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Risk of Myocardial Infarction with use of Selected Nonsteroidal Anti-Inflammatory Drugs in Spondyloarthritis and Osteoarthritis Patients

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Abstract

Objectives—Spondyloarthritis (SpA) is associated with an increased risk of myocardial infarction (MI) due to underlying inflammation and possibly due to medications such as certain non-steroidal anti-inflammatory drugs (NSAIDs). We sought to describe MI risk among patients with SpA who were prescribed NSAIDs, and to compare the pattern of risk in SpA to that in osteoarthritis (OA).

Methods—Nested case-control studies were performed using The Health Improvement Network (THIN). Underlying cohorts included adults with incident SpA or OA who had 1 NSAID prescription and no history of MI. Within each cohort, we matched each MI case to four controls without MI. NSAID use was categorized as: (A) current (prescription 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 244,339, there were 115 and 6287 MI cases, respectively. After adjustment, current diclofenac use in SpA was associated with an OR of 3.32 (95% CI 1.57–7.03) for MI. Naproxen was not associated with any increase (aOR 1.19, 95% CI 0.53–2.68). A ratio of ORs for SpA/diclofenac relative to OA/diclofenac was 2.64 (1.24–5.58).

Conclusions—MI risk in SpA is increased among current users of diclofenac, but not naproxen. The MI risk in with diclofenac in SpA appears to differ from that in OA.

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Keywords

spondyloarthritis; nonsteroidal anti-inflammatory drugs; myocardial infarction

Introduction

Myocardial infarction (MI) risk is increased in several systemic rheumatic diseases including rheumatoid arthritis (RA), psoriatic arthritis (PsA) and other forms of spondyloarthritis (SpA).^{1–4} Reasons for this increased risk are likely multifactorial, including a greater prevalence of traditional cardiovascular (CV) risk factors, systemic inflammation, and use of medications that may predispose to MI.^{5–9} While some risk factors 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 first-line therapy for axial SpA and PsA^{10–12} While NSAIDs may relieve pain and stiffness, use may be associated with risk of adverse events such as MI. In particular, several NSAIDs that selectively inhibit cyclooxygenase-2 (COX-2) were withdrawn from the market when their CV risk was publicized. Although drugs with predominantly COX-2 inhibition have been incriminated and limited or removed from the market, NSAIDs with lower COX-2 inhibition (“nonselective NSAIDs”) remain available. In fact, the top three NSAIDs, diclofenac, naproxen and ibuprofen are nonselective, and account for more than 12 million prescriptions annually in the UK.¹³

In people without CV disease, several nonselective NSAIDs have been shown to increase risk of CV events in a dose-dependent fashion. High dose diclofenac is associated with a 41% increase in risk, and high dose ibuprofen is also likely associated with an increased risk, though not statistically significant in meta-analysis (rate ratio [RR] 1.44, 95% CI 0.89–2.33).¹⁴ Naproxen, on the other hand, did not have an increased risk (RR 0.93, 95% CI 0.69–1.27), suggesting drug-specific effects, rather than a class effect. The proposed mechanisms for different effects include the relative degree of COX-2 inhibition compared to COX-1 (rather than the absolute amount of inhibition), drug half-life and platelet inhibition.

Despite the evidence of CV risk in the general population, risk has not been fully studied in systemic rheumatic diseases. We hypothesized that MI risk with specific NSAIDs would follow a similar pattern in SpA patients to that in the general population, but would be greater in SpA due to systemic inflammation. A competing theory is that NSAID use in inflammatory arthritis may protect against CV events by reducing systemic inflammation which itself increases risk for MI. For this reason, we examined the risk of MI associated with use of NSAIDs in SpA patients, and also assessed risk among patients with osteoarthritis (OA), a non-inflammatory form of arthritis.

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 UK. THIN currently contains data on over 11 million individuals, covering more than 6% of the UK population.

