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Risk of myocardial infarction with use of selected nonsteroidal anti-inflammatory drugs in spondyloarthritis patients

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RISK OF MYOCARDIAL INFARCTION WITH USE OF SELECTED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS IN SPONDYLOARTHRITIS PATIENTS

by

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ABSTRACT

Background: Spondyloarthritis (SpA) is associated with increased risk of myocardial infarction (MI); the risk may be due to the underlying inflammatory disease, or also due to medications that increase MI risk, such as certain non-steroidal anti-inflammatory drugs (NSAIDs).

Objectives:

1. To describe the risk of myocardial infarction (MI) among patients with spondyloarthritis who are prescribed NSAIDs
2. To compare the pattern of MI risk with specific NSAID use among spondyloarthritis patients with the pattern of risk among patients with osteoarthritis (OA)

Methods: Nested case-control studies were performed using 1994–2015 data from The Health Improvement Network (THIN). Underlying cohorts included adult patients with incident SpA or OA had ≥1 NSAID prescriptions and no history of MI. In each cohort, we matched cases of incident MI to four controls without MI. NSAID use was categorized as: (A) current (prescription end date 0–180

days prior to index date), (B) recent (181–365 days), or (C) remote (>365 days). We performed conditional logistic regression to compare the odds of current or recent NSAID use relative to remote use of any NSAID, considering diclofenac and naproxen specifically.

Results: Within the SpA cohort of 8140 and the OA cohort of 244,399, there were 115 and 6287 MI cases, respectively. After adjustment, among SpA subjects, current diclofenac use was associated with an OR of 3.05 (95% CI 1.48–6.29; Table 2) for MI. Naproxen use was not associated with any increase (adjusted OR 1.25, 95% CI 0.56–2.78). A ratio of ORs for SpA/diclofenac relative to OA/diclofenac was 2.35 (1.10–4.90).

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aOR: adjusted odds ratio

AS: ankylosing spondylitis

CI: confidence interval

CKD: chronic kidney disease

COX: cyclooxygenase

MI: myocardial infarction

NSAID: non-steroidal anti-inflammatory drug

OR: odds ratio

PsA: psoriatic arthritis

SpA: spondyloarthritis

THIN: The Health Improvement Network

THESIS

Background/Introduction

Risk of myocardial infarction (MI) is increased in several systemic rheumatic diseases including rheumatoid arthritis, psoriatic arthritis and other forms of inflammatory arthritis of the spine (spondyloarthritis; SpA).[1–4] Reasons for this increased risk are likely multifactorial, including a greater prevalence of traditional cardiovascular risk factors, system-wide inflammation, and use of medications that may predispose to MI.[5–9] While some risk factors (genetics) cannot be changed, other modifiable risk factors, specifically medication selection, offer an opportunity to prevent morbidity and reduce the premature mortality associated with SpA.

Nonsteroidal anti-inflammatory drugs (NSAIDs), are currently indicated as first-line treatment for SpA of the spine, and for psoriatic arthritis.[10–12] While NSAIDs may provide relief from pain and stiffness associated with SpA, their use may be associated with risk of adverse events such as MI. In particular, several NSAIDs that selectively inhibit the cyclooxygenase-2 (COX-2) enzyme were withdrawn from the market when their cardiovascular risk was publicly recognized. Although drugs with predominantly COX-2 inhibition have been incriminated and limited or removed from the market, NSAIDs with relatively lower COX-2 inhibition (“nonselective NSAIDs”) remain on the market. In fact, the top three NSAIDs, diclofenac, naproxen and ibuprofen account for more than 12 million

prescriptions annually in the United Kingdom.[13]

In people without known cardiovascular disease, several nonselective NSAIDs have been shown to increase risk of several major cardiovascular events in a dose-dependent fashion. High dose diclofenac has been associated with a 41% increase in risk, and high dose ibuprofen use is also likely associated with an increased risk, though this failed to reach statistical significance in meta-analysis (ARR 1.44, 95% CI 0.89–2.33).[14] Naproxen, on the other hand, did not have an increased risk (ARR 0.93, 95% CI 0.69–1.27), suggesting individual drug differences exist, rather than there being a class effect. The proposed mechanisms for the differences in effects include the relative degree of COX-2 enzyme inhibition (rather than the absolute degree of inhibition), as well as drug half-life and drug-specific effects on platelet inhibition.

