EXTENDED REPORT

Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden

Karin Bengtsson,[1] Helena Forsblad-d'Elia,[1,2] Elisabeth Lie,[1,3] Eva Klingberg,[1] Mats Dehlin,[1] Sofia Exarchou,[4] Ulf Lindström,[1] Johan Askling,[5] Lennart T H Jacobsson[1]

[1]Department of Rheumatology and Inflammation Research, Institute of Medicine, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden
[2]Department of Public Health and Clinical Medicine, Rheumatology, Umeå University, Umeå, Sweden
[3]Department of Rheumatology, Diakonhjemmet Hospital, Oslo, Norway
[4]Department of Clinical Sciences, Section of Rheumatology, Lund University, Malmö, Sweden
[5]Department of Medicine Solna, Clinical Epidemiology Unit and Rheumatology Unit, Karolinska Institutet, Stockholm, Sweden

Correspondence to
Dr Karin Bengtsson, Department of Rheumatology and Inflammation Research, Sahlgrenska Academy at University of Gothenburg, Gothenburg S-405 30, Sweden; karin.si.bengtsson@vgregion.se

Received 4 August 2017
Revised 30 October 2017
Accepted 21 November 2017
Published Online First
19 December 2017

ABSTRACT

Objectives To describe the incidence of atrioventricular (AV) block II–III, atrial fibrillation (AF), pacemaker implantation (PM) and aortic regurgitation in patients with ankylosing spondylitis (AS), undifferentiated spondyloarthritis (uSpA) and psoriatic arthritis (PsA) compared with the general population (GP) and with each other.

Methods A prospective nationwide study with cohorts of patients with AS (n=6448), PsA (n=16 063) and uSpA (n=5190) and a GP (n=2 66 435) cohort, identified in 2001–2009 in the Swedish National Patient and Population registers. Follow-up began on 1 January 2006 and ended at event, death, emigration or 31 December 2012. Age-standardised and sex-standardised incidence rates and hazard ratios (HRs) were calculated.

Results The highest incidence rates were noted for AF (5.5–7.4 events per 1000 person-years), followed by PM (1.0–2.0 events per 1000 person-years). HRs for AV block, AF, PM and aortic regurgitation were significantly increased in AS (HRs 2.3, 1.3, 2.1 and 1.9), uSpA (HRs 2.9, 1.3, 1.9 and 2.0) and PsA (HRs 1.5, 1.5, 1.6 and 1.8) compared with the GP cohort. The highest HRs were seen for AV block in male uSpA (HR 4.2) and AS (HR 2.5) compared with GP. Compared with PsA, significantly increased HRs were noted for PM (HR 1.5) in AS and for AV block (HR 1.8) in uSpA.

Conclusions Patients with SpA are at increased risk of aortic regurgitation, cardiac rhythm disturbances and, as a probable consequence, also PM. Particularly for AF, the most common arrhythmia, increased caution is warranted, whereas AV block should be looked for especially in men with AS or uSpA.

INTRODUCTION

Ankylosing spondylitis (AS) may increase the risk of cardiac manifestations, such as conduction disturbances and aortic regurgitation.[1 2] Most of the existing studies regarding these cardiac manifestations in patients with AS are small scaled, some lack controls from the general population (GP) and the results have been inconsistent.[3–10] In more recent studies of AS, the reported prevalence of (often subclinical) aortic regurgitation and conduction disturbances have been in the range of 10%–18% and 5%–33%, respectively.[5–8]

AS belongs to the spondyloarthritis (SpA), which is a cluster of rheumatic diseases with a spectrum of similar clinical features and a varying degree of association with HLA-B27.[11 12] In this cluster of diseases, reactive arthritis has been associated with similar cardiac manifestations as AS.[13–15] HLA-B27 has in itself been linked to conduction disturbances and aortic regurgitation, even in the absence of rheumatic disease.[16 17] Therefore, other SpA subtypes, such as psoriatic arthritis (PsA) and undifferentiated SpA (uSpA), may presumably also have an increased risk of such cardiac manifestations. Furthermore, the risk of atrial fibrillation (AF), a commonly occurring arrhythmia in the GP, has hardly been studied in patients with SpA irrespective of subtype.[18]

The main aim of this study was therefore to investigate the incidence and risk of cardiac rhythm disturbances (atrioventricular (AV) block II–III, AF) and aortic regurgitation in patients with AS, PsA and uSpA compared with the GP and with each other. We also aimed to investigate the incidence and risk of pacemaker implantation (PM) as a possible consequence of severe arrhythmia.

