EXTENDED REPORT

Ankylosing spondylitis and risk of ischaemic heart disease: a population-based cohort study

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ABSTRACT

Objective To investigate the incidence and risk of ischaemic heart disease (IHD) and acute myocardial infarction (AMI), including the role of non-steroidal anti-inflammatory drugs (NSAID), in patients with ankylosing spondylitis (AS) compared with population controls.

Methods All patients with newly diagnosed AS (n=3809) from the British Clinical Practice Research Datalink (1987–2012) were matched with up to seven persons without AS by year of birth, gender and practice (n=26 197). Incidence rate ratios (IRR) and HRs for development of IHD and AMI were calculated. Stepwise analyses were performed adjusting for age, gender, comorbidity and drug use, including NSAIDs.

Results At baseline, 4.3% of the patients had IHD and 1.8% had AMI compared with 3.4% and 1.4% of the controls, respectively. After exclusion of pre-existing IHD or AMI, the IRRs were 1.18 (95% CI 0.96 to 1.46) and 0.91 (95% CI 0.65 to 1.27) for IHD and AMI, respectively. Compared with controls, the age-gender adjusted HR for developing IHD was 1.20 (95% CI 0.97 to 1.48), and for AMI 0.91 (95% CI 0.65 to 1.28). In female patients, the risk of developing IHD was increased (HR 1.88, 95% CI 1.22 to 2.90), but after adjustment for all possible risk factors only a non-significant trend was found (HR 1.31, 95% CI 0.83 to 2.08). In particular, NSAID use explained this change (HR IHD adjusted for age-gender-NSAID use 1.57, 95% CI 0.99 to 2.48).

Conclusions Female patients with AS had an increased age-adjusted risk of developing IHD, but after adjustment for NSAID use only a non-significant trend towards increased risk was found.

INTRODUCTION

Ischaemic heart disease (IHD) is one of the leading causes of death and loss of quality of life worldwide.[1] In the last few decades, an excess in cardiovascular (CV) morbidity and mortality in patients with chronic inflammatory rheumatic disease, such as rheumatoid arthritis (RA) has been demonstrated.[2 3] This led to additional recommendations for CV risk assessment[4] and treatment guidelines to manage the CV risk in RA.[5] In ankylosing spondylitis (AS) conflicting results on the risk of CV disease have been reported.[6] An increased risk of IHD in AS was found in three studies.[7–9] Also, a statistically significantly increased risk for acute myocardial infarction (AMI) in AS was reported in some studies,[10–12] whereas, others failed to demonstrate this.[7 13 14] Differences in selection of populations or a flawed study design may have contributed to the contradictory results.[15]

Several aetiological mechanisms could be associated with the increased CV risk in AS. First, the systemic inflammation, which is a part of the pathophysiology of AS, may play an independent role in the onset of atherosclerosis.[6] Second, several studies have shown an increased prevalence of conventional risk factors in AS, including the metabolic syndrome and decreased levels of high density lipoprotein cholesterol.[6 11] Third, the long-term use of non-steroidal anti-inflammatory drugs (NSAID) may accelerate the atherosclerotic process.[6 16] NSAIDs are the cornerstone of the treatment of AS and are often prescribed on a long-term basis. According to a recent evaluation of all available evidence by the European Medicines Agency, NSAIDs, as a class, are associated with a small increased risk of atherosclerosis or atherothrombotic events, particularly in patients with underlying heart or circulatory conditions, or with certain CV risk factors.[17] Moreover, high-dose or long-term NSAID use may increase this risk.[18] Differences among the several types of NSAIDs with respect to the CV risk have been reported.[17 19]

To date, there are still some unsolved epidemiological issues on the CV risk of patients with AS. Studies comparing the CV risk in patients with AS with population-based controls are limited or had a flawed study design. Also, studies including adjustments for other potential risk factors besides age and gender when analysing the risk of CV disease in AS, are scarce. Furthermore, the role of NSAID use in the aetiology of AS-associated IHD has, to our knowledge, never been assessed. Therefore, the objective of the present study was to investigate the risk of a first event of IHD, including AMI, in patients with AS compared with population-based controls, and the role of NSAID use in this.