Despite the evidence of cardiovascular risk in the general population, the cardiovascular effects of NSAIDs have not been fully studied in persons with systemic rheumatic diseases. The hypothesis for this study was that that MI risk with specific NSAIDs would follow a similar pattern in SpA patients to the pattern in the general population, but that risk would be greater in SpA with each drug, because the systemic inflammation in SpA also contributes to risk of MI. However, a competing theory suggests that NSAID use in inflammatory arthritis may protect against adverse cardiovascular events by reducing systemic

inflammation which itself is a risk factor for MI. For this reason, we examined the risk of MI associated with use of NSAIDs in SpA patients, and also assessed this risk among patients with osteoarthritis (OA) separately, to compare the pattern of risk between the two diseases.

Methods

We performed a nested case-control study using 1994–2015 data from The Health Improvement Network (THIN), a database of medical records from over 600 general practitioners in the United Kingdom. THIN currently contains data on over 11 million unique individuals, covering more than 6% of the UK population.

THIN contains systematically and prospectively recorded data collected by GPs on demographics, diagnoses, consultation rates, referrals, hospitalizations, laboratory test results, and prescriptions among patients covered in the practices. Diagnoses are organized according to the Read classification,[15] which is akin to the ICD classification used in the US and elsewhere. Prescription data include the dose, strength and formulation of medications, and medications are categorized according to the drug dictionary, Multilex. Quality control checks are done regularly, and this database has been validated for several pharmaco-epidemiologic studies as well as for MI as an outcome.[16]

Rationale for case-control study design. The effect of NSAIDs on increasing risk of MI is theoretically short; with onset occurring within hours, and the effect lasting only up to four days following discontinuation of the drug. For this reason, a case-control study design was selected, with the exposure of greatest interest being current use of an NSAID on the index date. This design has the advantage of capturing the most recent NSAID prescription, and therefore greater likelihood of correctly classifying NSAID exposure among cases and controls. Although many patients use NSAIDs regularly or continuously, the specific NSAID used may change over time. In one study of administrative and prescription records for members of a large health plan, NSAID switches occurred in 15% of patients following the initial prescription, most commonly due to lack of efficacy and side effects.[17] Additionally, MI cases, while "common", occur in under 1% of patients, thus the case-control study will maximize the power of these relatively infrequent cases by including all of them (within the eligible cohort). Because the primary goal of this work was to compare the relative safety of NSAIDs, and inform shared decision making regarding NSAID selection in clinical practice, we elected to use a study design that maximizes the likelihood of correct exposure classification, namely the case-control design with assessment of the most recent NSAID prescription.

Underlying cohort establishment. We identified adult patients, aged 18–89 years who had a diagnosis of ankylosing spondylitis (AS) or psoriatic arthritis (PsA),

two forms of spondyloarthritis (SpA) in THIN, after at least 12 months' enrollment in the database without such a diagnosis (incident SpA cohort). Diagnosis was established using Read codes documented by the patient's GP. In previous studies, a Read code alone for PsA was found to have a positive predictive value (PPV) of 85% and the PPV of a single AS Read code was 72%.[18–19] As a control condition, we also identified a cohort of adults with osteoarthritis (OA, any site) documented by the GP. While the PPV of an OA diagnosis has not been assessed in THIN, the high disease prevalence makes it likely PPV will be high. Subjects were excluded if they had any history of MI to allow assessment of incident MI cases. Although the NSAIDs of primary interest for this study were diclofenac (which has high COX-2 inhibition) and naproxen (which has low COX-2 inhibition), we required all subjects to have been prescribed at least one NSAID of any type to minimize confounding by indication. NSAID never-users may potentially have had inactive arthritis, incomplete documentation of medications, or a contraindication to NSAID use. Therefore, the risk of MI in NSAID never-users was expected to be unpredictably but systematically different from the risk in SpA or OA patients who were prescribed an NSAID.