METHOD

Study design and register sources

This is a prospective nationwide population-based cohort study, including three separate cohorts of patients with AS, PsA and uSpA identified from the Swedish National Patient Register (NPR) and one GP cohort identified from the Swedish Population Register. Through the unique personal identification number of each Swedish resident, the subjects were linked to NPR, the Population Register, Swedish Rheumatology Quality Register (SRQ), the Swedish Prescribed Drug Register (PDR) and the Swedish Register of Education to identify outcomes as well as sociodemographic data, comorbidities and pharmacological treatment in order to characterise the populations.

NPR was established in 1964 and contains data of inpatient care (with full national coverage from 1987) and from 2001 also non-primary outpatient care. Primary and secondary diagnoses reported by the physician are recorded at each visit according to the International Classification of Diseases (ICD). The register also includes surgical procedure codes.

The Population Register holds information of residency, immigration, emigration and deaths for all the Swedish residents.

541

Table 1 Baseline characteristics of patients with AS, uSpA, PsA and GP comparators at start of follow-up

	AS (n=6448)	uSpA (n=5190)	PsA (n=16 063)	GP (n=266 435)
Sex				
Male	4390 (68.1)	2325 (44.8)	7217 (44.9)	131 807 (49.5)
Female	2058 (31.9)	2865 (55.2)	8846 (55.1)	134 628 (50.5)
Age (years)				
Mean (SD); men	50.3 (13.9)	44.2 (13.4)	52.6 (13.4)	53.5 (15.7)
Mean (SD); women	49.5 (13.8)	45.1 (13.1)	53.7 (14.1)	53.4 (16.0)
18–29 years	488 (7.6)	691 (13.3)	761 (4.7)	18 465 (6.9)
30–39 years	1120 (17.4)	1255 (24.2)	2047 (12.7)	36 805 (13.8)
40–49 years	1452 (22.5)	1406 (27.1)	3368 (21.0)	52 122 (19.6)
50–59 years	1670 (25.9)	1085 (20.9)	4385 (27.3)	63 559 (23.9)
60–69 years	1209 (18.8)	583 (11.2)	3638 (22.6)	52 626 (19.8)
70–79 years	414 (6.4)	132 (2.5)	1422 (8.9)	27 259 (10.2)
≥80 years	95 (1.5)	38 (0.7)	442 (2.8)	15 599 (5.9)
Start of follow-up				
2006–2007	4938 (76.6)	3725 (71.8)	11 926 (74.2)	266 234 (99.9)
2008–2010	1510 (23.4)	1465 (28.2)	4137 (25.8)	201 (0.1)
Level of education				
≤9 years	1423 (22.1)	804 (15.5)	4039 (25.1)	68 776 (25.8)
10–12 years	3096 (48.0)	2566 (49.4)	7983 (49.7)	119 681 (44.9)
>12 years	1858 (28.8)	1789 (34.5)	3931 (24.5)	74 587 (28.0)
Missing	71 (1.1)	31 (0.6)	110 (0.7)	3391 (1.3)
SpA-related comorbidities*				
Anterior uveitis	1342 (20.8)	771 (14.9)	252 (1.6)	1156 (0.4)
Inflammatory bowel disease	514 (8.0)	269 (5.2)	346 (2.2)	2565 (1.0)
Psoriasis	145 (2.2)	162 (3.1)	15 873 (98.8)	2190 (0.8)
SpA-related current medications†				
Any DMARD	1599 (24.8)	1579 (30.4)	6659 (41.5)	2542 (1.0)
TNF inhibitors	545 (8.5)	279 (5.4)	758 (4.7)	268 (0.1)
Methotrexate	494 (7.7)	609 (11.7)	5094 (31.7)	1104 (0.4)
Sulfasalazin	798 (12.4)	877 (16.9)	1396 (8.7)	493 (0.2)
NSAIDs	3543 (54.9)	2804 (54.0)	7801 (48.6)	28 467 (10.7)
Prednisone	659 (10.2)	778 (15.0)	2133 (13.3)	4234 (1.6)
Other comorbidities*				
Ischaemic heart disease	468 (7.3)	182 (3.5)	1091 (6.8)	14 849 (5.6)
Heart failure	203 (3.1)	53 (1.0)	386 (2.4)	5225 (2.0)
Cerebrovascular disease	160 (2.5)	79 (1.5)	454 (2.8)	7763 (2.9)
AV block II–III	56 (0.9)	22 (0.4)	48 (0.3)	710 (0.3)
AF	264 (4.1)	87 (1.7)	513 (3.2)	7430 (2.8)
PM	66 (1.0)	28 (0.5)	73 (0.5)	1221 (0.5)
Aortic regurgitation	73 (1.1)	20 (0.4)	62 (0.4)	676 (0.3)
Aortic valve surgery	41 (0.6)	9 (0.2)	41 (0.3)	573 (0.2)
Dispensed prescriptions†				
Oral antidiabetics or insulin	274 (4.2)	123 (2.4)	1077 (6.7)	11 372 (4.3)
Antihypertensive	1794 (27.8)	846 (16.3)	4853 (30.2)	59 053 (22.2)
Statins	657 (10.2)	307 (5.9)	1871 (11.6)	23 180 (8.7)
Aspirin	557 (8.6)	230 (4.4)	1519 (9.5)	23 655 (8.9)
Warfarin	174 (2.7)	52 (1.0)	277 (1.7)	4328 (1.6)

