

EXTENDED REPORT

Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study

Jesper Lindhardsen,^{1,2} Gunnar Hilmar Gislason,¹ Søren Jacobsen,² Ole Ahlehoff,³ Anne-Marie Schjerning Olsen,¹ Ole Rintek Madsen,⁴ Christian Torp-Pedersen,¹ Peter Riis Hansen¹

Handling editor Tore K Kvien

¹Department of Cardiology, Copenhagen University Hospital Gentofte, Hellerup, Denmark

²Department of Rheumatology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark

³Department of Cardiology, Copenhagen University Hospital Roskilde, Roskilde, Denmark

⁴Department of Internal Medicine–Rheumatology Section, Copenhagen University Hospital Gentofte, Hellerup, Denmark

Correspondence to

Dr Jesper Lindhardsen, Department of Cardiology, Copenhagen University Hospital Gentofte, Post 635 Niels Andersenvej 65, Hellerup, Denmark; jesper.lindhardsen@regionh.dk

Received 17 December 2012

Revised 3 May 2013

Accepted 7 May 2013

ABSTRACT

Objective To examine the risk of major cardiovascular disease associated with non-steroidal anti-inflammatory drugs (NSAIDs) in a large 'real-world' contemporary rheumatoid arthritis (RA) cohort.

Methods A longitudinal cohort study was conducted with use of Danish nationwide individual-level registry data on inpatient and outpatient health care provision, pharmacotherapy and income during 1997–2009.

17 320 RA patients were identified and matched with 69 280 controls (4 : 1) by age and sex. NSAID-associated risk of major cardiovascular disease defined as the combined endpoint of myocardial infarction, stroke or cardiovascular mortality was assessed in multivariable survival models.

Results During follow-up (median 4.9 years) 6283 events occurred. The cardiovascular risk associated with overall NSAID use was significantly lower in RA patients than in controls (HR 1.22 (95% CI 1.09 to 1.37) vs 1.51 (1.36 to 1.66), $p < 0.01$). The pattern of lower NSAID-associated risk in RA patients was generally found with the individual NSAIDs investigated. While use of rofecoxib (HR 1.57 (1.16 to 2.12)) and diclofenac (HR 1.35 (1.11 to 1.64)) was associated with increased cardiovascular risk in RA patients, there was no significant risk increase associated with use of other NSAIDs in these patients.

Conclusions The cardiovascular risk associated with NSAID use in RA patients was modest and significantly lower than in non-RA individuals. Moreover, only a few of the individual NSAIDs were associated with increased cardiovascular risk. NSAID use should be assessed in the individual patient based on the indication for pain relief and risk factors for adverse effects, and not automatically be avoided due to concerns of severe cardiovascular outcomes alone.

INTRODUCTION

Patients with rheumatoid arthritis (RA) face an increased risk of cardiovascular morbidity and mortality compared to the general population.¹ Several non-steroidal anti-inflammatory drugs (NSAIDs) have been reported to confer an excess risk of cardiovascular disease such as myocardial infarction (MI), stroke and cardiovascular death in both clinical trials and observational studies; consequently NSAIDs may be of particular concern in individuals who are already at increased risk of cardiovascular

disease such as RA patients.^{2–4} While chronic systemic inflammation and classical cardiovascular risk factors are important determinants of the increased cardiovascular risk in RA, the frequent use of NSAIDs among RA patients and the increased cardiovascular risk observed with NSAIDs in other populations, suggest that NSAIDs may contribute to the augmented cardiovascular risk in RA patients.^{1 5–7} However, limited data from placebo-controlled clinical trials and observational studies with NSAID use in RA populations do not indicate that NSAIDs other than rofecoxib confer additional cardiovascular risk.^{8–13} This may suggest that in RA patients the benefits of NSAIDs, for example pain relief and increased mobility, counterbalance potential adverse cardiovascular effects such as hypertension and atherothrombotic effects.¹ As NSAIDs are valuable in the management of many RA patients, it is important that clinicians have sufficient information available to consider the cardiovascular safety of individual NSAIDs in RA patients, and more such data have been called for.¹ This study therefore examined the incidence of adverse cardiovascular events in an unselected nationwide cohort of RA patients according to their NSAID use in the period 1997–2009.

METHODS**Data sources**

Based on the unique personal identifier given at birth, data from individual-level Danish nationwide registers were combined. Data on morbidity were obtained from the National Patient Register, where diagnoses from all hospital admissions (from 1978) and outpatient activities (from 1995) are listed according to the International Classification of Diseases (ICD) codes (ICD-8: 1978–1993; ICD-10: 1994–2009). This register also includes information on surgical procedures and other non-trivial treatments coded by use of SKS (a Danish coding system). Death certificates were gathered from the National Causes of Death Register. From 1995, all prescriptions dispensed from Danish pharmacies were available from the Danish Register of Medicinal Product Statistics, with data on drug Anatomical Therapeutic Chemical (ATC) class, drug strength, quantity and date of dispensing. Information on income and migration were available through the national statistical institute,

To cite: Lindhardsen J, Gislason GH, Jacobsen S, et al. *Ann Rheum Dis* Published Online First: [please include Day Month Year] doi:10.1136/annrheumdis-2012-203137

Clinical and epidemiological research

Statistics Denmark. All registers used have nationwide coverage and are considered effectively complete.^{14 15}

Cohort entry and follow-up

During the period 1997–2009, patients with RA were identified by ICD-10 codes M05–M06 in combination with dispensed disease-modifying antirheumatic drugs (DMARDs) within 1 year before or after the time of diagnosis. The last of either the prescription date or date of RA diagnosis was used as the starting point for the time at risk (RA index date). RA patients with prior RA diagnoses, stroke or MI were excluded. Each RA patient was matched with four controls randomly selected from the entire Danish population by gender and birth year conditioned on no prior stroke or MI at the RA index date. Controls were considered at risk from the RA index date of the corresponding RA patient match (baseline). Participants were followed until a study outcome, emigration, death or 31 December 2009.