METHODS

Design and data source

A retrospective cohort study was conducted using data from the Clinical Practice Research Datalink GOLD (CPRD), formerly known as the General Practice Research Database. CPRD contains computerised medical records of over 10 million patients under care of general practitioners (GP) in the UK. Since 1987, data are prospectively recorded, and include patient demographics, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and their major outcomes. Read codes classify diseases and symptoms.

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Practices only contribute to CPRD when their data quality is up to research standards. CPRD has been extensively validated.[20]

Study population

The study population consisted of all patients aged 16 years or older with at least one recording of AS during the period of CPRD data collection, which started for the present study in January 1987 and ended in December 2012. The start of valid data collection of each patient was defined as the date at which the practice was included into CPRD, the GP's dataset was approved as 'up-to-standard', and the patient moved into the practice. Patients with a first-ever diagnosis of AS were matched by year of birth, gender, calendar time and practice to up to seven control subjects without a diagnosis of AS at any time during their registration period. The date of the first record of AS defined the index date. Control patients were assigned the same index date as their matched case. The subjects in the study population were followed from their index date to the outcome of interest, the end of data collection, the date of transfer out of the practice area or death, whichever came first. Patients and controls with a record for another inflammatory rheumatic disease (RA, psoriatic arthritis, systemic lupus erythematous or vasculitis) any time during the enrolment were excluded from the current analysis.

Study outcome and risk factors

Outcomes of interest were a first event of IHD or AMI, specified by read codes. IHD was defined as all types of IHD, and included, for example, AMI, coronary artery bypass surgery and percutaneous coronary intervention. The total follow-up time was divided into 30-day intervals in order to adjust the analyses for the influence of potential confounders in a time-varying way. The computerised medical records before the start of each interval were reviewed for the occurrence of potential confounders. Baseline confounders considered included gender, body mass index (BMI), smoking status and alcohol use (the later three as dummy variables). The following time-varying confounders were considered: age, hypercholesterolaemia (including familial hypercholesterolaemia), a history of acute or chronic renal failure, as well as a prescription of antihypertensives, antidiabetics, antiplatelet agents, statins and asthma medication 6 months before the start of an interval. Exposure to NSAIDs was determined as the average defined daily doses (DDD) equivalent to 100 mg of diclofenac, based on WHO norms prior to the start of an interval.[21] NSAIDs were further categorised into cyclo-oxygenase-2 (COX-2) inhibitors, naproxen or other traditional NSAIDs 3 months prior the start of an interval (binary), because of the possible different impact on the risk of IHD or AMI.[17]

Statistical analysis

Dichotomous baseline characteristics (excluding gender and age) of patients and controls were compared using χ^2 tests. Stratified analyses for gender were done with respect to a history of IHD and AMI before the index date. After excluding patients with pre-existing IHD or AMI, incidence rates (IR) for IHD and AMI were calculated for patients (and their controls), respectively, and were estimated as the number of subjects with the event per 1000 person-years (pys). pys Were computed by adding all person-time from the index date to either the date of the first event or to the date of censoring if the event did not occur. Incidence rate ratios (IRR) were calculated by dividing the IR for patients by the IR for controls. IRRs were stratified

Table 1 Baseline characteristics of patients with ankylosing spondylitis (AS) and controls

