients. In addition, the cardiac and cerebrovascular event rates are in the range of what has been shown previously in the Swedish general population. The lack of power in this study makes it difficult to estimate whether small risk differences exist between the different types of NSAIDs. Also unmeasured confounders and confounding by indication might be affecting the observed results. Overall, the results of this study do not change the previously established favorable benefit-risk profile for etoricoxib.

Marketing Authorisation Holder

Merck Sharp & Dohme Corp.

Names and affiliations of principal investigators

PPD Sweden

2. List of abbreviations

AE	Adverse experience
AS	Ankylosing Spondylitis
ACE	Acetyl cholinesterase
CHMP	Committee Human Medicinal Products
CI	Confidence interval
COX-2	Cyclooxygenase-2
DDD	Defined daily dose
DMARD	Disease-Modifying Anti-Rheumatic Drug
DVT	Deep venous thrombosis
EDGE	Etoricoxib vs. Diclofenac Sodium GI Tolerability and Effectiveness study
EMEA	European Medicines Evaluation Agency
EMA	European Medicines Agency
GI	Gastrointestinal
GP	General Practitioner
GPRD	General Practice Research Database
MEDAL	Multinational Etoricoxib and Diclofenac Arthritis Long-term Program
MI	Myocardial infarction
NA	Not Applicable
NSAID	Nonsteroidal anti-inflammatory drugs
nsNSAID	non-selective NSAID
OA	Osteoarthritis
PASS	Post-authorization safety study
PE	Pulmonary embolism
Pts	Patients
PI	Principal Investigator
PUB	Perforations, ulcers or bleeding
PY	Person-years or patient-years
RA	Rheumatoid arthritis
RR	Relative Risk
SpA	Spondyloarthropathy
SPC	Summary of product characteristics
UK	United Kingdom
Yrs	Years

3. Investigators

PPD

Sweden

PPD

Merck

4. Other responsible parties

n/a

5. Milestones

Milestone	Planned date	Actual date	Comments
Start of data collection	*01 JAN 2011*	*15 NOV 2011*	Short delay due to revision requests for data extraction form
End of data collection	*01 MAR 2012*	*01 OCT 2012*	Legal issues regarding extraction of data from the Swedish biologics register delayed this process substantially
Registration in the EU PAS register	n/a	n/a	This study is not registered
Final report of study results	*30 JUN 2015*	TBD	

6. Rationale and background

The safety and efficacy of etoricoxib has been studied in patients with AS in a single Phase III Clinical Trial (MK-0663 Protocol 032) titled "A Double-Blind, Placebo- and Active-Comparator-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of MK-0663 in Ankylosing Spondylitis (AS)" [Ref. 5.3.5.4: 4072]. MK-0663 Protocol 032 was a double-blind, placebo- and active-comparator-controlled, parallel-group safety and efficacy study performed at 44 sites with 300 AS patients.

Because MK-0663 Protocol 032 was primarily designed to demonstrate efficacy, it provided only limited data on the safety profile of etoricoxib with respect to the incidence of GI clinical events (ulcers, gastrointestinal bleeding), thrombotic cardiovascular clinical events, congestive heart failure, or renovascular effects (hypertension, acute renal impairment / failure) in the treatment of patients with AS.

In addition to the above clinical trial data, a nested case-control post-authorization safety study of etoricoxib and other anti-inflammatory therapies in a cohort of patients with AS using data from general practice databases in the UK, France and Germany has been performed and reported to the CHMP annually since May 2010. Given the limited exposure to etoricoxib in the study, and the small numbers of patients with clinical outcome events of interest while exposed to etoricoxib, it was not possible to draw firm conclusions regarding the safety profile of etoricoxib for the indication of AS from the analysis.

As with other drugs in the same class, the SPC for etoricoxib which was agreed during the referral procedures in June 2008 (**Annex 2**) includes special warnings and precautions for use regarding:

- Upper gastrointestinal (GI) complications [perforations, ulcers or bleedings (PUBs)]
- Thrombotic events (especially myocardial infarction (MI) and stroke), relative to placebo and some NSAIDs.
- Impairment of renal function.
- Risk of fluid retention, edema and hypertension
- Risk of cardiac failure / left ventricular dysfunction

This study is being conducted by Merck & Co. Inc. as a post-licensure commitment to the European Medicines Agency (EMA). The rationale for the study is to provide additional post-marketing safety data regarding the use of etoricoxib for the indication of ankylosing spondylitis.

7. Research question and objectives

Objectives

The specific project objectives are to:

1. Describe the characteristics of Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS)
2. Describe the use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS. Describe potential predicators/confounders of use of etoricoxib, other COX-2 selective inhibitors, and non-selective NSAIDs
3. Describe incidence rates of outcomes of interest for etoricoxib, other coxibs, and nonspecific NSAIDs in Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS). Present incidence rates for outcomes of interest adjusted for potential confounders

Hypothesis

This study is for estimation purposes. The clinical outcomes of interest as stated in the objectives above are known to be associated with anti-inflammatory treatments (nsNSAIDs and COX-2 selective inhibitors) and are described in drug class labeling. Comparisons of clinical outcomes among the drugs of interest will be made by descriptive comparison of the point estimates for the incidence rates and their associated 95% CIs, using both clinical and epidemiological judgment and in light of the limitations of this observational study.

Note: The study was performed as 3 separate analyses corresponding to the 3 objectives. The majority of Section 9: Research Methods are applicable to all 3 analyses and are presented in a combined manner. Section 10: Results are presented separately for the 3 objectives, and Sections 11 onward are presented for the full report.

8. Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	11APR2011	Variables	Added clinical outcome of "Hypertension, severe" (defined as hospital admission with a primary diagnosis of hypertension)	
2	4Q12-2Q13	Various (Subjects, exposure, statistical methods)	See Section 9.9.5 for details	Increase the sample size, clarify data handling, simplify analyses due to small number of outcomes

9. Research methods

9.1. Study design

This study is a population- and register-based nationwide matched cohort study of ankylosing spondylitis and spondyloarthropathy patients treated with various classes of NSAIDs or untreated, using data from 1987-2009. This study is designed as a retrospective analysis of patient level data using a series of Swedish national health care-related registers. There will be no active enrolment or follow-up of patients, and no data will be collected directly from patients.

This study is for estimation purposes. The clinical outcomes of interest (gastrointestinal, renovascular, cardiovascular and cerebrovascular) as stated in the objectives above are known to be associated with anti-inflammatory treatments (nsNSAIDs and COX-2 selective inhibitors) and are described in drug class labelling. Comparisons of clinical outcomes among the drugs of interest will be made by descriptive comparison of the point estimates for the incidence rates and their associated 95% CIs, using both clinical and epidemiological judgment and in light of the limitations of this observational study.

9.2. Setting

Location: Sweden

Definitions of Time Points/Periods Used for Analyses

Study Period
The study period will begin on 1 Jan 2001 and end on 31 Dec. 2009 (or the latest date for which data are available from the various registers).

Baseline Period
Data prior to 2001 (as far back as 1987) will used as available to characterize baseline characteristics of the study population.

Refer to **Figure 1** for the time points and time periods that are relevant to the analyses.

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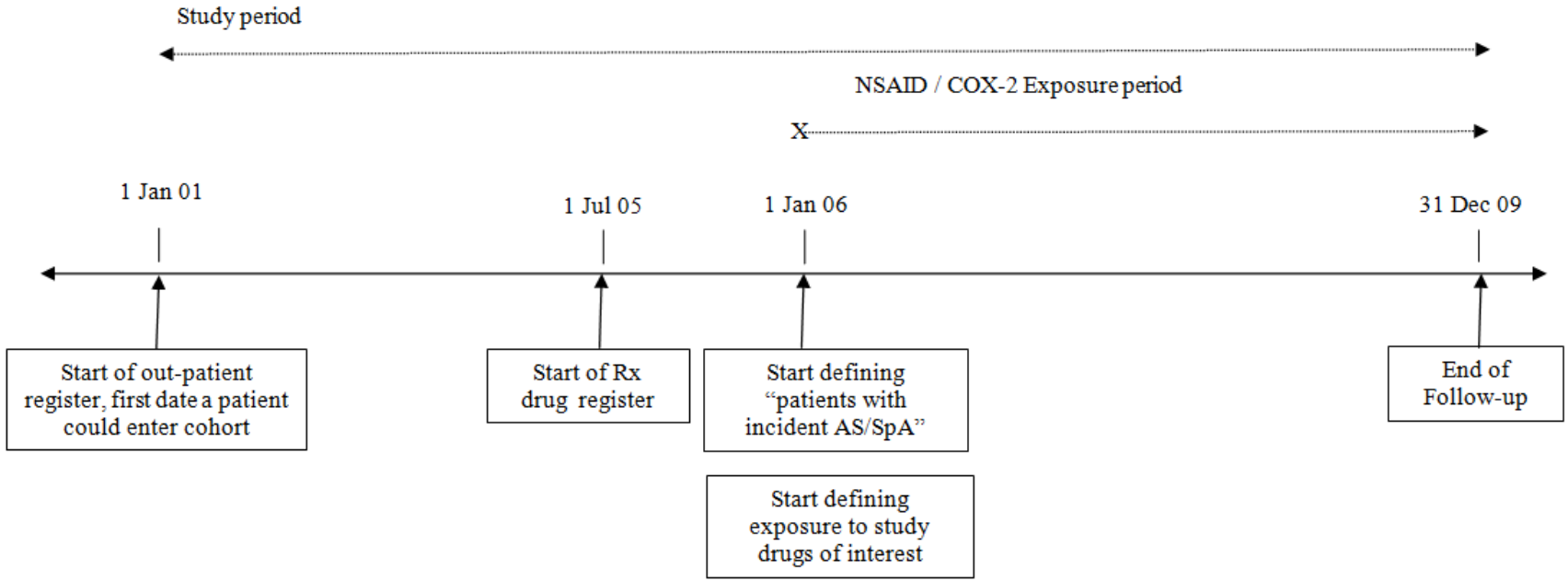
Figure 1. Study Design / Time Periods for Analysis



X

Baseline* is all time up to 01 Jan 2006 for patients who entered the cohort prior to 01 Jan 2006

X

Baseline*is all time up to the date of cohort entry for patients who entered the cohort on or after 01 Jan 2006

* Baseline can extend as far back as 1987 nationally and Jan 1969 for certain regions of Sweden

01 Jan 2001: The time point when the Swedish Patient Register for out-patient specialist care was started, and the start of the Study Period

01 Jan 2006: The time point after which prescriptions for nsNSAIDs or coxibs are considered for purposes of defining exposure to study drugs of interest. This time point was chosen instead of the start of the "The Swedish Prescribed Drug Register" in July 2005 (as described in the protocol, **Annex 6**) in order to accumulate information on medication for comorbidities prior to the evaluation of risk, and because the "prescription pattern" for nsNSAIDs and coxibs stabilized after 01 Jan 2006 both with regard to new patients being exposed to nsNSAIDs or coxibs and with regard to the total number of registered prescriptions (see Annex 2, figures A - D). At the initiation of the prescription drug register the number of new prescriptions for nsNSAIDs / coxibs was high then fell off dramatically. This is probably an artifact due to the registry being new in mid-2005 (mix of recent prevalent and new incident prescriptions coming into the database). Exposure from the start of the prescription drug registry to 01 Jan 2006 is handled as a covariate in the adjusted models predicting the clinical outcomes.

01 Jan 2006: For purposes of most validly addressing the study safety objectives vis-à-vis etoricoxib, it was necessary to define a group of patients with complete data on exposure to nsNSAIDs and coxibs from the time they are first diagnosed with AS/SpA. This group would be patients whose Study Entry Date occurs on or after the start of the Exposure Period following the start of the "The Swedish Prescribed Drug Register" (i.e., 01 Jan 2006). These are referred to as patients with "incident" AS/SpA diagnosis. Note this time point of 01 Jan 2006 was changed from 01 Jan 2007 (in the protocol, **Annex 6**) in order to enlarge the population that could be regarded as "incident" and less likely to be extensively exposed to nsNSAIDs or coxibs. Per the protocol, patients with >180 DDD's of exposure were originally going to be excluded. This was altered to include patients with >180 DDDs of exposure (about 10% of the incident cases) in order to enlarge the incident population due to low number of outcome events.

31 Dec 2009: The last date of follow-up of and the end of the Study Period.

9.3 Subjects

This study is designed as a retrospective analysis of patient level data using a series of Swedish national health care-related registers. There will be no active enrolment or follow-up of patients, and no data will be collected directly from patients.

Eligibility Criteria

A patient will be eligible for inclusion on the first date all of the following criteria are met:

- Attended an out-patient clinic 2001-2010
- Age >=16 years on the date attended the out-patient clinic
- Registered with an ICD-code corresponding to SPA/AS (i.e. ICD10: M46.1, M46.8, M46.9, and ICD9: 720B, 720C or 720X for the appropriate periods) and AS (i.e. ICD10: M459 and ICD9: 720A for the appropriate periods)

Patients were excluded if:

The medical record diagnosis indicated a previous/concomitant (before or on the date of entry into the study) diagnosis of systemic lupus erythematosus (SLE) or juvenile inflammatory arthritis (JIA). Patients with these conditions were excluded since patients with these diagnoses are unlikely to have AS/SpA, and these are not likely to be misdiagnoses. Patients with other arthritis diagnoses such as rheumatoid arthritis or psoriatic arthritis are included since these can either be initial misdiagnoses or comorbid conditions.

Patients were assigned to cohorts for various time periods based on coded NSAID (etoricoxib, other coxib, nsNSAID) prescriptions that were dispensed to the patients according to the prescription database or assigned to the untreated cohort as applicable. Assumptions concerning the actual use of the prescriptions dispensed apply.

Study Entry Date

The date that a given patient met all eligibility criteria was designated as the Study Entry Date.

Patient Follow-up

Patients were followed until the earliest of emigration, death, or the end of the study period.

Cohorts:

Analyses are performed for the cohorts of patients defined by combinations of the following:

For SpA / AS diagnosis (SpA only, AS only, combined);

For prevalent SpA/AS patients, for incident SpA/AS patients, for all SpA/AS patients NSAID use: etoricoxib, other coxibs, nsNSAIDs, no NSAID treatment.

Note: there is not a true "new user" analysis because the incident SpA/AS patients could have limited prior NSAID exposure and only their initial NSAID course could be included in such an analysis. All NSAID treatment courses are included in the current analyses.

9.4. Variables

Diagnosis Variables:

SpA / AS diagnosis – See ICD-10 diagnosis codes in **Annex 4**.

Patients with AS/SpA were classified as having "prevalent" or "incident" AS/SpA at the time of entry into the Exposure Period. Patients with "prevalent" AS/SpA were defined as those with a pre-existing diagnosis in their medical record prior to 01 Jan 2006 while those with "incident" AS/SpA were defined as those with a first time diagnosis in the medical record on or after 01 Jan 2006.

SpA/AS disease common comorbidities: (ever recorded occurrence of diagnosis code of uveitis, inflammatory bowel disease, psoriasis, urethritis, hip-joint replacement surgery, aortic valve surgery). See diagnosis codes in **Annex 4**.

Duration since first recorded SpA/AS diagnosis code.

Duration since first recorded diagnosis of Low Back Pain.

9.4.1 Exposure

NSAIDs: medications classified as "non-selective NSAIDs", "etoricoxib", or "other coxib". See **Annex 3** for ATC codes. Note use of "over the counter" NSAIDs were not captured in the Prescribed Drug Register.

Exposure Period

Exposure period: The period during which reliable information about nsNSAID and coxib exposure is available: 01 Jan 2006 through 31 Dec 2009.

Entry into the Exposure Period

Entry into the Exposure Period, and consequently the ability to accumulate "time at risk", starts on 01 Jan 2006 for those entering the cohort prior to that date and on the date of study entry for those entering the cohort on or after 01 Jan 2006.

Exposure Definition:

To facilitate the analysis, defined daily dosages (DDDs) are used throughout this report. DDDs are defined according to WHO standard of exposure (http://www.whocc.no/atc_ddd_index) as the assumed average maintenance dose per day for a drug used for its main indication in adults. The WHO standard dose for each NSAID is provided in Table 1a. The patient's prescribed dosage and amount dispensed are used to calculate the DDDs using the standard dose.

If patients started a prescription prior to entry into the exposure period, the remainder of their current prescription (DDDs) will be carried forward. Some of the analyses are performed with censoring of overlapping prescriptions. If one prescription is overlapping another, the remaining DDDs of the earlier prescription are censored. If 2 different prescriptions are received on the same date, the smaller prescription is censored. For example, if a patient is receiving 100 DDDs of naproxen and after 82 days receives 100 DDDs of diclofenac, the remaining 18 DDDs of naproxen are censored. Because the DDDs for each drug are based on the WHO standard rather than the prescribed dose, the assumed exposure period may be longer than the intended treatment period if the actual dose is greater than the standard dose. For example, if a patient is prescribed 90 mg of etoricoxib for 30 days (2700 mg), the DDDs are calculated as 2700 mg / 60 mg = 45 days. For etoricoxib and other coxibs, the recommended dosages can exceed the standard DDD up to 2-fold. As a result, if the patient receives another prescription for etoricoxib after 30 days, the prescriptions would appear to overlap and the first one would be censored.

Table1a DDDs according to WHO standard (http://www.whocc.no/atc_ddd_index)

M01AH05	Etoricoxib	60 mg
M01AH01	Celecoxib	0.2 g
M01AE14	Dexibuprofen	0.8 g
M01AB05	Diclofenac	0.1 g
M01AB55	Diclofenac, combinations	0.1 g
M01AE01	Ibuprofen	1.2 g
M01AB01	Indomethacin	0.1 g
M01AE03	Ketoprofen	0.15 g
M01AB15	Ketorolac	30 mg
M01AC05	Lornoxicam	12 mg
M01AC06	Meloxicam	15 mg
M01AX01	Nabumetone	1 g
M01AE02	Naproxen	0.5 g
M01AC01	Piroxicam	20 mg
M01AC02	Tenoxicam	20 mg

The degree of exposure is defined as number of prescribed DDDs divided by potential time of exposure and categorized as 0-24%, 25-49%, 50-74%, 75-99% and 100%.

Potential time of exposure is defined as the number of days from first date of prescription in the exposure period through the last date of prescription or to the end of follow-up, whichever comes first.

Rates of the outcomes will be calculated using 4 different approaches to exposure (on drug, on drug + 14 days, on drug + 30 days, and on drug + 90 days):

Exposure variables:

Mean total exposure in DDDs, cumulative drug quantity, and qualitative usage of etoricoxib, other coxibs, and nsNSAIDs (including subcategories of nsNSAIDs)

Degree of drug coverage/mean drug exposure (i.e., DDDs prescribed divided by time with actual prescriptions)

Major treatment sequences (looking at first and second line medication)

9.4.2 Outcome

(See **Annex 4** for ICD-10 diagnosis codes)

- Atherosclerotic / thrombotic cardiovascular: angina pectoris, acute myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting, death from acute MI, sudden death presumed to be of cardiac origin
- Congestive heart failure
- Atherosclerotic / thrombotic cerebrovascular: stroke (not classified as to type), ischemic stroke, hemorrhagic stroke
- Hypertension, severe (defined as hospital admission with a primary diagnosis of hypertension)
- Renovascular: renal insufficiency (chronic and acute), dialysis
- Gastrointestinal: varix bleeding, esophageal gastric and duodenal ulcer (with and without complications of bleeding or perforation), intestinal bleeding

9.4.3 Covariates

Demographics (age in ten-year bands, sex, educational level using a three-level scale, county of residence)

(See **Annex 3** for ATC codes)

Baseline medications:

a) Treatments for rheumatic conditions: non-biologic disease modifying anti-rheumatic drugs (DMARDs), oral corticosteroids
b) Gastro-protective medications: proton pump inhibitors (PPI), histamine 2 receptor blockers (H2s), misoprostol
c) Cardiovascular / lipid medications: diuretics, anti-hypertensives, treatments for heart failure, lipid-lowering drugs
d) Diabetes medications: insulin, oral anti-diabetic
e) Anticoagulants / antiplatelet therapy: warfarin, low molecular weight heparin (LMWH), tranexamic acid, other anti-coagulants or anti-platelet drugs
f) Prescription aspirin (any dose)
g) Narcotic and non-narcotic analgesics: codeine, morphine / morphine derivatives, tramadol hydrochloride, prescription paracetamol (hereafter referred to as acetaminophen), etc.

Baseline comorbidities (ever recorded hospitalisation / outpatient visit for any condition). See **Annex 4**.

a) Cardiovascular: cardiac valvular disease, arrhythmia
b) Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)
c) Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia
d) Renal: hypertension, nephritis (any type), and chronic kidney failure (CKD)
e) Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain
f) Hepatic: alcoholism, liver failure
g) SpA / AS-related: Prior recorded diagnosis of SpA, AS, and Low Back Pain

9.5. Data sources and measurement

Data Sources

For this study, data from the following registers will be utilized:

- *The Swedish Patient Register (of Hospital Discharges and Outpatients Visits)*

In this register, close to 100% of all hospital discharges 1987 and onwards are registered, including date of discharge, discharging hospital and department, and medical discharge diagnoses (assigned by physicians) according to ICD-10. Since 2001, this register also contains information on outpatient visits (dates, diagnoses, and department) for non-GP care (e.g., pediatric outpatient departments).This register will be used to identify the study population of patients with SpA/AS, determine baseline characteristics, and to identify clinical outcomes. Validations against medical files suggest that for many diagnoses (including Rheumatoid Arthritis), the validity is around 90%.

- *Swedish Register of Total Population and Population Changes*

This is the Swedish census register, updated weekly, covering information on all residents in Sweden, including certain basic demographic information. This register will be used to determine baseline characteristics and to ascertain end of follow-up.

- *The Swedish Cancer Register*

The Swedish Cancer Register is a nationwide register, in operation since 1958, to which reporting is mandatory for clinicians and pathologists, resulting in a completeness of cancer reporting of approximately 99% [Ref. 5.4: 6061]. This register is used to assess baseline history of gastrointestinal cancer based on ICD7-10 and ICD-0 codes.

- *The Swedish Cause of Death Register*

This register includes data on date and cause (ICD-7-10) of death for all deaths among Swedish residents 1952 and onwards. This register will be used to identify clinical outcomes and to ascertain end of follow-up.

- *The Swedish Biologics Register*

This is a profession-based rheumatology register of patients with rheumatic diseases (RA initially) >16 years of age starting treatment with a biologic drug. The register includes an estimated 90% of all AS/SpA patients receiving biological therapy in Sweden. Currently, some 2500 patients with SpA/AS starting a biologic are also registered because of the biologic start. This register is used to identify treatment with biologics as a covariate for the analyses of clinical outcomes.

The Swedish Prescribed Drug Register

In operation since Q3 2005, this nationwide register covers information on dispensed drugs in the out-patient setting including treatments given by "consultant rheumatologists" in out-patient care. This register will be used to determine baseline medication use and to exposure to etoricoxib, other COX-2 inhibitors, and nsNSAIDs prescribed in the out-patient setting. It does not capture drugs given while in hospital and includes only a proportion of non-dispensed drugs such as infusion biologics for SpA/AS. The latter treatments are captured in the Swedish Biologics Register for those patients included in that register.

For SpA, a previously published validation study supports the validity of defining AS or SpA diagnoses based on once having received such ICD-code by a specialist in rheumatology or internal medicine [Ref. 5.4: 6062]. Furthermore, preliminary unpublished results from ongoing validation of approximately 500 AS/SpA patients using this definition suggest that > 90% of AS cases fulfill New York criteria and patients with SpA diagnoses fulfill ASAS criteria for either peripheral or axial SpA to a similar extent [Ref. 5.4: 6066, 6067].

9.5.1 Study Procedures

Study Results Reporting

This report contains data from the Swedish registers through 2009. A second report with an updated data linkage will be provided in 2015.

9.6. Bias

There is potential for channeling bias in this study because it is feasible that patients prescribed etoricoxib or another of the drugs of interest are those patients at greater risk of some of the clinical outcomes. For example, those with prior GI bleeding or those who use low dose aspirin may be preferentially prescribed etoricoxib over non-selective

Channeling could also occur if patients who are high risk for CV or GI events are not prescribed any NSAIDs. A variety of models adjusted for various combinations of covariates will be used to try to adjust for the effect of specific individual risk factors (e.g., age) as well as combinations of risk factors.