Case and control ascertainment. We identified cases of MI as the first recording of an MI Read code by the GP, a definition that had a PPV of 95% in previous THIN study.[20] In the SpA and OA cohorts separately, each MI case was matched to 1–4 control subjects who did not have an MI, according to age (within

2 years), gender, and year of diagnosis of SpA or OA.

Exposure assessment. For each subject NSAID use was categorized as "current" if the most recent NSAID prescription was calculated to end 0–180 days prior to index date, "recent" if the prescription ended 180–365 days prior or "remote" if more than 365 days prior to the index date. This approach of prescription recency was pioneered by Graham et al. but has since been adopted by our research group in the study of rheumatic disease populations.[21 22] Prescription end date was calculated according to details of the prescriptions issued by the GP. In the event that the instructions for a prescription lacked detail on the quantity of medication to be used each day, we estimated the daily quantity as follows: for diclofenac, each specific formulation was reviewed and an expert clinician reviewed the available quantity frequencies to select the frequency that was thought to me most likely; for naproxen the default number of daily tablets was two.

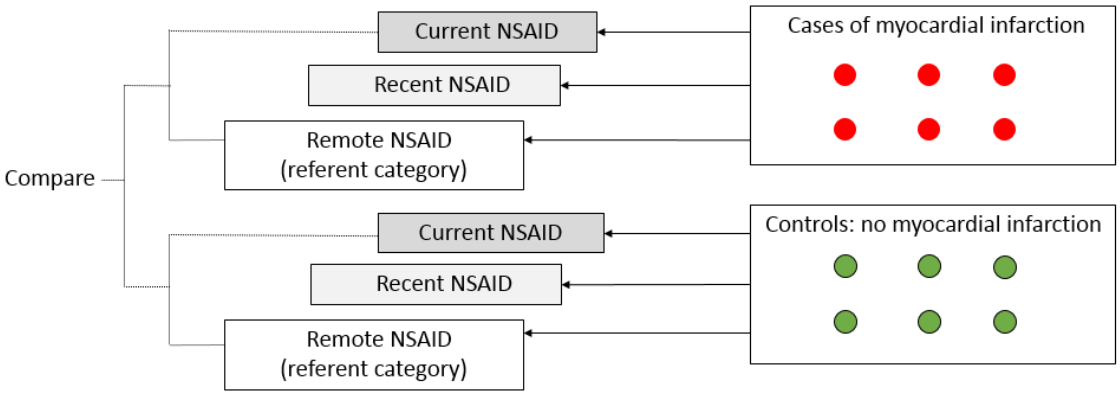

Figure 1. Case-control study design. The study begins on the right, with selection of MI cases and matched controls, who did not have MI. Subjects' exposure to NSAIDs was assessed as "Current" (within 180 days), "Recent" (180–365 days), or "Remote" (>365 days). NSAID non-users were excluded. Remote NSAID use was considered the referent category.

Covariate assessment. We assessed for the presence of potential confounders of the relationship between NSAID use and MI using diagnostic records, including any prior diagnosis of hypertension, hyperlipidemia, diabetes mellitus, gastrointestinal bleeding, ischemic heart disease and chronic kidney disease. We assessed use of medications that are potential confounders, using prescription records from the year period preceding the index date. We included use of: aspirin, anti-hypertensives, and lipid lowering agents (statins and fibrates). Body mass index (BMI) and smoking status were also considered, and classified according to the most recent recording prior to the index date, within 5 years. For the primary analysis, missing values of BMI and smoking status were imputed using multiple imputation.[23]

Statistical analysis. We generated descriptive statistics for MI cases and controls, including mean age, sex, prevalence of comorbidities and medication use, and BMI and smoking categories. Statistical comparison between cases and controls was not be performed for descriptive statistics.