Outcome

The study outcome was the combined endpoint of MI (ICD-10: I21–I22), stroke (ICD-10: I60, I61, I63 and I64) or cardiovascular death (ICD-10 code: I00–I99 listed as the primary cause of death).^{16–18}

NSAID treatment

NSAID use was determined from dispensed prescriptions for the following 10 most prescribed NSAIDs in Denmark during the study period: ibuprofen (ATC code: M01AE01), diclofenac (M01AB05), etodolac (M01AB08), celecoxib (M01AH01), piroxicam (M01AC01), rofecoxib (M01AH02), naproxen (M01AE02), ketoprofen (M01AE03), nabumetone (M01AX01) and indometacin (M01AB01). Due to very low usage, indometacin exposure was only included in overall NSAID analyses. In order to allocate exposure as accurately as possible, it was necessary to determine NSAID use on a day to day basis. In brief, for each prescription the number of pills dispensed was divided by the estimated daily dosage to calculate the treatment duration, where the estimated daily dosage was based on standard dosage as well as prescription data from up to three preceding prescriptions.

Prespecified cardiovascular outcome predictors

Besides sex and age at baseline, the following endpoint predictors were included (specified before analysis): an age-standardised socioeconomic index (from 1 to 5 based on the mean income 5 years prior to baseline); baseline cardiovascular pharmacotherapy as a proxy for established cardiovascular risk factors based on prescriptions in the year preceding the participants' baseline (table 1); diabetes, defined as use of glucose-lowering drugs; hypertension, defined as concurrent use of at least two antihypertensive agents; heart failure, ischaemic heart disease, atrial fibrillation and chronic obstructive pulmonary disease defined by hospitalisations and/or outpatient visits before baseline by ICD codes.¹⁹ Details on ATC and ICD codes used in the study are listed in online supplementary table S1.

Statistical analysis

Overall event rates as well as rates according to RA status and NSAID exposure were calculated. Also, rates were standardised based on rates among controls stratified by sex and age in 10-year intervals. The risk associated with NSAID use was estimated as HRs by fitting proportional-hazard regression models. The potential influence of prespecified baseline confounders was addressed by running several models with successive

Table 1 Baseline characteristics of study participants

n (%)	Rheumatoid arthritis n (%)	Controls n (%)
Women	12 231 (70.6)	48 924 (70.6)
Men	5 089 (29.4)	20 356 (29.4)
Total	17 320 (100)	69 280 (100)
Age, mean (SD)	58.9 (14.4)	58.9 (14.4)
Socioeconomic index, mean (SD)	2.98 (1.41)	3.02 (1.41)
β-blocker	815 (4.7)	2 956 (4.3)
Lipid lowering agent	600 (3.5)	2 713 (4.0)
RAS blocker	1 148 (6.6)	4 309 (6.2)
Loop diuretic	659 (3.8)	1 818 (2.6)
Spironolactone	146 (0.8)	357 (0.5)
Vitamin K antagonist	208 (1.2)	586 (0.9)
Clopidogrel	24 (0.1)	71 (0.1)
Aspirin	677 (3.9)	2 574 (3.7)
Thiazide	1 111 (6.4)	3 871 (5.6)
Calcium channel blocker	632 (3.7)	2 338 (3.4)
NSAID	13480 (77.8)	15 477 (22.3)
Gastroprotective agent	3657 (21.1)	7 119 (10.3)
Hypertension	2 746 (15.9)	10 317 (14.9)
Ischaemic heart disease	832 (4.8)	2 580 (3.7)
Heart failure	336 (1.9)	880 (1.3)
Atrial fibrillation	488 (2.8)	1 326 (1.9)
Diabetes	868 (5.0)	2 894 (4.2)
Chronic obstructive pulmonary disorder	775 (4.5)	2 077 (3.0)
Chronic kidney disease	106 (0.6)	319 (0.5)

Values are absolute numbers (frequencies) unless otherwise indicated. NSAID, non-steroidal anti-inflammatory drug; RAS, renin-angiotensin system.

inclusion of covariates. Exposures to individual NSAIDs were included as time-dependent variables. To evaluate differences between RA and non-RA individuals, models which examined the impact of NSAID use were stratified according to RA status (within-model stratification). CIs were set to 95% and two-tailed p values less than 0.05 were considered significant. Analyses were carried out in Stata 11.2.

RESULTS

A total of 17 320 RA patients without prior stroke or MI were identified and matched with four controls each. The cohort consisted of 70% women, and the mean age was 59 years (table 1). Except for a high use of NSAIDs and gastroprotective drugs in the RA group, there were only small absolute differences compared to controls. The median follow-up was 4.9 (IQR 2.3 to 8.1) years in RA patients and 5.1 (2.4 to 8.5) years in controls; 552 participants (0.6%) emigrated during the study.