Age is given in mean (SD). All other data are presented in number (%). Parts of the baseline characteristics in Table 1 have previously been published.[31]

*Prevalent comorbidity at baseline, defined by identification of specified International Classification of Diseases codes or surgical procedure codes in the National Patient Register prior to start of follow-up.

†Dispensed prescription in Prescribed Drug Register or intravenous biologic DMARD in Swedish Rheumatology Quality register within 6 months prior to start of follow-up.

AF, atrial fibrillation/flutter; AS, ankylosing spondylitis; AV, atrioventricular; DMARD, disease-modifying antirheumatic drug; GP, general population; NSAID, non-steroidal anti-inflammatory drug; PsA, psoriatic arthritis; PM, pacemaker implantation; TNF, tumour necrosis factor; uSpA, undifferentiated spondyloarthritis.

PDR started in July 2005 and contains information regarding all dispensed prescriptions of pharmacological treatment, registered according to the Anatomical Therapeutic Chemical Classification (ATC) system.

SRQ started in 1995 and includes information on treatment with biological disease-modifying antirheumatic drugs (bDMARDs), with an estimated national coverage of 85% for patients with SpA treated with bDMARDs.[19]
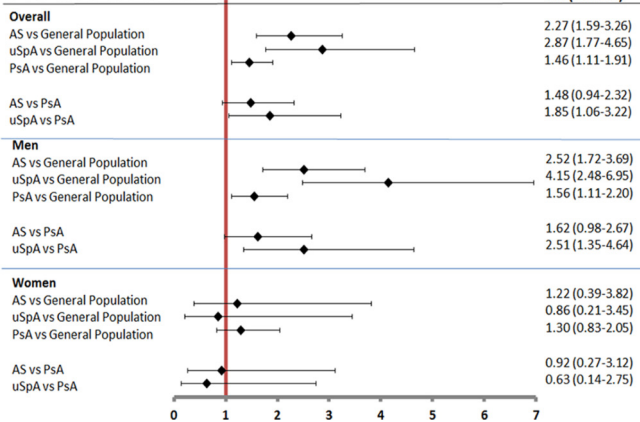
AV block II-III

Figure 1 Age-adjusted and sex-adjusted HRs for AV block II–III, overall and stratified by sex, in patients with AS, uSpA and PsA using general population comparators and patients with PsA as reference. AS, ankylosing spondylitis; AV, atrioventricular; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthritis.