For the primary analysis, we calculated a crude odds ratio for the odds of current NSAID use relative to remote NSAID use for cases and controls. To adjust for potential confounders, a conditional logistic regression model was used, adjusting for baseline presence of potential confounders (outlined above), for the SpA and OA cohorts separately. For each odds ratios (OR), we calculated a

95% confidence interval (CI) for each category of NSAID exposure (current and recent) relative to remote use of any NSAID (the referent).

To compare the ORs between the SpA and OA cohorts, we calculated the ratio of the odds ratios with 95% CI.[24]

Sensitivity analyses

To assess the robustness of the primary analysis findings, we conducted several sensitivity analyses. Firstly, because the OA subjects had a mean age more than 10 years greater than the SpA subjects, we performed an analysis restricted to subjects aged 55–70 years. Secondly, we re-matched the original SpA cohort cases to controls, using all the original matching factors, and additionally matching on SpA subtype (AS or PsA; within the SpA cohort only). We then examined the effect estimates within the SpA population, stratified by SpA subtype. Finally, while the primary analysis used imputation for missing data on BMI and smoking status, we also performed a complete case analysis, excluding any subjects who did not have data on both BMI and smoking.

All analyses were performed using SAS 9.3 or 9.4 (SAS Institute, Cary, NC).

Results

Subject characteristics. From an original SpA cohort of 8140, we identified 115 MI cases and 455 matched controls. From the OA cohort of 244,399, we identified 6287 MI cases and 25164 matched controls. In each cohort, MI cases

had a greater prevalence of traditional MI risk factors, including CKD, diabetes, hyperlipidemia, hypertension, IHD, obesity and smoking (Table 1). MI cases also tended to have greater use of medications for treatment of hypertension and diabetes, including aspirin, ACE-inhibitors, beta-blockers, and lipid lowering agents. Among subjects in the SpA cohort, disease modifying anti-rheumatic drug (DMARD) use was present in 35% of MI cases and 30% of controls. Biologic use was rare, as expected, occurring in only 1 SpA control subject.

NSAID prescriptions. Among subjects with current diclofenac use, the majority (92%) were prescribed a daily dosage or 100 mg or more, with 150 mg daily being the most common prescription (74%). The daily dosage or diclofenac was 100 mg or more in 92% of OA subjects, 95% of AS subjects and 92% of PsA subjects, respectively. For naproxen, the most common daily dosage was 1000 mg (55%). The daily dosage was 1000 mg or greater in 56% of OA subjects, 63% of AS subjects and 72% of PsA subjects. Among all subjects whose most recent prescription was an NSAID other than diclofenac or naproxen, the most common drug was ibuprofen (55%), followed by celecoxib (11%), meloxicam (10%), rofecoxib (7%), etoricoxib (5%), indomethacin (3%) and etodolac (3%). All other NSAIDs accounted for 2% or less of prescriptions.

Table 1. Characteristics of cases and controls derived from the underlying SpA and OA cohorts