9.7. Study size

To estimate the expected numbers of incident clinical outcomes that might be available for analysis (overall and with use of etoricoxib) in the unexposed to etoricoxib group, rates from a prior population-based cohort study done by Merck of patients of all ages (mean age 46, median age 45) with AS from general medical practices in the UK, Germany and France were used (see table below). The rates (note rates are per 1000 / PY) shown include events regardless of treatment and are restricted to persons without a prior history of a given event.

The 2008 census of Sweden indicated that there were about 3.84 million women and 3.75 million men in Sweden aged 16 years and older. The best available estimates of the prevalence of undifferentiated SpA and AS together (that is axial SpA) are 0.19% in women and 0.25% in men. **Therefore, it is expected that about 16,671 persons (7296 women and 9375 men) with a diagnosis of AS / SpA will be identified in this study.** Assuming that all identified patients in the study have a minimum of 5 years of treatment data in the Swedish Prescribed Drug Register, it is estimated that there will be a total of about 83,355 PY of follow-up with treatment data.

Pharmaceutical sales data for Sweden indicate that from 4Q2005 through 2010 among patients with a diagnosis of AS or SpA approximately 2175 patient years of Etoricoxib therapy were sold. Given the study design it is expected that the 2175 person years of therapy hold in this analysis. This represents about 2.6% of the expected total PY of follow-up time in the study with treatment data. For simplicity it will be also assumed that 2.6% of the study population, or 433 patients (with 2165 PY), will be exposed to etoricoxib, leaving 16,237 patients (with 81,185 PY) unexposed to etoricoxib.

To estimate the expected numbers of incident clinical outcomes that might be available for analysis (overall and with use of etoricoxib) in the unexposed to etoricoxib group, rates from a prior population-based cohort study done by Merck of patients of all ages (mean age 46, median age 45) with AS from general medical practices in the UK, Germany and France were used (see table below). The rates (note rates are per 1000 / PY) shown include events regardless of treatment and are restricted to persons without a prior history of a given event.

Table

Number (%) Of Patients and Incidence Of Clinical Outcomes Overall During Follow-Up*
Patients Without A Medical History Of The Respective Outcome
UK (GPRD, THIN & IMS), Germany (IMS) and France (IMS)

Clinical Outcome	n/N (%)	Incidence /1000 py‡
Gastrointestinal Ulcer, Perforation or Bleeding	401 /11071 (3.62)	5.59
All Vascular Events	941 /11169 (8.43)	13.33
Ischemic / Thrombotic Cardiac Events:	340 / 11166 (3.04)	4.65
Acute Myocardial Infarction	196 / 11091 (1.77)	2.67
Unstable Angina Pectoris	162 / 11136 (1.45)	2.20
Ischemic / Thrombotic Cerebrovascular Events:	343 / 11168 (3.07)	4.68
Ischemic Stroke	97 / 11143 (0.87)	1.30
Stroke NOS†	218 / 11110 (1.96)	2.97
Transient Ischemic Attack	112 / 11147 (1.00)	1.51
Hemorrhagic Cerebrovascular Events:	19 / 11167 (0.17)	0.25
Hemorrhagic Stroke	19 / 11167 (0.17)	0.25
Thromboembolic Peripheral Vascular Events	316 / 11169 (2.83)	4.31
Deep Venous Thrombosis	271 / 11121 (2.44)	3.70
Pulmonary Embolism	47 / 11159 (0.42)	0.63
Arterial Embolism / Thrombosis	17 / 11166 (0.15)	0.23
Sudden / Unexplained Death	63 / 11169 (0.56)	0.84
Acute Renal Failure	146 / 11127 (1.31)	1.98
Congestive Heart Failure / Left Ventricular Dysfunction	310 / 11044 (2.81)	4.26
Hypertension	1332 / 10093 (13.20)	21.38

* Each row is not mutually exclusive; an individual patient may be counted in more than one row, but is counted only once in a given row.
† NOS=not otherwise specified as ischemic or hemorrhagic.
‡ py=person years

Thus, assuming that the gender and age distributions are similar in the above prior study and the current one, using the above rates and the estimated 83,355 PY of follow-up with treatment data, it is expected that the following numbers of clinical outcomes (disregarding treatment) will be available for analysis among AS patients, with accompanying treatment data, in the current study.

	Approximate rate / 1000 pt-yrs	Expected no. of cases in the current study	
Type of event		Overall	In those not exposed to etoricoxib
Cardiovascular			
Acute MI	2.67	223	217
Sudden death (presumed cardiac)	0.84	70	68
Heart Failure	4.26	355	346
Cerebrovascular			
Stroke NOS	0.30	25	24
Ischemic stroke	0.13	11	11
Hemorrhagic stroke	0.03	3	2
Gastrointestinal			
Upper GI PUB	5.59	466	454

Based on the above information the estimated power (based on the normal approximation with continuity correction) to detect various relative increases in the rates of the outcomes expected to occur most often [MI, heart failure (HF), and PUBs] with etoricoxib exposure relative to nsNSAIDs in the current study are as shown in the following table.

	Power (%)		
RR	MI	HF	PUB
1.5	10	3	4
2.0	16	14	21
2.5	22	35	48
3.0	28	60	76
3.5	32	82	93
4.0	39	94	98
4.5	42	99	100
5.0	46	100	100

* Assumes 2.6% prevalence of exposure to etoricoxib and a 2-sided alpha of 0.05

source: http://www.openepi.com/OE2.3/Power/PowerCohort.htm

Thus, if the assumptions of the study power analysis hold, this study will have low power to detect an increased RR of <3.0 for HF and PUBs, and very low power to detect any increased RR of MI (or the other less frequent outcomes) with etoricoxib relative to the comparison groups. The statistical power will be further reduced in the various stratified / subgroup analyses that are planned. However, the assumptions used in these estimations, which came from other EU countries, may not hold in Sweden. For example, the mean age of the AS population is Sweden is approximately 10 years older than that in the prior population-based observational study that generated the rates above. Therefore, the clinical outcomes rates for some of the outcomes in this study may in fact be higher than in the previous study.

Nevertheless, given the above information is based on outcome event rate data from other studies in different countries and assumptions regarding exposure to etoricoxib, the information should be viewed as rough estimates only.

9.8. Data transformation

See section 9.4 above for variable definitions.

9.8.1 Data management

De-identified data will be stored on a secure server. Access will be limited to the co-workers of this project.

For this study, the following data linkages will be performed at Statistics Sweden and at the National Board of Health and Welfare; the data will be delivered to the PI as a de-identified dataset for analysis:

1. *Assembly of a national cohort of individuals with Spondyloarthropathy including those given a diagnoses of AS:*

Through ICD-codes for SpA and AS all individuals who meet entry criteria will be identified. The out-patient and any available hospitalisation data for a given patient will be assembled.

2. *Assessment of vital status throughout follow-up:*

Through linkage of all unique individuals in (i) to the Swedish Cause of Death Register and to the Swedish Register of Total Population and Population Changes, a last date of potential follow-up (and all deaths including underlying and contributory causes of death) will be identified. These registers will include data on vital status through 2010, and causes of death through 2009.

3. Assessment of baseline prior medications:

Through linkage to the Swedish Prescribed Drug Register, all dispensing of drugs during the baseline period will be identified, including substance (ATC-coding), amount dispensed, and date of dispensing, for purposes of baseline characteristics or for adjustment of potential confounders during analyses of clinical outcomes will also be identified, including:

a) Treatments for rheumatic conditions: non-biologic and biologic disease modifying anti-rheumatic drugs (DMARDs),oral corticosteroids
b) Gastro-protective medications: proton pump inhibitors (PPI), histamine 2 receptor blockers (H2s), misoprostol
c) Cardiovascular / lipid medications: diuretics, anti-hypertensives, treatments for heart failure, lipid-lowering drugs
d) Diabetes medications: insulin, oral anti-diabetic
e) Anticoagulants / antiplatelet therapy: warfarin, low molecular weight heparin (LMWH), tranexamic acid, other anti-coagulants or anti-platelet drugs
f) Prescription aspirin (any dose)
g) Narcotic and non-narcotic analgesics: codeine, morphine / morphine derivatives, tramadol hydrochloride, prescription acetaminophen, etc.

4. Assessment of baseline comorbid conditions

Through linkage of all unique individuals with SpA/AS to the Swedish Patient Register, all out-patient records and all hospitalisations during the baseline period will be identified (date, ICD-code, duration of hospital stay, hospital and department type (medical specialty). These records will be used for purposes of baseline characteristics or for adjustment of potential confounders during analyses of clinical outcomes. Baseline comorbid conditions will be identified based on ICD-codes for the following diagnoses (by body system):

a) Cardiovascular: cardiac valvular disease, arrhythmia
b) Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)
c) Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia
d) Renal: hypertension, nephritis (any type)
e) Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain
f) Hepatic: alcoholism, liver failure
g) SpA / AS-related: Prior recorded diagnosis of SpA, AS, and Low Back Pain

In addition, recorded diagnoses of any of the clinical outcomes (see below) will also be tabulated during the baseline period.

5. Assessment of exposure to etoricoxib and other NSAIDs:

Through linkage of all above-mentioned individuals to the Swedish Prescribed Drug Register, all dispensing of etoricoxib, other COX-2 selective inhibitors, and nsNSAID treatments Q3 2005-2010 will be identified, including substance (ATC-coding), amount and strength of tablets dispensed, and date of dispensing.

6. Assessment of clinical outcomes

Through linkage of all unique individuals with SpA/AS to the Swedish Patient Register, all hospitalisations and all outpatients visits for each study subject following cohort entry date through study end date will be identified (date, ICD-code, duration of hospital stay, hospital and department type (medical specialty). Using these data the first occurrence of each clinical outcome in a given patient will be identified based on ICD-codes for the following diagnoses of interest (by body system):

a) Atherosclerotic / thrombotic cardiovascular: angina pectoris, acute myocardial infarction (MI), percutaneous transluminal coronary angioplasty (PTCA), coronary artery bypass grafting, death from acute MI, sudden death presumed to be of cardiac origin
b) Congestive heart failure
c) Atherosclerotic / thrombotic cerebrovascular: stroke (not classified as to type), ischemic stroke, hemorrhagic stroke.
d) Hypertension, severe (defined as hospital admission with a primary diagnosis of hypertension)
e) Renovascular: renal insufficiency (chronic & acute), dialysis
f) Gastrointestinal: varix bleeding,, esophageal, gastric and duodenal ulcer (with and without complications of bleeding or perforation), intestinal bleeding.

9.9. Statistical methods

9.9.1. Main summary measures

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Objective 1: Description of the Characteristics of Swedish Patients with Inflammatory Spondyloarthropathy / Ankylosing Spondylitis (SpA/AS)

Analyses for Objective 1 involve: the number (%) of patients, proportions and / or univariate statistics for the below characteristics:

- Demographics (age in ten-year bands, sex, educational level using a three-level scale, county of residence)
- SpA/AS disease phenotype (ever recorded occurrence of diagnosis code indicating: an AS-diagnosis, uveitis, inflammatory bowel disease, psoriasis, urethritis, hip-joint replacement surgery, aortic valve surgery)

- Duration since first recorded SpA/AS diagnosis code
- Duration since first recorded diagnosis of Low Back Pain
- Baseline Prior Medications (ever recorded dispensing of any medication listed in section 9.8.1 (*Assessment of baseline prior medications (other than nsNSAIDs and coxibs)).*
- Baseline co-morbid conditions (ever recorded hospitalisation / outpatient visit for any condition listed in section 9.8.1)

Objective 2: Description of the exposure to etoricoxib, other coxibs, and nonselective NSAIDs for Swedish Patients with Inflammatory Spondyloarthropathy / Ankylosing Spondylitis (SpA/AS)

Analyses for objective 2 involve the number (%) of patients, proportions and / or univariate statistics for the below characteristics for three groups (all AS and SpA, only AS patients and only SpA patients):

- Mean total exposure in DDDs, cumulative drug quantity, and qualitative usage of etoricoxib, other coxib, and nsNSAID (including subcategories of nsNSAID)
- Degree of drug coverage/mean drug exposure
- Major treatment sequences (looking at first and second line medication)
- Demographic information, frequencies of baseline medications, SpA phenotypes, comorbidities and outcome events at baseline in relation to nsNSAID, etoricoxib, other coxib exposure, and no NSAID exposure.

Objective 3: Incidence rates (unadjusted and adjusted) for clinical outcomes (described in section 9.4.2) for etoricoxib, other coxibs, non-selective NSAIDs, and patients with no NSAID treatment for Swedish patients with Inflammatory Spondyloarthropathy / Ankylosing Spondylitis (SpA/AS)

Analyses for Objective 3 involve the number of events of interest, exposure, time and incidence rates for four groups (etoricoxib, nsNSAID, other coxibs, no NSAID treatment).

9.9.2. Main statistical methods

Statistical analyses were performed using R version 2.15.2. Data were exported as comma-separated files from SAS.

Event rates were calculated for all patients and in the following groups / subgroups, using 4 different approaches to exposure (on drug, on drug + 14 days, on drug + 30 days, and on drug + 90 days):

- By SpA / AS diagnosis (SpA only, AS only, combined)
- By prevalent SpA / AS / incident SpA/AS and combined
- By combinations of both of the above

A clinical outcome event is associated with one of the study drugs of interest if the date of the diagnosis falls within the exposure time window for the specific analysis. Outcome events that occur in patients who are not exposed are also tabulated and reported. Patients dying because of an outcome of interest are recorded as such. Patients dying for other reasons (or emigrating) are censored at that time and thus do not contribute further to the "time at risk".

Incidence rates of outcomes associated with exposure to etoricoxib (referent) are compared with the corresponding incidence rates attributed to exposure to the other drugs of interest using 95% confidence intervals. Adjusted rates are also presented. Potential confounders included in the models are age, sex, prior incidence of outcome of interest, and a compound risk factor individualized to the outcome of interest. The compound baseline risks were defined as any presence of the listed conditions/drugs at entry into the exposure period:

For Atherosclerotic cardiovascular events, the compound baseline risk factors include the following:

- Atherosclerotic cardiovascular event
- Atherosclerotic cerebrovascular event
- Severe hypertension
- Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia co-morbidity
- Cardiovascular drugs
- ASA for atherosclerotic prevention

For Atherosclerotic cerebrovascular events, the compound baseline risk factors include the following:

- Atherosclerotic cardiovascular event
- Atherosclerotic cerebrovascular event
- Severe hypertension
- Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia co-morbidity
- Cardiovascular drugs
- ASA for atherosclerotic prevention
- Anti-coagulants

For Severe hypertension events, the compound baseline risk factors include the following:

- Renal insufficiency
- Corticosteroids
- NSAID overall

For Congestive heart failure events, the compound baseline risk factors include the following:

- NSAID overall
- Severe hypertension
- Renal insufficiency
- Cardiovascular: cardiac valvular disease, arrhythmia

For Gastrointestinal (perforation, ulcer, bleeding or varix bleeding) events, the compound baseline risk factors include the following:

- Gastroprotective drugs
- NSAID overall
- Aspirin overall
- Anti-coagulants
- Corticosteroids
- Hepatic: alcoholism, liver failure

For Renal insufficiency events, the compound baseline risk factors include the following:

- Anti-diabetic drugs
- Severe hypertension
- Hepatic: alcoholism, liver failure
- Cardiovascular drugs

Incidence rates, their adjustments and relative rates were modelled using a generalized linear model with poisson response with log-link. Confidence intervals are adjusted such that 95%-family-wise CI's are presented using the R-package multcomp version 1.2-14 [Ref. 5.4: 6063].

All adjustments are made additively, i.e. without interactions between adjustment factor and the treatment-groups since the numbers are too low to fit many parameters. Age as a continuous covariate was included in the models using thin-plate regression splines in generalised additive models to avoid making an unwarranted linearity assumption, using the R-package mgcv version 1.7-22.

9.9.3. Missing values

Approximately 0.1% of the subjects were excluded prior to data extraction due to obvious errors with regard to their personal identification number (PIN). Reasons for this include human data handling errors, usage of a pre-existing PIN in some cases for immigrants, or PINs that for legal or safety reasons are kept secret [Ref. 5.4: 6064].

In the event analysis, subjects with missing values (less than 1%) were censored. No imputations were performed

9.9.4. Sensitivity analyses

The following sensitivity analyses were performed:

- According to whether a patient has a recorded AS diagnosis during follow-up, because subjects may switch from the SpA group to the AS group and possibly back again
- For thrombotic/embolic cardiovascular (MIs and sudden deaths) and cerebrovascular (ischemic stroke) clinical outcomes - the nsNSAIDs group

will exclude exposure to naproxen, since it has demonstrated potent anti-platelet inhibitory properties

- With censoring of patients at biologics exposure
- Because some diagnoses recorded long before cohort entry may no longer be active, with baseline medications and comorbidities limited to those recorded within two years prior to cohort entry
- Extending each exposure period by 14, 30 or 90 days

9.9.5. Amendments to the statistical analysis plan

- Definition of an incident case: In the original protocol, an incident case is defined as "SpA/AS individuals with no SpA/AS diagnosis codes in the patient register before 1 Jan 2007, and less than 6 months of accumulated exposure to any of the drugs of interest between July 2005 and January 2007" (Page 18). This date was altered from Jan 1st 2007 to Jan 1st 2006 in order to enlarge the population that could be regarded as "incident" and less likely to be extensively exposed to nsNSAIDs or coxibs.
- Outcomes for incident cases: Per the protocol, patients with >180 DDD's of exposure were originally going to be excluded. This was altered to include patients with >180 DDDs of exposure (about 10% of the incident cases) in order to enlarge the incident population due to low number of outcome events. Therefore, the incidence rates are calculated for all patients with a first diagnosis after Jan 1st 2006.
- Handling of exposure when 2 prescriptions overlap: The original protocol listed multiple options (p. 19) for handling exposure when 2 prescriptions overlap. The decision was made to censor the first drug class exposure when a prescription from another drug class was recorded. We believe this is appropriate for several reasons. First, as shown in Table 2.2 (in objective 2) the overlap in exposure periods between the three drug classes that are compared is modest (ranging from 0.4 to 8.5%). Second, it is a reasonable assumption that patients discontinue the first prescription when a prescription from another drug class is received, although there is no way to assure this. Nevertheless, incidence rates assuming extended exposure periods of 14, 30 and 90 days were computed (see **Annex 5**) with various sensitivity analysis for outcomes of interest) to evaluate the impact of assuming an extended exposure period on incidence rates.
- Handling of 2 prescriptions recorded on the same date: The original protocol did not specify how multiple prescriptions on the same date would be handled. The decision was made that if two different prescriptions were checked out on the same date, the smallest prescription is censored, again. We considered this justified, since this occurred in < 2% of patients irrespective of drug class (i. e. etoricoxib, celecoxib, nsNSAID) or restriction of case group (i.e. AS, SpA, AS/SpA, incident or prevalent cases).We did not consider it as meaningful to perform separate analyses of this very limited exposure time with two prescription checked out simultaneously.

- Analyses stratifying by < and > 1 year of accumulated exposure (page 21 in the original protocol): Analyses stratified by < and > 2 year of exposure were not performed due to the low number of events for almost all outcomes occurring in the etoricoxib and celecoxib groups.
- Adjustment of confounding by propensity scoring methods: The original protocol suggested that adjustment for confounding using propensity score methods would be considered ; however, this was not performed for several reasons. First, we did do a large number of sensitivity analyses according to the protocol, without any indication of a major effect on the overall results or conclusions. Second, the number of events for almost all outcomes occurring in the etoricoxib and celecoxib groups were very low.

9.10. Quality control

All data extracts and data linkages from the national registers were performed by experienced personnel from Statistics Sweden and the National Board of Health and Welfare. The correctness of program scripts were assessed by having at least two persons perform the overall analysis for each objective.

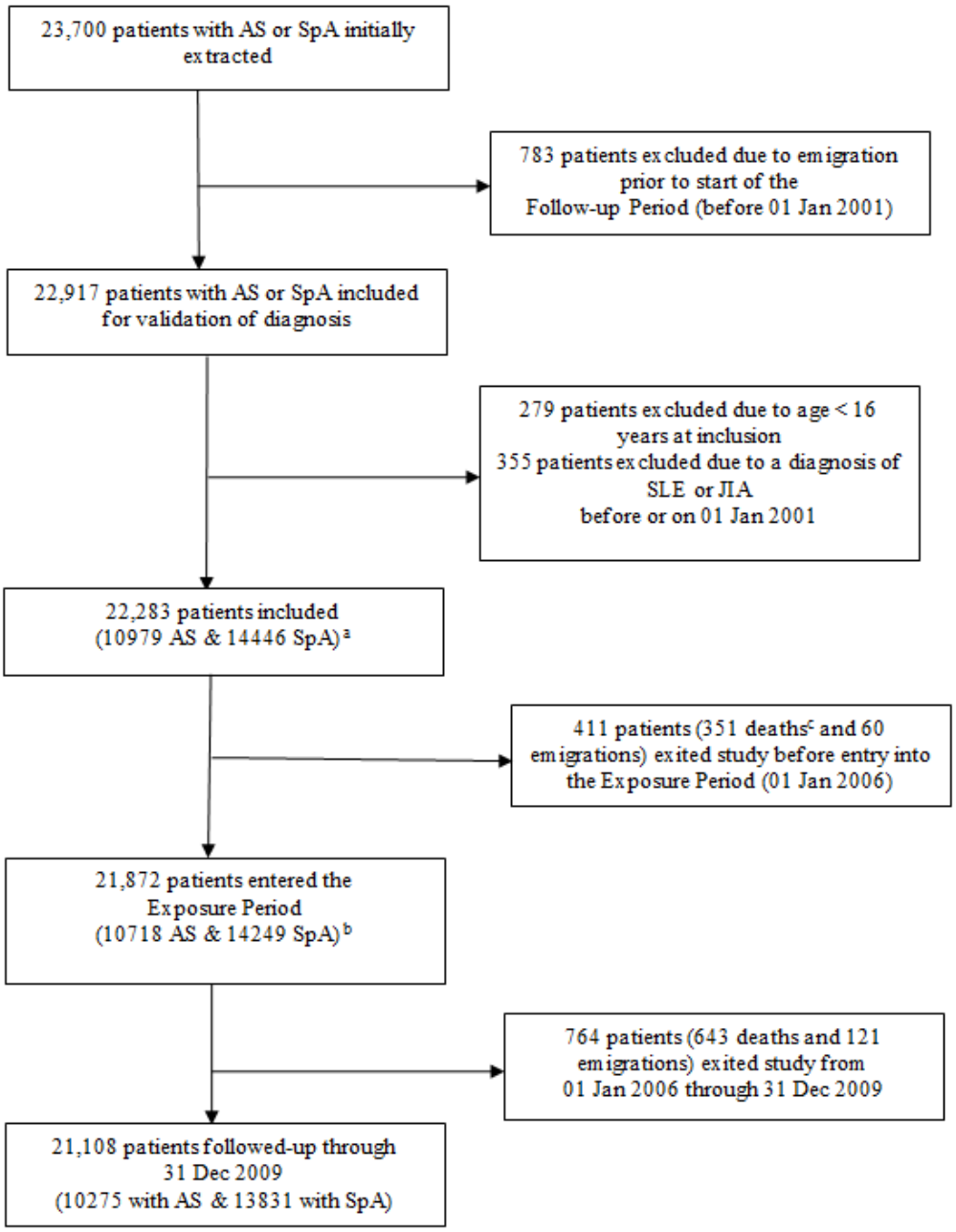
10. Results

10.1. Participants

Study Flow

Figure 2 displays the flow of selection and exit of patients with either AS or SpA from prior to and during the follow-up period (01 Jan 2001 through 31 Dec 2009). It can be seen that 22,283 patients were included during the study period, 21,872 patients entered the Exposure Period, and 21,108 patients were available for follow-up at the end of the study (31 Dec 2009). AS (ankylosing spondylitis) patients were defined as having at least one diagnosis of AS recorded after 01 Jan 2001. Date of first diagnosis is the cohort entry date. Likewise, SpA patients were entered the study at first recorded diagnosis of SpA after 01 Jan 2001. Note that some patients may have both an AS and a SpA diagnosis (overlap patients). These persons are represented both in the SpA and the AS subgroup in the descriptive tables. The Study Entry Date for the overlapping patients is fist recorded AS diagnosis when presented in the AS subgroup, first recorded SpA diagnosis when presented in the SpA subgroup, and earliest diagnosis of AS or SpA when presented in the overall group.