NSAID exposure

RA patients were exposed to any NSAID during 24% of the follow-up compared to 5% in the controls. However, the relative distributions of exposure to the individual NSAIDs were similar in the two groups, with ibuprofen and diclofenac being most commonly used (table 2). The proportion of RA patients who did not use NSAIDs was stable at approximately 40% until 2003, increasing gradually to 60% in 2009 (figure 1). In both groups, the temporal trends in specific NSAID use reflected the introduction of the cyclooxygenase-2 (COX-2) inhibitors rofecoxib and celecoxib in 2000 and the withdrawal of rofecoxib from the market in 2004 (figure 2). After 2004, celecoxib was practically abandoned, while ibuprofen and etodolac seemed to

Table 2 Number of events, time at risk, and crude and standardised incidence rates in rheumatoid arthritis patients and controls according to non-steroidal anti-inflammatory drug (NSAID) exposure

	Rheumatoid arthritis				Controls			
	Events (n)	Time at risk (% of follow-up)*	Crude incidence rate†	Standardised incidence rate‡	Events (n)	Time at risk (% of follow-up)*	Crude incidence rate†	Standardised incidence rate‡
Total	1574	91.7 (100)	17.2	17.7	4709	381.1 (100)	12.4	–
No NSAID	1186	69.6 (75.9)	17.0	17.0	4276	362.9 (95.2)	11.8	11.9
Any NSAID	388	22.1 (24.1)	17.5	20.1	433	18.2 (4.8)	23.8	19.2
Individual NSAIDs								
Ibuprofen	115	7.5 (8.1)	15.4	18.0	189	8.4 (2.2)	22.6	20.0
Diclofenac	111	6.0 (6.5)	18.6	22.1	115	4.8 (1.3)	23.9	19.8
Etodolac	50	3.2 (3.5)	15.7	20.9	40	1.7 (0.4)	23.6	18.3
Celecoxib	42	2.0 (2.2)	21.2	20.2	23	0.8 (0.2)	29.5	13.6
Piroxicam	44	1.4 (1.5)	16.9	18.5	35	0.7 (0.2)	29.3	21.3
Rofecoxib	7	0.6 (0.6)	31.2	26.5	8	0.7 (0.2)	52.4	32.9
Naproxen	8	0.5 (0.5)	17.7	12.6	15	0.5 (0.1)	12.0	8.5
Ketoprofen	7	0.7 (0.7)	10.3	11.7	8	0.4 (0.1)	14.3	21.6
Nabumetone	10	0.7 (0.8)	13.4	15.6	7	0.3 (0.1)	20.1	12.0

*Time at risk per 1000 person-years (percent of total time at risk).

†Unadjusted incidence rate per 1000 person-years.

‡Incidence rate standardised by sex and age.

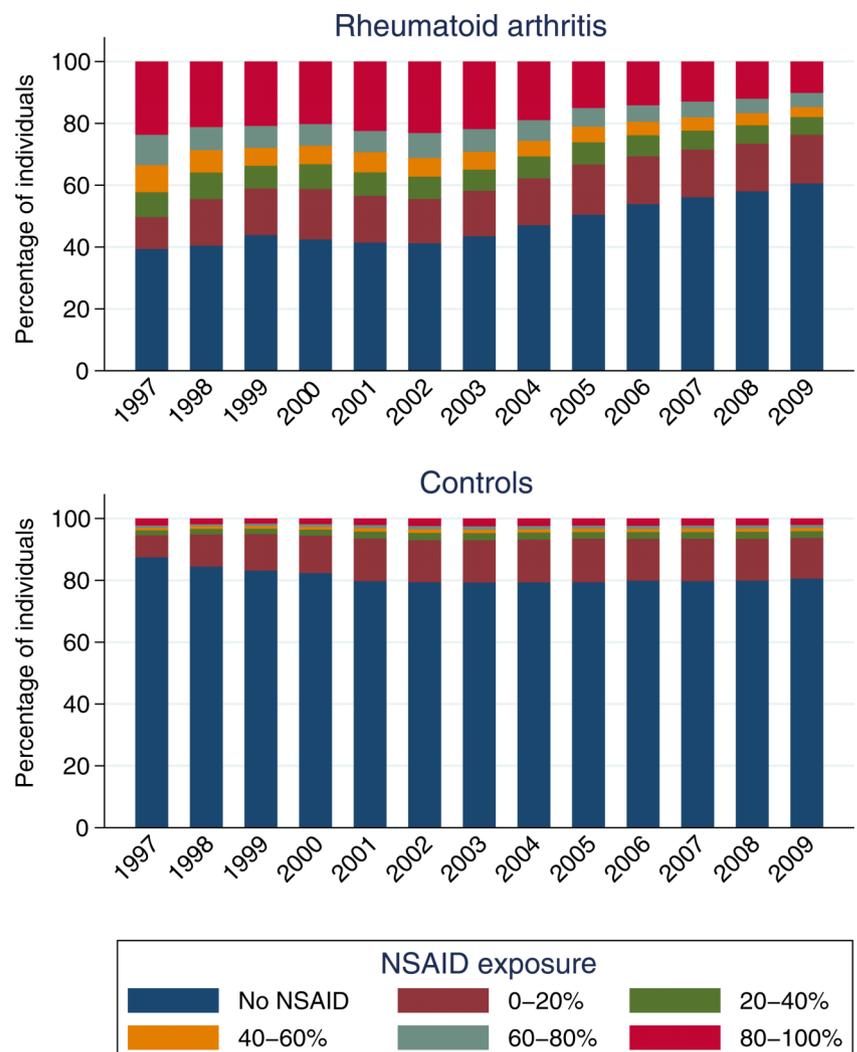
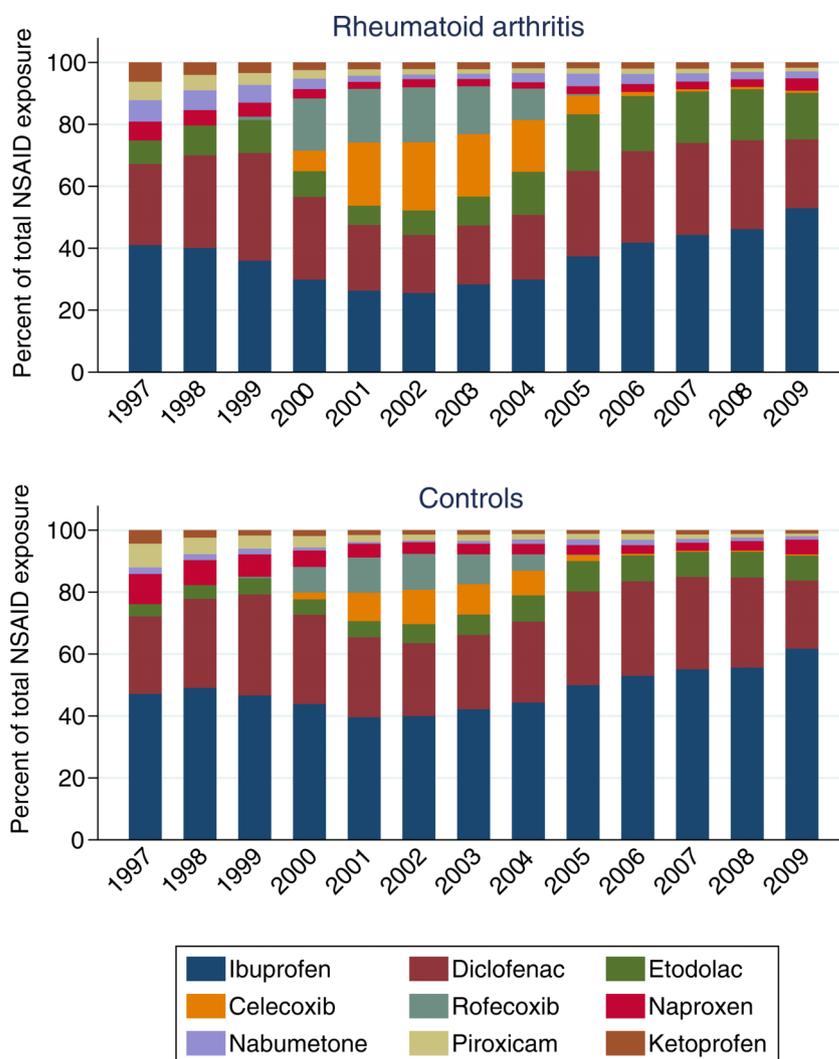
Figure 1 Temporal trends in non-steroidal anti-inflammatory drug (NSAID) treatment. NSAID exposure was categorised into 'no NSAID' exposure or quintile of NSAID exposure (in percentage of follow-up) based on individual-level data.