	Patients with AS		Controls		
Characteristic	n=3809	(%)	n=26 197	(%)	p Value
Males	2686	(70.5)	18 519	(70.7)	–
Age at index date (years)					
16–29	728	(19.1)	5085	(19.4)	–
30–39	1038	(27.3)	7172	(27.4)	–
40–49	817	(21.4)	5674	(21.7)	–
50–59	570	(15.0)	3870	(14.8)	–
60–69	376	(9.9)	2551	(9.7)	–
70–79	206	(5.4)	1399	(5.3)	–
80+	74	(1.9)	446	(1.7)	–
BMI					
<20	204	(5.4)	1280	(4.9)	0.21
20–25	1046	(27.5)	6934	(26.5)	0.20
25–30	879	(23.1)	6066	(23.2)	0.91
>30	447	(11.7)	3086	(11.8)	0.94
Unknown	1223	(32.4)	8831	(33.7)	0.10
Smoking status					
Never	1668	(43.8)	11 962	(45.7)	**0.03**
Current	1403	(36.8)	8256	(31.5)	**<0.01**
Ex	569	(14.9)	3605	(13.8)	**0.05**
Unknown	169	(4.4)	2374	(9.1)	**<0.01**
Alcohol use					
Yes	2612	(68.6)	17 468	(66.7)	**0.02**
No	596	(15.6)	3251	(12.4)	**<0.01**
Unknown	601	(15.8)	5478	(20.9)	**<0.01**
Disease history					
Any cardiovascular disease	216	(5.7)	1317	(5.0)	0.09
IHD	164	(4.3)	898	(3.4)	**<0.01**
AMI	69	(1.8)	354	(1.4)	**0.02**
Stroke	44	(1.2)	317	(1.2)	0.77
Heart failure	24	(0.6)	108	(0.4)	0.06
Peripheral vascular disease	38	(1.0)	246	(0.9)	0.73
Hypertension	316	(8.3)	2007	(7.7)	0.17
Acute renal failure	3	(0.1)	16	(0.1)	0.69
Chronic renal failure	2	(0.1)	62	(0.2)	**0.02**
Hypercholesterolaemia	165	(4.3)	1127	(4.3)	0.93
Diabetes mellitus	150	(3.9)	795	(3.0)	**<0.01**
History of drug use 6 months before the index date					
Any antihypertensives	509	(13.4)	2902	(11.1)	**<0.01**
β-blockers	199	(5.2)	1276	(4.9)	0.35
Loop diuretics	92	(2.4)	380	(1.5)	**<0.01**
Thiazide diuretics	173	(4.5)	967	(3.7)	**0.01**
ACE-I or ANG-II-R	248	(6.5)	1449	(5.5)	**0.01**
Calcium channel antagonist	177	(4.7)	985	(3.8)	**<0.01**
Antiplatelet agents	206	(5.4)	1142	(4.4)	**<0.01**
Nitrates	94	(2.5)	391	(1.5)	**<0.01**
Antidiabetics*	107	(2.8)	586	(2.2)	**0.03**
Statins	233	(6.1)	1363	(5.2)	**0.02**
Asthma medication†	289	(7.6)	1661	(6.3)	**<0.01**
NSAIDs	1731	(45.4)	2163	(8.3)	**<0.01**
COX-2 inhibitors	225	(5.9)	114	(0.4)	**<0.01**
Naproxen only	303	(8.0)	298	(1.1)	**<0.01**
Other traditional NSAIDs	1582	(41.5)	2071	(7.9)	**<0.01**

Bold typeface indicates statistical significance (p<0.05).
A χ^2 test was performed to compare patients with AS and controls.
*Antidiabetics, including insulin.
†Asthma medication, including bronchodilators, inhaled corticosteroids, leukotriene receptor antagonists, β-2 agonists and theophylline.
AMI, acute myocardial infarction; ANG-II-R, angiotensin II receptor antagonist; AS, ankylosing spondylitis; BMI, body mass index; COX-2 inhibitors, cyclo-oxygenase-2 inhibitors; IHD, ischaemic heart disease; NSAIDs, non-steroidal anti-inflammatory drugs.

based on gender and age categories (16–39, 40–49, 50–59, 60–69, 70–79 and ≥80 years). The overall prevalence of IHD and AMI was estimated using Kaplan–Meier methods, and also included patients (and controls, respectively) with an event at baseline. Furthermore, the attributable risk per 1000 pys was calculated for IHD and AMI.

The risk of developing a first IHD or AMI after the index date was estimated by HRs using time-dependent Cox proportional hazard models for those patients (and controls) without the outcome of interest before the index date. Three step-wise models were created with adjustment for potential confounders: (1) adjustment for age and gender, (2) adjustment for age, gender and the DDD of NSAID use, (3) adjustment for age, gender, DDD of NSAID use, and all confounders that changed the β coefficient of the HR more than 1% in the age-gender adjusted analysis. Stratified analyses were done for gender.