Figure 2
Study Flow Chart Showing Selection and Exit of Patients Before and During the Study Period



[a] Patients could have both an AS and a SpA diagnosis during the Study Period (n=3142); thus the total number of AS/SpA is not the sum of AS and SpA subgroups
[b] Patients could have both an AS and a SpA diagnosis during the Exposure Period (n=3095)
[c] Causes of death (split according to outcome of interest): atherosclerotic cardiovascular: 58, congestive heart failure: 4, atherosclerotic / thrombotic cerebrovascular: 19, hypertension, severe: 0, renal disease: 4; gastrointestinal: 6, other: 260

10.2. Descriptive data

Objective 1: Describe the characteristics of Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS)

10.2.1 Demographics

Table 1.1 shows demographics and age at study entry. A greater proportion of men comprise the group diagnosed with AS, while a greater proportion of women comprise those with a diagnosis of SpA. The combined AS/SpA group is about equally men and women. The mean age at study entry is about 46 years of age. The variable "Disease Duration" at study entry as described in the protocol is renamed to "Time Since First Diagnosis" since the variable does not describe a true time since disease onset; rather it represents time in years from the first SpA/AS diagnosis in the Swedish Patient Register to the Study Entry Date. The mean Time Since First Diagnosis is about 3.2 years in the AS group, 0.8 years in the SpA group, and about 1.7 years overall.

"Disease Duration" at entry into the Exposure Period is, in a similar fashion, called "Time Since First Diagnosis" for the same reasons as above.

Educational level is categorized as a 3-level scale: short <=9 years., intermediate >9 and <=12 years., and long >12 years. of formal school.

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Table 1.1
Baseline Demographics at Study Entry and at Entry into the Exposure Period[a]

Baseline Demographics at Study Entry n (%)	**AS** 10979[b]	**SpA** 14446[b]	**AS or SpA/Total** 22283
Male Sex	7148 (65.1%)	6250 (43.3%)	11617 (52.1%)
Educational level			
Low	2484 (22.6%)	2681 (18.6%)	4600 (20.6%)
Intermediate	5170 (47.1%)	7011 (48.5%)	10680 (47.9%)
Long	3186 (29.0%)	4639 (32.1%)	6779 (30.4%)
Missing	139 (1.2%)	115 (0.8%)	224 (1.0%)
Time since first recorded diagnosis of AS/SpA[c]			
Mean years (sd)	3.17 (6.79)	0.83 (3.47)	1.68 (5.09)
IQR range	0.00-0.00	0.00-0.00	0.00-0.00
Age			
Mean years (sd)	47.23 (4.20)	45.03 (14.96)	46.40 (14.87)
IQR range	37.00-57.00	34.00-55.00	35.00-57.00
Baseline Demographics at Entry into Exposure Period (All Patients[d])			
	10718[*]	14249[**]	21872[***]
Time since first recorded diagnosis of AS/SpA[e]			
Mean years (sd)	5.51 (8.06)	1.92 (3.39)	3.58 (6.25)
IQR range (years)	0.00-4.96	0.00-3.04	0.00-4.14
Age at baseline, mean years (sd, IQR, range)			
Mean years (sd)	49.30 (14.35)	46.59 (14.80)	48.07 (14.84)
IQR range (years)	38.00-60.00[f]	36.00-57.00[g]	37.00-59.00[h]
Baseline Demographics at Entry into Exposure Period (Prevalent AS/SpA Patients Only)			
	7335	**7965**	**13601**
Time since first recorded diagnosis of AS/SpA[‡]			
Mean years (sd)	8.05 (8.64)	3.44 (3.92)	5.76 (7.09)
IQR range (years)	2.22-11.84	1.11-4.26	1.66-4.92
Age at baseline, mean years (sd, IQR, range)			
Mean years (sd)	50.70 (13.46)	46.69 (14.18)	48.84 (14.12)
IQR range (years)	41-60	36-56	38-59

[a] The Study Entry Date is defined as the date that a given patient met all eligibility criteria.
[b] Patients could have both an AS and a SpA diagnosis during the Study Period (n=3142); thus the total number of AS/SpA is not the sum of AS and SpA subgroups.
[c] Time in years from the first SpA/AS diagnosis in the Swedish Patient Register to the Study Entry Date. Although a patient could have a diagnosis as far back as 1969 in the Swedish Patient Register for Hospital Discharge, a fresh recording of AS/SpA during 01 Jan 2001 through 31 Dec 2009 was required to be included in the study.
[d] Includes patients with a prevalent AS/SpA diagnosis at the start of the Exposure Period (01 Jan 2006) and patients with new incident diagnoses of AS/SpA after start of the Exposure Period.
[e] Time in years from the first SpA/AS diagnosis in the Swedish Patient Register to the start of the Exposure Period. Although a patient could have a diagnosis as far back as 1969 in the Swedish Patient Register for Hospital Discharge, a fresh recording of AS/SpA during 01 Jan 2001 through 31 Dec 2009 were required to be included in the study.
[f] n=10715 (264 patients in this group died or emigrated prior to the start of the Exposure Period).
[g] n=14248 (198 patients in this group died or emigrated prior to the start of the Exposure Period).
[h] n=21872 (411 patients in this group died or emigrated prior to the start of the Exposure Period).

Table 1.2 presents frequency and percentage of patients in age groups split in 10-year bands at study entry (i.e., the time of first diagnosis recorded on or after 01 Jan 2001.

The distribution of age at study entry is similar for both the AS and SpA groups. A large majority of patients are between 30 and 60 years old at the time of entry in the study.

Note that identification of patients started from 1969 using the Swedish Patient Register for Hospital Discharge, however a fresh recording of AS/SpA during the Study Period of 01 Jan 2001 through 31 Dec 2009 was required to be included in the study. Thus patients included in the study might have been followed for several years prior to study entry, and many of the patients enrolled during the first years of the Study Period would be patients with a "prevalent" (i.e., pre-existing) AS/SpA diagnosis. Thus age at study entry is expected to be higher than seen in a study that enrolled only patients with incident AS/SpA.

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Table 1.2

Frequency and Percentage of Patients by Age at Time of First Diagnosis after Study Entry[a] in 10-Year Age Bands -All Patients[b] Included N (%)

Age Band	AS n=10979[c]	SpA n=14446[c]	AS or SpA/Total n=22283
16-19	185 (1.7)	342 (2.4)	456 (2.0)
20-29	1150 (10.5)	1904 (13.2)	2548 (11.4)
30-39	2279 (20.8)	3460 (24.0)	4871 (21.9)
40-49	2587 (23.6)	3463 (24.0)	5272 (23.7)
50-59	2682 (24.4)	2795 (19.3)	4851 (21.8)
60-69	1402 (12.8)	1525 (10.6)	2699 (12.1)
70-79	546 (5.0)	688 (4.8)	1177 (5.3)
>= 80	148 (1.4)	269 (1.8)	409 (1.8)

a The date, on or after 01 Jan 2001, that a given patient met all eligibility criteria.

b Includes patients with a prevalent AS/SpA diagnosis at study entry and those with an incident diagnosis during the Study Period.

c Patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3142, and thus total number of AS/SpA is not the sum of AS and SpA subgroups.

10.2.2 Baseline Medication

The following results pertain to analyses of all patients (both those with prevalent and incident SpA/AS diagnoses as described previously).

Baseline medication is defined qualitatively (any use yes/no) expressed as the frequency and percentage of patients prescribed any of the medications mentioned prior to entry into the Exposure Period (i.e., at 01 Jan 2006 for patients diagnosed before 2006 and at the Study Entry Date for the patient entering the study on or after 01 Jan 2006).

The following categories of medications (see **Annex 3** for ATC codes) were used for this analysis:

- Anti-rheumatic: medications classified as “Biologics” or “DMARD” or “Corticosteroids”
- Gastro-protective: proton pump inhibitors (PPI), histamine 2 receptor blockers (H2s), misoprostol)
- Cardiovascular: medications classified as" antihypertensive” or “diuretics” or “beta blockers” or “Ca-antagonists” or “ACE & ATII blockers” or “cholesterol lowering agents” or “nitrates
- Analgesics: narcotic and non-narcotic analgesics including codeine, morphine / morphine derivatives, tramadol hydrochloride, and prescription acetaminophen. Note use of “over the counter” analgesics was not captured in the Prescribed Drug Register
- NSAID: medications classified as "non-selective NSAID", “etoricoxib”, or “coxib other”. Note use of “over the counter” NSAID was not captured in the Prescribed Drug Register
- Anti-diabetic: medications classified as “Anti-diabetics”
- Anticoagulants: medications classified as" Anticoagulants“. Note acetylsalicylic acid (ASA) preparations except for ASA in combination with persantine (dipyridamole) is omitted from this category
- Aspirin: medications classified as ”Aspirin overall”
- Aspirin used for atherosclerotic prevention: a subgroup of aspirin defined as medications classified as ”Aspirin used for atherosclerotic prevention”

Table 1.3 presents baseline usage of medications for all patients. In this analysis, the majority of patients had their diagnosis before baseline which explains the high level of anti-rheumatic therapy (including conventional DMARDs and biologics) and NSAID usage at baseline. With respect to biologics, patients may have received these drugs for other conditions such as psoriasis, inflammatory bowel disease, etc.

Note that the exposure frequencies in this table compared to both those seen for all patients during the Exposure Period (**Table 1.4**) and for the “incident” patients (**Table 1.7**) often are lower due to the fact that, at baseline, patients have had less time to be prescribed medications.

Also note that the proportion of patients prescribed drugs can be higher in both AS and SpA subgroups compared to the overall group of patients. This is due to an overlapping population of 3095 patients (accounted for in both the AS and the SpA subgroup) who have both an AS and a SpA diagnosis. This group has had more overall contact with the healthcare system and thus more exposure to certain medications.

The high proportion of patients receiving analgesics is due to the high frequency of acetaminophen usage. Again it should be noted that "over the counter" usage of acetaminophen and other analgesic drugs is not captured in the Prescribed Drug Register.

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Table 1.3
Frequency and Proportion of Patients with Prescribed Medications
Prior to Entry into the Exposure Period[a] - All Patients[b] Included
N (%)

Medication Category	AS n=10718[c]	SpA n=14249[c]	AS or SpA/Total n=21872
Anti-rheumatic overall	3170 (29.6)	3782 (26.5)	5440 (24.9)
Corticosteroids	1351 (12.6)	1853 (13.0)	2574 (11.8)
DMARDs	2130 (19.9)	2476 (17.4)	3567 (16.3)
Biologics	836 (7.8)	780 (5.5)	1067 (4.9)
Gastroprotective[d]	2743 (25.6)	3611 (25.3)	5313 (24.3)
NSAID overall	6183 (57.7)	8028 (56.3)	12152 (55.6)
Coxib other	288 (2.7)	372 (2.6)	550 (2.5)
Etoricoxib	342 (3.2)	458 (3.2)	653 (3.0)
Nonselective NSAID	5902 (55.1)	7732 (54.3)	11673 (53.4)
Aspirin overall	981 (9.2)	1019 (7.2)	1802 (8.2)
ASA for atherosclerotic prevention	937 (8.7)	965 (6.8)	1722 (7.9)
Analgesics[e]	4215 (39.3)	6477 (45.5)	9145 (41.8)
Cardiovascular	3200 (29.9)	3373 (23.7)	5818 (26.6)
Anti-coagulants	362 (3.4)	404 (2.8)	689 (3.2)
Anti-diabetics	449 (4.2)	482 (3.4)	848 (3.9)

[a] Entry into the Exposure Period is defined as 01 Jan 2006 for patients diagnosed before 2006 and at Study Entry Date for the patient entering the study on or after 01 Jan 2006.

[b] Includes patients with a prevalent AS/SpA diagnosis at the beginning of the Exposure Period and those with an incident diagnosis during the Study Period.

[c] Patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3095, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups. Also, the proportion of patient prescribed drugs can be higher in both AS and SpA subgroups compared to the total group of patients who have at least one AS and one SpA diagnosis.

[d] Including any of the registered PPI's, H2-blockers, or misoprostol.

[e] Mainly acetaminophen.

Table 1.4 displays the frequency and proportion of patients prescribed any of the medication categories described above from entry into the Exposure Period until the end of the Study Period (i.e., any prescription after 01 Jan 2006 until the end of the Study Period for patients diagnosed before 2006, and from study entry until the end of the Study Period for the patients entering the study on or after 01 Jan 2006).

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Table 1.4
Frequency and Proportion of Patients Prescribed Medications from Entry into the Exposure Period until the End of the Study Period[a] - All Patients[b] Included
N (%)

Prescribed Medication Category	AS n=10718[c]	SpA n=14249[c]	AS or SpA/Total n=21872
Anti-rheumatic overall	4716 (44.0)	5434 (38.1)	8308 (38.0)
Corticosteroids	2455 (22.9)	3100 (21.8)	4661 (21.2)
DMARDs	3209 (29.9)	3834 (26.9)	5754 (26.3)
Biologics	1669 (15.6)	1535 (10.8)	2362 (10.8)
Gastroprotective[d]	4512 (42.1)	5638 (39.6)	8739 (40.0)
NSAID overall	8004 (74.7)	10193 (71.5)	15804 (72.3)
Coxib other	455 (4.2)	506 (3.6)	813 (3.7)
Etoricoxib	797 (7.4)	1098 (7.7)	1635 (7.5)
Nonselective NSAID	7639 (71.3)	9807 (68.8)	15162 (69.3)
Aspirin overall	1560 (14.6)	1491 (10.5)	2746 (12.6)
ASA for atherosclerotic prevention	1505 (14.0)	1405 (9.9)	2627 (12.0)
Analgesics[e]	6388 (59.6)	8629 (60.6)	12997 (59.4)
Cardiovascular	4467 (41.7)	4737 (33.2)	8151 (37.3)
Anti-coagulants	908 (8.5)	913 (6.4)	1610 (7.4)
Anti-diabetics	658 (6.1)	686 (4.8)	1218 (5.6)

[a] Entry into the Exposure Period is defined as 01 Jan 2006 for patients diagnosed before 2006 and at Study Entry Date for the patient entering the study on or after 01 Jan 2006.

[b] Includes patients with a prevalent AS/SpA diagnosis at the beginning of the Exposure Period and those with an incident diagnosis during the Study Period.

[c] Patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3095, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups. Also, the proportion of patient prescribed drugs can be higher in both AS and SpA subgroups compared to the total group of patients who have at least one AS and one SpA diagnosis.

[d] Including any of the registered PPI's, H2-blockers, or misoprostol.

[e] Mainly acetaminophen.

Table 1.5 presents the cumulative frequency and proportion of patients prescribed any of the medication categories described above from the beginning of the Swedish Prescribed Drug Register in Q3 2005 through 31 Dec 2009. Note this analysis includes prescriptions during the time period from the beginning of the Swedish Prescribed Drug Register until 01 Jan 2006, which were not included in **Table 1.4**.

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Table 1.5
Cumulative Frequency and Proportion of Patients Prescribed Medications at Any Time During the Study Period[a] - All Patients[b] Included
N (%)

Prescribed Medication Category	AS n=10718[c]	SpA n=14249[c]	AS or SpA/Total n=21872
Anti-rheumatic overall	5092 (47.5)	5973 (41.9)	9046 (41.4)
Corticosteroids	2879 (26.9)	3741 (26.3)	5502 (25.2)
DMARDs	3490 (32.6)	4197 (29.5)	6202 (28.4)
Biologics	1933 (18.0)	1743 (12.2)	2672 (12.2)
Gastroprotective[d]	4989 (46.5)	6457 (45.3)	9797 (44.8)
NSAID overall	8760 (81.7)	11549 (81.1)	17629 (80.6)
Coxib other	573 (5.3)	706 (5.0)	1081 (4.9)
Etoricoxib	964 (9.0)	1367 (9.6)	1983 (9.1)
Nonselective NSAID	8490 (79.2)	11277 (79.1)	17163 (78.5)
Aspirin overall	1676 (15.6)	1670 (11.7)	3001 (13.7)
ASA for atherosclerotic prevention	1603 (15.0)	1556 (10.9)	2846 (13.0)
Analgesics[e]	7029 (65.6)	9827 (69.0)	14598 (66.7)
Cardiovascular	4634 (43.2)	5012 (35.2)	8532 (39.0)
Anti-coagulants	1012 (9.4)	1094 (7.7)	1858 (8.5)
Anti-diabetics	668 (6.2)	710 (5.0)	1249 (5.7)

[a] Before and after entry into the Exposure Periods, from start of the *Prescription Drug Registry* through 31 Dec 2009.
[b] Includes patients with a prevalent AS/SpA diagnosis at the beginning of the Exposure Period and those with an incident diagnosis during the Study Period.
[c] Patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3095, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups. Also, the proportion of patient prescribed drugs can be higher in both AS and SpA subgroups compared to the total group of patients who have at least one AS and one SpA diagnosis.
[d] Including any of the registered PPI's, H2-blockers, or misoprostol.
[e] Mainly acetaminophen.

The following results pertain to analyses of the subset of patients with an incident SpA/AS diagnosis defined by having a first diagnosis on or after 01 Jan 2006.

Table 1.6 presents the frequency and proportion of patients with incident AS/SpA diagnosis who were prescribed any of the medication categories described above prior to entry into the Exposure Period.

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Table 1.6

Frequency and Proportion of Patients with an Incident SpA/AS Diagnosis[a] Prescribed Medications at the Time of Entry into the Exposure Period or First Recorded Diagnosis

N (%)

Prescribed Medication Category	***AS*** 2483[b]	***SpA*** 4872[b]	***AS or SpA/Total*** 6223[c]
Anti-rheumatic overall	526 (21.2%)[c]	890 (18.3%)[c]	1110 (17.8%)
Corticosteroids	334 (13.5%)	649 (13.3%)	814 (13.1%)
DMARDs	293 (11.8%)	428 (8.8%)	526 (8.5%)
Biologics	87 (3.2%)	83 (1.7%)	83 (1.3%)
Gastroprotective[d]	564 (22.7%)	1264 (25.9%)	1589 (25.5%)
NSAID overall	1405 (56.6%)	2978 (61.1%)	3932 (63.2%)
Coxib other	45 (1.8%)	89 (1.8%)	117 (1.9%)
Etoricoxib	86 (3.5%)	182 (3.7%)	232 (3.7%)
Nonselective NSAID	1353 (54.5%)	2898 (59.5%)	3824 (61.4%)
Aspirin overall	224 (9.0%)	396 (8.1%)	577 (9.3%)
ASA for atherosclerotic prevention	208 (8.4%)	378 (7.8%)	547 (8.8%)
Analgesics[e]	993 (40.0%)	2504 (51.4%)	3134 (50.4%)
Cardiovascular	586 (23.6%)	1132 (23.2%)	1552 (24.9%)
Anti-coagulants	85 (3.4%)	181 (3.7%)	242 (3.9%)
Anti-diabetics	95 (3.8%)	167 (3.4%)	249 (4.0%)

[a] Subset of patients receiving their first diagnosis on or after 01 Jan 2006 and having less than 180 DDDs of NSAID prior to entry into the Exposure Period.

[b] Patients could have both an AS and a SpA diagnosis during the Study Period. Also a patient may have an incident diagnosis of either AS or SpA, but if the patient also received the alternative diagnosis prior to 01 Jan 2006 this patient will not be an incident case in the overall AS/SpA population following entry into the Exposure Period, and thus total number of AS/SpA will not be the sum of the individual AS and SpA subgroups.

[c] The proportion of patient prescribed drugs can be higher in both AS and SpA subgroups compared to the total group of patients due to an overlapping population of patients (accounted for in both the AS and the SpA subgroup) who have at least one AS and one SpA diagnosis. Also a patient may have an incident diagnosis of either AS or SpA, but if the patient also received the alternative diagnosis prior to 01 Jan 2006 this patient will not be an incident case in the overall AS/SpA population following entry into the Exposure Period.

[d] Including any of the registered PPI's, H2-blockers, or misoprostol.

[e] Mainly acetaminophen.

Table 1.7. presents the cumulative frequency and proportion of patients with incident AS/SpA diagnosis prescribed any of the categories of medications described above at time of entry into the Exposure Period through 31 Dec 2009.

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Table 1.7
Cumulative Frequency and Proportion of Patients with Incident[a] AS/SpA Diagnosis Prescribed Medications from Start of the Prescription Drug Registry (01 July 2005) through the End of the Study Period
N (%)

Prescribed Medication Category	AS 2483[b]	SpA 4872[b]	AS or SpA/Total 6223[c]
Anti-rheumatic overall	984 (39.6%)	1665 (34.2%)	2224 (35.7%)
Corticosteroids	574 (23.1%)	1160 (23.8%)	1487 (23.9%)
DMARDs	633 (25.5%)[c]	1091 (22.4%)[c]	1430 (23.0%)
Biologics	344 (13.9%)	346 (7.1%)	493 (7.9%)
Gastroprotective[d]	938 (37.8%)	2019 (41.4%)	2618 (42.1%)
NSAID overall	1790 (72.1%)[c]	3879 (79.6%)[c]	5113 (82.2%)
Coxib other	91 (3.7%)	183 (3.8%)	237 (3.8%)
Etoricoxib	189 (7.6%)	442 (9.1%)	567 (9.1%)
Nonselective NSAID	1742 (70.2%)	3812 (78.2%)	5011 (80.5%)
Aspirin overall	300 (12.1%)	528 (10.8%)	769 (12.4%)
ASA for atherosclerotic prevention	284 (11.4%)	499 (10.2%)	728 (11.7%)
Analgesics[e]	1374 (55.3%)	3248 (66.7%)	4154 (66.8%)
Cardiovascular	777 (31.3%)	1522 (31.2%)	2076 (33.4%)
Anti-coagulants	180 (7.2%)	345 (7.1%)	469 (7.5%)
Anti-diabetics	117 (4.7%)	223 (4.6%)	322 (5.2%)

[a] Subset of patients receiving their first diagnosis on or after 01 Jan 2006

[b] Patients could have both an AS and a SpA diagnosis during the Study Period. Also a patient may have an incident diagnosis of either AS or SpA, but if the patient also received the alternative diagnosis prior to 01 Jan 2006 this patient will not be an incident case in the overall AS/SpA population following entry into the Exposure Period, and thus total number of AS/SpA will not be the sum of the individual AS and SpA subgroups.

[c] The proportion of patient prescribed drugs can be higher in both AS and SpA subgroups compared to the total group of patients due to an overlapping population of patients (accounted for in both the AS and the SpA subgroup) who have at least one AS and one SpA diagnosis. Also a patient may have an incident diagnosis of either AS or SpA, but if the patient also received the alternative diagnosis prior to 01 Jan 2006 this patient will not be an incident case in the overall AS/SpA population following entry into the Exposure Period.

[d] Including any of the registered PPI's, H2-blockers, or misoprostol.

[e] Mainly acetaminophen.

10.2.3 Comorbidities

The following results pertain to analyses of all patients (both those with prevalent and incident SpA/AS diagnosis as described previously).