	SpA cohort		OA cohort	
	Cases	**Controls**	**Cases**	**Controls**
Subjects (n)	115	455	6287	25164
Age, mean ± SD	63.0 ± 11.5	62.7 ± 11.4	72.6 ± 10.3	72.5 ± 10.2
Female	35 (30.4%)	138 (30.3%)	2927 (46.6%)	11716 (46.6%)
Comorbidities*				
Chronic kidney disease	14 (12.2%)	52 (11.4%)	1043 (16.6%)	3248 (12.9%)
Diabetes	23 (20.0%)	52 (11.4%)	1153 (18.3%)	3195 (12.7%)
Gastrointestinal Bleeding	5 (4.3%)	17 (3.7%)	339 (5.4%)	1011 (4.0%)
Hyperlipidemia	22 (19.1%)	58 (12.7%)	1211 (19.3%)	3898 (15.5%)
Hypertension	66 (57.4%)	188 (41.3%)	3626 (57.7%)	12491 (49.6%)
Ischemic Heart Disease	44 (38.3%)	39 (8.6%)	2707 (43.1%)	3048 (12.1%)
Medication Use*				
Aspirin	29 (25.2%)	71 (15.6%)	2354 (37.4%)	6400 (25.4%)
ACE-inhibitors	32 (27.8%)	87 (19.1%)	1732 (27.5%)	5568 (22.1%)
Beta Blockers	19 (16.5%)	66 (14.5%)	1687 (26.8%)	4697 (18.7%)
Lipid Lowering Drugs	42 (36.5%)	111 (24.4%)	2382 (37.9%)	7956 (31.6%)
DMARDs	41 (35.7%)	137 (30.1%)	196 (3.1%)	488 (1.9%)
Biologics	0 (0.0%)	1 (0.2%)	0 (0.0%)	0 (0.0%)
BMI*- missing	29 (25.2%)	154 (33.8%)	1580 (25.1%)	7197 (28.6%)
Underweight	5 (4.3%)	9 (2.0%)	168 (2.7%)	546 (2.2%)
Normal	15 (13.0%)	64 (14.1%)	1016 (16.2%)	4181 (16.6%)
Overweight	32 (27.8%)	126 (27.7%)	1929 (30.7%)	7405 (29.4%)
Obese	34 (29.6%)	102 (22.4%)	1594 (25.4%)	5835 (23.2%)
Smoking* missing	6 (5.2%)	21 (4.6%)	184 (2.9%)	786 (3.1%)
Non-smoker	27 (23.5%)	170 (37.4%)	2364 (37.6%)	11428 (45.4%)
Ex-smoker	46 (40.0%)	183 (40.2%)	2506 (39.9%)	9894 (39.3%)
Current smoker	36 (31.3%)	81 (17.8%)	1233 (19.6%)	3056 (12.1%)

Values expressed are N (%) unless otherwise noted. SpA: spondyloarthritis, OA: osteoarthritis, DMARDs: disease modifying anti-rheumatic drugs, BMI: body mass index.

*Assessed prior to study entry; comorbidities and any time prior to study, medications within the year prior; most recent BMI/smoking status within 5 years

Associations of NSAID use with MI. In the primary analysis, among SpA subjects, current diclofenac use was associated with an OR of 2.23 (95% CI 1.22–4.05), which after adjustment for covariates, and imputation for missing values of BMI and smoking, increased to 3.05 (95% CI 1.48–6.29; Table 2). Current naproxen use was not associated with an increased OR for MI (adjusted OR [aOR] 1.25, 95% CI 0.56–2.78], nor was current or recent use of other NSAIDs (aORs 1.32 [0.67–2.60] and 1.05 [0.38–2.92], respectively).

Table 2. Primary outcome: Odds of myocardial infarction with current use of diclofenac, naproxen or other NSAIDs, and recent use of an NSAID, relative to remote use of NSAIDs, among patients with spondyloarthritis and osteoarthritis.

	SpA				OA			
	Cases (n=115)	**Controls (n=455)**	**Crude OR**	**aOR***	**Cases (n=6287)**	**Controls (n=25164)**	**Crude OR**	**aOR***
Current⁺ diclofenac	25	62	2.23 (1.2–4.1)	3.05 (1.5–6.3)	843	2981	1.23 (1.1–1.3)	1.30 (1.2–1.4)
Current naproxen	14	46	1.60 (0.8–3.2)	1.25 (0.6–2.8)	339	1365	1.06 (0.9–1.2)	1.04 (0.9–1.2)
Current other NSAID	29	107	1.48 (0.8–2.6)	1.32 (0.7–2.6)	1224	4491	1.18 (1.1–1.3)	1.21 (1.1–1.3)
Recent⁺ NSAID	8	39	1.05 (0.5–2.4)	1.05 (0.4–2.9)	684	2805	1.05 (0.96–1.2)	1.04 (0.9–1.2)
Remote⁺ NSAID	39	201	1.0 (ref)	1.0 (ref)	3197	13522	1.0 (ref)	1.0 (ref)