In a separate analysis, the role of NSAIDs in the risk of IHD was evaluated. For this, all patients were stratified according to the recent use of any NSAIDs, naproxen, COX-2 inhibitors or other traditional NSAIDs. HRs were calculated, in which patients were compared with controls, irrespective of their NSAID use. Additionally, patients with a history of NSAID use were compared with patients without a history of the same class of NSAIDs, using the Wald test. This analysis was also stratified for gender. All statistical analyses were conducted using SAS V.9.1.

RESULTS

Baseline results

Baseline characteristics of patients with AS (n=3809) and their matched controls (n=26197, 92% had seven controls) are presented in table 1. The mean duration of follow-up for patients and controls was 6.6 years. At baseline, patients were more likely to have been diagnosed with IHD (4.3% vs 3.4%) or AMI (1.8% vs 1.4%) compared with controls (table 1). In the stratified analyses, male patients were more likely to have been diagnosed with IHD (3.4% vs 2.8%, p=0.04) and AMI (1.7% vs 1.2%, p=0.01) compared with male controls, and female patients were more likely to have been diagnosed with IHD (0.9% vs 0.6%, p=0.04), but not with AMI (0.1% vs 0.1%, p=0.06) compared with female controls. Within the AS population, male patients had, more often, a history of IHD (p=0.01) and AMI (p<0.01) compared with female patients.

Incidence and overall prevalence of IHD and AMI

In table 2, a trend towards a higher incidence of developing a first IHD event in patients compared with controls (IRR 1.18, 95% CI 0.96 to 1.46) is shown. In particular, the IRR of IHD was increased among female patients versus female controls (IRR 1.72, 95% CI 1.12 to 2.64), whereas, male patients were not at increased risk of IHD (IRR 1.07, 95% CI 0.84 to 1.37). The IRR of developing a first AMI event was not increased in patients versus controls (IRR 0.91, 95% CI 0.65 to 1.27). Figure 1 visualises the overall prevalence of IHD and AMI over time compared with controls, including events prior to baseline. At baseline, differences in the prevalence of IHD and AMI between patients and controls were found, which remained unchanged during follow-up. The overall prevalence of IHD was 10.8% in patients and 9.0% in controls, after 15 years of follow-up. The overall prevalence of AMI was 4.6% in patients and 4.1% in controls, after 15 years of follow-up. The

Table 2 Incidence rates of ischaemic heart disease and acute myocardial infarction in patients with ankylosing spondylitis (AS) and controls

	Patients with AS			Controls				
	Event	Person-years	Incidence rate*	Event	Person-years	Incidence rate*	Incidence rate ratio†	95% CI
Ischaemic heart disease‡	102	23 719	4.30	600	165 176	3.63	1.18	(0.96 to 1.46)
By gender								
Male	76	16 495	4.61	497	115 956	4.29	1.07	(0.84 to 1.37)
Female	26	7224	3.60	103	49 219	2.09	**1.72**	**(1.12 to 2.64)**
By age (years)								
16–39	3	7674	0.39	17	52 690	0.32	1.21	(0.36 to 4.13)
40–49	9	6367	1.41	74	43 523	1.70	0.83	(0.42 to 1.66)
50–59	27	4779	5.65	135	33 636	4.01	1.41	(0.93 to 2.13)
60–69	35	3081	11.36	180	21 435	8.40	1.35	(0.94 to 1.94)
70–79	20	1321	15.14	128	10 112	12.66	1.20	(0.75 to 1.92)
80+	8	495	16.16	66	3763	17.54	0.92	(0.44 to 1.92)
Acute myocardial infarction§	38	24 560	1.55	291	170 551	1.71	0.91	(0.65 to 1.27)
By gender								
Male	31	17 053	1.82	248	120 175	2.06	0.88	(0.61 to 1.28)
Female	7	7507	0.93	43	50 375	0.85	1.09	(0.49 to 2.43)
By age category (years)								
16–39	1	7683	0.13	9	52 823	0.17	0.76	(0.10 to 6.03)
40–49	4	6388	0.63	35	43 887	0.80	0.79	(0.28 to 2.21)
50–59	12	4921	2.44	59	34 680	1.70	1.43	(0.77 to 2.67)
60–69	9	3346	2.69	76	23 144	3.28	0.82	(0.41 to 1.63)
70–79	7	1594	4.39	68	11 601	5.86	0.75	(0.34 to 1.63)
80+	5	626	7.98	44	4399	10.00	0.80	(0.32 to 2.01)