Baseline comorbidities are expressed as frequency and proportion of patients with any of the comorbidities mentioned (registered *from The Swedish Patient Register for Hospital Discharge* starting 01 Jan 1969) prior to entry into the Exposure Period. See **Annex 4** for definitions (i.e., ICD10/9/8 codes) for the various comorbidities mentioned below. The following categories are cumulated diagnoses from the subgroups defined in **Annex 4**:

- Endocrine / metabolism is defined as any registration of diagnosis under the labels "Diabetes" or "Diabetes type 1" or "Diabetes type 2" or "Hyperlipidemia"
- Hypertension or renal disease is defined as any registration of diagnoses under the labels "hypertension" or "renal insufficiency"
- Cardiovascular is defined as any registration of diagnoses under the labels "cardiac valvular disease" or "arrhythmia"
- Peripheral vascular is defined as any registration of diagnoses under the labels "deep venous thrombosis (DVT)" or "pulmonary embolism (PE)"
- "Severe hypertension" is defined as the "primary" hospital discharge diagnosis using the codes for hypertension shown in **Annex 4**
- "Renal insufficiency" and "dialysis" is defined as any registration of both diagnoses under the labels "renal insufficiency" and "renal dialysis"

Table 1.8 displays baseline comorbidities for all patients. In general, as expected, the prevalence of spondyloarthropathy-related comorbidities is high compared with the general population. The low frequency of urethritis may be due to the fact that the diagnosis is derived from hospital registries (either out-patient register or in-hospital) when in fact the vast majority of urethritis is diagnosed and treated in the primary care setting. Thus it is likely that there is a large number of patients with unrecorded urethritis diagnoses in the study population. The low frequency of a diagnosis of "Lower Back Pain" most likely reflects the fact that patients included in the study are those receiving a diagnosis during admission to a hospital or during a visit to an out-patient specialty clinic, in these settings a non-specific diagnosis of "low back pain" is not likely to be recorded. Other comorbidities of rheumatoid arthritis and psoriatic arthritis are also high compared with what is typically observed in the general population. These may represent initial rule out or misdiagnoses.

The baseline prevalence of diagnosis codes related to the clinical outcomes of interest in this study are as expected for a population of this type, except for that of "severe hypertension". The high frequency of this outcome is likely due to the broad categories of ICD-10 codes used for hypertension (see Annex 4). It is not possible to properly isolate "severe" or malignant hypertension in this cohort of patients using the available diagnosis codes. Consequently this outcome, defined though the Swedish National Hospital registers likely has poor validity.

Table 1.8
Frequency and Proportion of Patients with Comorbidities (Registered Since 01 Jan 1969) Prior to Entry into the Exposure Period[a] - All Patients[b] Included
N (%)

Co-morbidity	*AS* n=10718[c]	*SpA* n=14249[c]	*AS or SpA/Total* n=21872
Spondyloarthropathy related			
Uveitis	2066 (19.3)	1472 (10.3)	2871 (13.1)
Inflammatory bowel disease	764 (7.1)	654 (4.6)	1171 (5.4)
Psoriasis skin/nail	594 (5.5)	872 (6.1)	1210 (5.5)
Urethritis[d]	33 (0.3)	52 (0.4)	68 (0.3)
Hip-replacement surgery	527 (4.9)	399 (2.8)	796 (3.6)
Lower back pain	1010 (9.4)	2189 (15.4)	2836 (13.0)
Aortic valve insufficiency	96 (0.9)	52 (0.4)	130 (0.6)
Other comorbidities			
Psoriatic arthritis	421 (3.9)	632 (4.4)	836 (3.9)
Rheumatoid arthritis	840 (7.8)	1097 (7.7)	1537 (7.0)
Hypertension or renal disease	1308 (12.2)	1209 (8.5)	2209 (10.1)
Cardiovascular: cardiac valvular disease, arrhythmia	383 (3.6)	376 (2.6)	666 (3.0)
Hypertension	1264 (11.8)	1172 (8.2)	2137 (9.8)
Hepatic: alcoholism, liver failure	198 (1.8)	286 (2.0)	429 (2.0)
Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)	204 (1.9)	251 (1.8)	402 (1.8)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	717 (6.7)	767 (5.4)	1338 (6.1)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	1260 (11.8)	2172 (15.2)	2982 (13.6)
Outcome related comorbidities			
Atherosclerotic cardiovascular event	737 (6.9)	683 (4.8)	1273 (5.8)
Atherosclerotic cerebrovascular event	272 (2.5)	232 (1.6)	493 (2.3)
Severe hypertension	1144 (10.7)	1088 (7.6)	1957 (8.9)
Congestive heart failure	285 (2.7)	224 (1.6)	464 (2.1)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	400 (3.7)	443 (3.1)	705 (3.2)
Renal insufficiency	134 (1.3)	105 (0.7)	211 (1)
Renal insufficiency and dialysis	20 (0.2)	18 (0.1)	29 (0.1)

[a] 01 Jan 2006 for patients diagnosed before 2006 and at Study Entry Date for the patient entering the study on or after 01 Jan 2006.
[b] Includes patients with a prevalent AS/SpA diagnosis at the beginning of the Exposure Period and those with an incident diagnosis during the Study Period.
[c] Note patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3095, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups.
[d] The frequency of urethritis is derived from hospital registries (either out-patient register or in hospital); however the vast majority of urethritis is handled in primary care and thus we expect there is a large unrecorded number of urethritis diagnoses in our population which would account for the low frequency seen here.

Table 1.9 displays the cumulative frequency of comorbidities during the entire Study Period for all patients. This includes, in addition to baseline comorbidities, any comorbidities during the Exposure Period.

Table 1.9
Frequency and Proportion of Patients with Comorbidities
During the Entire Study Period – All Patients[a] Included
N (%)

Co-morbidity	*AS* n=10718[b]	*SpA* n=14249[b]	*AS or SpA/Total* n=21872
Spondyloarthropathy related			
Uveitis	2580 (24.1)	1782 (12.5)	3553 (16.2)
Inflammatory bowel disease	881 (8.2)	766 (5.4)	1364 (6.2)
Psoriasis skin/nail	833 (7.8)	1220 (8.6)	1713 (7.8)
Urethritis	39 (0.4)	66 (0.5)	87 (0.4)
Hip-replacement surgery	685 (6.4)	532 (3.7)	1043 (4.8)
Lower back pain	1400 (13.1)	2960 (20.8)	3899 (17.8)
Aortic valve insufficiency	132 (1.2)	82 (0.6)	187 (0.9)
Other comorbidities			
Psoriatic arthritis	576 (5.4)	912 (6.4)	1239 (5.7)
Rheumatoid arthritis	1122 (10.5)	1495 (10.5)	2093 (9.6)
Hypertension or renal disease	2154 (20.1)	1940 (13.6)	3604 (16.5)
Cardiovascular: cardiac valvular disease, arrhythmia	589 (5.5)	591 (4.1)	1041 (4.8)
Hypertension	2084 (19.5)	1892 (13.3)	3501 (16.0)
Hepatic: alcoholism, liver failure	286 (2.7)	384 (2.7)	588 (2.7)
Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)	292 (2.7)	340 (2.4)	558 (2.6)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	1077 (10.0)	1118 (7.8)	1962 (9.0)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	1800 (16.8)	2974 (20.9)	4157 (19.0)
Outcome related comorbidities			
Atherosclerotic cardiovascular event	1020 (9.5)	909 (6.4)	1729 (7.9)
Atherosclerotic cerebrovascular event	424 (4.0)	432 (3.0)	772 (3.5)
Severe hypertension	1995 (18.6)	1817 (12.8)	3356 (15.3)
Congestive heart failure	491 (4.6)	379 (2.7)	789 (3.6)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	643 (6.0)	704 (4.9)	1141 (5.2)
Renal insufficiency	264 (2.5)	184 (1.3)	394 (1.8)
Renal insufficiency and dialysis	38 (0.4)	24 (0.2)	55 (0.3)

[a] Includes patients with a prevalent AS/SpA diagnosis at the beginning of the Study Period and those with an incident diagnosis during the Study Period.
[b] Patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=3095, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups.

Table 1.10 displays comorbidities for the subset of patients with an incident diagnosis of AS/SpA, defined as patients with a first diagnosis on or After 01 Jan 2006

Table 1.10
Frequency and Proportion of Patients with Incident[a] AS/SpA Diagnosis with Comorbidities at the Time of Study Entry or at the Time of First Recorded Diagnosis
N (%)

Co-morbidity	AS 2483[b]	SpA 4872[b]	AS or SpA/Total 6223
Spondyloarthropathy related			
Uveitis	369 (14.9%)	399 (8.2%)	628 (10.1%)
Inflammatory bowel disease	121 (4.9%)	199 (4.1%)	255 (4.1%)
Psoriasis skin/nail	93 (3.7%)	172 (3.5%)	218 (3.5%)
Urethritis	10 (0.4%)	14 (0.3%)	23 (0.4%)
Hip-replacement surgery	32 (1.3%)	98 (2.0%)	112 (1.8%)
Lower back pain	254 (10.2%)	740 (15.2%)	906 (14.6%)
Aortic valve insufficiency	11 (0.4%)	18 (0.4%)	25 (0.4%)
Other comorbidities			
Psoriatic arthritis	61 (2.5%)	101 (2.1%)	129 (2.1%)
Rheumatoid arthritis	97 (3.9%)	140 (2.9%)	177 (2.8%)
Hypertension or renal disease	209 (8.4%)	392 (8.0%)	537 (8.6%)
Cardiovascular: cardiac valvular disease, arrhythmia	71 (2.9%)	137 (2.8%)	188 (3.0%)
Hypertension	207 (8.3%)	375 (7.7%)	520 (8.4%)
Hepatic: alcoholism, liver failure	46 (1.9%)	106 (2.2%)	142 (2.3%)
Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)	40 (1.6%)	82 (1.7%)	113 (1.8%)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	117 (4.7%)	255 (5.2%)	351 (5.6%)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	296 (11.9%)	797 (16.4%)	999 (16.1%)
Outcome related comorbidities			
Atherosclerotic cardiovascular event	118 (4.8%)	225 (4.6%)	318 (5.1%)
Atherosclerotic cerebrovascular event	52 (2.1%)	86 (1.8%)	127 (2.0%)
Severe hypertension	195 (7.9%)	355 (7.3%)	491 (7.9%)
Congestive heart failure	52 (2.1%)	92 (1.9%)	128 (2.1%)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	61 (2.5%)	123 (2.5%)	156 (2.5%)
Renal insufficiency	21 (0.8%)	47 (1.0%)	59 (0.9%)
Renal insufficiency and dialysis	4 (0.1%)	6 (0.1%)	9 (0.1%)

[a] Subset of patients receiving their first diagnosis on or after 01 Jan 2006
[b] Note patients could have both an AS and a SpA diagnosis during the Study Period. These overlap patients constitute n=517, and thus total number of AS/SpA will not be the sum of AS and SpA subgroups.

Table 1.11 displays for the subset of patients with an incident AS/SpA diagnosis (patients with a first diagnosis on or after 01 Jan 2006) the cumulative frequency of comorbidities during the entire Study Period. This includes, in addition to baseline comorbidities, any comorbidities during the Exposure Period.

Table 1.11
Frequency and Proportion of Patients with Incident AS/SpA Diagnosis with Comorbidities During the Entire Study Period
N (%)

Co-morbidity	AS 2483[a]	SpA 4872[a]	AS or SpA/Total 6223
Spondyloarthropathy related			
Uveitis	432 (17.4%)	448 (9.2%)	716 (11.5%)
Inflammatory bowel disease	146 (5.9%)	244 (5.0%)	319 (5.1%)
Psoriasis skin/nail	134 (5.4%)	281 (5.8%)	351 (5.6%)
Urethritis	11 (0.4%)	18 (0.4%)	28 (0.4%)
Hip-replacement surgery	54 (2.2%)	126 (2.6%)	157 (2.5%)
Lower back pain	346 (13.9%)	1082 (22.2%)	1317 (21.2%)
Aortic valve insufficiency	17 (0.7%)	29 (0.6%)	42 (0.7%)
Other comorbidities			
Psoriatic arthritis	87 (3.5%)	194 (4.0%)	239 (3.8%)
Rheumatoid arthritis	141 (5.7%)	229 (4.7%)	287 (4.6%)
Hypertension or renal disease	330 (13.3%)	577 (11.8%)	815 (13.1%)
Cardiovascular: cardiac valvular disease, arrhythmia	110 (4.4%)	200 (4.1%)	280 (4.5%)
Hypertension	322 (13.0%)	560 (11.5%)	793 (12.7%)
Hepatic: alcoholism, liver failure	57 (2.3%)	128 (2.6%)	172 (2.8%)
Peripheral vascular: deep venous thrombosis (DVT), pulmonary embolism (PE)	50 (2.0%)	96 (2.0%)	135 (2.2%)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	172 (6.9%)	349 (7.2%)	486 (7.8%)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	367 (14.8%)	1026 (21.1%)	1267 (20.4%)
Outcome related comorbidities			
Atherosclerotic cardiovascular event	164 (6.6%)	277 (5.7%)	407 (6.5%)
Atherosclerotic cerebrovascular	72 (2.9%)	125 (2.6%)	180 (2.9%)
Severe hypertension	313 (12.6%)	538 (11.0%)	764 (12.3%)
Congestive heart failure	79 (3.2%)	139 (2.9%)	194 (3.1%)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	89 (3.6%)	198 (4.1%)	248 (4.0%)
Renal insufficiency	38 (1.5%)	74 (1.5%)	99 (1.6%)
Renal insufficiency and dialysis	6 (0.2%)	9 (0.2%)	12 (0.2%)

[a] Subset of patients receiving their first diagnosis on or after 01 Jan 2006. Note patients could have both an AS and a SpA diagnosis during the Study Period. Also a patient may have an incident diagnosis of either AS or SpA, but if the patient also received the alternative diagnosis prior to 01 Jan 2006 this patient will not be an incident case in the overall population following entry into the Exposure Period, and thus total number of AS/SpA will not be the sum of the individual AS and SpA subgroups.

Objective 2: Describe the use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS. Describe potential predictors/confounders of use of etoricoxib, other COX-2 selective inhibitors, and non-selective NSAIDs.

10.2.4 Drug exposure

Tables 2.1a through 2.1c show drug exposures to etoricoxib, other coxibs and nsNSAIDs and cumulative dosages during the exposure period. The tables are presented for all AS/SpA patients, AS patients only and SpA patients only. Patients could have both an AS and a SpA diagnosis during the study period. Entry into the exposure period is defined as 01 Jan 2006 for patients diagnosed and entering the study before that date and at study entry for patients diagnosed and entering the study on or after 01 Jan 2006. Exposure to etoricoxib, other coxibs, and nsNSAIDs during the period between 01Jul05 and 01Jul06 when the drug registry was established and not yet stabilized is handled qualitatively as a yes/no covariate in the analysis of clinical outcomes in Part 3.

Overall, 7.6% of patients are exposed to etoricoxib. The mean cumulative DDDs during the exposure period is 90 (sd=311) and the mean cumulative quantity in mg is 5400 (sd=18661). Overall, 3.9% of patients are exposed to other coxibs, however the mean DDDs and cumulative quantity of those is greater than for etoricoxib. In general, the fraction of patients exposed to etoricoxib, other coxibs and nsNSAID are similar for patients with AS compared with SpA; however, the mean exposure to the coxibs is generally larger for AS patients compared to SpA patients. For both AS and SpA patients, the mean exposure to etoricoxib is less than that to other coxibs. Overall, exposure to nsNSAIDs is 71.2%, and variable by specific drug. The greatest exposures are to diclofenac, ketoprofen, ibuprofen, and naproxen. This pattern holds for both AS and SpA patients.

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Table 2.1a
Drug Exposures From Entry Into The Exposure Period
To The End Of The Study Period
All patients (n=21872)*

	Patients Exposed		Cumulative DDDs[a]		Cumulative Quantity (mg)	
Variable	**n**	**(%)**	**Mean (sd)**	**IQR**	**Mean (sd)**	**IQR**
Etoricoxib	1655	(7.6%)	90 (311)	30-282	5400 (8661)	1800-16920
Other coxibs	858	(3.9%)	100 (389)	32-392	20000 (77832)	6400-78450
nsNSAIDs	15581	(71.2%)	218 (415)	69-668	NA[b]	NA
Dexibuprofen	350	(1.6%)	38 (168)	15-76	30400 (134016)	12000-61000
Diclofenac	7054	(32.3%)	50 (234)	25-150	5000 (23408)	2500-15000
Diclofenac-comb	738	(3.4%)	75 (323)	20-304	7500 (32334)	2000-30425
Ibuprofen	3261	(14.9%)	88 (303)	34-263	105600 (363165)	40800-315000
Indomethacin	918	(4.2%)	147 (394)	50-596	14650 (39384)	5000-59550
Ketoprofen	5046	(23.1%)	266 (446)	98-686	39900 (66836)	14700-102938
Ketorolac	1	(0.0%)	5 (NA)	NA	150 (NA)	NA
Lornoxicam	33	(0.2%)	93 (175)	21-255	1116 (2105)	252-3054
Meloxicam	473	(2.2%)	180 (375)	50-527	2700 (5628)	750-7898
Nabumetone	1277	(5.8%)	83 (320)	23-227	83000 (320482)	23000-227000
Naproxen	3315	(15.2%)	125 (367)	50-393	62500 (183514)	25000-196500
Piroxicam	192	(0.9%)	262 (431)	50-824	5230 (8622)	1005-16485
Tenoxicam	332	(1.5%)	200 (447)	63-783	4000 (8945)	265-15665

* 17.3% of the patients were not treated with etoricoxib, other coxibs, or nsNSAIDs.
[a] DDD is defined according to WHO standard (http://www.whocc.no/atc_ddd_index). Please note if one prescription is overlapping another, the remaining DDDs are censored. If 2 different prescriptions are checked out at the same date the smallest prescription is censored. Also patients may have started a prescription prior entry into the exposure period; these patients will carry forward the remainder of their current prescription.
[b] NA = not applicable

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Table 2.1b
Drug Exposure From Entry Into The Exposure Period To End Of The Study Period
AS patients (n=10718)*

	Patients Exposed		Cumulative DDDs[a]		Cumulative Quantity (mg)	
Variable	**n**	**(%)**	**Mean (sd)**	**IQR**	**Mean (sd)**	**IQR**
Etoricoxib	819	(7.6%)	262 (340)	30-394	15734 (20395)	2400-21240
Other coxibs	472	(4.4%)	320 (409)	40-457	63934 (81802)	8000-91300
nsNSAIDs	7845	(73.2%)	468 (442)	100-752	NA[b]	NA
Dexibuprofen	131	(1.2%)	86 (188)	15-69	68519 (150105)	12000-55200
Diclofenac	3061	(28.6%)	168 (264)	25-180	16753 (26392)	2500-18000
Diclofenac-comb	366	(3.4%)	272 (353)	30-394	27164 (35296)	3000-39425
Ibuprofen	1565	(14.6%)	245 (331)	34-303	294553 (397372)	40800-363600
Indomethacin	650	(6.1%)	399 (413)	50-665	39917 (41346)	5000-66525
Ketoprofen	2847	(26.6%)	474 (459)	114-749	71080 (68827)	17100-112350
Ketorolac	0	(0.00%)	0 (NA)	NA	0 (NA)	NA
Lornoxicam	16	(0.1%)	221 (1219)	24-458	2657 (2630)	291-5490
Meloxicam	286	(2.7%)	371 (379)	65-596	5567 (5687)	975-8936
Nabumetone	652	(6.1%)	257 (345)	31-337	257288 (345210)	30500-336750
Naproxen	1663	(15.5%)	368 (409)	66-554	184136 (204722)	33000-277000
Piroxicam	142	(1.3%)	509 (442)	88-889	10175 (8845)	1750-17780
Tenoxicam	182	(1.7%)	491 (474)	95-908	9828 (9486)	1890-18155

* 14.8% of the patients were not treated with etoricoxib, other coxibs, or nsNSAIDs.

[a] DDD is defined according to WHO standard (http://www.whocc.no/atc_ddd_index). Please note if one prescription is overlapping another, the remaining DDDs are censored. If 2 different prescriptions are checked out at the same date the smallest prescription is censored. Also patients may have started a prescription prior entry into the exposure period; these patients will carry forward the remainder of their current prescription.

[b] NA = not applicable

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Table 2.1c
Drug Exposure From Entry Into The Exposure Period To The End Of The Study Period
SpA patients (n=14249)*

Variable	Patients Exposed		Cumulative DDDs[a]		Cumulative Quantity (mg)	
	n	(%)	Mean (sd)	IQR	Mean (sd)	IQR
Etoricoxib	1108	(7.8%)	82 (286)	28-250	4890 (17188)	1680-14985
Other coxibs	542	(3.8%)	100[b] (376)	30-369	20000 (75210)	6000-73750
nsNSAIDs	10096	(70.9%)	189 (389)	60-524	NA[b]	NA
Dexibuprofen	264	(1.9%)	38 (167)	15-79	30400 (133330)	12000-62800
Diclofenac	4868	(34.2%)	50 (219)	25-143	5000 (21860)	2500-14300
Diclofenac-comb	464	(3.3%)	60 (282)	15-232	6000 (28248)	1500-23150
Ibuprofen	2215	(15.5%)	87 (282)	34-246	104400 (338540)	40800-295200
Indomethacin	446	(3.1%)	100 (371)	38-426	10000 (37095)	3800-42625
Ketoprofen	3169	(22.2%)	234 (424)	91-634	35100 (63648)	13575-95025
Ketorolac	1	(0.0%)	5 (NA)	NA	150 (NA)	NA
Lornoxicam	23	(0.2%)	81 (154)	21-253	972 (1846)	252-3036
Meloxicam	282	(2.0%)	158 (364)	50-500	2363 (5466)	750-7504
Nabumetone	836	(5.9%)	73 (308)	20-200	73000 (307558)	20000-200000
Naproxen	2110	(14.8%)	106 (325)	50-316	52750 (162409)	25000-158000
Piroxicam	76	(0.5%)	115 (357)	20-378	2300 (7137)	400-7550
Tenoxicam	209	(1.5%)	166 (421)	58-646	3320 (8423)	1160-12920

* 17.5% of the patients were not treated with etoricoxib, other coxibs, or nsNSAIDs.

[a] DDD is defined according to WHO standard (http://www.whocc.no/atc_ddd_index). Please note if one prescription is overlapping another, the remaining DDDs are censored. If 2 different prescriptions are checked out at the same date the smallest prescription is censored. Also patients may have started a prescription prior entry into the exposure period; these patients will carry forward the remainder of their current prescription.

[b] NA = not applicable

Table 2.2 presents the frequency of prescribed DDDs that overlap for nsNSAID, etoricoxib and other coxibs in relation to each other, illustrating the amount of prescribed DDDs that are "discarded" when censoring exposure at the time of a new prescription. In general, censoring truncates exposure to one prescription at the time of new prescription (to the same or another class of NSAIDs). When two prescriptions completely overlap, the one with the longest exposure was counted.

For example, 21% of nsNSAID exposure is "discarded" when the exposure is censored with a new prescription for a different nsNSAID. Data is for all AS/SpA patients during the exposure period.

Table 2.2
Total and Overlapping Frequency of Prescribed DDDs accumulated from All Patients for nsNSAIDs, etoricoxib and other coxibs
N (%)

Days (%)	nsNSAID	Etoricoxib	Other Coxib
Total exposure	10,066,274	609,526	463,257
Overlapping prescriptions of:			
nsNSAID	2,095,741 (20.8%)	52,089 (8.5%)	32,678 (7.1%)
Etoricoxib	52,089 (0.6%)	137,725 (22.6%)	4730 (1.0%)
Other Coxib	32,678 (0.4%)	4730 (0.8%)	122,873 (26.5%)

Tables 2.3a, 2.3b and 2.3c and Tables 2.4a, 2.4b, and 2.4c present the frequency of patients with different degrees of exposed time during the prescription of nsNSAID, etoricoxib and other coxibs after inclusion into the exposure period. The degree of exposure is defined as the number of prescribed DDDs divided by the potential time of exposure and categorized as 0-24%, 25-49%, 50-74%, 75-99% and 100%. Potential time of exposure is defined as the number of days from first date of prescription in the exposure period through the last date of prescription or to the end of follow-up, whichever comes first.

Tables 2.3a, 2.3b and 2.3c reflect degrees of exposure calculated based on DDDs with censoring of overlapping DDDs, that is truncating exposure to one prescription at the time of new prescription.

Tables 2.4a, 2.4b, and 2.4c present in a similar fashion the degree of exposure based on DDDs without censoring of overlapping prescriptions, that is adding DDDs from a new prescription to the DDDs of the previous prescription, without discarding any prescribed DDDs.

It can be seen that the total number of various drug exposures are higher (in **Tables 2.4a-c** vs. **Tables 2.3 a-c**) when including data from overlapping prescriptions. This is due to censoring of an entire prescription if it completely overlapped with another prescription. In such cases of completely overlapping prescriptions, the one with the longest exposure was counted. Thus some of the actual exposures are censored (due to overlapping), however, the number of included patients are the same.