Informed consent was not needed due to the register-based study design.

Study population

This study is part of a large-scale nationwide register linkage project, which identified all patients with a registered diagnosis of AS, PsA or uSpA, given at a visit to a physician, in NPR 1968 through 2009. From the Population Register, up to five controls per patient were identified, matched on birth year, sex and place of residence at the date when the index patient received his/her first SpA diagnosis in NPR.

AS, uSpA and PsA cohorts

From these larger groups of patients with SpA, we selected all patients with at least one physician visit with an AS, PsA or uSpA diagnosis in rheumatology or internal medicine outpatient care between 2001 and 2009, at the ages 18–99 years, alive and living in Sweden at start of follow-up. These patients were included in the AS (n=6448), PsA (n=16 063) or uSpA (n=5190) cohorts. Patients who also had received an ICD code indicating rheumatoid arthritis or systemic lupus erythematosus were excluded.
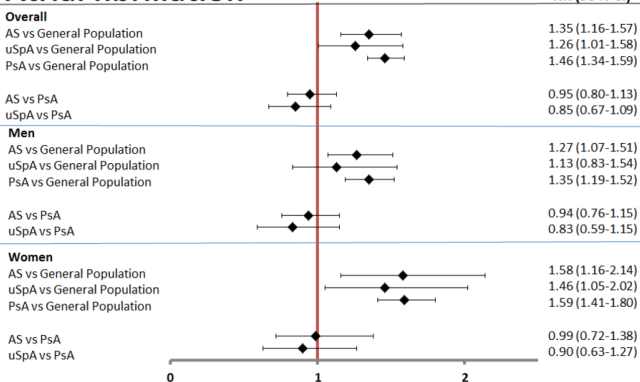
Atrial fibrillation

Figure 2 Age-adjusted and sex-adjusted HRs for atrial fibrillation, overall and stratified by sex, in patients with AS, uSpA and PsA using general population comparators and patients with PsA as reference. AS, ankylosing spondylitis; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthritis.

The ICD codes (online supplementary table S1) used to identify eligible patients have previously been validated. In patients with AS and available data of imaging and/or HLA-B27 status, the positive predicted values (PPVs) for fulfilling the modified New York criteria and any set of SpA criteria were 80% and 97%, respectively.[20] The corresponding PPVs in uSpA were 26% and 89%, respectively.[20] The PPVs of an ICD code for PsA within primary or specialised care was within the range of 63%–92%, where the highest proportion of confirmed PsA was noted if the PsA was diagnosed in specialised care (as the patients with PsA in the present study) and at least on two occasions.[21]

Patients diagnosed with ≥2 subtypes of SpA

Patients with ICD codes for more than one subtype of SpA diagnosis before start of follow-up were not included in the AS, PsA or uSpA cohorts but analysed separately to avoid case mixing (n=1082).

GP cohort

All initially identified GP controls from the first register extraction, at the ages 18–99 years, alive and living in Sweden at start of follow-up, were included in the GP cohort (n=266 435) and analysed as unmatched GP comparators. GP comparators were excluded from the GP cohort if they had been diagnosed with AS, uSpA or PsA before start of follow-up (n=340).

Definition of outcome

The primary outcomes were incident AV block II–III, AF, PM and aortic regurgitation. Each outcome was analysed separately. The outcomes were identified in NPR and defined as follows:

1. First occurrence of AV block II–III reported as a primary or secondary diagnosis from either inpatient or outpatient care.
2. First occurrence of AF reported as a primary or secondary diagnosis from either inpatient or outpatient care.
3. First occurrence of PM reported as a surgical procedure code in either inpatient or outpatient care.
4. First occurrence of isolated aortic regurgitation reported as a primary or secondary diagnosis in either inpatient or outpatient care. Aortic regurgitation in combination with stenosis was not included.