Bold typeface indicates statistical significance (p<0.05).
*Number of patients or controls with an event/1.000 person-years.
†The incidence rate ratio is calculated as the incidence rate for patients divided by the incidence rate of controls.
‡Because patients with a history of ischaemic heart disease before or at the index date were excluded, the total number of patients with AS was 3640 and the total number of controls was 25 299.
§Because patients with a history of acute myocardial infarction before or at the index date were excluded, the total number of patients with AS was 3738 and the total number of controls was 25 843.

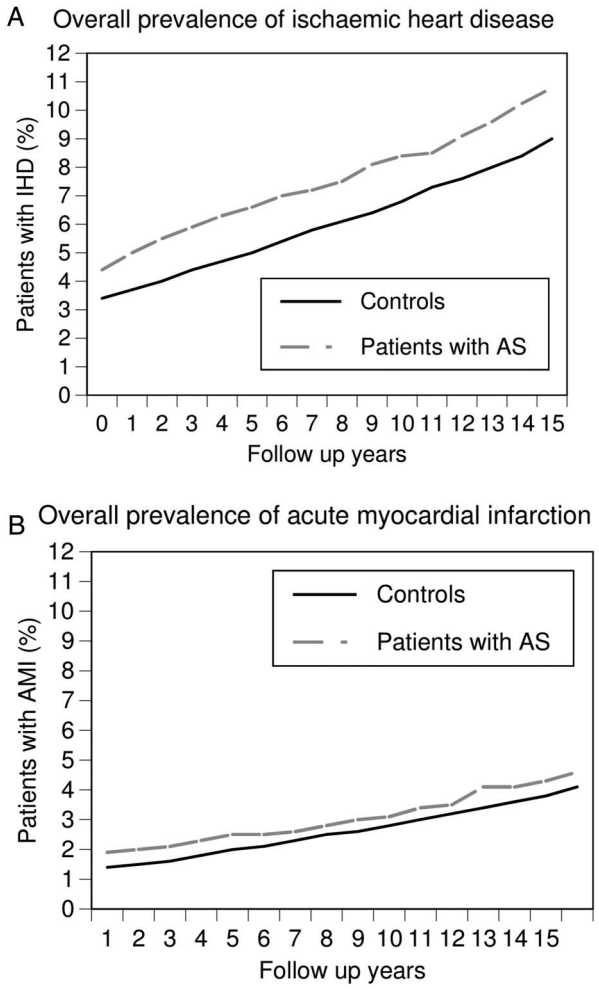

Figure 1 Visualisation of the overall prevalence over time, including baseline values, of IHD and AMI in patients with AS and controls. (A) IHD; (B) AMI. For the calculation of the overall prevalence over time, also the patients (controls) are included with an event at baseline. AMI, acute myocardial infarction; IHD, ischaemic heart disease; AS, ankylosing spondylitis.

attributable risk of AS for developing IHD was 0.7 per 1000 pys and for developing an AMI −0.2 per 1000 pys.

Risk of developing a first event of IHD or AMI

Table 3 shows that the risk of IHD or AMI was similar among patients with AS and controls. Female patients with AS had a 1.9-fold age-gender adjusted risk of IHD (HR 1.88, 95% CI 1.22 to 2.90), but it was no longer significantly increased after adjustment for the DDD of NSAIDs use (age-gender adjusted HR1.57, 95% CI 0.99 to 2.48). Additionally, table 4 shows that the risk of IHD in patients with AS was 1.4-fold increased with recent use of NSAIDs (fully adjusted HR 1.36, 95% CI 1.00 to 1.85), and 3.0-fold increased with recent use of COX-2 inhibitors (fully adjusted HR 3.03, 95% CI 1.61 to 5.69) compared with all controls irrespective of their NSAID use. Moreover, patients with AS using COX-2 inhibitors had an increased risk of IHD compared with patients who did not use this drug (data not shown).