Table 2.3a
Degree Of Exposed Time after Cohort Entry (based On DDDs) With Censoring Of Overlapping Prescriptions (All Patients)
N (%)

Degree of exposure	nsNSAID n=15581	Etoricoxib# n=1655	Other coxibs# n=858
0-24%	2524 (16.2%)	122 (7.4%)	75 (8.7%)
25-49%	2960 (19.0%)	217 (13.1%)	112 (13.1%)
50-74%	2353 (15.1%)	225 (13.6%)	158 (18.4%)
75-99%	3551 (22.8%)	334 (20.2%)#	179 (20.9%)#
100%	4193 (26.9%)	757 (45.7%)#	334 (38.9%)#

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

Table 2.4a
Degree Of Exposed Time after Cohort Entry (based On DDDs) Without Censoring Of Overlapping Prescriptions (All Patients)
N (%)

Degree of exposure	nsNSAID n=15612	Etoricoxib# n=1688	Other coxibs# n=874
0-24%	2264 (14.5%)	69 (4.1%)	45 (5.1%)
25-49%	2560 (16.4%)	138 (8.2%)	67 (7.7%)
50-74%	2108 (13.5%)	143 (8.5%)	102 (11.7%)
75-99%	1842 (11.8%)	182 (10.8%)	115 (13.2%)
100%	6838 (43.8%)	1156 (68.5%)	545 (62.4%)

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

Table 2.3b
Degree Of Exposed Time after Cohort Entry (based On DDDs) With Censoring Of Overlapping Prescriptions (AS Patients Only)
N (%)

Degree of exposure	nsNSAID n=7845	Etoricoxib# n=819	Other coxibs# n=472
0-24%	1036 (13.2%)	56 (6.8%)	31 (6.6%)
25-49%	1483 (18.9%)	107 (13.1%)	72 (15.2%)
50-74%	1467 (18.7%)	112 (13.7%)	87 (18.5%)
75-99%	1938 (24.7%)	195 (23.8%)#	107 (22.7%)#
100%	1921 (24.5%)	349 (42.6%)#	175 (37.1%)#

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

Table 2.4b
Degree Of Exposed Time after Cohort Entry (based On DDDs) Without Censoring Of Overlapping Prescriptions (As Patients Only)
N (%)

Degree of exposure	nsNSAID n=7863	Etoricoxib# n=834	Other coxibs# n=479
0-24%	912 (11.6%)	30 (3.6%)	27 (5.6%)
25-49%	1274 (16.2%)	73 (8.7%)	37 (7.8%)
50-74%	1132 (14.4%)	79 (9.5%)	56 (11.7%)
75-99%	1030 (13.1%)	98 (11.8%)	63 (13.1%)
100%	3515 (44.7%)	554 (66.5%)	296 (61.8%)

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

Table 2.3c
Degree Of Exposed Time after Cohort Entry (based On DDDs) With Censoring Of Overlapping Prescriptions (SpA Patients Only)
N (%)

Degree of exposure	nsNSAID n=10096	Etoricoxib# n=1108	Other coxibs# n=542
0-24%	1757 (17.4%)	84 (7.6%)	44 (8.1%)
25-49%	1908 (18.9%)	140 (12.6%)	71 (13.1%)
50-74%	1656 (16.4%)	150 (13.5%)	100 (18.5%)
75-99%	1928 (19.1%)	207 (18.7%)#	109 (20.1%)#
100%	2847 (28.2%)	527 (47.6%)#	218 (40.2%)#

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

Table 2.4c
Degree Of Exposed Time after Cohort Entry (based on DDDs) Without Censoring Of Overlapping Prescriptions (SpA Patients Only)
N (%)

Degree of exposure	nsNSAID n=10114	Etoricoxib# n=1131	Other coxibs# n=553
0-24%	1588 (15.7%)	44 (3.9%)	23 (4.2%)
25-49%	1649 (16.3%)	87 (7.7%)	40 (7.2%)
50-74%	1325 (13.1%)	88 (7.8%)	66 (11.9%)
75-99%	1133 (11.2%)	124 (11.0%)	68 (12.3%)
100%	4419 (43.7%)	788 (69.7%)	356 (64.4%)

Etoricoxib & other coxibs have a larger degree of complete exposure; this can be attributed to the fact that the recommended dosages can exceed the standard DDD up to 2-fold. Moreover, it is possible that larger dosages of COX-2 inhibitors a generally well tolerated.

10.2.5 Major treatment sequences

Table 2.5 presents the frequency of patients with different sequences of treatment with nsNSAIDs, etoricoxib and other coxibs. Different permutations of the first two classes of treatment are included as well as the number of patients only exposed to one drug class. Patients with exposure to all 3 categories irrespective of sequence are included as a lumped group to illustrate the size of this population of patients.

Table 2.5a
Major Treatment Sequences for First and Second Line Medication (from beginning of the Prescription Registry 01 Jul 2005 to the end of the study period)
N (%)

Sequence	AS n=10718	SpA n=14249	Overall AS/SpA n=21872
nsNSAID only	7313 (68.2%)	9626 (67.6%)	14766 (67.5%)
nsNSAID prior to etoricoxib	675 (6.3%)	1017 (7.1%)	1435 (6.6%)
nsNSAID prior to other coxib	274 (2.6%)	358 (2.5%)	539 (2.5%)
Etoricoxib only	140 (1.3%)	139 (1.0%)	242 (1.1%)
Etoricoxib prior to nsNSAID	132 (1.2%)	184 (1.3%)	267 (1.2%)
Etoricoxib prior to other coxib	35 (0.3%)	47 (0.3%)	68 (0.3%)
Other coxib only	118 (1.1%)	109 (0.8%)	192 (0.9%)
Other coxib prior to nsNSAID	157 (1.5%)	204 (1.4%)	299 (1.4%)
Other coxib prior to etoricoxib	55 (0.5%)	100 (0.7%)	128 (0.6%)
Exposed to all irrespective of sequence (nsNSAID, etoricoxib and other coxibs)	77 (0.7%)	126 (0.9%)	168 (0.8%)

Table 2.5b
Major Treatment Sequences for First and Second Line Medication (from 01 Jan 2006 for patients entering the study before 2006 and at cohort entry date for patients entering the study on or after 01 Jan 2006).
N (%)

Sequence	**AS** n=10718	**SpA** n=14249	**Overall AS/SpA** n=21872
nsNSAID only	6963 (65.0%)	8902 (62.5%)	13793 (63.0%)
nsNSAID prior to etoricoxib	447 (4.2%)	675 (4.7%)	973 (4.4%)
nsNSAID prior to other coxib	177 (1.7%)	208 (1.5%)	325 (1.5%)
Etoricoxib only	196 (1.8%)	220 (1.5%)	350 (1.6%)
Etoricoxib prior to nsNSAID	139 (1.3%)	177 (1.2%)	270 (1.2%)
Etoricoxib prior to other coxib	23 (0.2%)	29 (0.2%)	45 (0.2%)
Other coxib only	137 (1.3%)	136 (1.0%)	230 (1.1%)
Other coxib prior to nsNSAID	128 (1.2%)	158 (1.1%)	239 (1.1%)
Other coxib prior to etoricoxib	39 (0.4%)	63 (0.4%)	82 (0.4%)
Exposed to all irrespective of sequence (nsNSAID, etoricoxib and other coxibs)	56 (0.5%)	78 (0.5%)	107 (0.5%)

Note, it is only the exposure time that decreases compared to table 5a, the actual patients included are the same.

10.2.6 Description of potential predictors/confounders of etoricoxib, other coxib and nsNSAID exposure.

Tables 2.6a, 2.6b and 2.6c present demographics, co-medications and comorbidities for patients prior to entry into the exposure period. The tables are divided into (a) all patients (b) patients with AS and (c) patients with SpA, and the numbers are presented as frequencies and percentages.

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Table 2.6a
Patient Characteristics Prior To Entry Into Exposure Period
According To Exposure Of Interest (Classified As Any Exposure During The Exposure Period)
(All Patients, N=21,872)
N (%)

	Etoricoxib		Other coxib		nsNSAIDs		None	
Characteristic	**Yes (1655)**	**No (20,217)**	**Yes (858)**	**No (21014)**	**Yes (15580)**	**No (6292)**	**Yes (4260)**	**No (17612)**
Demographics								
Male Sex	799 (48.2)	10542 (52.1)	419 (48.8)	10922 (52.0)	8048 (51.6)	3293 (52.3)	2271 (53.2)	9080 (51.5)
Educational level*								
Low	298 (18.0)	4179 (20.7)	165 (19.2)	4312 (20.5)	3037 (19.5)	1440 (22.9)	999 (23.5)	3478 (19.7)
Intermediate	839 (50.7)	9716 (48.1)	395 (46.0)	10160 (48.4)	7575 (48.0)	2980 (47.4)	2005 (47.1)	8550 (48.5)
High	505 (30.5)	6193 (30.6)	292 (34.0)	6406 (30.5)	4873 (31.3)	1825 (29.0)	1225 (28.8)	5473 (31.1)
Missing	13 (0.8)	129 (0.6)	6 (0.7)	136 (0.7)	95 (0.6)	52 (0.8)	31 (0.6)	111 (0.7)
Age								
16-19 years	18 (1.1)	301 (1.5)	6 (0.7)	313 (1.5)	207 (1.3)	112 (1.8)	79 (18)	240 (1.4)
20-29 years	155 (9.4)	1888 (9.3)	65 (7.6)	1978 (9.4)	1512 (9.7)	531 (8.4)	334 (7.8)	1709 (9.7)
30-39 years	380 (23.0)	4034 (20.0)	172 (20.1)	4242 (20.2)	3255 (20.9)	1159 (18.4)	715 (16.8)	3709 (21.0)
40-49 years	432 (26.1)	4717 (23.3)	227 (26.5)	4922 (23.4)	3885 (25.0)	1264 (20.1)	838 (19.7)	4311 (24.5)
50-59 years	401 (24.2)	4533 (22.4)	205 (23.9)	4729 (22.5)	3578 (23.0)	1356 (21.6)	932 (21.9)	4002 (22.7)
60-69 years	20012.1)	3035 (15.0)	136 (15.9)	3099 (14.8)	2222 (14.3)	1013 (16.1)	715 (16.8)	2520 (14.3)
70-79 years	58 (3.6)	1251 (6.2)	37 (4.3)	1272 (6.1)	742 (4.7)	567 (9.0)	416 (9.8)	893 (5.1)
>= 80 years	11 (0.7)	458 (2.3)	10 (1.2)	459 (2.2)	179 (1.2)	290 (4.6)	231(5.5)	238(1.4)

*Educational level is categorized as a 3-level scale: short <=9 years, intermediate >9 and <=12 years, and long >12 years of formal school

Table 2.6a (cont.)

Characteristic	Etoricoxib		Other coxib		nsNSAIDs		None	
	Yes (1655)	No (20,217)	Yes (858)	Yes (5653)	Yes (15580)	No (6292)	Yes (4260)	No (17612)
Prescribed Medications								
Anti-rheumatic treatments overall	421(25.4)	5019(24.8)	266(31.0)	5174(24.6)	3905(25.1)	1535(24.4)	974 (22.9)	4466 (25.3)
Corticosteroids	198(12.0)	2376(11.8)	115(13.4)	2459(11.7)	1743(11.1)	831(13.2)	486 (11.4)	2088 (11.9)
DMARDs	275(16.6)	3292(16.3)	172(20.0)	3395(16.2)	2649(17.0)	918(14.6)	586 (13.8)	2981 (16.9)
Biologics	853(5.1)	982(4.9)	61(7.1)	1006(4.8)	749(4.8)	318(5.1)	228 (5.4)	839 (4.8)
Gastroprotective§	538(32.9)	4769(23.6)	315(36.7)	4998(23.8)	3926(25.2)	1387(22.0)	715 (16.8)	4598 (26.1)
NSAID overall	1190(71.9)	10962(54.2)	609(71.0)	11543(54.9)	10327(66.3)	6292(29.0)	0 (0)	12152 (69.0)
Coxib other	81(4.9)	469(2.3)	331(38.6)	219(1.0)	347(2.2)	203(3.2)	0 (0)	550 (3.1)
Etoricoxib	346(20.9)	307(1.5)	29(3.4)	624(3.0)	391(2.5)	262(4.2)	0 (0)	653 (3.7)
Nonselective NSAID	982(59.3)	10691(52.9)	389(45.3)	11284(53.7)	10106(64.9)	1567(24.9)	0 (0)	11673 (66.2)
Aspirin overall	98(5.9)	1704(8.4)	60(7.0)	1742(8.3)	1124(7.2)	678(10.8)	476 (11.2)	1326 (7.5)
Aspirin used for atherosclerotic prevention	87(5.3)	1635(8.1)	56(6.5)	1666(7.9)	1068(6.9)	654(10.4)	464 (10.9)	1258 (7.1)
Analgesics¤	844(51.0)	8301(41.1)	434(50.6)	8711(41.5)	6668(42.8)	2477(39.4)	1322 (31.1)	7823 (44.4)
Cardiovascular	406(24.5)	5412(26.8)	224(26.1)	5594(26.6)	3900(25.0)	1918(30.5)	1340 (31.5)	4478 (25.4)
Anti-coagulants	40(2.4)	649(3.2)	21(2.5)	668(3.2)	320(2.1)	369(5.9)	264 (6.2)	425 (2.4)
Anti-diabetics	52(3.1)	796(3.9)	27(3.2)	821(3.9)	513(3.3)	335(5.3)	240 (5.7)	608 (3.5)
Spondyloarthropathy related comorbidities								
Uveitis	213(12.9)	2658(13.2)	123(14.4)	2748(13.0)	2164(13.9)	707(11.3)	488 (11.5)	2383 (13.5)
Inflammatory bowel disease	62(3.8)	1109(5.5)	75(8.7)	1096(5.2)	620(4.0)	551(8.8)	430 (10.1)	741 (4.2)
Psoriasis skin/nail	102(6.2)	1108(5.5)	57(6.6)	1153(5.5)	894(5.7)	316(5.0)	215 (5.1)	995 (5.7)
Urethritis	3(0.2)	65(0.3)	3(0.4)	65(0.3)	51(0.3)	17(0.3)	10 (0.2)	58 (0.3)
Hip-replacement surgery	55(3.3)	741(3.7)	33(3.9)	763(3.6)	546(3.5)	250(4.0)	196 (4.7)	600 (3.4)
Lower back pain	255(15.4)	2581(12.8)	149(17.4)	2687(12.8)	2036(13.1)	800(12.7)	486 (11.4)	2350 (13.3)
Aortic valve insufficiency	7(0.4)	123(0.6)	2(0.2)	128(0.6)	54(0.4)	76(1.2)	59 (1.4)	71 (0.4)

Table 2.6a (cont.)

Characteristic	Etoricoxib		Other coxib		nsNSAIDs		None	
	Yes (1655)	No (20,217)	Yes (858)	No (21014)	Yes (15580)	No (6292)	Yes (4260)	No (17612)
Other comorbidities								
Psoriatic arthritis	81(4.9)	782(3.9)	46(5.4)	817(3.9)	649(4.2)	214(3.4)	145 (3.4)	718 (4.1)
Rheumatoid arthritis	109(6.6)	1428(7.1)	67(7.1)	1470(7.0)	1123(7.2)	414(6.6)	217 (5.1)	1234 (7.0)
Hypertension or renal disease	--	--	--	--	--	--	--	--
Cardiovascular: cardiac valvular disease, arrhythmia	33(2.0)	633(3.1)	21(2.5)	645(3.1)	375(2.4)	291(4.6)	276(4.9)	449 (2.6)
Hypertension	127(7.7)	2010(9.9)	858(8.3)	2066(9.8)	1351(8.7)	786(12.5)	577 (13.6)	1560 (8.9)
Hepatic: alcoholism, liver failure	34(2.1)	395(2.0)	18(2.1)	411(2.0)	260(1.7)	169(2.7)	103 (2.4)	326 (1.9)
Peripheral vascular: DVT, PE	28(1.7)	374(1.9)	15(1.8)	387(1.8)	225(1.4)	177(2.8)	127 (3.0)	275 (1.6)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	66(4.0)	1272(6.3)	46(5.4)	1292(6.2)	824(5.3)	514(8.2)	382 (9.0)	956 (5.4)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	268(16.2)	2714(13.4)	173(20.2)	2809(13.4)	2087(13.4)	895(14.2)	502 (11.8)	2480 (14.1)
Outcome related comorbidities								
Atherosclerotic cardiovascular event	56(3.4)	1217(6.0)	45(5.2)	1228(5.8)	765(4.9)	508(8.1)	389 (9.1)	884 (5.0)
Atherosclerotic cerebrovascular (cerebrovascular)	22(1.3)	471(2.3)	10(1.2)	483(2.3)	252(1.6)	241(3.8)	203 (4.8)	290 (1.7)
Severe hypertension	120(7.3)	1837(9.1)	60(7.0)	1897(9.0)	1233(7.9)	724(11.5)	533 (12.5)	1424 (8.1)
Congestive heart failure	17(1.0)	447(2.2)	14(1.6)	450(2.1)	197(1.3)	267(4.2)	214 (5.1)	250 (1.4)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	56(3.4)	649(3.2)	38(4.4)	667(3.2)	429(2.8)	276(4.4)	192 (4.5)	513 (2.9)
Renal insufficiency	4(0.2)	207(1.0)	4(0.5)	207(1.0)	83(0.5)	128(2.0)	110 (2.6)	101 (0.6)
Renal insufficiency and dialysis	0 (0)	29(0.1)	0(0)	29(0.1)	7(0.0)	22(0.4)	19 (0.5)	10 (0.1)

Table 2.6b
Patient Characteristics Prior To Entry Into Exposure Period
According To Exposure Of Interest (Classified As Any Exposure During The Exposure Period)
(AS Patients, N=10,718)
N (%)

	Etoricoxib		Other coxib		nsNSAIDs		None	
Characteristic	**Yes (819)**	**No (9899)**	**Yes (472)**	**No (10246)**	**Yes (7844)**	**No (2874)**	**Yes (1961)**	**No (8757)**
Demographics								
Male Sex	518 (63.3)	6434 (65.0)	281 (59.5)	6671 (65.1)	5029 (64.1)	1923 (66.9)	1341 (66.4)	5611 (64.1)
Educational level								
Low	163 (19.9)	2244 (22.7)	101 (21.4)	2306 (22.5)	1701 (21.7)	706 (24.6)	513 (26.1)	1894 (21.6)
Intermediate	404 (49.3)	4690 (47.4)	208 (44.1)	4886 (47.7)	3730 (47.6)	1364 (47.5)	922 (47.0)	4172 (47.6)
High,	242 (30.0)	2892 (29.2)	160 (33.9)	2974 (29.0)	2357 (30.1)	777 (27.0)	512 (26.1)	2622 (29.9)
Missing	10 (1.2)	73 (0.7)	3 (0.6)	80 (0.8)	56 (0.7)	27 (0.9)	14 (0.7)	69 (0.8)
Age								
16-19 years	6 (0.7)	116 (1.2)	5 (1.1)	117 (1.1)	73 (1.1)	49 (1.7)	34 (1.7)	88 (1.0)
20-29 years	60 (7.3)	753 (7.6)	29 (6.1)	784 (7.7)	624 (8.0)	189 (6.6)	98 (5.0)	715 (8.2)
30-39 years	192 (23.4)	1818 (18.4)	84 (17.8)	1926 (18.8)	1567 (20.0)	443 (15.4)	263 (13.4)	1747 (20.0)
40-49 years	204 (24.9)	2176 (22.0)	129 (27.3)	2251 (22.0)	1832 (23.4)	548 (19.1)	352 (18.0)	2028 (23.2)
50-59 years	222 (27.1)	2461 (24.9)	125 (26.5)	2558 (25.0)	1989 (25.4)	694 (24.2)	506 (25.8)	2177 (24.8)
60-69 years	105 (12.8)	1742 (17.6)	79 (16.7)	1768 (17.3)	1303 (16.6)	544 (18.9)	395 (20.1)	1452 (16.6)
70-79 years	28 (3.4)	650 (6.6)	19 (4.)	659 (6.4)	395 (5.0)	283 (9.9)	211 (10.8)	467 (5.4)
>= 80 years	2 (0.2)	183 (1.9)	2 (0.4)	183 (1,8)	61 (0.8)	124 (4.3)	102(5.2)	83(0.9)

Table 2.6b (cont.)

Characteristic	Etoricoxib		Other coxib		nsNAIDs		None	
	Yes (819)	**No (9899)**	**Yes (472)**	**No (10246)**	**Yes (7845)**	**No (2874)**	**Yes (1961)**	**No (8757)**
Prescribed Medications								
Anti-rheumatic treatments overall, n	250 (30.5)	2920 (29.5)	172 (36.4)	2998 (9.3)	2275 (29.0)	895 (31.1)	586 (29.9)	2584 (29.5)
Corticosteroids	101 (12.3)	1251 (12.6)	64 (13.6)	1288 (12.6)	901 (11.5)	451 (15.7)	287 (14.6)	1065 (12.2)
DMARDs	160 (19.5)	1970 (19.9)	113 (23.9)	2017 (19.7)	1583 (20.2)	547 (19.0)	338 (17.2)	1792 (20.5)
Biologics	63 (7.7)	773 (7.8)	51 (10.8)	785 (7.7)	575 (5.4)	261 (9.1)	173 (8.8)	663 (7.8)
Gastroprotective§	265 (32.4)	2478 (25.0)	175 (37.1)	2568 (25.1)	2062 (26.3)	681 (23.7)	371 (18.9)	2372 (27.1)
NSAID overall,	601(73.4)	5582(56.4)	338(71.6)	5845(57.1)	5382(68.6)	801(27.9)	0 (0)	6183 (70.6)
Coxib other	29 (3.5)	259 (2.6)	189 (40.0)	99 (0.9)	172 (2.2)	116 (4.0)	0 (0)	288 (3.3)
Etoricoxib	206 (25.2)	136 (1.4)	19 (4.0)	323 (3.2)	194 (2.5)	148 (5.2)	0 (0)	342 (3.9)
Nonselective NSAID	475 (58.0)	5427 (54.8)	205 (43.4)	5697 (55.6)	5264 (67.1)	638 (22.2)	0 (0)	5902 (67.4)
Aspirin overall,	40 (4.9)	941 (9.5)	36 (7.6)	945 (9.2)	633 (8.1)	348 (12.1)	262 (13.4)	719 (8.2)
Aspirin used for atherosclerotic prevention	36 (4.4)	901 (9.1)	34 (7.2)	903 (8.8)	604 (7.7)	333 (11.6)	255 (13.0)	682 (7.8)
Analgesics¤	379 (46.3)	3836 (38.8)	237 (50.2)	3978 (38.8)	3147 (40.1)	1068 (37.2)	603 (30.8)	3612 (41.3)
Cardiovascular	213 (26.0)	2987 (30.2)	125 (26.5)	3075 (30.0)	2204 (28.1)	996 (34.7)	734 (37.4)	2466 (28.2)
Anti-coagulants	20 (2.4)	342 (3.5)	10 (2.1)	352 (3.4)	170 (2.2)	192 (6.7)	144 (7.4)	218 (2.5)
Anti-diabetics	29 (3.5)	420 (4.2)	18 (3.8)	431 (4.2)	288 (3.7)	161 (5.6)	123 (6.3)	326 (3.7)
Spondyloarthropathy related comorbidities								
Uveitis	156 (19.1)	1910 (19.3)	82 (17.4)	1984 (19.4)	1559 (19.9)	507 (17.6)	346 (17.6)	1720 (19.6)
Inflammatory bowel disease	38 (4.6)	726 (7.3)	54 (11.4)	710 (6.9)	422 (5.4)	342 (11.9)	272 (13.9)	492 (5.6)
Psoriasis skin/nail	51 (6.2)	543 (5.5)	27 (5.7)	567 (5.5)	425 (5.4)	169 (5.9)	119 (6.1)	475 (5.4)
Urethritis	2 (0.2)	31 (0.3)	3 (0.6)	30 (0.3)	25 (0.3)	8 (0.3)	2(0.1)	31 (0.4)
Hip-replacement surgery	35 (4.3)	492 (5.0)	27 (5.7)	500 (4.9)	369 (4.7)	158 (5.5)	131 (6.7)	396 (4.5)
Lower back pain	106 (12.9)	904 (9.1)	76 (16.1)	934 (9.1)	764 (9.7)	246 (8.6)	132 (6.7)	878 (10.0)
Aortic valve insufficiency	6 (0.7)	90 (0.9)	1 (0.2)	95 (0.9)	43 (0.6)	53 (1.8)	878 (2.1)	55 (0.6)

Table 2.6b (cont.)