SpA: spondyloarthritis (includes ankylosing spondylitis and psoriatic arthritis), OA: osteoarthritis, OR: odds ratio, aOR: adjusted OR
*Adjusted for potential confounders, using imputed BMI/smoking when missing
⁺Current use: prescription end date 0–180 days prior to index date; recent use: 180–365 days and remote use: >365 days

The OR for risk of MI with current diclofenac use was also increased among OA subjects, but was lesser in magnitude than that in SpA; crude OR 1.23 (95% CI 1.12–1.34), aOR 1.30 (1.18–1.43). Current naproxen was not associated with an increased OR, but current use of other NSAIDs was (aOR 1.21, 95% CI 1.11–1.32) in the OA cohort.

Ratio of ratios. Using the results from the primary analysis, the ratio of odds ratios for current diclofenac (OA as the referent) was 2.35 (95% CI 1.10–4.90), suggesting that the risk of MI with current diclofenac use was more than twice as great in SpA patients as it was in OA. When these results were repeated using the ORs from the SpA subtype matched analysis, the ratio of ORs was 1.85 (95% CI 0.90–4.90; Table 3).

Table 3. Ratio of odds ratios for current diclofenac use in SpA relative to OA

	Original SpA cohort, *unmatched* by SpA Subtype		**Sensitivity analysis: SpA cohort, *matched* by SpA subtype**	
	SpA	OA	SpA	OA
*aOR	3.05	1.30	2.34	1.30
Ratio of odds ratios (95% CI)	2.35 (1.1–4.9)		1.80 (0.9–4.9)	

* From the fully adjusted model including imputed values for BMI and smoking when missing

Sensitivity analyses. With restriction to subjects aged 55–70 in both the SpA and OA cohorts, the results were not meaningfully changed (Table 4); current

diclofenac aORs were: for SpA 3.36 (95% CI 0.9–12.8), and for OA 1.30 (95% CI 1.1–1.5). When we re-matched subjects within the SpA cohort based on the SpA subtype (AS or PsA) in addition to the other matching factors, the crude OR for diclofenac use within the whole SpA sample remained similar (OR 2.08 versus 2.23 with the original design), however the aOR was only 2.34 (95% CI 1.1–4.9; original aOR 3.05). When stratified by SpA subtype, the crude and adjusted ORs for current diclofenac were similar in the subtypes, but confidence intervals were much wider, due to smaller numbers (8 AS cases and 17 PsA cases). For AS, aOR for current diclofenac use was 1.93 (95% CI 0.2–14.9) and for PsA, aOR 1.79 (95% CI 0.7–4.5) (Table 4). Interestingly, naproxen continued to have no association with MI among AS subjects, but had an increased point estimate (with wide CI) among PsA subjects (aOR 2.59, 95% CI 0.89–7.52). When we restricted analyses to only subject with complete data on BMI and smoking, the results were not meaningfully changed for either SpA or OA subjects (data not shown).

Table 4. Sensitivity analyses: (A) Age restricted to 55–70 years, (B) SpA cases and controls rematched and stratified by SpA subtype. Odds of myocardial infarction with current use of diclofenac, naproxen or other NSAIDs relative to remote use of NSAIDs.