DISCUSSION

The present study investigated the incidence and risk of IHD and AMI, including the role of NSAIDs, in patients with AS compared with population-based matched controls. While the incidence of IHD was not increased in male patients, a significant increase was found in female patients compared with controls. After adjustment for NSAIDs use, however, only a non-significant trend towards increased risk of IHD in female patients was found. Recent use of NSAIDs and, in particular COX-2 inhibitors, resulted in a 1.4-fold and 3.0-fold fully adjusted overall risk of IHD in patients with AS compared with controls. An increased risk of AMI could not be demonstrated, and no gender differences were found.

In the literature, an increased risk of IHD in patients with AS has been reported earlier. Claims data from the Canadian province, Quebec, showed increased IHD risks in 4836 male patients of all age categories (prevalence ratio ranging from 1.17 to 1.75) and in 3169 female patients younger than 60 years of age (prevalence ratio ranging from 1.54 to 1.97), but not in 701 female patients older than 60 years (prevalence ratio 1.08, 95%

Table 3 Risk of ischaemic heart disease and acute myocardial infarction in patients with AS compared with controls

Population	Number of events	Age-gender adj HR	95% CI	NSAID-adj HR[1]	95% CI	Fully adj HR[2]	95% CI
Ischaemic heart disease*							
Controls	600	Reference		Reference		Reference	
Patients with AS	102	1.20	(0.97 to 1.48)	1.04	(0.83 to 1.30)	1.00	(0.80 to 1.25)
Gender							
Female	26	**1.88**	**(1.22 to 2.90)**	1.57	(0.99 to 2.48)	1.31	(0.83 to 2.08)
Male	76	1.07	(0.84 **to** 1.37)	0.94	(0.72 to 1.21)	0.94	(0.73 to 1.21)
Acute myocardial infarction†							
Controls	291	Reference		Reference		Reference	
Patients with AS	38	0.91	(0.65 to 1.28)	0.80	(0.56 to 1.15)	0.76	(0.53 to 1.09)
Gender							
Female	7	1.16	(0.52 to 2.58)	0.97	(0.42 to 2.23)	0.85	(0.36 to 1.98)
Male	31	0.87	(0.60 to 1.27)	0.80	(0.54 to 1.19)	0.77	(0.52 to 1.15)

Bold typeface indicates statistical significance (p<0.05).
*Because patients with a history of ischaemic heart disease before the index date were excluded, the total number of patients with AS was 3640 and the total number of controls was 25 299.
†Because patients with a history of acute myocardial infarction before the index date were excluded, the total number of patients with AS was 3738, and the total number of controls was **25 843**.
The controls are used as reference group with an HR of 1.0.
1) Adjusted for: age, gender and the DDD of NSAID use.
2) Adjusted for: age, gender, DDD of NSAID use, as well as smoking status, BMI, and use of antihypertensives, antiplatelets, antidiabetics, statins in the past 6 months.
Adj, adjusted; AS, ankylosing spondylitis; BMI, body mass index; DDD, defined daily doses; NSAID, non-steroidal anti-inflammatory drugs.