THIN contains systematically and prospectively recorded data collected by GPs on demographics, diagnoses, consultations, referrals, hospitalizations, testing, and prescriptions. Diagnoses are organized according to the Read classification.¹⁵ Prescription data include the dose, strength and formulation of medications, categorized according to the drug dictionary, Multilex. Quality control checks are done regularly, and this database has been validated for several pharmacoepidemiologic studies as well as for MI as an outcome.¹⁶

Underlying cohort establishment

We identified adults, aged 18–89 years in THIN with a diagnosis of ankylosing spondylitis (AS) or psoriatic arthritis (PsA), two forms of spondyloarthritis (SpA), after at least 12 months' enrollment without such a diagnosis (incident SpA cohort). Diagnosis was established using Read codes documented by the GP. In previous studies, a Read code alone for PsA had a positive predictive value (PPV) of 85% and the PPV of an AS code was 72%.^{17–18} As a control condition, we also identified a cohort of adults with incident 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 identification of incident MIs. 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.

Case and control ascertainment

We identified cases of MI as the first recording of an MI Read code, a definition with a PPV of 95% in a previous THIN study.¹⁹ In SpA and OA separately, each MI case was matched using risk set sampling to 1–4 control subjects without an MI, according to age (within 2 years), date of SpA or OA diagnosis (within 2 years), and sex (Figure 1).

Exposure assessment

For each subject, NSAID use was categorized as “current” if the most recent NSAID prescription was 0–180 days prior to the index date, “recent” if 181–365 days prior, or “remote” if more than 365 days. This approach of prescription recency has been used previously in the study of rheumatic diseases.^{20,21}

Covariate assessment

Potential confounders included any prior diagnosis of hypertension, hyperlipidemia, diabetes mellitus, gastrointestinal bleeding, ischemic heart disease and chronic kidney disease. We

assessed use of medications in the year preceding the index date, including aspirin, anti-hypertensives (beta-blockers and ACE-inhibitors), lipid lowering agents (statins and fibrates), proton pump inhibitors and disease modifying anti-rheumatic drugs (DMARDs) or biologics used in the treatment of SpA. Body mass index (BMI) was classified using the most recent value prior to the index date within 5 years, and smoking status as the most recent value. Missing values for BMI and smoking were imputed using multiple imputation, in which 5 datasets were generated.^{22–25} The imputation model was constructed using all variables used in the analytic model (below).

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.

For the primary analysis, we calculated a crude odds ratio (OR) for the odds of current NSAID use relative to remote NSAID use for cases and controls. A conditional logistic regression model was used to adjust for baseline confounders. The SpA and OA cohorts were analyzed separately. For each OR we calculated a 95% confidence interval (CI) for current and recent NSAID exposure categories relative to remote use of any NSAID (the referent).

To assess the robustness of the primary analysis findings, we conducted several sensitivity analyses. Firstly, because the mean age in OA was 10 years greater than that in SpA, we performed an analysis restricted to subjects aged 55–70 years to allow a comparison of relative risks among cohorts of comparable ages. Secondly, we re-matched the original SpA cases to controls, using all the original matching factors, and additionally matched on SpA subtype (AS or PsA; within the SpA cohort only) and stratified to assess for effects by SpA subtype. Thirdly, out of concern that aspirin use among subjects may be an indication of preexisting ischemic heart disease, we performed an analysis restricted to subjects free of baseline aspirin use.

Finally, to assess for effect modification between arthritis type (SpA versus OA) and the effect of diclofenac, we calculated the ratio of the adjusted odds ratios with 95% CI.²⁶ Analyses were performed using SAS 9.3 or 9.4 (SAS Institute, Cary, NC).