The ICD codes used to identify the outcomes are described in online supplementary table S1. Importantly, subjects with a history of the outcome of interest prior to start of follow-up were excluded from that specific analysis.

Follow-up

The follow-up started on 1 January 2006 for subjects receiving their first AS, uSpA or PsA diagnosis in rheumatology or internal medicine outpatient care prior to 30 June 2005 and 6 months after the date of first diagnosis for those with a first registered diagnosis after 30 June 2005. This was done to make the rates comparable in SpA contra GP, by reducing the risk for detection bias in the SpA cohorts as a result of increased surveillance in connection with receiving an SpA diagnosis. For GP subjects, the follow-up began on 1 January 2006 or the date of immigration if this occurred later than 1 January 2006.

All subjects were followed until first occurrence of outcome, emigration, death or 31 December 2012, whichever occurred first. Subjects were censored in the GP cohort if diagnosed with an SpA diagnosis and subsequently eligible to enter the corresponding SpA cohort. Patients were censored from their original SpA cohort if diagnosed with a different SpA subtype

Table 2 Incidence rates of atrioventricular block, atrial fibrillation, pacemaker implantation and aortic regurgitation in patients with AS, uSpA, PsA and in GP comparators

	AS	uSpA	PsA	GP
Atrioventricular block II–III				
Subjects at risk, n	6392	5168	16 015	265 725
Incident events, n (male/female)	31 (28/3)	17 (15/2)	55 (35/20)	936 (616/320)
Person-years at risk, n	35 995	27 771	91 664	1 771 585
Overall incidence rates				
Crude rates	0.9 (0.6 to 1.2)	0.6 (0.3 to 0.9)	0.6 (0.4 to 0.8)	0.5 (0.5 to 0.6)
Standardised rates*	0.9 (0.6 to 1.3)	1.2 (0.5 to 1.9)	0.7 (0.5 to 0.9)	
Male incidence rates				
Crude rates	1.1 (0.7 to 1.6)	1.2 (0.6 to 1.9)	0.9 (0.6 to 1.1)	0.7 (0.7 to 0.8)
Standardised rates†	1.6 (0.9 to 2.2)	1.8 (0.8 to 2.8)	1.0 (0.6 to 1.3)	
Female incidence rates				
Crude rates	0.3 (0 to 0.6)	0.1 (0 to 0.3)	0.4 (0.2 to 0.6)	0.4 (0.3 to 0.4)
Standardised rates†	0.4 (0 to 0.8)	0.6 (0 to 1.6)	0.4 (0.2 to 0.6)	
Atrial fibrillation				
Subjects at risk, n	6184	5103	15 550	259 005
Incident events, n (male/female)	174 (132/42)	77 (40/37)	560 (281/279)	9484 (5638/3846)
Person-years at risk, n	34 592	27 299	87 967	1 711 828
Overall incidence rates				
Crude rates	5.0 (4.3 to 5.8)	2.8 (2.2 to 3.5)	6.4 (5.8 to 6.9)	5.5 (5.4 to 5.7)
Standardised rates*	7.1 (5.6 to 8.6)	6.4 (4.6 to 8.3)	7.4 (6.7 to 8.0)	
Male incidence rates				