Characteristic	Etoricoxib		Other coxib		nsNSAIDs		None	
	Yes (819)	**No (9899)**	**Yes (472)**	**No (10246)**	**Yes (7845)**	**No (2874)**	**Yes (1961)**	**No (8757)**
Other comorbidities								
Psoriatic arthritis	40(4.9)	381(3.9)	23(4.9	398(3.9))	298(3.8)	123(4.3)	83 (4.2)	338 (3.9)
Rheumatoid arthritis	59(7.2)	781(7.9)	41(8.7)	799(7.8)	613(7.8)	227(7.9)	168 (8.6)	672 (7.7)
Hypertension or renal disease	--	--	--	--	--	--	--	--
Cardiovascular: cardiac valvular disease, arrhythmia	15 (1.8)	368 (3.7)	14 (3.0)	369 (3.6)	222 (2.8)	161 (5.6)	124 (6.3)	259 (3.0)
Hypertension	69 (8.4)	1195 (12.1)	43 (9.1)	1221 (11.9)	832 (10.6)	432 (15.0)	331(16.9)	933 (10.7)
Hepatic: alcoholism, liver failure	17 (2.1)	181 (1.8)	8 (1.7)	190 (1.9)	120 (1.5)	78 (2.7)	47 (2.4)	151 (1.7)
Peripheral vascular: DVT, PE	14 (1.7)	190 (1.9)	7 (1.5)	197 (1.9)	120 (1.5)	84 (2.9)	64 (3.3)	140 (1.6)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	33 (4.0)	684 (6.9)	27 (5.7)	690 (6.7)	467 (6.0)	250 (8.7)	202 (10.3)	515 (5.9)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain	107 (13.1)	1153 (11.7)	90 (19.1)	1170 (11.4)	908 (11.6)	352 (12.3)	201 (10.3)	1059 (12.1)
Outcome related comorbidities								
Atherosclerotic cardiovascular event	32 (3.9)	705 (7.1)	30 (6.4)	707 (6.9)	463 (5.9)	274 (9.5)	222261(11.3)	515 (5.9)
Atherosclerotic cerebrovascular	11 (1.3)	261 (2.6)	6 (1.3)	266 (2.6)	148 (1.9)	124 (4.3)	106 (5.4)	166152(1.9)
Severe hypertension	65 (7.9)	1079 (10.9)	39 (8.3)	1105 (10.8)	746 (7.0)	398 (13.9)	302 (15.4)	842 (9.6)
Congestive heart failure	8 (1.0)	277 (2.8)	11 (2.3)	274 (2.7)	119 (1.5)	166 (5.8)	135 (6.9)	150 (1.7)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	36 (4.4)	364 (3.7)	28 (5.9)	372 (3.6)	246 (3.1)	154 (5.4)	106 (5.4)	294 (3.4)
Renal insufficiency	2 (0.2)	132 (1.3)	3 (0.6)	131 (1.3)	43 (0.6)	91 (0.9)	79 (4.0)	55 (0.6)
Renal insufficiency and dialysis	0 (0)	20 (0.2)	0 (0)	20 (0.2)	4 (0.2)	16 (0.6)	14 (0.7)	6(0.1)

Table 2.6c
Patient Characteristics Prior To Entry Into Exposure Period
According To Exposure Of Interest (Classified As Any Exposure During The Exposure Period)
(SpA Patients, N=14,249)
N (%)

	Etoricoxib		Other coxib		nsNSAIDs		None	
Characteristic	**Yes (1108)**	**No (13141)**	**Yes (542)**	**No (13707)**	**Yes (10096)**	**No (4153)**	**Yes (2710)**	**No (11539)**
Demographics								
Male Sex	435 (39.3)	5704 (43.4)	220 (40.6)	5919 (43.2)	4327 (42.9)	1812 (43.6)	1171 (43.3)	4968 (43.1)
Educational level								
Low	179 (16.2)	2447 (18.6)	95 (21.4)	2531 (18.5)	1743 (17.3)	883 (21.3)	579 (21.3)	2047 (17.8)
Intermediate	575 (51.9)	6374 (48.5)	257 (47.4)	6692 (48.8)	4984 (49.4)	1965 (47.3)	1279 (47.3)	5670 (49.2)
Long	351 (31.7)	4244 (32.3)	187 (34.5)	4408 (32.2)	3311 (32.8)	1284 (30.9)	837 (30.9)	3758 (32.6)
Missing	3 (0.3)	76 (0.6)	3 (0.6)	76 (0.6)	58 (0.6)	21 (0.5)	15 (0.5)	64 (0.6)
Age								
16-19 years	15 (1.4)	211 (1.6)	2 (0.4)	224 (1.6)	154 (1.5)	72 (1.7)	47 (1.7)	179 (1.6)
20-29 years	119 (10.7)	1435 (10.9)	52 (9.6)	1502 (11.0)	1139 (11.3)	415 (10.0)	270 (10.0)	1284 (11.1)
30-39 years	269 (24.3)	2902 (22.1)	122 (22.5)	3049 (22.2)	2289 (22.7)	882 (21.2)	540 (20.0)	2631 (22.8)
40-49 years	300 (27.1)	3264 (24.8)	138 (25.5)	3426 (25.0)	2684 (26.6)	880 (20.3)	569 (21.0)	2995 (26.0)
50-59 years	244 (22.0)	2687 (20.5)	118 (21.8)	2813 (20.5)	2089 (20.7)	842 (20.3)	530 (19.6)	2401 (20.8)
60-69 years	121 (10.9)	1659 (12.6)	82 (15.1)	1698 (12.4)	1211 (12.0)	569 (13.7)	389 (14.3)	1391 (12.1)
70-79 years	31 (2.8)	691 (5.3)	20 (3.7	702 (5.1)	403 (4.0)	319 (7.7)	230 (8.5)	492 (4.3)
>= 80 years n	9 (0.8)	292 (2.2)	8 (1.5)	293 (2.1)	127 (1.3)	174 (4.2)	135(4.4)	166(1.5)

Table 2.6c (cont.)

Characteristic	Etoricoxib		Other coxib		nsNSAIDs		None	
	Yes (1108)	No (13141)	Yes (542)	No (13707)	Yes (10096)	No (4153)	Yes (2710)	No (11539)
Prescribed Medications								
Anti-rheumatic treatments overall	298 (26.9)	3484 (26.1)	186 (34.3)	3596 (26.2)	2729 (27.0)	1053 (25.4)	613 (22.7)	3169 (27.5)
Corticosteroids	148 (13.4)	1705 (13.0)	90 (16.6)	1763 (12.9)	1271 (12.6)	582 (14.0)	291 (10.8)	1562 (13.5)
DMARDs	194 (17.5)	2282 (17.4)	118 (21.8)	2358 (17.2)	1841 (18.2)	635 (15.3)	379 (14.0)	2097 (18.2)
Biologics	64 (5.8)	716 (5.5)	41 (7.6)	739 (5.4)	541 (5.4)	239 (5.8)	160 (5.9)	620 (5.4)
Gastroprotective§	376 (33.9)	3235 (24.6)	200 (36.9)	3411 (24.9)	2662 (26.4)	949 (22.9)	442 (16.4)	3169 (27.5)
NSAID overall	800(72.2)	7228(55.0)	382(70.5)	7646(55.8)	6707(66.4)	1321(31.8)	0 (0)	8028 (69.5)
Coxib other	64 (5.8)	308 (2.3)	211 (38.9)	161 (1.2)	245 (2.4)	127 (3.1)	0 (0)	372 (3.2)
Etoricoxib	214 (19.3)	244 (1.9)	15 (2.8)	443 (3.2)	271 (2.7)	187 (4.5)	0 (0)	458 (4.0)
Nonselective NSAID	674 (60.8)	7058 (53.7)	251 (43.3)	7481 (54.6)	6560 (65.0)	1172 (28.2)	0 (0)	7732 (67.0)
Aspirin overall	69 (6.2)	950 (7.2)	31 (5.7)	988 (7.2)	633 (6.3)	386 (9.3)	245 (9.1)	774 (6.7)
Aspirin used for atherosclerotic prevention	60 (4.4)	905 (6.9)	28 (5.2)	937 (6.8)	592 (5.9)	373 (9.0)	239 (8.8)	726 (6.3)
Analgesics¤	612 (55.2)	5865 (44.6)	291 (53.7)	6186 (45.2)	4703 (46.6)	1774 (42.7)	889 (32.9)	5588 (48.4)
Cardiovascular	248 (22.4)	3125 (23.8)	138 (25.5)	3235 (23.6)x	2226 (22.1)	1147 (27.6)	740 (27.4)	2633 (22.8)
Anti-coagulants	24 (2.2)	380 (2.9)	15 (2.8)	389 (2.8)	201 (2.0)	203 (4.9)	132 (4.9)	272 (2.4)
Anti-diabetics	28 (2.5)	454 (3.5)	13 (2.4)	469 (3.4)	284 (2.8)	198 (4.8)	132 (4.9)	350 (3.0)
Spondyloarthropathy related comorbidities								
Uveitis	122 (11.0)	1350 (10.3)	72 (13.3)	1400 (10.2)	1107 (11.0)	365 (8.8)	228 (8.4)	1244 (10.8)
Inflammatory bowel disease	39 (3.5)	615 (4.7)	43 (7.9)	611 (4.5)	330 (3.3)	324 (7.8)	238 (8.8)	416 (3.6)
Psoriasis skin/nail	79 (7.1)	793 (6.0)	47 (8.7)	825 (6.0)	661 (6.6)	211 (5.1)	138 (5.1)	734 (6.4)
Urethritis	1 (0.1)	51 (0.4)	3 (0.6)	49 (0.4)	39 (0.4)	13 (0.3)	9 (0.3)	40(0.4)
Hip-replacement surgery	29 (2,6)	370 (2.8)	14 (2.6)	385 (2.8)	272 (2.7)	127 (3.1)	93 (3.2)	306 (2.7)
Lower back pain	200 (18.1)	1989 (15.1)	105 (19.4)	2084 (15.2)	1563 (15.4)	626 (15.1)	384 (14.2)	1805 (15.6)
Aortic valve insufficiency	3 (0.3)	49 (0.4)	1 (0.2)	51 (0.4)	22 (0.2)	30 (0.7)	23 (0.9)	29 (0.3)

Table 2.6c (cont.)

Characteristic	Etoricoxib		Other coxib		nsNSAIDs		None	
	Yes (1108)	No (13141)	Yes (542)	No (13707)	Yes (10096)	No (4153)	Yes (2710)	No (11539)
Other comorbidities								
Psoriatic arthritis	60(5.4)	572(4.4)	37(6.8)	595(4.3)	491(4.9)	141(3.4)	94 (3.5)	538 (4.7)
Rheumatoid arthritis	82(7.4)	1015(7.7)	54(10.0)	1043(7.6)	803(8.0)	294(7.1)	205 (7.6)	892 (7.7)
Hypertension or renal disease	--	--	--	--	--	--	--	--
Cardiovascular: cardiac valvular disease, arrhythmia	23 (2.1)	353 (2.7)	10 (1.9)	366 (2.7)	215 (2.1)	161 (3.9)	114 (4.2)	262 (2.3)
Hypertension	79 (7.1)	1093 (8.3)	37 (6.8)	1135 (8.3)	729 (7.2)	443 (10.7)	298 (11.0)	874 (7.6)
Hepatic: alcoholism, liver failure	23 (2.1)	263 (2.0)	13 (2.4)	273 (2.0)	171 (1.7)	115 (2.8)	71 (2.6)	215 (1.9)
Peripheral vascular: DVT, PE	18 (1.6)	233 (1.7)	9 (1.7)	242 (1.8)	143 (1.4)	108 (2.6)	72 (2.7)	179 (1.6)
Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia	43 (3.9)	724 (5.1)	25 (4.6)	742 (5.4)	465 (4.6)	302 (7.3)	207 (7.7)	560 (4.9)
Gastrointestinal: colorectal cancer, dyspeptic and other abdominal pain n	210 (19.0)	1962 (14.3)	120 (22.1)	2052 (15.0)	1510 (15.0)	662 (15.9)	365 (13.5)	1807 (15.7)
Outcome related comorbidities								
Atherosclerotic cardiovascular event	28(2.5)	655 (5.0)	23 (4.2)	660 (4.8)	407 (4.0)	276 (6.6)	196 (7.3)	487 (4.2)
Atherosclerotic cerebrovascular	13 (1.2)	258 (2.0)	5 (0.9)	266 (1.9)	132 (1.3)	139 (3.4)	115 (4.3)	156 (1.4)
Severe hypertension	73 (6.6)	1015 (7.7)	29 (5.4)	1059 (7.7)	677 (6.7)	411 (9.9)	281 (10.4)	807 (6.7)
Congestive heart failure	9 (0.8)	215 (1.6)	4 (0.7)	220 (1.6)	100 (1.0)	124 (3.0)	94 (3.5)	130 (1.1)
Gastrointestinal (perforation, ulcer, bleeding or varix bleeding)	37 (3.3)	406 (3.1)	20 (3.7)	423 (3.1)	267 (2.6)	176 (4.2)	120 (4.4)	323 (2.8)
Renal insufficiency	2 (0.2)	103 (0.8)	1 (0.2)	104 (0.8)	48 (0.5)	57 (1.4)	47 (1.7)	58 (0.5)
Renal insufficiency and dialysis	0 (0)	12 (0.1)	0 (0)	12 (0.1)	5 (0.1)	7 (0.2)	6(0.2)	6(0.1)

10.3. Outcome data

Objective 3: Describe incidence rates of outcomes of interest for etoricoxib, other coxibs, and nonspecific NSAIDs in Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS). Present incidence rates for outcomes of interest adjusted for potential confounders.

Number of events and, incidence rates (unadjusted and adjusted) for outcomes of interest – All patients, incident and prevalent

Tables 3.1a through 3.1c show events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs during the exposure period. The tables are presented for (3.1a) all AS/SpA patients, (3.1b) AS patients only and (3.1c) SpA patients only. Entry into the exposure period is defined as 01 Jan 2006 for patients diagnosed and entering the study before that date and at study entry for patients diagnosed and entering the study on or after 01 Jan 2006. Also, patients could have both an AS and a SpA diagnosis during the study period. Patients were censored when the event of interest occurred (or death or emigration) explaining why person time-at-risk differs for the different outcomes studied. Exposure was assessed in a time-dependent manner; i.e., if subjects exposure status changed from one stratum of NSAID exposure to another during the course of the study, the person-time at risk was computed within the appropriate category. Etoricoxib was used as the referent group for all analyses. For comparison, incidence rates were also calculated for the subgroup that were totally unexposed to any of the three NSAID groups during the theoretical exposure period. Rates were also calculated using extended approaches to exposure (on drug + 14 days, on drug + 30 days, on drug + 90 days). These results along with a variety of additional adjusted models and sensitivity analyses are presented in **Annex 5**. Moreover, death due to any cause during the different exposures is also tabulated in the appended files. The actual numbers of deaths are low, and do not allow for meaningful analysis of relative risks or adjustments. No differences in death rates were detected between the different exposure groups.

It should be noted that patients experiencing an outcome event of interest are censored after the first occurrence of the particular outcome. However, censoring occurs only for the specific outcome of interest, and the patient remains in the denominator, eligible for experiencing the other outcomes.

Based on the rather low number of outcome related events, the number of covariates that should be used in multivariate regression models is limited. Obvious confounders to control for are age, sex, previous exposure to the different NSAID classes, and previous incidence of the outcome of interest. Further, it is important to control for outcome related comorbidities and outcome related medications as well as disease severity (usage of concomitant biological therapy).

The outcome related baseline characteristics were chosen based on clinical/ pathophysiologic reasoning. For example when studying gastric bleeding, ulcers and perforation, we controlled for usage of gastroprotective medicine, glucocorticoids, and baseline hepatic/gastrointestinal disease and/or alcoholism. Following a similar line of

thought, different sets of confounding factors were adjusted for in the analyses of the different outcomes.

The compound baseline risks were defined as presence of any of the listed conditions/drugs at entry into the exposure period:

For Atherosclerotic cardiovascular events, the compound baseline risk factors include the following:

- Atherosclerotic cardiovascular event
- Atherosclerotic cerebrovascular event
- Severe hypertension
- Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia co-morbidity
- Cardiovascular drugs
- ASA for atherosclerotic prevention

For Atherosclerotic cerebrovascular events, the compound baseline risk factors include the

following:- Atherosclerotic cardiovascular event
- Atherosclerotic cerebrovascular event
- Severe hypertension
- Endocrine / metabolism: diabetes mellitus (DM), hyperlipidemia co-morbidity
- Cardiovascular drugs
- ASA for atherosclerotic prevention
- Anti-coagulants

For Severe hypertension events, the compound baseline risk factors include the following:

- Renal insufficiency
- Corticosteroids
- NSAID overall

For Congestive heart failure events, the compound baseline risk factors include the following:

- NSAID overall
-Severe hypertension
- Renal insufficiency
- Cardiovascular: cardiac valvular disease, arrhythmia

For Gastrointestinal (perforation, ulcer, bleeding or varix bleeding) events, the compound baseline risk factors include the following:

- Gastroprotective drugs
- NSAID overall
- Aspirin overall
- Anti-coagulants
- Corticosteroids
- Hepatic: alcoholism, liver failure

For Renal insufficiency events, the compound baseline risk factors include the following:

- Anti-diabetic drugs
- Severe hypertension
- Hepatic: alcoholism, liver failure
- Cardiovascular drugs

Table 3.1a.
Events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
AS and SpA Combined Cohort (Incident + Prevalent)

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Atherosclerotic Cardiac Events				
Unique individuals in exposure group [Total 20302] §§	1630	15400	840	4260
Events	8	262	6	317
Time (yrs.)	1000	16500	686	14200
Incidence rates (/1000yrs)	8.0	15.9	8.75	22.3
CI for Incidence rates (/1000yrs)	3.32 - 19.3	13.7 - 18.6	3.16 - 24.2	19.4 - 25.7
Relative risks (CI)	1	1.99 (0.89 - 4.45)	1.09 (0.325 - 3.67)	**2.79 (1.25 - 6.23)**
Rates adjusted for potential confounding factors* (CI)	1.33 (0.5 - 3.56)	2.23 (1.34 - 3.7)	1.15 (0.383 - 3.46)	1.9 (1.17 - 3.1)
RR adjusted for potential confounding factors* (CI)	1	1.67 (0.728 - 3.84)	0.864 (0.247 - 3.02)	1.43 (0.619 - 3.28)
Atherosclerotic Cerebrovascular Events				
Unique individuals in exposure group [Total 20427] §§	1650	15500	858	4260
Events	5	83	6	155
Time (yrs.)	1000	16800	694	14600
Incidence rates (/1000yrs)	5.0	4.94	8.65	10.6
CI for Incidence rates (/1000yrs)	1.64 - 15.2	0.00376 - 0.00649	0.00313 - 0.0239	0.00869 - 0.013
Relative risks (CI)	1	0.989 (0.352 - 2.78)	1.73 (0.445 - 6.73)	2.12 (0.766 - 5.88)
Rates adjusted for potential confounding factors* (CI)	1.9 (0.564 - 6.39)	1.47 (0.81 - 2.68)	2.39 (0.77 - 7.42)	2.03 (1.2 - 3.44)
RR adjusted for potential confounding factors* (CI)	1	0.776 (0.269 - 2.24)	1.26 (0.312 - 5.08)	1.07 (0.369 - 3.09)
Combined Atherosclerotic Thrombotic (cerebrovascular and cardiac)				
Unique individuals in exposure group [Total 20263]	1630	15400	840	4260
Events	13	325	11	433

	Etoricoxib	nsNSAID	Other Coxib	Not exposed to NSAIDs
Time (yrs.)	989	16400	684	13400
Incidence rates (/1000yrs)	13.14	19.85	16.08	32.24
CI for Incidence rates (/1000yrs)	6.59 - 26.23	17.29 - 22.79	7.59 - 34.08	28.6 - 36.34
Relative risks (CI)	1	1.51 (0.8 - 2.85)	1.22 (0.49 - 3.07)	**2.45 (1.3 - 4.62)**
Rates adjusted for potential confounding factors* (CI)	2.92 (1.36 - 6.27)	3.67 (2.49 - 5.39)	2.79 (1.23 - 6.3)	3.76 (2.63 - 5.37)
RR adjusted for potential confounding factors* (CI)	1	1.25 (0.65 - 2.41)	0.95 (0.37 - 2.45)	1.28 (0.67 - 2.48)
Hypertension, severe events				
Unique individuals in exposure group [Total 20184] §§	1580	15300	827	4260
Events	29	665	26	558
Time (yrs.)	959	15800	654	13700
Incidence rates (/1000yrs)	30.2	42.0	39.8	40.7
CI for Incidence rates (/1000yrs)	19.0 - 48.0	38.2 - 46.3	24.4 - 64.8	36.6 - 45.3
Relative risks (CI)	1	1.39 (0.907 - 2.13)	1.31 (0.715 - 2.42)	1.35 (0.877 - 2.07)
Rates adjusted for potential confounding factors* (CI)	5.91 (3.49 - 10.0)	7.14 (5.33 - 9.57)	6.75 (3.9 - 11.7)	6.85 (5.22 - 8.99)
RR adjusted for potential confounding factors* (CI)	1	1.21 (0.777 - 1.88)	1.14 (0.609 - 2.14)	1.16 (0.74 - 1.81)
Congestive Heart Failure Events				
Unique individuals in exposure group [Total 20420] §§	1650	15500	853	4260
Events	4	83	2	226
Time (yrs.)	1010	16800	694	14400
Incidence rates (/1000yrs)	3.96	4.94	2.88	15.7
CI for Incidence rates (/1000yrs)	1.14 - 13.8	3.76 - 6.49	0.495 - 16.8	13.3 - 18.5
Relative risks (CI)	1	1.25 (0.392 - 3.97)	0.727 (0.103 - 5.15)	3.95 (1.26 - 12.4)
Rates adjusted for potential confounding factors* (CI)	1.12 (0.301 - 4.15)	1.22 (0.717 - 2.07)	0.587 (0.10 - 3.55)	2.43 (1.55 - 3.81)
RR adjusted for potential confounding factors* (CI)	1	1.09 (0.335 - 3.54)	0.525 (0.0714 - 3.86)	2.17 (0.668 - 7.07)
Gastrointestinal Events				
Unique individuals in exposure group [Total 20443]	1630	15500	845	4260
Events	13	178	6	87
Time (yrs.)	985	16700	681	14800

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Incidence rates (/1000yrs)	13.2	10.7	8.81	5.88
CI for Incidence rates (/1000yrs)	6.62 - 26.3	8.84 - 12.8	3.19 - 24.4	4.5 - 7.68
Relative risks (CI)	1	0.807 (0.416 - 1.57)	0.667 (0.214 - 2.08)	**0.446 (0.224 - 0.885)**
Rates adjusted for potential confounding factors* (CI)	8.98 (4.09 - 19.7)	7.1 (4.62 - 10.9)	5.35 (1.82 - 15.8)	3.43 (2.36 - 4.98)
RR adjusted for potential confounding factors* (CI)	1	0.791 (0.402 - 1.56)	0.596 (0.186 - 1.91)	**0.382 (0.183 - 0.799)**
Renovascular Events				
Unique individuals in exposure group [Total 20446] §§	1650	15600	854	4260
Events	3	57	0	125
Time (yrs.)	1010	16900	695	14700
Incidence rates (/1000yrs)	2.97	3.38	N/A	8.53
CI for Incidence rates (/1000yrs)	0.705 - 12.5	2.43 - 4.7	N/A	6.83 - 10.7
Relative risks (CI)	1	1.14 (0.292 - 4.45)	N/A	2.87 (0.75 - 11)
Rates adjusted for potential confounding factors* (CI)	0.593 (0.125 - 2.82)	0.5 (0.235 - 1.06)	N/A	0.592 (0.277 - 1.27)
RR adjusted for potential confounding factors* (CI)	1	0.842 (0.208 - 3.41)	N/A	0.998 (0.248 - 4.02)