Results

From an original SpA cohort of 8140, we identified 115 MI cases and 455 matched controls. From the OA cohort of 244,339, we identified 6287 MI cases and 25164 matched controls. In each cohort, MI cases had a greater prevalence of traditional MI risk factors and greater use of medications for treatment of hypertension and diabetes, including aspirin, ACE-inhibitors, beta-blockers, and lipid lowering agents (Table 1). Among SpA subjects, 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 those classified as diclofenac users, the majority (92%) were prescribed a daily dosage of 100 mg or more, with 150 mg daily being most common (74%). The daily dosage of diclofenac was 100 mg or more in 92% of OA subjects, 95% of AS subjects and 92% of PsA subjects. For naproxen, the most common daily dosage was 1000 mg (55%) and 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 (Supplementary Table 1).

Associations of NSAID use with MI

In the primary analysis, among SpA subjects, current diclofenac was associated with a greater than 2-fold increase in the crude risk of MI compared to remote NSAID use (OR 2.23, 95% CI 1.22–4.05), which after adjustment for covariates and imputation for missing values of BMI and smoking increased to 3.32 (95% CI 1.57–7.03; Table 2). With current naproxen use and current other NSAID use, ORs were not significantly increased; the adjusted OR (aOR) for naproxen was 1.19 (95% CI 0.53–2.68), current other NSAIDs aOR 1.23 (0.61–2.46), and recent other NSAID aOR 1.03 (0.36–2.93).

The OR for risk of MI with current diclofenac use was also increased among OA subjects; aOR 1.26 (1.14–1.39). Current naproxen was not associated with an increased aOR (0.98, 95% CI 0.85–1.13), but current use of other NSAIDs was (aOR 1.17, 95% CI 1.07–1.28) in the OA cohort.

Sensitivity analyses

With restriction to ages 55–70, results were not meaningfully changed (Table 3); the aOR for current diclofenac in SpA was 3.36 (95% CI 0.88–12.79), and for OA 1.30 (95% CI 1.10–1.53). When we re-matched subjects in the SpA cohort based on SpA subtype, the unadjusted OR for diclofenac use within the whole SpA sample remained similar (OR 2.08). When stratified by SpA subtype, the unadjusted ORs for current diclofenac were similar; for AS, 2.83 (95% CI 0.92–8.68) and for PsA, 1.76 (95% CI 0.85–3.64). Interestingly, naproxen did not have an increased OR in AS, but had an increased point estimate in PsA (unadjusted OR 2.09, 95% CI 0.90–4.85). SpA subtype stratified results could not be adjusted for confounders due to small event numbers. With restriction to subjects free of aspirin use at baseline, results were unchanged. The unadjusted OR for diclofenac in SpA was 2.31 (95% CI 1.16–4.61) and for naproxen was 1.76 (0.81–3.85). In OA, the crude OR of diclofenac was 1.28 (1.15–1.42), and for naproxen was 1.06 (0.90–1.23).

Because current diclofenac was associated with increased MI risk, we also assessed whether recent use (181–365 days from prescription date) conferred risk. In SpA, the unadjusted OR for recent diclofenac was 1.45 (0.50–4.19) and in OA was 0.94 (0.80–1.11). Recent naproxen was not associated with an increased or decreased risk in either SpA or OA (results not shown).

Ratio of ratios

Using the results from the primary analysis, the ratio of aORs for current diclofenac (OA as the referent) was 2.64 (95% CI 1.24–5.58), suggesting an interaction between the underlying form of arthritis (SpA versus OA) and MI risk with diclofenac use, meaning that MI risk differed between the two groups. When these calculations were repeated using the population from the age restricted sensitivity analysis, the point estimate was similar but no longer statistically significant (Table 5).

Discussion

This nested case-control study, performed using GP electronic medical records, demonstrated that MI risk was increased among SpA patients using diclofenac, and that risk with diclofenac differed between SpA and OA subjects. This novel study design, comparing current NSAID users to remote NSAID users, minimized confounding by indication in that all subjects were judged to have an indication for prescription NSAID use by their GP.