Crude rates	5.6 (4.7 to 6.6)	3.4 (2.3 to 4.4)	7.2 (6.4 to 8.1)	6.8 (6.6 to 7.0)
Standardised rates†	7.2 (5.8 to 8.5)	7.1 (4.3 to 9.9)	8.5 (7.4 to 9.5)	
Female incidence rates				
Crude rates	3.8 (2.6 to 4.9)	2.4 (1.6 to 3.2)	5.7 (5.0 to 6.4)	4.4 (4.2 to 4.5)
Standardised rates†	7.1 (4.5 to 9.7)	5.8 (3.2 to 8.4)	6.3 (5.5 to 7.1)	
Pacemaker implantation				
Subjects at risk, n	6382	5162	15 990	265 214
Incident events, n (male/female)	53 (39/14)	21 (18/3)	113 (58/55)	1776 (1109/667)
Person-years at risk, n	35 887	27 732	91 364	1 766 293
Overall incidence rates				
Crude rates	1.5 (1.1 to 1.9)	0.8 (0.4 to 1.1)	1.2 (1.0 to 1.5)	1.0 (1.0 to 1.1)
Standardised rates*	2.0 (1.3 to 2.7)	1.5 (0.7 to 2.2)	1.5 (1.2 to 1.8)	
Male incidence rates				
Crude rates	1.6 (1.1 to 2.1)	1.5 (0.8 to 2.2)	1.4 (1.1 to 1.8)	1.3 (1.2 to 1.4)
Standardised rates†	2.1 (1.4 to 2.9)	2.6 (1.1 to 4.1)	1.7 (1.3 to 2.2)	
Female incidence rates				
Crude rates	1.2 (0.6 to 1.9)	0.2 (0.0 to 0.4)	1.1 (0.8 to 1.4)	0.7 (0.7 to 0.8)
Standardised rates†	1.9 (0.7 to 3.1)	0.4 (0 to 0.8)	1.3 (0.9 to 1.6)	
Aortic regurgitation				
Subjects at risk, n	6375	5170	16 001	265 759
Incident events, n (male/female)	24 (20/4)	13 (7/6)	62 (28/34)	744 (453/291)
Person-years at risk, n	35 927	27 787	91 531	1 771 918
Overall incidence rates				
Crude rates	0.7 (0.4 to 0.9)	0.5 (0.2 to 0.7)	0.7 (0.5 to 0.8)	0.4 (0.4 to 0.5)
Standardised rates*	0.7 (0.4 to 1.1)	0.7 (0.3 to 1.1)	0.7 (0.5 to 0.9)	
Male incidence rates				
Crude rates	0.8 (0.5 to 1.2)	0.6 (0.1 to 1.0)	0.7 (0.4 to 0.9)	0.5 (0.5 to 0.6)
Standardised rates†	1.0 (0.6 to 1.5)	0.9 (0.2 to 1.7)	0.7 (0.5 to 1.0)	
Female incidence rates				
Crude rates	0.3 (0.0 to 0.7)	0.4 (0.1 to 0.7)	0.7 (0.4 to 0.9)	0.3 (0.3 to 0.4)
Standardised rates†	0.5 (0.0 to 0.9)	0.5 (0.0 to 0.9)	0.7 (0.5 to 1.0)	

Rates are presented as number of events per 1000 person-years at risk. All rates are calculated with 95% CI given in parentheses.

*Age-adjusted and sex-adjusted with the GP cohort as reference.

†Age-adjusted with the GP cohort as reference.

AS, ankylosing spondylitis; GP, general population; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthritis.
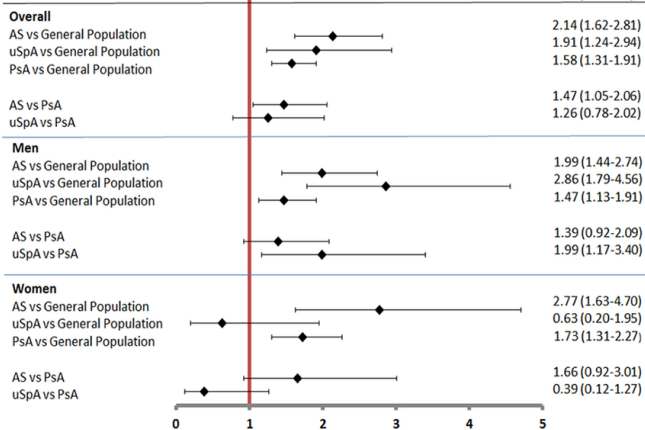
Figure 3 Age-adjusted and sex-adjusted HRs for pacemaker implantation, overall and stratified by sex, in patients with AS, uSpA and PsA using general population comparators and patients with PsA as reference. AS, ankylosing spondylitis; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthritis.

during follow-up and subsequently eligible to enter the SpA cohort with ≥2 subtypes of SpA (described above).