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

Table 3.1b.
Events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
AS Only Combined Cohort (Incident + Prevalent)

	Etoricoxib	nsNSAID	Other Coxib	Not exposed to NSAIDs
Atherosclerotic Cardiac Events				
Unique individuals in exposure group [Total 10061] §§	808	7750	458	1960
Events	5	208	3	179
Time (yrs)	579	9690	406	6540
Incidence rates (/1000yrs)	8.63	21.5	7.4	27.4
CI for Incidence rates (/1000yrs)	2.83 - 26.3	18.1 - 25.5	1.76 - 31.2	22.7 - 33.0
Relative risks (CI)	1	2.49 (0.899 - 6.88)	0.857 (0.166 - 4.42)	**3.17 (1.14 - 8.79)**
Rates adjusted for potential confounding factors* /1000yrs (CI)	2.09 (0.62 - 7.09)	4.27 (2.36 - 7.72)	1.22 (0.27 - 5.53)	2.9 (1.62 - 5.2)
RR adjusted for potential confounding factors* (CI)	1	2.04 (0.715 - 5.83)	0.582 (0.107 - 3.16)	1.39 (0.482 - 3.99)
Atherosclerotic Cerebrovascular Events				
Unique individuals in exposure group [Total 10133]	813	7810	472	1960
Events	5	53	5	83
Time (yrs)	578	9960	411	6800
Incidence rates (/1000yrs)	8.66	5.32	12.2	12.2
CI for Incidence rates (/1000yrs)	2.84 - 26.4	3.78 - 7.49	3.99 - 37.0	9.28 - 16.0
Relative risks (CI)	1	0.615 (0.213 - 1.78)	1.4 (0.335 - 5.9)	1.41 (0.496 - 4.01)
Rates adjusted for potential confounding factors* /1000yrs (CI)	4.04 (1.08 - 15.2)	1.68 (0.746 - 3.77)	4.01 (1.08 - 15.0)	2.34 (1.12 - 4.9)
RR adjusted for potential confounding factors* (CI)	1	0.415 (0.138 - 1.25)	0.992 (0.225 - 4.37)	0.579 (0.19 - 1.77)
Hypertension, severe Events				
Unique individuals in exposure group [Total 9991]	780	7660	452	1960
Events	18	472	18	317
Time (yrs)	550	9250	383	6280
Incidence rates (/1000yrs)	32.7	51.0	47.0	50.5

	Etoricoxib	nsNSAID	Other Coxib	Not exposed to NSAIDs
CI for Incidence rates (/1000yrs)	18.2 - 58.8	45.5 - 57.2	26.1 - 84.5	43.9 - 58.1
Relative risks (CI)	1	1.56 (0.908 - 2.68)	1.44 (0.678 - 3.04)	1.54 (0.894 - 2.66)
Rates adjusted for potential confounding factors* /1000yrs (CI)	6.78 (3.44 - 13.3)	9.11 (6.21 - 13.4)	8.25 (4.2 - 16.2)	8.26 (5.72 - 11.9)
RR adjusted for potential confounding factors* (CI)	1	1.35 (0.77 - 2.35)	1.22 (0.561 - 2.64)	1.22 (0.69 - 2.15)
Congestive Heart Failure Events				
Unique individuals in exposure group [Total 10126]	814	7810	470	1960
Events	4	61	2	142
Time (yrs)	585	9950	412	6660
Incidence rates (/1000yrs)	6.84	6.13	4.86	21.3
CI for Incidence rates (/1000yrs)	1.97 - 23.8	4.46 - 8.43	0.834 - 28.3	17.3 - 26.3
Relative risks (CI)	1	0.896 (0.277 - 2.9)	0.71 (0.0991 - 5.08)	3.12 (0.985 - 9.88)
Rates adjusted for potential confounding factors* /1000yrs (CI)	2.28 (0.586 - 8.84)	1.8 (0.932 - 3.47)	1.12 (0.181 - 6.96)	3.43 (1.93 - 6.11)
RR adjusted for potential confounding factors* (CI)	1	0.79 (0.237 - 2.63)	0.493 (0.0656 - 3.71)	1.51 (0.45 - 5.05)
Gastrointestinal Events				
Unique individuals in exp group [Total 10146]	806	7820	464	1960
Events	10	104	4	50
Time (yrs)	568	9910	406	6900
Incidence rates (/1000yrs)	17.6	10.5	9.85	7.25
CI for Incidence rates (/1000yrs)	8.0 - 38.7	8.22 - 13.4	2.83 - 34.2	5.1 - 10.3
Relative risks (CI)	1	0.596 (0.276 - 1.29)	0.56 (0.142 - 2.21)	**0.412 (0.184 - 0.921)**
Rates adjusted for potential confounding factors* /1000yrs (CI)	15.8 (6.21 - 40.1)	9.08 (5.17 - 16.0)	7.64 (2.01 - 29.0)	5.14 (3.11 - 8.5)
RR adjusted for potential confounding factors* (CI)	1	0.575 (0.262 - 1.26)	0.484 (0.119 - 1.97)	**0.325 (0.136 - 0.778)**
Renovascular Events				
Unique individuals in exposure group [Total 10146]	817	7830	469	1960
Events	3	43	0	86
Time (yrs)	586	10000	412	6770
Incidence rates (/1000yrs)	5.12	4.3	NA	12.7
CI for Incidence rates (/1000yrs)	1.21 - 21.6	2.94 - 6.29	NA	9.72 - 16.6

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Relative risks (CI)	1	0.84 (0.211 - 3.34)	NA	2.48 (0.639 - 9.65)
Rates adjusted for potential confounding factors* /1000yrs (CI)	1.64 (0.333 - 8.05)	0.993 (0.427 - 2.31)	NA	1.17 (0.487 - 2.8)
RR adjusted for potential confounding factors* (CI)	1	0.606 (0.147 - 2.5)	NA	0.713 (0.173 - 2.95)

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

Table 3.1c.
Events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
SpA Only Combined Cohort (Incident + Prevalent)

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Atherosclerotic Thrombotic Cardiac Events				
Unique individuals in exposure group [Total 13108]§§	1100	10000	536	2710
Events	3	99	4	158
Time (yrs)	602	9640	422	9030
Incidence rates (/1000yrs)	4.99	10.3	9.49	17.5
CI for Incidence rates (/1000yrs)	1.18 - 21.0	8.0 - 13.2	2.73 - 33.0	14.4 - 21.3
Relative risks (CI)	1	2.06 (0.562 - 7.56)	1.9 (0.35 - 10.4)	3.51 (0.963 - 12.8)
Rates adjusted for potential confounding factors* (CI)	0.634 (0.12 - 3.34)	1.04 (0.399 - 2.7)	1.13 (0.249 - 5.1)	1.12 (0.443 - 2.82)
RR adjusted for potential confounding factors* (CI)	1	1.64 (0.423 - 6.33)	1.78 (0.305 - 10.3)	1.76 (0.455 - 6.83)
Atherosclerotic Thrombotic Cerebrovascular Events				
Unique individuals in exposure group [Total 13182]	1100	10100	542	2710
Events	2	46	4	85
Time (yrs)	603	9770	425	9200
Incidence rates (/1000yrs)	3.32	4.71	9.41	9.24
CI for Incidence rates (/1000yrs)	0.57 - 19.3	3.26 - 6.8	2.71 - 32.7	7.05 - 12.1
Relative risks (CI)	1	1.42 (0.288 - 7)	2.83 (0.418 - 19.2)	2.78 (0.573 - 13.5)
Rates adjusted for potential confounding factors* (CI)	0.952 (0.148 - 6.14)	1.23 (0.555 - 2.71)	2.13 (0.522 - 8.72)	1.57 (0.78 - 3.16)
RR adjusted for potential confounding factors* (CI)	1	1.29 (0.251 - 6.6)	2.24 (0.314 - 15.9)	1.65 (0.32 - 8.48)
Hypertension, severe events				
Unique individuals in exposure group [Total 13049]	1060	9940	525	2710
Events	16	321	17	291
Time (yrs)	577	9310	401	8730

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Incidence rates (/1000yrs)	27.7	34.5	42.4	33.3
CI for Incidence rates (/1000yrs)	14.9 - 51.7	30.0 - 39.6	23.2 - 77.6	28.8 - 38.6
Relative risks (CI)	1	1.24 (0.699 - 2.21)	1.53 (0.699 - 3.35)	1.2 (0.675 - 2.14)
Rates adjusted for potential confounding factors* (CI)	5.24 (2.56 - 10.7)	5.96 (3.98 - 8.92)	7.76 (3.85 - 15.6)	5.74 (3.96 - 8.33)
RR adjusted for potential confounding factors* (CI)	1	1.14 (0.628 - 2.06)	1.48 (0.66 - 3.33)	1.1 (0.598 - 2.01)
Congestive heart failure Events				
Unique individuals in exposure group [Total 13175]	1110	10100	539	2710
Events	0	32	1	103
Time (yrs)	605	9770	425	9150
Incidence rates (/1000yrs)	NA	3.27	2.36	11.3
CI for Incidence rates (/1000yrs)	NA	2.11 - 5.09	0.195 - 28.4	8.8 - 14.4
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* (CI)	NA	0.763 (0.346 - 1.68)	0.528 (0.040 - 6.8)	1.97 (1.04 - 3.75)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Gastrointestinal Events				
Unique individuals in exposure group [Total 13178]	1090	10100	533	2710
Events	10	102	4	48
Time (yrs)	590	9700	412	9290
Incidence rates (/1000yrs)	17.0	10.5	9.7	5.17
CI for Incidence rates (/1000yrs)	7.72 - 37.3	8.22 - 13.5	2.79 - 33.7	3.61 - 7.4
Relative risks (CI)	1	0.62 (0.287 - 1.34)	0.572 (0.144 - 2.26)	**0.305 (0.136 - 0.684)**
Rates adjusted for potential confounding factors* (CI)	8.46 (3.31 - 21.6)	5.15 (2.88 - 9.2)	4.48 (1.17 - 17.2)	2.57 (1.56 - 4.24)
RR adjusted for potential confounding factors* (CI)	1	0.609 (0.277 - 1.34)	0.53 (0.13 - 2.16)	**0.304 (0.125 - 0.736)**
Renovascular Events				
Unique individuals in exposure group [Total 13184]	1110	10100	541	2710
Events	0	24	0	52
Time (yrs)	606	9790	426	9270
Incidence rates (/1000yrs)	NA	2.45	NA	5.61

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
CI for Incidence rates (/1000yrs)	NA	1.47 - 4.07	NA	3.97 - 7.92
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* (CI)	NA	0.32 (0.098 - 1.05)	NA	0.374 (0.114 - 1.23)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

Incident patients

Tables 3.2a through 3.2c show events, number of person years at risk, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs during the exposure period for incident patients. The tables are presented for (3.2a) all AS/SpA patients, (3.2b) AS patients only, and (3.2c) SpA patients only. Entry into the exposure period is defined as 01 Jan 2006 for patients diagnosed and entering the study before that date and at study entry for patients diagnosed and entering the study on or after 01 Jan 2006. Also, patients could have both an AS and a SpA diagnosis during the study period. Patients were censored when the outcome of interest occurred explaining different time of exposure for different outcome events observed. However, rates were also calculated using extended approaches to exposure (on drug + 14 days, on drug + 30 days, on drug + 90 days). These results along with a variety of additional adjusted models and sensitivity analyses are presented in **Annex 5**.

Table 3.2a.
Events, number of exposed patient years, unadjusted and adjusted incidence rates
for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
AS and SpA Incident Cohort

	Etoricoxib	**nsNSAID**	**Other Coxib**	**Not exposed to NSAIDs**
Atherosclerotic Cardiac Events				
Unique individuals in exposure group [Total 7083] §§	631	5700	249	1110
Events	1	47	1	90
Time (yrs)	302	3980	115	2230
Incidence rates (/1000yrs)	3.32	11.8	8.66	40.33
CI for Incidence rates (/1000yrs)	0.275 - 40.0	8.22 - 17.0	0.718 - 105.0	31.0 - 52.55
Relative risks (CI)	1	3.56 (0.378 - 33.6)	2.61 (0.113 - 60.5)	**12.2 (1.3 - 114)**
Rates adjusted for potential confounding factors* /1000yrs (CI)	0.454 (0.03 - 6.13)	2.05 (0.764 - 5.5)	1.23 (0.09 - 16.8)	2.94 (1.16 - 7.44)
RR adjusted for potential confounding factors* (CI)	1	4.51 (0.452 - 45.1)	2.71 (0.109 - 67.7)	6.48 (0.653 - 64.3)
Atherosclerotic Cerebrovascular Events				
Unique individuals in exposure group [Total 7128]	635	5740	256	1110
Events	0	19	0	33
Time (yrs)	303	4030	119	2320
Incidence rates (/1000yrs)	0	4.72	0	14.2
CI for Incidence rates (/1000yrs)	NA	2.66 - 8.36	NA	9.21 - 21.9
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	0.866 (0.186 – 4.03)	NA	1.36 (0.329 – 5.64)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Combined Atherosclerotic Thrombotic				
Unique individuals in exposure group [Total 7074]	630	5690	249	1110
Events	1	63	1	112
Time (yrs)	301	3960	115	2130
Incidence rates (/1000yrs)	3.32	15.9	8.68	52.59

CI for Incidence rates (/1000yrs)	0.28 - 40.1	11.61 - 21.76	0.72 - 104.78	41.56 - 66.55
Relative risks (CI)	1	4.79 (0.51 - 44.57)	2.61 (0.11 - 59.9)	**15.83 (1.71 - 146.34)**
Rates adjusted for potential confounding factors* /1000yrs (CI)	0.43 (0.03 - 5.63)	2.41 (1 - 5.82)	1.01 (0.08 - 13.25)	3.61 (1.59 - 8.2)
RR adjusted for potential confounding factors* (CI)	1	5.61 (0.57 - 54.83)	2.34 (0.1 - 57.32)	8.38 (0.86 - 81.79)
Hypertension, severe Events				
Unique individuals in exposure group [Total 7051]	612	5660	248	1110
Events	7	176	2	142
Time (yrs)	289	3850	114	2150
Incidence rates (/1000yrs)	24.3	45.8	17.6	66.2
CI for Incidence rates (/1000yrs)	9.46 - 62.2	37.9 - 55.2	3.02 - 102.0	53.7 - 81.6
Relative risks (CI)	1	1.89 (0.782 - 4.55)	0.724 (0.116 - 4.52)	2.73 (1.13 - 6.61)
Rates adjusted for potential confounding factors* /1000yrs (CI)	3.38 (1.1 - 10.4)	5.5 (2.77 - 10.9)	1.55 (0.248 - 9.65)	6.21 (3.25 - 11.9)
RR adjusted for potential confounding factors* (CI)	1	1.63 (0.655 - 4.04)	0.458 (0.0689 - 3.04)	1.84 (0.724 - 4.66)
Congestive Heart Failure Events				
Unique individuals in exposure group [Total 7124]	635	5740	254	1110
Events	0	15	0	63
Time (yrs)	303	4030	118	2280
Incidence rates (/1000yrs)	0	3.72	NA	27.7
CI for Incidence rates (/1000yrs)	NA	1.96 - 7.09	NA	20.2 - 37.9
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	0.997 (0.337 - 2.95)	NA	3.63 (1.51 - 8.72)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Gastrointestinal Events				
Unique individuals in exposure group [Total 7127]	629	5740	253	1110
Events	1	51	3	20
Time (yrs)	300	4010	117	2350
Incidence rates (/1000yrs)	3.34	12.7	25.6	8.51
CI for Incidence rates (/1000yrs)	0.277 - 40.3	8.97 - 18.0	6.07 - 108.0	4.88 - 14.9
Relative risks (CI)	1	3.81 (0.417 - 34.8)	7.65 (0.61 - 96)	2.55 (0.27 - 24)

Rates adjusted for potential confounding factors* /1000yrs (CI)	1.7 (0.124 - 23.4)	6.27 (2.44 - 16.1)	10.5 (1.96 - 56.0)	3.82 (1.68 - 8.69)
RR adjusted for potential confounding factors* (CI)	1	3.69 (0.385 - 35.3)	6.15 (0.463 - 81.7)	2.25 (0.215 - 23.5)
Renovascular Events				
Unique individuals in exposure group [Total 7130]	635	5740	255	1110
Events	0	16	0	31
Time (yrs)	304	4030	119	2340
Incidence rates (/1000yrs)	NA	3.97	NA	13.2
CI for Incidence rates (/1000yrs)	NA	2.13 - 7.4	NA	8.47 - 20.7
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	0.242 (0.04 - 1.54)	NA	0.318 (0.05 - 2.12)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

Table 3.2b.
Events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
AS only Incident Cohort

	Etoricoxib	**nsNSAID**	**Other.Coxib**	**Totally.unexposed**
Atherosclerotic Cardiac Events				
Unique individuals in exposure group [Total 2925]§§	264	2350	110	430
Events	0	34	0	45
Time (yrs)	150	1900	62.5	804
Incidence rates (/1000yrs)	NA	17.9	NA	56.0
CI for Incidence rates (/1000yrs)	NA	11.7 - 27.5	NA	38.6 - 81.1
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	8.58 (2.46 - 30.0)	NA	6.06 (1.79 - 20.6)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Atherosclerotic Cerebrovascular Events				
Unique individuals in exposure group [Total 2947]	264	2370	114	430
Events	1	11	0	16
Time (yrs)	151	1930	64.2	851
Incidence rates (/1000yrs)	6.64	5.71	NA	18.8
CI for Incidence rates (/1000yrs)	0.55 - 80.1	2.69 - 12.1	NA	10.1 - 35.1
Relative risks (CI)	1	0.86 (0.076 - 9.73)	NA	2.83 (0.259 - 31.1)
Rates adjusted for potential confounding factors* /1000yrs (CI)	0.231 (0.005 - 9.3)	0.169 (0.009 - 3.0)	NA	0.457 (0.030 - 6.92)
RR adjusted for potential confounding factors* (CI)	1	0.733 (0.0585 - 9.17)	NA	1.98 (0.151 - 25.9)
Hypertension, severe Events				
Unique individuals in exposure group [Total 2908]	251	2330	111	430
Events	7	109	2	68
Time (yrs)	138	1820	62.6	771
Incidence rates (/1000yrs)	50.8	59.9	31.9	88.2
CI for Incidence rates (/1000yrs)	19.8 - 130.0	47.3 - 76.2	5.49 - 186.0	65.2 - 119.0

Relative risks (CI)	1	1.18 (0.481 - 2.9)	0.629 (0.0991 - 4)	1.74 (0.696 - 4.34)
Rates adjusted for potential confounding factors* /1000yrs (CI)	7.13 (1.83 - 27.7)	5.73 (1.99 - 16.5)	2.79 (0.387 - 20.2)	5.26 (1.88 - 14.7)
RR adjusted for potential confounding factors* (CI)	1	0.804 (0.314 - 2.05)	0.392 (0.0571 - 2.69)	0.738 (0.273 - 1.99)
Congestive Heart Failure Events				
Unique individuals in exposure group [Total 2947]	264	2370	113	430
Events	0	7	0	29
Time (yrs)	151	1930	63.9	829
Incidence rates (/1000yrs)	NA	3.63	NA	35.0
CI for Incidence rates (/1000yrs)	NA	1.41 - 9.3	NA	22.0 - 55.5
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	0.38 (0.05 - 2.77)	NA	2.35 (0.452 - 12.2)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Gastrointestinal Events				
Unique individuals in exposure group [Total 2949]	262	2380	114	430
Events	0	25	2	9
Time (yrs)	149	1920	64	868
Incidence rates (/1000yrs)	NA	13.0	31.2	10.4
CI for Incidence rates (/1000yrs)	NA	7.91 - 21.4	5.37 - 182.0	4.52 - 23.8
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	7.68 (1.79 - 33.0)	15.2 (1.65 - 139.0)	4.73 (1.24 - 18.1)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Renovascular Events				
Unique individuals in exposure group [Total 2948]	265	2380	113	430
Events	0	8	0	11
Time (yrs)	152	1930	64.1	866
Incidence rates (/1000yrs)	NA	4.15	NA	12.7
CI for Incidence rates (/1000yrs)	NA	1.72 - 10.0	NA	6.0 - 26.9
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* /1000yrs (CI)	NA	0.628 (0.07 - 5.43)	NA	0.497 (0.04 - 5.52)

RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

Table 3.2c.
Events, number of exposed patient years, unadjusted and adjusted incidence rates for the outcomes of interest for etoricoxib, nsNSAID, and other coxibs
From Entry into the Exposure Period to the End of the Study Period
SpA only Incident Cohort

	Etoricoxib	**nsNSAID**	**Other.Coxib**	**Totally.unexposed**
Atherosclerotic Thrombotic Cardiac				
Unique individuals in exposure group [Total 5362] §§	480	4370	197	800
Events	1	31	1	51
Time (yrs)	211	2980	101	1650
Incidence rates (/1000yrs)	4.73	10.4	9.87	31.0
CI for Incidence rates (/1000yrs)	0.392 - 57.1	6.65 - 16.3	0.818 - 119.0	21.9 - 43.9
Relative risks (CI)	1	2.2 (0.227 - 21.3)	2.09 (0.0886 - 49.1)	6.54 (0.686 - 62.4)
Rates adjusted for potential confounding factors* (CI)	0.375 (0.02 - 6.16)	0.933 (0.214 - 4.07)	1.06 (0.06 - 17.3)	1.46 (0.357 - 5.97)
RR adjusted for potential confounding factors* (CI)	1	2.49 (0.238 - 26)	2.82 (0.107 - 74.3)	3.89 (0.374 - 40.4)
Atherosclerotic Thrombotic Cerebrovascular				
Unique individuals in exposure group [Total 5391]	484	4390	200	800
Events	0	10	1	20
Time (yrs)	212	3010	103	1700
Incidence rates (/1000yrs)	NA	3.32	9.73	11.8
CI for Incidence rates (/1000yrs)	NA	1.51 - 7.3	0.806 - 117.0	6.74 - 20.5
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* (CI)	NA	1.04 (0.178 - 6.13)	1.52 (0.08 - 29.1)	1.76 (0.355 - 8.7)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Hypertension, severe				
Unique individuals in exposure group [Total 5339]	467	4340	193	800
Events	3	114	1	87
Time (yrs)	205	2900	99.3	1580
Incidence rates (/1000yrs)	14.6	39.4	10.1	55.0
CI for Incidence rates (/1000yrs)	3.47 - 61.5	31.2 - 49.7	0.834 - 122.0	42.1 - 71.9

Relative risks (CI)	1	2.69 (0.715 - 10.1)	0.689 (0.0503 - 9.44)	3.77 (0.995 - 14.3)
Rates adjusted for potential confounding factors* (CI)	2.42 (0.488 - 12.1)	6.08 (2.73 - 13.6)	1.23 (0.09 - 15.7)	7.81 (3.71 - 16.4)
RR adjusted for potential confounding factors* (CI)	1	2.51 (0.64 - 9.82)	0.507 (0.0342 - 7.53)	3.22 (0.805 - 12.9)
Congestive heart failure				
Unique individuals in exposure group [Total 5385]	484	4390	199	800
Events	0	11	0	39
Time (yrs)	212	3010	103	1670
Incidence rates (/1000yrs)	NA	3.66	NA	23.3
CI for Incidence rates (/1000yrs)	NA	1.73 - 7.75	NA	15.7 - 34.8
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* (CI)	NA	1.17 (0.351 - 3.91)	NA	4.04 (1.54 - 10.6)
RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA
Gastrointestinal				
Unique individuals in exposure group [Total 5387]	479	4390	197	800
Events	3	38	1	14
Time (yrs)	208	2990	102	1710
Incidence rates (/1000yrs)	14.4	12.7	9.83	8.2
CI for Incidence rates (/1000yrs)	3.43 - 60.8	8.47 - 19.0	0.814 - 119.0	4.21 - 15.9
Relative risks (CI)	1	0.879 (0.218 - 3.55)	0.68 (0.0464 - 9.97)	0.567 (0.129 - 2.49)
Rates adjusted for potential confounding factors* (CI)	8.42 (1.47 - 48.2)	7.48 (2.6 - 21.5)	5.53 (0.389 - 78.7)	4.86 (2.04 - 11.6)
RR adjusted for potential confounding factors* (CI)	1	0.888 (0.214 - 3.69)	0.657 (0.0423 - 10.2)	0.577 (0.113 - 2.96)
Renovascular				
Unique individuals in exposure group [Total 5391]	483	4400	200	800
Events	0	10	0	23
Time (yrs)	212	3010	103	1700
Incidence rates (/1000yrs)	NA	3.32	NA	13.5
CI for Incidence rates (/1000yrs)	NA	1.51 - 7.3	NA	8.03 - 22.7
Relative risks (CI)	NA	NA	NA	NA
Rates adjusted for potential confounding factors* (CI)	NA	0.125 (0.009 - 1.66)	NA	0.265 (0.02 - 3.45)

RR adjusted for potential confounding factors* / 1000yrs (CI)	NA	NA	NA	NA

§§ Please note that patients experiencing an event prior to NSAID exposure will be censored thus n can vary slightly from outcome to outcome. Also patients are partially exposed to NSAID, i.e. exposed from 01 07 2005 till 01 01 2006 and then unexposed – these patients are not accounted for, giving a total n that differs slightly from the demographic baseline tables. Also all incident patients are included (i.e. despite previous accumulated DDD exposure > 180 DDDs) to allow for more exposure time.