While the risk of MI with specific NSAIDs has been studied in the general population, relatively little data exists among patients with inflammatory arthritides. One cohort study, in rheumatoid arthritis (RA), found that the risk of CV disease (composite outcome) 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.²⁷ A 2014 meta-analysis of NSAIDs in RA and PsA found that COX-2 inhibitors were associated with increased CV risk, possibly due to rofecoxib alone, while nonselective NSAIDs, in combination, were not (RR 1.02, 95% CI 0.94–1.24). Notably, only one study of diclofenac met inclusion criteria, finding a significantly increased HR of 1.35.²⁸ Subsequently, a subgroup analysis of RA patients from the PRECISION trial (10% of the sample) reported no significant increased risk of the composite CV outcome with celecoxib relative to both naproxen and ibuprofen.²⁹

In AS, Essers and colleagues performed a cohort study using the British Clinical Practice Research Datalink (CPRD), a database with 60% overlap with THIN. The authors reported that ischemic heart disease in women was increased (HR 1.88, 95% CI 1.22–2.90), but that risk was attenuated after adjustment for NSAID use (HR 1.57, 95% CI 0.99–2.48). These results are consistent with our current study findings that specific NSAIDs do increase ischemic heart disease risk.³⁰

A cohort study using the Ontario health administrative data assessed the effect of NSAIDs on CV mortality in a subset analysis among AS patients aged 66 and older.⁴ This older adult subset was selected because prescription data was available only in this group. Authors reported a HR of 0.1 with NSAID use (95% CI 0.01–0.61) and broadly stated that “lack of NSAID exposure” is a risk factor for vascular death. This finding, that NSAID use is associated with 90% reduction in CV mortality in an older adult 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, chronic kidney disease or cancer, illustrates the same bias. In contrast to this study, our 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 demonstrates the findings of the Ontario study should not be assumed to hold true in a younger SpA population.

The present study has several limitations and strengths. Although this study applied validated algorithms for identification of SpA, it was not possible to confirm SpA diagnosis for included subjects. We expect that misclassification of non-diseased persons as having SpA would bias study results toward the null. Secondly, while prescription data is detailed in THIN, the nature of the data did not allow us to determine 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). We provided conservative estimates by using the prescription date to define the exposure window. This may have led to misclassification of some current users as recent or remote users, potentially overestimating MI risk in recent or remote use categories and biasing results for current NSAID users toward the null. Thirdly, 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 subject at risk. Because it was not possible to assess disease activity within this study, we consider the results of this study to be suggestive of an increased risk of MI with diclofenac and worthy of further exploration. Nonetheless, differential risk of NSAIDs would not be expected if these findings were driven by pain since any type of NSAID may be prescribed for pain. Fourthly, while we estimate the ratio of odds ratios to provide some insight into differences in the effect estimates for diclofenac use in SpA relative to OA, we did not perform a formal test for interaction. Nonetheless, it is unlikely that formally accounting for interaction (eg- in the imputation model) would have substantially changes the results of these sub-analyses. Finally, the ratio of ORs, indicated a difference in the effect of diclofenac in SpA as compared to OA, but failed to reach statistical significance in our sensitivity analysis, and therefore warrants further investigation. Even so, one may speculate that this finding indicates a greater propensity for MI among SpA patients than OA patients.

This study has strength in the use of a large, GP-derived database reflecting real world NSAID use and risk, in contrast to the highly selected populations in trials. Secondly, the requirement that all subjects had at least one NSAID prescription reduces confounding by indication, 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 diagnostic codes, the PPV using this method was high in a previous validation study, and our internal validation study confirmed MI in 89% of cases. Finally, the sensitivity analyses overall agreed with the primary findings of increased risk with diclofenac use in SpA suggesting these results are robust given the assumptions made in our analytical approach.

In conclusion, this study found that current use of diclofenac in SpA was associated with two- to three-fold risk of MI relative to remote use of any NSAID. The risk associated with diclofenac in SpA differed from the risk in OA. Current naproxen use 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 has the important implication for SpA patients and clinicians that MIs could be prevented 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 in SpA.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Case-control study design. The study began 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.