Figure 2 Temporal trends of individual non-steroidal anti-inflammatory drug (NSAID) use.



replace previous COX-2 inhibitor use. NSAID exposure was different across age groups, that is, RA patients had lower NSAID exposure with increasing age, while the opposite was observed in controls (see online supplementary figure S1).

Cardiovascular risk associated with NSAIDs

The overall event rate was higher in RA patients than in controls, resulting in an RA-associated unadjusted HR of 1.39 (95% CI 1.31 to 1.47) and a fully adjusted HR of 1.32 (1.25 to 1.40), however the models revealed significant interaction between overall NSAID use and RA status ($p < 0.01$). This indicated that NSAID-associated risk differed between RA patients and controls and further analysis where stratified by RA status. All pre-specified outcome predictors listed in table 1, except for vitamin K use, were statistically significant when included into the models; however, except for age, their influence on the NSAID-associated risk was negligible. In general, their inclusion slightly decreased the risk estimates of the control group, while the opposite, albeit more subtle, effect was observed in RA patients. Only loop diuretics affected the NSAID-related HR, and this was only in the control group (decrease in HR from 1.57 to 1.51). The results presented hereafter are fully adjusted for the prespecified cardiovascular risk predictors.

Crude and standardised outcome data according to overall and individual NSAID exposure are shown in table 2. Cox regression stratified by RA status showed that overall NSAID

exposure was associated with a 22% risk increase in RA patients compared to a 51% increase in non-RA patients (figure 3). With naproxen as the exception, this pattern of lower NSAID-associated risk in RA patients was consistent across the individual NSAIDs, although the magnitude and difference in risk increase between RA patients and controls varied significantly (figure 3). Rofecoxib was associated with the highest risk in both RA patients (HR 1.57) and controls (HR 2.19), while naproxen, ketoprofen and nabumetone seemed to be associated with a low or even slightly reduced risk, although these latter estimates were less reliable due to low drug exposure.

Among RA patients, the other NSAIDs were associated with increased risk estimates that were between 11% (celecoxib) and 35% (diclofenac) higher than the risk without NSAID exposure, whereas the corresponding risk estimates in the control group were considerably higher.

With the exception of naproxen, the risk estimates consistently increased with higher daily dosages of NSAIDs in both RA patients and controls (figure 4). The HRs with low NSAID dosages were very close to 1 in both groups, while high dosages generally were associated with more pronounced risk increases in controls than in RA patients.