* Potential confounding factors are age, sex, prior incidence of outcome of interest and compound risk factors, which are individualized for the outcome of interest as defined here. See text for description of the compound risk factors for each outcome.

10.4. Main results

Please refer to Section 10.3 of this report.

10.5. Other analyses

See a variety of adjusted models and sensitivity analyses for the various combinations of cohorts (Incident, Prevalent, All; AS, SpA, combined) in **Annex 5**.

10.6. Adverse events/adverse reactions

No reporting of individual cases to regulatory agencies is planned as part of this retrospective observational database study. This is consistent with the pharmacovigilance guidelines drawn up by the European Commission in accordance with Article 106 of Directive 2001/83/EC of the European Parliament and the Council are published as Volume 9A of The Rules Governing Medicinal Products in the EU section 7.4.2 Reporting of Adverse Reactions: "In certain study designs, such as case-control or retrospective cohort studies…in which it is not feasible or appropriate to make an assessment of causality between medical events recorded and the medicinal products at individual case level, expedited reporting of Individual Case Safety Reports is not required." Because there is no access to individual patient charts for this study, no specific attribution of cases is possible.

11. Discussion

11.1. Key results

Objective 1: Describe the characteristics of Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS)

11.1.1 Demographics

This study identified patients with AS/SpA using ICD-9 and -10 diagnosis codes. A study done in the southernmost county of Sweden validated the diagnostic coding for spondyloarthritis and its subtypes by reviewing the medical records of patients who had visited the rheumatology clinic at PPD (a major rheumatology clinic within the county) [Ref. 5.4: 6062]. The medical records of 347 patients were reviewed with regard to the items included in the classification criteria for AS, psoriatic arthritis, undifferentiated SpA as well as a diagnosis of inflammatory bowel disease. A valid spondyloarthritis diagnosis was found in 340 (98%) of the cases. Thus the ICD diagnosis codes used in this study would appear to have high validity.

The number of identified AS/SpA patients is at a level that would be expected from a Swedish national population of around 7.55 million people (i.e., 22,283 patients / 7,549,326 persons 17 years. or older at the end of 2009 according to official statistics = 0.30%) considering that only patients with a hospital referral for AS/SpA are included in

the study population. The predominance of male patients among those with a diagnosis of AS is also as would be expected. However, it should be noted that the average age for patients at study entry is rather high (peak enrollment age 40-49 years.). Explanations for this relatively high age include: the nature of the study design, where patients enrolled during the first year of the entry period are patients with prevalent AS/SpA diagnosis known for years rather than patients with incident AS/SpA diagnosis; patient delay in seeking care; and a time lag between diagnoses by GPs and later referral for care to a specialist clinic.

11.1.2 Medications

In general, the high frequency of usage of anti-rheumatic drugs and nsNSAIDs or coxibs reflects a patient group with moderate to severe AS/SpA. In addition, it should be noted that due to the study design, the majority of patients had their diagnosis before the start of the baseline period (and also before their entry into the Exposure Period; n=13,601, 62.2%), which explains the high level of biologic therapy and conventional DMARD usage at baseline. Also patients may have received these drugs for other conditions such as psoriasis, inflammatory bowel disease, etc. This would explain the prior usage of biological therapies for the patients with incident AS/SpA diagnosis.

Again it should be mentioned that "over the counter" prescriptions are immeasurable given the study design. This is reflected in the prescription of acetylsalicylic acid where the vast majority of prescriptions comprise prescriptions for cardiovascular prophylaxis. Thus "over the counter" sale of ASA, acetaminophen and NSAIDs cannot be accounted for. However, exposure to such medications is expected to be limited because prescribed drugs are cheaper than "over the counter" medications, and thus it is less costly for patients to get their analgesic medications through a doctor's prescription.

As noted in the data tables, the proportion of patients prescribed anti-rheumatic drugs and NSAIDs can be higher in both the AS and SpA subgroups individually compared to the total group of all patients combined. This is due to an overlapping population of up to 3095 patients (accounted for in both the AS and the SpA subgroups) who have received both a diagnosis of AS and SpA. It is therefore likely that this group has had more overall contact with the healthcare system and thus is more exposed to certain medications.

11.1.3 Comorbidities

The frequency of comorbidities is generally as expected for this study population of AS/SpA with a mean age of about 46 years. The frequency of urethritis is lower than expected both at baseline and cumulatively over the entire Study Period. This is probably due to the fact that the diagnosis of urethritis was derived from hospital registries (either out-patient register or in-hospital). Since the vast majority of urethritis is diagnosed and managed in primary care, it is likely that there are a large number of patients with unrecorded urethritis diagnoses in the study population.

Also the frequency of chronic low back pain is lower than would be expected both at baseline and cumulatively over the entire Study Period. This is likely because a diagnosis chronic low back pain is mainly assigned in the primary care setting. Subsequently, when these patients are referred to specialist care at hospitals, they then receive an AS/SpA diagnosis and are unlikely to also receive a chronic low back pain diagnosis. Due to the very low number of patients with chronic low back pain both at baseline and cumulatively over the entire Study Period, the protocol-specified variable "average time with previous low back pain" is not of much value and has been omitted from this report.

Notably, the recording of “severe hypertension” showed a rather high baseline and cumulative frequency. This is believed to be due to the broad categories of ICD-10 codes for hypertension. It is not possible to properly isolate “severe” or malignant hypertension in this cohort of patients using ICD diagnosis codes. Consequently this outcome, defined through registers, has limited validity and it is recommended that it be omitted from further analysis regarding risk relation to different nsNSAID/Coxib exposure.

Objective 2: Describe the use of etoricoxib and other COX-2 inhibitors / nsNSAIDs in Swedish patients with SpA/AS. Describe potential predicators/confounders of use of etoricoxib, other COX-2 selective inhibitors, and non-selective NSAIDs.

11.1.4 Exposure to etoricoxib, other coxibs and nsNSAIDs

The mean exposure to the different COX inhibitors is generally larger than the mean exposure to nsNSAIDs for AS and SpA patients. This may be in part a function of the way exposure is defined in terms of defined daily doses (DDD). The definition of DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults. It should be emphasized that the DDD is a unit of measurement and does not necessarily reflect the recommended or prescribed daily dose. Doses for individual patients and patient groups will often differ from the DDD and will necessarily be based on specific patient characteristics (e.g. diagnosis, age and weight) and other considerations such as comorbidities and potential interaction with other drugs. Moreover, as described above, the standard DDDs for etoricoxib and other coxibs tend to be low compared to prescribed doses which may be up to twice the DDDs per day (e.g., for etoricoxib, the WHO standard DDD is 60 mg/day, but some patients are prescribed 90 or 120 mg/day), whereas DDDs for nsNSAIDs in general are closer to the prescribed doses which tend to only be 25% to 50% more. As a result, patients receiving coxibs may appear to have more intense dosing as measured in DDDs/exposed time compared to patients receiving nsNSAIDs.

Moreover, note in **Table 2.1** if one prescription is overlapping another, the remaining DDDs are censored. This is done because DDDs do not actually reflect the true exposure time for the reasons mentioned above. Moreover, in **Table 2.2** it can be seen that the actual overlap between drug classes is rather small (ranging from 0.4 to 8.5%), whereas the overlap within a specific drug class is more extensive (>20%), especially for etoricoxib and other coxibs. This is further illustrated in **Table 2.3** and **Table 2.4** where the fraction of patients with >75% drug coverage increases when no censoring of

overlapping DDDs is performed (**Table 2.4** vs. **Table 2.3**). Based on the moderate size of this potential overlap of exposures (**Tables 2.2, 2.3 and 2.4**) and that it makes sense to assume that patients in general do not take DDDs from overlapping prescriptions simultaneously, it is reasonable to censor overlapping DDDs when computing time at risk for different exposures. To address the potential problem with overlapping prescriptions, we specify the number of events occurring during the possible overlap periods between two prescriptions when reporting absolute risks in the supplemental tables. With this approach, we also compensate for overestimated exposure time for drug classes that might have relative low DDDs, with minimal censoring of DDDs during drug overlap between different classes as seen in **Table 2.2**.

Finally, if 2 different prescriptions are checked out on the same date, the smaller prescription (in terms of DDD's) is censored. This is the reason why the number of patients exposed is different between **Tables 2.3 and 2.4** with respect to degree of exposure calculated with or without censoring.

11.1.5 Treatment sequences

In general, the majority of patients have been exposed to nsNSAID only. It should be noted that patients can have different permutations of treatment sequences and thus appear in more than one group in **Tables 2.5a and 2.5b** (except for the nsNSAID, other coxib and etoricoxib ONLY groups); however, the number of patients exposed to all three categories is quite modest and the overlapping population (that might be represented in different permutation groups) has therefore limited impact on the overall exposure time. Based on the fact that few patients have been exposed to all three types of NSAIDs, it is sufficient to only adjust for previous exposure to the individual drug classes (nsNSAID, etoricoxib and other coxibs) when performing risk analysis in Objective 3 of the study protocol. Moreover, looking at treatment sequences during the entire period as opposed to the exposure period only (i.e. **Table 2.5a** vs. **Table 2.5b**), the relative distribution remains the same. This further suggests that controlling for exposure prior to entry into the exposure period and subsequently looking at first and second line exposure during the exposure period will be sufficient when calculating risk rates for the outcomes of interest. nsNSAIDs were more likely to precede COX-2 inhibitor treatment than the other way around. Thus patients receiving COX-2 inhibitors are more likely to represent a selected group of patients "channeled" to this treatment.

11.1.6 Potential predictors/confounders of exposure to etoricoxib, other coxibs or nsNSAID

Overall the baseline medications, comorbidities and phenotype characteristics presented in **Tables 2.6a-c** reflect that of a moderate to severe population of AS/SpA patients. This is consistent with the study design capturing only patients with referral to hospital centers' outpatient clinic and/or in-hospital departments. Notably, the usage of conventional DMARDs and glucocorticoids are higher than the use of biologicals for these cohorts. The reasons for this are most likely due to the frequent peripheral manifestations in this patient group, as well as historical standard of care treatment in

these patients during the reporting period. Moreover, whether concomitant DMARD treatment should be used with biologicals is still an open question.

The proportion of patients with diagnoses of RA or Psoriatic Arthritis at baseline is 3-9% and somewhat higher in the SpA cohort than in the AS cohort. This may be due to initial misdiagnosis, the fact that the initial symptoms of AS and SpA may be arthritis (without psoriasis), comorbid conditions, or true misclassification. Based on the validation studies cited above, the true misclassification rate for the AS and SpA patients is likely to be very low and will not affect the validity of results and conclusions.

Moreover, as expected, patients with AS have a higher proportion of men, a higher degree of drug exposure and more comorbidities than the SpA patients, thus reflecting a population with a larger burden of disease.

Overall (in both AS and SpA patients), women seem to have greater exposure to nsNSAIDs. Patients receiving other coxibs tend to have higher education levels, have greater exposure to antirheumatics (i.e. DMARDs and biologics), and have slightly higher rates of comorbidities at baseline (either outcome related or not outcome related). This might represent a confounding by indication or channeling bias in the way that the more vulnerable patients tend to receive COX-2 inhibitors (in this case other coxibs) than the less severe patients, and needs to be kept in mind when interpreting regression models for the outcome analysis for Objective 3.

Objective 3: Describe incidence rates of outcomes of interest for etoricoxib, other coxibs, and nonspecific NSAIDs in Swedish patients with inflammatory spondyloarthropathy / ankylosing spondylitis (SpA/AS). Present incidence rates for outcomes of interest adjusted for potential confounders.

Number of events and, incidence rates (unadjusted and adjusted) for outcomes of interest – All patients, incident and prevalent disease

When comparing etoricoxib, other coxibs and nsNSAIDs, no major differences were found in relation to the outcomes of interest. The incidence rates found in the overall patient group were somewhat higher than estimated in the study protocol. Thus with the rates and exposure found for etoricoxib (see table 3.1a), our results were powered to >90% to detect a change in RR of 3 and >50% to detect a change in RR of at least 2 (http://www.openepi.com/OE2.3/Power/PowerCohort.htm) for atherosclerotic cardiovascular events. The power is lower for cerebrovascular events and heart failure, however higher to detect differences in gastrointestinal events.

Overall, the incidence rates (see table 3.1a & 3.2a) for atherosclerotic cerebrovascular and cardiovascular events for patients exposed to various NSAIDs were in range of what has been shown previously in the Swedish general population i.e. 2.5-5.0 per 1,000 patient years (PY) [Ref. 5.4: 6068]. However, patients unexposed to NSAIDs had somewhat higher rates of atherosclerotic cardiac and cerebrovascular events, potentially reflecting confounding by indication or channelling bias in this group of patients (Table 3.1a & 3.2a). For the overall group of patients, a combined endpoint of either

cerebrovascular or cardiac atherosclerotic events was calculated. In this combined group of patients, the unadjusted relative risk was also higher in the group of patients unexposed to NSAIDs compared to patients exposed to etoricoxib (Table 3.1a & 3.2a).

Also the event rates for patients exposed to NSAIDs are within range, but somewhat higher than the rates reported from a prior population-based cohort study done by Merck of patients of all ages (mean age 46, median age 45) with AS from general medical practices in the UK, Germany and France (See table in section 9.7 with event rates used for estimate of study power). In that study, the rates for ischemic cardiac atherosclerotic events were 4.65 events per 1000 PY, and the corresponding rate were 4.68 events per 1000 PY for ischemic cerebrovascular events. However, the UK, German and French study includes events regardless of exposure to treatment and is restricted to persons without a prior history of a given outcome. Thus it would be expected that these patients would have naturally lower event rates for atherosclerotic events. It should be noted that the present study population is selected from out-patient and in-hospital registers for care provided by non-GP specialists, and are thus more likely to have a larger burden of disease than a study population recruited from primary care. Also the definition of gastrointestinal events in this report is rather broad (including abdominal pain unspecified), which is also reflected by the somewhat higher rate observed in this study compared to the UK, German, French study (about 6.13 events per 1,000 PY in the present study compared to 5.59 per 1,000 PY) .

As stated previously, no major consistent differences were found between the groups of patients receiving etoricoxib, nsNSAIDs and other coxibs. Nonetheless, for atherosclerotic events there was a non-significant trend for lower event rates in the group of patients taking etoricoxib compared to nsNSAIDs and other coxibs (table 3.1a). On the other hand, the relative risk for gastrointestinal events was numerically higher in the etoricoxib group compared to nsNSAIDs and other coxibs (table 3.1a). The trends were less clear when studying different subgroups of patients, and the association was opposite for incident AS/SpA patients having numerically higher risks for GI events for unexposed patients, nsNSAIDs and patients using other coxibs compared to etoricoxib patients (see table 3.2a). Moreover, it should be noted that this open-labelled study was conducted in the era where a lot of attention has been brought to risks associated with nsNSAIDs and selective COX-2 -inhibitors. Thus it would be expected that the patients assigned different treatments were preselected based on perceived or actual risk for the various outcomes, and a confounding by indication underlying the results obtained is likely. This may also be supported by the fact that the totally unexposed group tended to have higher risk for cardiac atherosclerotic events and a lower risk for gastrointestinal events (ulcers, bleeding and perforation) compared to etoricoxib despite adjustment for potential measurable confounders (Table 3.1a). In other words, the patients are “channelled” into different treatments or no NSAID treatment at all based on the patient’s baseline medical conditions, and it may be these baseline medical conditions that are associated with the differences in the rates observed rather than (or in addition to) the different exposures of interest. We refer to this as channelling bias or confounding by indication.

In addition, the definition of GI events also included abdominal pain unspecified, which might confound the results obtained. One could speculate that if a patient was to receive

some type of NSAID for his AS/SpA one would choose a selective coxib if the patient had unspecified upper GI problems at baseline. Thus the coxib exposed patients would have higher GI event rates compared to other groups due to this preselection.

Several adjusted models were tested and numerous sensitivity analyses were performed including stepwise adjustment for sex and age, extension of the exposure period by 14, 30 or 90 days, as well as looking at different subgroups of patients (i.e. those with prior events of interest). Making these additional sensitivity analyses and adjustments (i.e. from unadjusted to age or sex adjusted and finally to the fully adjusted model) only gradually changed the RR estimates, and showed no consistent significant findings or unified trends for differences among the exposure groups of interest. This further supports the findings of no major drug specific hazards when using etoricoxib, nsNSAID or other coxibs in Swedish AS/SpA patients.

Overall, the results of this study do not change the previously established favourable benefit-risk profile for etoricoxib.

11.2. Limitations

Some limitations for the present analyses should also be considered. Firstly, some misclassification regarding case definition, comorbidities and outcomes of interest could occur. For the case definitions of AS and SpA published [Ref. 5.4: 6062] and unpublished data suggest that this occurs in less than 10%. Regarding, outcomes such as Acute Coronary Events, misclassification is less than 5% [Ref. 5.4: 6065]. Secondly, by basing our case definition strictly on ICD-codes recorded by a specialist in rheumatology or internal medicine, we might create a selection bias towards more severe cases being included. However, a previous study indicates that also including patients diagnosed in primary care, would increase the number of cases by approximately 15% [Ref. 5.4: 6062], but this would probably be at the expense of a larger degree of misclassification. Thirdly, there are limitations in precisely determining the exposure period. These include using DDDs based on the WHO standard to estimate exposure, a relatively low DDD set for etoricoxib, and not being able to include “over the counter” sales of NSAIDs.

The fact that this is not a true incident user design is also a limitation of this study. Some patients in the incident disease cohorts have some prior NSAID exposure and the analyses of outcomes are not restricted to the first course of NSAID therapy.

This study has been designed to reduce the potential for confounding through features of the study design and the analytic methods. Nevertheless, there is likely some degree of residual confounding in the assessment of the associations between the drugs under study and the clinical outcomes due to inaccurately measured or unmeasured confounders. For example, data regarding lifestyle factors such as smoking are not completely available in the databases, and data regarding the use of over the counter medicines, such as aspirin, are not captured at all. Control for potential confounding was attempted by including relevant covariates in the analysis, however it not likely that confounding was fully controlled and the net effect of any resulting “residual” confounding is not able to be measured.

In addition, there is potential for channeling bias in this study because it is feasible that patients prescribed etoricoxib or another of the drugs of interest are those patients at greater risk of some of the clinical outcomes. For example, those with prior GI bleeding or those who use low dose aspirin may be preferentially prescribed etoricoxib over non-selective NSAIDs. Channeling could also occur if patients who are at high risk for CV or GI events are not prescribed any NSAIDs.

11.3. Interpretation

Given the Swedish national population of 7.55 million, 22,283 Swedish patients with inflammatory AS/SpA represents almost all patients with such diagnoses in Sweden from 1987 through the end of the Study Period. The baseline demographic characteristics of the study population, and the frequency of medication usage and comorbidities are as expected for patients with moderate to severe AS/SpA drawn from patients attending out-patient specialist (i.e. non-GP) clinics.

The AS/SpA patients in this study demonstrate primarily usage of nsNSAID, with limited usage of etoricoxib and other coxibs. Only a few patients have been exposed to all 3 types of NSAIDs, however quite a few have taken more than one type. Sex and age appear to be important potential confounders that were controlled for when evaluating the association of exposure to outcomes. Other potential confounders are a baseline history of the outcome of interest and previous exposure to other classes of NSAIDs. Additional covariates were based on clinical reasoning; however, given the low rates of outcomes, the number of covariates capable of being fit into a regression model were limited.

Overall, the results of the third analysis, addressing Objective 3, show no significantly increased risks for etoricoxib compared to nsNSAIDs and other coxibs in this population of AS and SpA patients. In addition, the cardiac and cerebrovascular event rates are in the range of what has been shown previously in the Swedish general population. The lack of power in this study made it difficult to estimate whether small risk differences exist between the different types of NSAIDs. Also unmeasured confounders and confounding by indication might have affected the results found in the combined patient group analysis (all AS/SpA patients), potentially decreasing the observed risk of cardiovascular and cerebrovascular atherosclerotic events in the NSAID exposed patients compared to patients unexposed to NSAIDs, as well as potentially increasing the GI risks in the etoricoxib treated patients compared to the other patient groups.

These data are consistent with the results of the UK, French, German study of the safety of etoricoxib in AS patients, and do not demonstrate any major increased risk of the outcomes of interest (cardiovascular, cerebrovascular, congestive heart failure, renovascular, severe hypertension, and gastrointestinal events).

11.4. Generalisability

This study includes 21,872 patients with AS and/or SpA diagnoses which includes nearly all Swedish patients diagnosed with these conditions since 1987. Given that there is no reason to believe that Swedish patients with AS or SpA are not typical and the

consistency of the results of this study and the study of UK, German, and French patients, the results should be generalizable to patients with AS or SpA treated with etoricoxib

12. Other information

Not applicable

13. Conclusion

Overall, the results of this analysis suggest, given the characteristics of the patient population, the safety profile of etoricoxib in the treatment of AS and SpA is consistent with the safety profile of the product as labelled and as previously demonstrated during clinical development and through post-marketing pharmacovigilance.

14. References

[Ref. 5.3.5.4: 4072] MRL Clinical Study Report (Synopsis), Multicenter Study: A Double-Blind, Placebo- and Active-Comparator-Controlled, Parallel-Group Study to Assess the Safety and Efficacy of MK-0663 in Ankylosing Spondylitis (Protocol 032).

[Ref. 5.4: 6061] Cancer incidence in Sweden 2004, 2006.

[Ref. 5.4: 6062] Haglund E, Bremander AB, Petersson IF, Strömbeck B, Bergman S, Jacobsson LTH, et al. Prevalence of spondyloarthritis and its subtypes in southern Sweden. Ann Rheum Dis 2011;70:943-8.

[Ref. 5.4: 6063] Hothorn T, Bretz F, Westfall P. Simultaneous inference in general parametric models. Biom J 2008;3:346-63.

[Ref. 5.4: 6064] Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol 2009;24:659-67.

[Ref. 5.4: 6065] Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim J-L, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:1-16.

[Ref. 5.4: 6066] Rudwaleit M, Van der Heijde D, Landewé R, Listing J, Akkoc N, Brandt J, et al. The development of assessment of spondyloarthritis international society classification criteria for axial spondyloarthritis (part II): validation and final selection. Ann Rheum Dis 2013;68:777-83.

[Ref. 5.4: 6067] Rudwaleit M, Van Der Heijde D, Landewé R, Akkoc N, Brandt J, Chou CT, et al. The assessment of spondyloarthritis international society classifcation criteria for peripheral spondyloarthritis and for spondyloarthritis in general. Ann Rheum Dis 2013;70:25-31.

[Ref. 5.4: 6068] Wilhelmsen L, Welin L, Svärdsudd K, Wedel H, Eriksson H, Hansson P-O, et al. Secular changes in cardiovascular risk factors and attack rate of myocardial infarction among men aged 50 in Gothenburg, Sweden. accurate prediction using risk models. J Intern Med 2008;263:636-43.