Table 4 Risk of ischaemic heart disease stratified by NSAID exposure in patients with AS compared with controls

	Total				Men				Female			
Exposure to NSAIDs	**Number of subjects**	**Number of IHD events**	**Fully adj HR**	**95% CI**	**Number of subjects**	**Number of IHD events**	**Fully adj HR**	**95% CI**	**Number of subjects**	**Number of IHD events**	**Fully adj HR**	**95% CI**
Controls (n=25 299)			Reference				Reference				Reference	
No NSAIDs	902	541			856	455			7046	86		
Any NSAID	1391	59			923	42			474	17		
Naproxen	438	9			294	7			144	2		
COX-2 inhibitors	89	8			48	4			41	4		
Other NSAIDs 899		42			599	31			300	11		
AS (n=3640)												
Any NSAID*												
No	2407	59	1.01	(0.77 to 1.32)	1660	42	0.85	(0.62 to 1.16)	747	17	1.50	(0.89 to 2.53)
Yes	1233	43	**1.36**	**(1.00 to 1.85)**	893	34	1.35	(0.95 to 1.92)	340	9	1.68	(0.84 to 0.334)
Naproxen†												
No	3349	101	1.10	(0.88 to 1.37)	2347	75	1.02	(0.79 to 1.31)	1002	26	1.47	(0.94 to 2.32)
Yes	291	1	0.26	(0.04 to 1.84)	206	1	0.29	(0.04 to 2.05)	85	0	–	–
COX-2 inhibitors‡												
No	3353	92	1.10	(0.82 to 1.29)	2351	68	0.94	(0.72 to 1.22)	1002	24	1.45	(0.91 to 2.30)
Yes	287	10	**3.03**	**(1.61 to 5.69)**	202	8	**3.11**	**(1.54 to 6.29)**	85	2	**1.98**	**(1.34 to 2.92)**
Other NSAIDs§												
No	2948	70	0.98	(0.77 to 1.27)	2039	51	0.89	(0.66 to 1.19)	909	19	1.46	(0.88 to 2.41)
Yes	692	32	1.32	(0.93 to 1.89)	514	25	1.27	(0.85 to 1.90)	178	7	1.55	(0.71 to 3.37)

Bold typeface indicates statistical significance ($p<0.05$).
Patients with AS with or without recent NSAID use were compared with all controls, irrespective of the use of NSAIDs in the control group. The controls are the reference group with an HR of 1.0.
*HR adjusted for: age, gender, as well as smoking status, BMI and use of antihypertensives, antiplatelets, antidiabetics, statins in the past 6 months.
†HR adjusted for: age, gender, use of COX-II inhibitors and other traditional NSAIDs other than naproxen in the previous 3 months, as well as smoking status, BMI and use of antihypertensives, antiplatelets, antidiabetics, statins in the past 6 months.
‡HR adjusted for: age, gender, use naproxen and other traditional NSAIDs in the previous 3 months, as well as smoking status, BMI and use of antihypertensives, antiplatelets, antidiabetics, statins in the past 6 months.
§HR adjusted for: age, gender, use of naproxen and COX-II inhibitors in the previous 3 months, as well as smoking status, BMI and use of antihypertensives, antiplatelets, antidiabetics, statins in the past 6 months.
AS, ankylosing spondylitis; adj, adjusted; BMI, body mass index; COX-2 inhibitors, cyclo-oxygenase-2 inhibitor; IHD, ischaemic heart disease; NSAID, non-steroidal anti-inflammatory drugs.

CI 0.99 to 1.17) compared with a general population cohort.[9] Two other population-based studies, not stratified for gender, reported an increased risk of IHD in patients with AS after adjustment for age and gender (n=935, standardised morbidity ratio 2.20, 95% CI 1.27 to 2.70[7]), and after adjustment for hypertension and hyperlipidaemia only (n=4794, HR 1.47 95% CI 1.13 to 1.92).[16] Various explanations can be found for the differences between reported risks and our results. Although sample sizes were large and comparable, our study included only newly diagnosed patients with AS, whereas, other studies included both prevalent and incident patients. At baseline, we found a higher prevalence of IHD in patients with AS compared with controls, which is in line with a cross-sectional study, which also found a 1.5 higher relative risk (95% CI 1.0 to 1.5) of IHD in patients with AS compared with matched controls.[8] Furthermore, in contrast with other studies, we were able to statistically adjust for a wide range of confounders, including the use of NSAIDs. In this study, we demonstrated that use of NSAIDs explained a substantial proportion of the association between AS and risk of IHD. Our results are in line with the growing evidence that also COX-2 inhibitors may increase the risk of IHD.[6 22] In general, NSAIDs inhibit the activity of both COX-1 (thromboxane; thrombogenic and arthrogenic) and COX-2 activity (prostacyclin; opposes thromboxane). A COX-2 inhibitor-associated disruption of this balance might increase the risk of atherosclerosis, thrombogenesis and CV complications.[22]