Additional analyses

Since NSAID exposure differed across age groups in RA patients and controls, the main analyses were repeated with age (instead

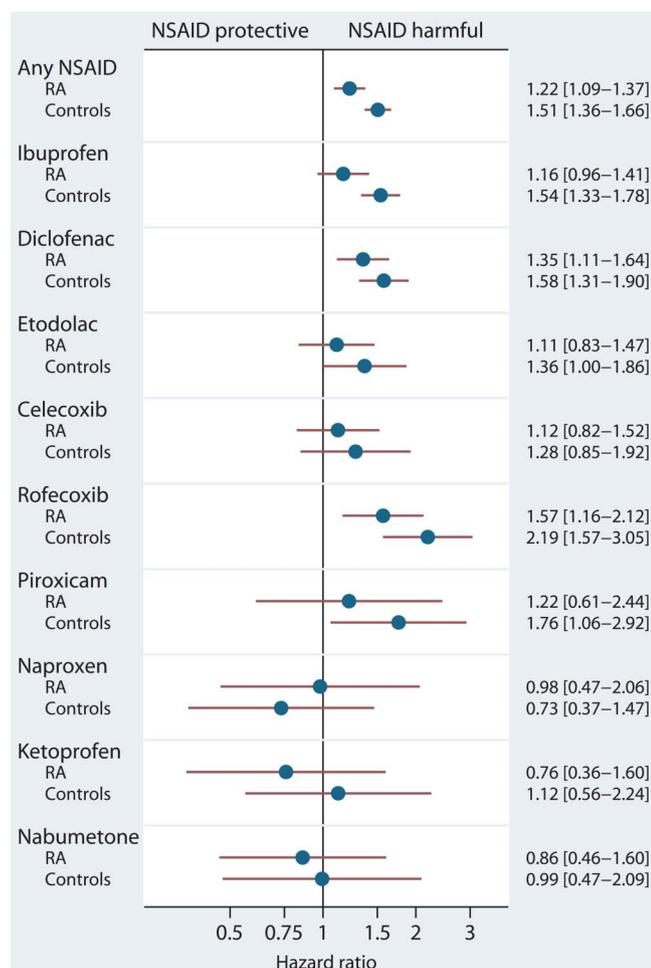


Figure 3 Cardiovascular risk associated with non-steroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis (RA) and controls. Reference: non-exposure in the RA and control group, respectively.

of follow-up) as timescale to adjust more carefully for the influence of age, without significant changes of the results. Results restricted to the period before 2002, where over-the-counter use of ibuprofen was not available and the general awareness of potential harmful cardiovascular effects of NSAID use was minimal, also yielded comparable results. In addition, several different dosage schemes, where typical, minimum and maximum dosages were both increased and decreased, were used to estimate NSAID exposure with no noteworthy changes to the primary results.

Even though DMARD use was required in the case definition, adverse effects, lack of efficacy, and/or disease remission could lead to a change of treatment strategy. As DMARD therapy (traditional and biological—see online supplementary table S1) may be related to the outcome, RA-specific therapy was determined every 6 months based on the prescription of DMARDs and the administration of biologicals. The NSAID-associated risk estimates were virtually identical to the primary results when DMARD therapy was included in the regression models, and no effect modification was noted between DMARD and NSAID therapy.

DISCUSSION

In this contemporary nationwide cohort of unselected RA patients there was a 32% increased risk of the composite

endpoint of MI, stroke or cardiovascular death compared to sex- and age-matched controls. NSAID exposure was associated with a 22% risk increase of cardiovascular events among RA patients, which was significantly lower than the NSAID-associated risk increase (51%) observed in controls. This pattern was consistent across individual NSAIDs, which generally exhibited an exposure-dependent risk increase with little or no risk associated with low and moderate dosages of any NSAID in RA patients. Sensitivity analyses, which included time-dependent inclusion of RA-specific treatment, supported these findings.

Clinical cardiovascular safety data on NSAIDs predominantly originate from randomised trials designed to evaluate the efficacy and safety of COX-2 inhibitors compared to either traditional NSAIDs or placebo, but rarely to both.² Consequently, previous data on cardiovascular risk associated with the most often used traditional NSAIDs, such as ibuprofen and diclofenac, were derived from either indirect comparisons of results from randomised trials or from observational studies.^{2–4} Of note, the magnitude of risk associated with individual NSAIDs in our control population was generally in agreement with previous results.^{2–20–22} For example, a recently published analysis of cardiovascular safety data from randomised trials reported that ibuprofen and diclofenac increased cardiovascular risk to the same or even a higher extent than celecoxib and rofecoxib, while naproxen was found to be the least harmful NSAID.² Very similar findings were reported in a recent meta-analysis of observational studies.⁴ Nonetheless, only a minority of the randomised studies included RA patients and, with exception of the VIGOR (rofecoxib vs naproxen) study, they did not show significant differences in cardiovascular events between groups treated with traditional NSAIDs (ibuprofen and diclofenac) and COX-2 inhibitors, respectively.^{8–10–23–24} The lack of placebo groups in these trials precluded direct comparison with the current findings of limited cardiovascular risk of NSAIDs in RA patients, but the few available observational studies which included RA populations have reported comparable results. Solomon *et al* analysed the risk of MI, stroke and cardiovascular mortality, including a subgroup with RA patients, in two elderly Medicare-beneficiary cohorts, and found an increased risk associated with rofecoxib use in RA patients, but not with other NSAIDs examined.¹¹ This pattern of increased risk restricted to rofecoxib was also found in two case-control studies of risk of stroke and heart failure in RA patients, respectively.^{12–25} Also, a small beneficial effect of NSAIDs in general on the risk of cardiovascular mortality was reported in an inception cohort of inflammatory polyarthritis patients, although here NSAID exposure was only based on patient interviews.¹³ Furthermore, current use of naproxen was found to reduce the risk of thromboembolic cardiovascular events in RA patients.²⁶ Interestingly, our data showed that in addition to naproxen, several NSAIDs, which have only rarely been investigated in relation to cardiovascular risk, were associated with cardiovascular risk estimates below or close to an HR of 1 in the RA population. However, reliability of these estimates was impeded by the relatively low use of respective NSAIDs.