Baseline characteristics

Cardiovascular and SpA-related comorbidities were regarded as prevalent at baseline if the specified ICD codes and surgical procedure codes (online supplementary table S1) were identified in NPR before start of follow-up. Pharmacological treatment at baseline was defined as a dispensed prescription within 6 months before start of follow-up according to specified ATC codes in PDR (online supplementary table S1). Current treatment with the intravenous tumour necrosis factor-inhibitor infliximab was retrieved from SRQ. From the Register of Education, we retrieved level of education as a measure of socioeconomic status.

Statistical analyses

Descriptive statistics are presented as number (percentage) or mean±SD. For each outcome, incidence rates, overall and stratified by sex, were calculated from the number of
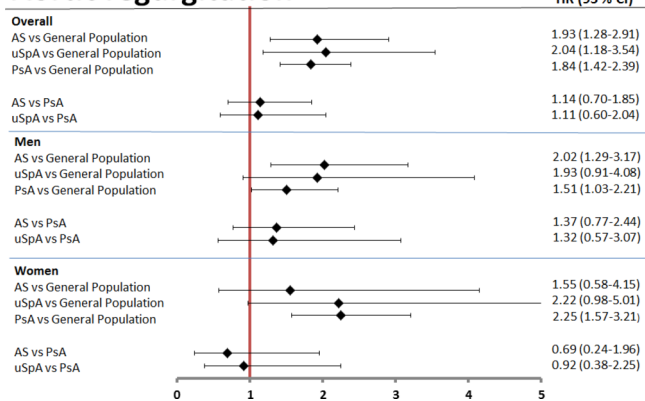

Figure 4 Age-adjusted and sex-adjusted HRs for aortic regurgitation, overall and stratified by sex, in patients with AS, uSpA and PsA using general population comparators and patients with PsA as reference. AS, ankylosing spondylitis; PsA, psoriatic arthritis; uSpA, undifferentiated spondyloarthritis.

incident events and person-years at risk. To enable comparison between the cohorts, standardised incidence rates were calculated, using the age and sex distribution in the GP cohort as standard. For incidence rates, we assumed a Poisson distribution when estimating 95% CI. For the risk assessment, age-adjusted and sex-adjusted HRs were calculated using Cox proportional hazard regression analyses, with the GP cohort and the largest SpA cohort—the PsA cohort—as the reference populations. The proportional hazards assumption for the Cox regression analyses was evaluated graphically and considered fulfilled in all analyses. Further adjusted HRs, with additional selected covariates from baseline characteristics, were calculated (online supplementary data). We also calculated age-standardised and sex-standardised prevalence and corresponding prevalence ratio (PR) at baseline for prior AV block, AF, PM and aortic regurgitation in the SpA cohorts, using the age and sex distribution in the GP cohort as standard/reference. Statistical analyses were performed by PASW Statistics V.19 and SAS V.9.3.

RESULTS
Study population

Cohorts of patients with AS (n=6448), PsA (n=16 063) and uSpA (n=5190) and one with GP comparators (n=2 66 435) were identified. Baseline characteristics are presented in table 1. All SpA cohorts had a significantly increased age-standardised and sex-standardised PR for prior AV block, AF, PM and aortic regurgitation compared with the GP cohort (online supplementary table S2).