A. Age-restricted to 55–70 years

	SpA				OA			
	Cases (n=115)	**Controls (n=455)**	**Crude OR**	**aOR***	**Cases (n=6287)**	**Controls (n=25164)**	**Crude OR**	**aOR***
Current⁺ diclofenac	11	29	2.13 (0.9–5.1)	3.36 (0.9–12.8)	349	1263	1.19 (1.0–1.4)	1.30 (1.1–1.5)
Current naproxen	8	26	1.64 (0.6–4.2)	1.11 (0.3–4.5)	144	595	1.02 (0.8–1.3)	0.95 (0.8–1.2)
Current other NSAID	14	49	1.55 (0.7–3.4)	1.60 (0.5–5.1)	394	1517	1.12 (1.0–1.3)	1.15 (1.0–1.3)
Recent⁺ NSAID	3	16	0.95 (0.2–3.8)	0.59 (0.1–4.2)	250	963	1.11 (1.0–1.3)	1.11 (0.9–1.3)
Remote⁺ NSAID	18	96	1.0 (ref)	1.0 (ref)	898	3802	1.0 (ref)	1.0 (ref)

B. SpA Subtype Matched and Stratified

	Ankylosing Spondylitis				Psoriatic Arthritis			
Current⁺ diclofenac	8	14	2.83 (0.9–8.7)	1.83 (0.2–14.9)	17	49	1.76 (0.9–3.6)	1.79 (0.7–4.5)
Current naproxen	3	14	1.14 (0.3–4.9)	0.32 (0.02–4.9)	11	27	2.09 (0.9–4.9)	2.59 (0.9–7.5)
Current other NSAID	12	38	1.60 (0.6–4.1)	0.82 (0.1–5.9)	17	81	1.05 (0.5–2.1)	0.85 (0.4–2.0)
Recent⁺ NSAID	1	16	0.33 (0.04, 2.8)	**	7	22	1.55 (0.6–4.0)	1.38 (0.4–4.4)
Remote⁺ NSAID	11	53	1.0 (ref)	1.0 (ref)	27	131	1.0 (ref)	1.0 (ref)

SpA: spondyloarthritis (includes ankylosing spondylitis and psoriatic arthritis), OA: osteoarthritis, OR: odds ratio, aOR: adjusted OR
*Adjusted for potential confounders, using imputed BMI/smoking when missing
⁺Current use: prescription end date 0–180 days prior to index date; recent use: 180–365 days and remote use: >365 days

Discussion

This nested case-control study performed using general practitioner electronic medical records, demonstrates an increased risk of MI among SpA patients using diclofenac. Relative to patients with OA, SpA patients appeared to have about twice the risk of MI with diclofenac use. This novel design used in this study, comparing current NSAID users to remote NSAID users, minimizes confounding by indication by comparing diclofenac users to remote NSAID users, all of whom were judged to have an indication for prescription NSAID use by their GP. While these findings warrant confirmation in other large SpA populations, the increased risk of MI with current diclofenac use and the absence of an increased risk among current naproxen users, has important implications for clinicians who prescribe or recommend NSAIDs to SpA patients. Given that NSAIDs are recommended as first-line therapy in both North America and Europe, there are hundreds of thousands of SpA patients whose MI risk may be reduced by treatment with naproxen rather than diclofenac.

While the risk of MI with specific NSAIDs has been studied in the general population, little data exists among patients with inflammatory arthritis, such as SpA. One cohort study, in rheumatoid arthritis, found that the risk of cardiovascular disease (combined endpoint of MI, stroke and cardiovascular mortality) was *lower* in RA than in controls without RA. Specific NSAIDs such as

rofecoxib and diclofenac were associated with increased risk, but others were not.[25]

In ankylosing spondylitis, Essers and others performed a cohort study using the British Clinical Practice Research Datalink (CPRD), a large medical records database with 60% overlap with THIN. The results indicate no increased rate of MI among AS patients overall. The investigators did find an increased incidence rate of ischemic heart disease in women (HR 1.88 [95% CI 1.22–2.90]), which was attenuated after NSAID use was adjusted for in the multivariable model (HR 1.57 [95% CI 0.99–2.48]). These results are consistent with the current study findings that the selected NSAIDs do increase heart disease risk.[26]