Explanations for a potentially more benign adverse cardiovascular risk profile of NSAIDs in RA patients compared to non-RA individuals are likely to be complex. However, relief of joint pain and other symptoms may itself, or through increased mobility, attenuate adverse effects of NSAIDs. Also, a potential pathophysiological threshold for development of adverse cardiovascular effects in response to NSAIDs may be altered in patients with RA, for example if such effects are dependent on

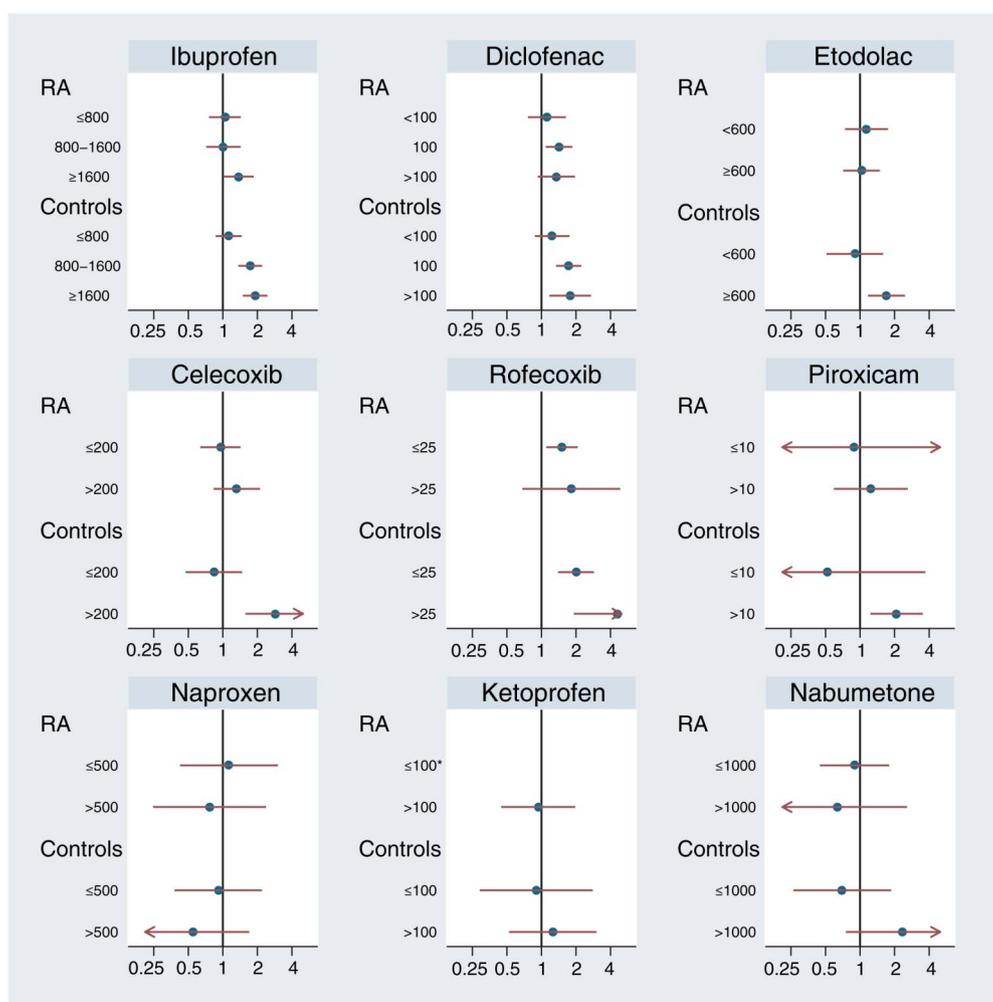


Figure 4 Cardiovascular risk stratified associated with non-steroidal anti-inflammatory drugs (NSAIDs) in patients with rheumatoid arthritis (RA) and controls stratified by NSAID type and daily dosages in milligrams. Reference: non-exposure in the RA and control group, respectively. *No outcomes observed.

shared inflammatory mechanisms between RA and cardiovascular disease.¹³

Study strengths and limitations

The overall strengths of the study design were the large unselected population, which offered a more ‘real world’ setting than most randomised trials, the large number of RA participants and the completeness of the data. However, this approach also introduced several methodological issues. One of the most important limitations may be confounding by indication/severity, that is, if NSAID use was only a marker and not a maker of increased cardiovascular disease risk; especially since NSAID use would intuitively be more common in active RA disease, which is also likely to increase risk of cardiovascular morbidity.²⁷ Consequently, the possibility of overestimating the NSAID-associated cardiovascular risk in RA patients (and perhaps even more so in controls) should be acknowledged, even though our findings were consistent with previous reports. Of note, we did not have information on the reasons for choosing one NSAID over another, thus selection bias may have occurred if the proportion of patients with (unmeasured) high cardiovascular risk was larger among those who avoided particular (or all) NSAIDs, for example due to gastrointestinal adverse effects, or because of increased awareness of harmful cardiovascular effects of

individual NSAIDs in the last years of the study period; however, NSAID-associated cardiovascular risk in RA patients before 2002 closely resembled the overall results.