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 $\pm$ SD	63.0 $\pm$ 11.5	62.7 $\pm$ 11.4	72.6 $\pm$ 10.3	72.5 $\pm$ 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%)
Proton pump inhibitors	57 (49.6%)	149 (32.7%)	2520 (40.1%)	7470 (29.7%)
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%)

	SpA cohort		OA cohort	
	Cases	Controls	Cases	Controls
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 index date; comorbidities and any time prior to study, medications within the year prior; most recent BMI and smoking status

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 (1.22–4.05)	3.32 (1.57–7.03)	843	2981	1.23 (1.12–1.34)	1.26 (1.14–1.39)
Current naproxen	14	46	1.60 (0.81–3.18)	1.19 (0.53–2.68)	339	1365	1.06 (0.93–1.20)	0.98 (0.85–1.13)
Current other NSAID	29	107	1.48 (0.84–2.61)	1.23 (0.61–2.46)	1224	4491	1.18 (1.09–1.28)	1.17 (1.07–1.28)
Recent ⁺ NSAID	8	39	1.05 (0.45–2.44)	1.03 (0.36–2.93)	684	2805	1.05 (0.96–1.15)	1.01 (0.91–1.12)
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 and smoking when missing.

[†] Current use: prescription date 0–180 days prior to index date; recent use: 180–365 days and remote use: >365 days

Table 3

Sensitivity analysis: Age restricted to 55–70 years. Odds of myocardial infarction with current use of diclofenac, naproxen or other NSAIDs relative to remote use of NSAIDs.

SpA				OA				
	Cases (n=54)	Controls (n=216)	Crude OR	aOR*	Cases (n=2035)	Controls (n=8140)	Crude OR	aOR*
Current [†] diclofenac	11	29	2.13 (0.88–5.14)	3.36 (0.88–12.79)	349	1263	1.19 (1.03–1.37)	1.30 (1.10–1.53)
Current naproxen	8	26	1.64 (0.64–4.19)	1.11 (0.27–4.50)	144	595	1.02 (0.84–1.25)	0.95 (0.75–1.19)
Current other NSAID	14	49	1.55 (0.71–3.37)	1.60 (0.50–5.08)	394	1517	1.12 (0.97–1.28)	1.15 (0.98–1.34)
Recent [†] NSAID	3	16	0.95 (0.24–3.76)	0.59 (0.08–4.20)	250	963	1.11 (0.95–1.31)	1.11 (0.92–1.33)
Remote [†] NSAID	18	96	1.0 (ref)	1.0 (ref)	898	3802	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.

[†] Current use: prescription date 0–180 days prior to index date; recent use: 181–365 days and remote use: >365 days

Sensitivity analysis: SpA cases and controls re-matched and stratified by SpA subtype. Odds of myocardial infarction with current use of diclofenac, naproxen or other NSAIDs relative to remote use of NSAIDs.

Table 4

	Ankylosing Spondylitis			Psoriatic Arthritis		
	Cases (n=35)	Controls (n=135)	Crude OR	Cases (n=79)	Controls (n=310)	Crude OR
Current [‡] diclofenac	8	14	2.83 (0.92–8.68)	17	49	1.76 (0.85–3.64)
Current naproxen	3	14	1.14 (0.26–4.94)	11	27	2.09 (0.90–4.85)
Current other NSAID	12	38	1.60 (0.62–4.14)	17	81	1.05 (0.53–2.08)
Recent [‡] NSAID	1	16	0.33 (0.04–2.76)	7	22	1.55 (0.60–3.97)
Remote [‡] NSAID	11	53	1.0 (ref)	27	131	1.0 (ref)

OR: odds ratio.

[‡] Current use: prescription end date 0–180 days prior to index date; recent use: 181–365 days and remote use: >365 days

Table 5

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

	Original SpA cohort		Sensitivity analysis: restricted to subjects aged 55–70 years	
	SpA	OA	SpA	OA
* aOR	3.32	1.26	3.36	1.30
Ratio of odds ratios (95% CI)	2.64 (1.24–5.58)		1.86 (0.40–4.33)	

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