In a cohort study using the Ontario health administrative data, the effect of NSAIDs on cardiovascular mortality was assessed in a subset analysis among those aged 66 and older. [4] This older adult subset was selected because prescription data was limited to this group. Authors report the multivariable adjusted HR of 0.1 with NSAID use (95% CI 0.01–0.61) and broadly state that "lack of NSAID exposure" is a risk factor for vascular death. This finding, that NSAID use is associated with 90% reduction in cardiovascular mortality in this population lacks face validity. But more importantly, the study design raises concern for prevalent user bias; that persons with AS who survive to late adulthood without a complication from or contraindication to NSAID use reflect

the healthiest stratum of AS patients. The same analysis, demonstrating no increased mortality risk with statin use, hypertension, CKD or cancer, illustrates the same bias. In contrast to the Toronto study, the present study is not limited to older adults and therefore is less likely to suffer from bias due to prevalent NSAID use. In fact, our analysis restricted to persons aged 55–70 years demonstrates the findings of the Toronto study should not be assumed to hold true in a younger SpA population.

The present study has several limitations and strengths that warrant discussion. Although this study applied validated algorithms for identification of SpA, it was not possible to confirm SpA diagnosis for included subjects. However we expect that any misclassification non-diseased persons as having SpA subjects would bias study results toward the null. Additionally, while prescription data is detailed in THIN, we cannot know if patients adhered to therapy. Some patients may take NSAIDs inconsistently, only on an as-needed basis for pain, and the pattern of use may differ according to the indication for use (SpA versus OA). To provide conservative estimates for this study, this study assumed complete medication adherence, using an estimate of the shortest possible exposure window for a given prescription. This may have led to misclassification of some current users as recent or remote users, potentially overestimating effects in recent or remote use categories and biasing results for current NSAID users toward the null. Finally, confounding by indication still remains a potential concern in that an

NSAID prescription may indicate a period of pain or increased disease activity, and it may be that painful condition or disease activity that truly puts a study subject at risk. Because it was not possible to assess disease activity within this study, we consider the results of this study to be exploratory or suggestive of an increased risk of MI with diclofenac, but not alone enough to change treatment guidelines. Finally, the ratio of odds ratios, indicated diclofenac use had approximately twice the risk of MI among SpA relative to OA, but failed to reach statistical significance in our sensitivity analysis, and therefore warrant further investigation.

This study has several strengths worth noting. Firstly, our use of a large, general practitioner-derived database reflects real world NSAID use and real world risk, in contrast to the relatively great drug adherence and highly selected population that would be present in medication trials. Secondly, the requirement that all included subjects had at least one NSAID prescription likely reduces confounding by indication, at least to some degree, and offers an advantage over previous studies that included SpA subjects who had not received NSAIDs at all.
While the primary outcome of MI was established through the use of diagnostic codes, the PPV using this method was high in a previous validation study, and an internal validation study of MI cases confirmed MI in 89% of cases.
Additionally, our series of sensitivity analysis, all confirming the primary finding of increased risk with diclofenac use in SpA with variations in the study population

and design, supports that our primary results are robust given the assumptions made in our analytical approach.

Conclusions

This study found that among SpA patients, current use of diclofenac was associated with two- to three-fold risk of MI relative to remote use of any NSAID. The risk associated with diclofenac in SpA was approximately double the risk in OA patients. Current naproxen use, on the other hand, did not increase MI risk in SpA or OA, though effects should be further investigated in SpA subtypes. These results suggest that diclofenac use contributes to risk of MI in SpA patients, and suggests that in the SpA population, overall MI risk could be lowered through preferential use of naproxen. If confirmed in other large SpA data sets, these findings may motivate a change in practice guidelines to recommend naproxen as the preferred first-line NSAID.

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