Also, we did not have exact data on the ingested daily NSAID dosages, and relied on an algorithm based on predefined typical, minimum and maximum dosages and prior prescription patterns. This algorithm assumed that all reimbursed NSAIDs were taken regularly and at a stable mean daily dosage between prescription claims. As precision of the daily dosage estimates improves with continued use, NSAID exposure was probably more accurate in the RA population than in controls. Nonetheless, the results were robust to changes in the NSAID exposure algorithm, in terms of both typical dosages and number of prior prescriptions used to estimate daily dosages. From October 2001, low dose ibuprofen (200 mg, maximum of 100 tablets) was available over-the-counter (and low dose diclofenac during part of 2008). Since only redeemed prescriptions are reimbursed in Denmark, this may have caused selection of high dosage and/or frequent users and thereby increased the ibuprofen-related cardiovascular risk estimate. The exclusion criteria restricted the results to RA patients without prior MI and/or stroke. Furthermore, our definition of RA relied on register diagnoses as well as DMARD initiation in order to ensure a cohort receiving contemporary RA treatment and to avoid

misclassification based on RA diagnoses alone.^{28 29} Finally, other unmeasured confounders may have influenced the findings despite inclusion of a range of cardiovascular risk markers in the analyses.

Clinical implications

Our current findings were in line with the ‘lowest possible dose for the shortest possible duration’ recommendation for NSAID use,³⁰ although the overall cardiovascular risk associated with most NSAIDs was modest in RA patients. While naproxen also proved risk neutral in an RA population, the adverse cardiovascular risks of diclofenac seem especially important due to the frequent use and availability over-the-counter in many countries. The choice between the other common NSAIDs (ibuprofen, celecoxib and naproxen) will hopefully be informed by the large ongoing randomised trial in patients with osteoarthritis or RA with high cardiovascular risk.³¹

In conclusion, the cardiovascular risk associated with overall NSAID use in RA patients was modest and significantly lower than in non-RA individuals. Moreover, only a few of the individual NSAIDs were associated with excess cardiovascular risk. These observations are in line with previous findings and indicate that in RA patients, NSAID use should not automatically be avoided due to concerns of severe cardiovascular outcomes alone but needs to be assessed in the individual patient based on the indication for pain relief, risk factors for adverse effects and the specific NSAID safety profiles.

Contributors JL made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. PRH helped to write the first draft. GG, CTP and PRH contributed to the study design. All authors had unrestricted access to data and contributed to the interpretation of results, critical revision of the manuscript and approved the final manuscript. JL is the guarantor.

Competing interests None.