A broad definition of IHD was used in this study and consisted of several of ischaemic heart conditions and symptoms, among which is angina pectoris. It is possible that misdiagnosis has occurred, because chest pain may also be caused by other conditions. Therefore, a more 'reliable' measure for IHD, that is, AMI, which was diagnosed on objective findings on electrocardiogram and blood abnormalities, was investigated. Earlier studies reported conflicting results with respect to the risk of AMI in AS. Two population-based studies with, respectively, 935 and 1686 patients with AS, failed to demonstrate an increased risk of developing AMI,[7 14] which is similar to our results. By contrast, a cross-sectional survey from The Netherlands among 383 patients with AS (age 50–75 years) under the care of a rheumatologist reported a 3.1-fold increased risk of AMI (95% CI 1.89 to 5.09) compared with patients selected from a general practitioner database.[12] The association in this cross-sectional survey is probably largely explained by information bias due to differential recording of exposure and outcome between both cohorts: the quality of AS recording has not been validated, and there is clear evidence that AMI is substantially under-recorded.[15]

Interestingly, we found a difference in the IHD risk between female and male patients, but we could not show this difference for the AMI risk. A possible explanation might be that female patients suffer more from enthesitis[23] and widespread ('fibromyalgia-like') pain[24] compared with male patients, which might be misdiagnosed as IHD.

Some limitations of the present study need to be addressed. First, an association between AS and IHD or AMI may have been masked by non-differential misclassification of exposure (AS, NSAID use) or outcome (IHD, AMI). Linkage of a different regional UK GP dataset with a rheumatology registry showed that 24% of the patients with an AS diagnoses were not captured by the GP.[14] We do not have information on this within CPRD. Additionally, a recent study showed a 25% under-recording rate of AMI in CPRD.[25] Furthermore, information on over-the-counter use of NSAIDs was lacking, which could have resulted in misclassification of NSAID exposure, however, it is difficult to quantify the degree of misclassification. The second limitation is our operational definition of 'incident' patients with AS. A proportion of the patients may have suffered from AS for a longer time, either because of a delay in diagnosis, or because the first diagnostic code for AS in CPRD did not correspond with the actual diagnostic date of AS. Third, the positive associations that we have reported may also be explained by diagnostic bias. Patients with AS may have visited their healthcare provider more regularly because of their disease, and as such, IHD and AMI may have been earlier or more frequently diagnosed compared with controls. Furthermore, as described above, chest pain is a feature of AS, and may therefore be misclassified as IHD, which can also explain the different findings with the lack of association between AS and AMI. Fourth, we did not have information on patient disease characteristics including HLA-B27 status, physical activity, disease activity and prescriptions of biologicals. Inflammation might accelerate the progress of atherosclerosis, and it is uncertain whether biologicals have a beneficial effect on subclinical atherosclerosis in AS.[26] Moreover, NSAID use might be a surrogate for disease activity, because patients with a higher disease activity are more likely to use NSAIDs.

The strengths of this study are the large sample size and substantial duration of follow-up. CPRD is representative for the total UK population. By contrast with most previous studies, we had a population-based comparison group which was randomly selected from CPRD. Additionally, we were the first study that could statistically adjust for a wide range of potential confounders, including smoking status, BMI, comorbidities and the use of comedications, including NSAIDs.

In conclusion, this study showed that female patients with AS seemed to be at an increased risk of developing IHD compared with female population-based controls in an age-adjusted analysis, but after adjustment for recent NSAID use there was only a trend towards increased risk. There was no increased risk of AMI in patients with AS compared with controls. Although it cannot be excluded that NSAID use is (partly) a reflection of disease activity, rheumatologists should carefully balance the beneficial effects of NSAIDs and the increased risk of IHD in patients with AS.

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