Ethics approval The study was approved by the Danish Data Protection Agency (reference 2008-41-2685). Approval from an ethics committee is not required for administrative register studies in Denmark.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- Peters MJL, Symmons DPM, McCarey D, *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. *Ann Rheum Dis* 2010;69:325–31.
- Trelle S, Reichenbach S, Wandel S, *et al*. Cardiovascular safety of non-steroidal anti-inflammatory drugs: network meta-analysis. *BMJ* 2011;342:c7086.
- Kearney PM, Baigent C, Godwin J, *et al*. Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised trials. *BMJ* 2006;332:1302–8.
- McGettigan P, Henry D. Cardiovascular risk with non-steroidal anti-inflammatory drugs: systematic review of population-based controlled observational studies. *PLoS Med* 2011;8:e1001098.
- Solomon DH, Kremer J, Curtis JR, *et al*. Explaining the cardiovascular risk associated with rheumatoid arthritis: traditional risk factors versus markers of rheumatoid arthritis severity. *Ann Rheum Dis* 2010;69:1920–5.
- Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis. *Am J Med* 2008;121:S21–31.
- Fosbøl EL, Gislason GH, Jacobsen S, *et al*. The pattern of use of non-steroidal anti-inflammatory drugs (NSAIDs) from 1997 to 2005: a nationwide study on 4.6 million people. *Pharmacoepidemiol Drug Saf* 2008;17:822–33.
- Bombardier C, Laine L, Reicin A, *et al*. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. *N Engl J Med* 2000;343:1520–8.
- Cannon CP, Curtis SP, FitzGerald GA, *et al*. Cardiovascular outcomes with etoricoxib and diclofenac in patients with osteoarthritis and rheumatoid arthritis in the Multinational Etoricoxib and Diclofenac Arthritis Long-term (MEDAL) programme: a randomised comparison. *Lancet* 2006;368:1771–81.
- Silverstein FE, Faich G, Goldstein JL, *et al*. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. *JAMA* 2000;284:1247–55.
- Solomon DH, Glynn RJ, Rothman KJ, *et al*. Subgroup analyses to determine cardiovascular risk associated with nonsteroidal antiinflammatory drugs and coxibs in specific patient groups. *Arthritis Rheum* 2008;59:1097–104.
- Nadareishvili Z, Michaud K, Hallenbeck JM, *et al*. Cardiovascular, rheumatologic, and pharmacologic predictors of stroke in patients with rheumatoid arthritis: a nested, case-control study. *Arthritis Rheum* 2008;59:1090–6.
- Goodson NJ, Brookhart AM, Symmons DPM, *et al*. Non-steroidal anti-inflammatory drug use does not appear to be associated with increased cardiovascular mortality in patients with inflammatory polyarthritis: results from a primary care based inception cohort of patients. *Ann Rheum Dis* 2009;68:367–72.
- Andersen TF, Madsen M, Jørgensen J, *et al*. The Danish National Hospital Register. A valuable source of data for modern health sciences. *Dan Med Bull* 1999;46:263–8.
- Gaist D, Sørensen HT, Hallas J. The Danish prescription registries. *Dan Med Bull* 1997;44:445–8.
- Frost L, Andersen LV, Vestergaard P, *et al*. Trend in mortality after stroke with atrial fibrillation. *Am J Med* 2007;120:47–53.
- Krarp L-H, Boysen G, Janjua H, *et al*. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150–4.
- Madsen M, Davidsen M, Rasmussen S, *et al*. The validity of the diagnosis of acute myocardial infarction in routine statistics: a comparison of mortality and hospital discharge data with the Danish MONICA registry. *J Clin Epidemiol* 2003;56:124–30.
- Lindhardsen J, Ahlehoff O, Gislason GH, *et al*. Risk of atrial fibrillation and stroke in rheumatoid arthritis: Danish nationwide cohort study. *BMJ* 2012;344:e1257.
- Gislason GH, Jacobsen S, Rasmussen JN, *et al*. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal antiinflammatory drugs after acute myocardial infarction. *Circulation* 2006;113:2906–13.
- Schjerning Olsen A-M, Fosbøl EL, Lindhardsen J, *et al*. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: a nationwide cohort study. *Circulation* 2011;123:2226–35.
- Fosbøl EL, Gislason GH, Jacobsen S, *et al*. Risk of myocardial infarction and death associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs) among healthy individuals: a nationwide cohort study. *Clin Pharmacol Ther* 2009;85:190–7.
- Geusens P, Alten R, Rovinsky J, *et al*. Efficacy, safety and tolerability of lumiracoxib in patients with rheumatoid arthritis. *Int J Clin Pract* 2004;58:1033–41.
- Emery P, Zeidler H, Kvien TK, *et al*. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis: randomised double-blind comparison. *Lancet* 1999;354:2106–11.
- Bernatsky S, Hudson M, Suissa S. Anti-rheumatic drug use and risk of hospitalization for congestive heart failure in rheumatoid arthritis. *Rheumatology (Oxford)* 2005;44:677–80.
- Watson DJ, Rhodes T, Cai B, *et al*. Lower risk of thromboembolic cardiovascular events with naproxen among patients with rheumatoid arthritis. *Arch Intern Med* 2002;162:1105–10.
- Wolfe F, Michaud K, Gefeller O, *et al*. Predicting mortality in patients with rheumatoid arthritis. *Arthritis Rheum* 2003;48:1530–42.
- Singh JA, Holmgren AR, Noorbaloochi S. Accuracy of Veterans Administration databases for a diagnosis of rheumatoid arthritis. *Arthritis Rheum* 2004; 51:952–7.
- Kim SY, Servi A, Polinski JM, *et al*. Validation of rheumatoid arthritis diagnoses in health care utilization data. *Arthritis Res Ther* 2011;13:R32.
- American College of Rheumatology Ad Hoc Group on Use of Selective and Nonselective Nonsteroidal Antiinflammatory Drugs. Recommendations for use of selective and nonselective nonsteroidal antiinflammatory drugs: an American College of Rheumatology white paper. *Arthritis Rheum* 2008;59:1058–73.
- Becker MC, Wang TH, Wisniewski L, *et al*. Rationale, design, and governance of Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen Or Naproxen (PRECISION), a cardiovascular end point trial of nonsteroidal antiinflammatory agents in patients with arthritis. *Am Heart J* 2009;157:606–12.



Non-steroidal anti-inflammatory drugs and risk of cardiovascular disease in patients with rheumatoid arthritis: a nationwide cohort study

Jesper Lindhardsen, Gunnar Hilmar Gislason, Søren Jacobsen, et al.

Ann Rheum Dis published online June 8, 2013
doi: 10.1136/annrheumdis-2012-203137

Updated information and services can be found at:
<http://ard.bmj.com/content/early/2013/06/07/annrheumdis-2012-203137.full.html>

These include:

Data Supplement

"Supplementary Data"
<http://ard.bmj.com/content/suppl/2013/06/10/annrheumdis-2012-203137.DC1.html>

References

This article cites 31 articles, 9 of which can be accessed free at:
<http://ard.bmj.com/content/early/2013/06/07/annrheumdis-2012-203137.full.html#ref-list-1>

P<P

Published online June 8, 2013 in advance of the print journal.

Email alerting service

Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:
<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:
<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:
<http://group.bmj.com/subscribe/>

Topic Collections

Articles on similar topics can be found in the following collections

[Epidemiology](#) (1065 articles)
[Connective tissue disease](#) (3300 articles)
[Degenerative joint disease](#) (3576 articles)
[Immunology \(including allergy\)](#) (3897 articles)
[Musculoskeletal syndromes](#) (3834 articles)
[Rheumatoid arthritis](#) (2501 articles)
[Biological agents](#) (399 articles)
[Drugs: musculoskeletal and joint diseases](#) (532 articles)

Notes

Advance online articles have been peer reviewed, accepted for publication, edited and typeset, but have not yet appeared in the paper journal. Advance online articles are citable and establish publication priority; they are indexed by PubMed from initial publication. Citations to Advance online articles must include the digital object identifier (DOIs) and date of initial publication.

To request permissions go to:

<http://group.bmj.com/group/rights-licensing/permissions>

To order reprints go to:

<http://journals.bmj.com/cgi/reprintform>

To subscribe to BMJ go to:

<http://group.bmj.com/subscribe/>