AV block II–III

During follow-up, 31, 17 and 55 AV block events occurred in the AS, uSpA and PsA cohorts, respectively, resulting in standardised incidence rates of 0.9, 1.2 and 0.7 AV block events per 1000 person-years at risk compared with 0.5 in the GP cohort (table 2). The age-adjusted and sex-adjusted HRs (95% CI) were significantly increased in AS (2.3 (1.6 to 3.3)), uSpA (2.9 (1.8 to 4.7)) and PsA (1.5 (1.1 to 1.9)) compared with the GP cohort. In the sex-stratified analyses, the highest age-adjusted HR point estimates were noted for male uSpA (4.2 (2.5 to 7.0)) and AS (2.5 (1.7 to 3.7)) compared with the male GP cohort. When compared with PsA, significantly increased HRs were noted for uSpA patients overall and for male uSpA in the sex-stratified analyses. No statistically increased HRs for AV block were noted for any of the groups of female patients with SpA neither compared with female GP comparators nor compared with female patients with PsA. (figure 1)

Atrial fibrillation

Based on 174, 77 and 560 AF events in the AS, uSpA and PsA cohorts, respectively, the standardised incidence rates were 7.1, 6.4 and 7.4 AF events per 1000 person-years at risk compared with 5.5 in the GP cohort (table 2). The age-adjusted and sex-adjusted HRs were significantly increased in AS (1.3 (1.2 to 1.6)), uSpA (1.3 (1.0 to 1.6)) and PsA (1.5 (1.3 to 1.6)) compared with the GP cohort. There were no significant differences between AS and uSpA compared with the PsA cohort. (figure 2)

Pacemaker implantation

During follow-up, 53, 21 and 113 PM events occurred in the AS, uSpA and PsA cohorts, respectively, resulting in standardised incidence rates of 2.0, 1.5 and 1.5 PM events per

1000 person-years at risk compared with 1.0 in the GP cohort (table 2). The age-adjusted and sex-adjusted HRs were significantly increased in AS (2.1 (1.6 to 2.8)), uSpA (1.9 (1.2 to 2.9)) and PsA (1.6 (1.3 to 1.9)). In the sex-stratified analyses, the highest age-adjusted HR point estimate was noted for male patients with uSpA (2.9 (1.8 to 4.6)). A significantly increased age-adjusted and sex-adjusted HR was noted in AS (1.5 (1.0 to 2.1)) compared with PsA (figure 3).

As a sensitivity analysis, subjects with prior AF/AV block at baseline were excluded from the PM analysis, resulting in only slightly attenuated HRs (data not shown).

Aortic regurgitation
Based on 24, 13 and 62 aortic regurgitation events in the AS, uSpA and PsA cohorts, respectively, the standardised incidence rates were 0.7, 0.7 and 0.7 events per 1000 person-years at risk compared with 0.4 in the GP cohort (table 2). The age-adjusted and sex-adjusted HRs were significantly increased in AS (1.9 (1.3 to 2.9)), uSpA (2.0 (1.2 to 3.5)) and PsA (1.8 (1.4 to 2.4)) compared with the GP cohort. (figure 4)

Supplementary data
Subjects (n=1931) excluded prior to study entry or censored during follow-up based on ICD codes for two or more different SpA subtypes were analysed separately (online supplementary tables S3 and S4). The majority (n=1169) had an overlap of AS and uSpA diagnoses. Incidence rates and HRs for the outcomes did not diverge substantially from the main results.

Characteristics of the subjects with AV block/AF/PM/aortic regurgitation and co-occurrence during follow-up are available in online supplementary tables S5–S8. For PM, the majority had an AV block or/and AF at baseline or during follow-up.

Overall HRs, adjusting for multiple confounders in addition to age/sex, resulted in slightly lower point estimates compared with the age/sex-adjusted main analyses (online supplementary table S9).

DISCUSSION
In this nationwide prospective population-based cohort study, we found an increased risk of aortic regurgitation, AV block, AF and accordingly an increased risk of PM in all three studied SpA subtypes compared with GP. Patients with AS and uSpA had a twofold increased risk for PM compared with GP, and AS also had a significantly increased risk compared with PsA.

These results confirm the previously known association between AS and conduction disturbances and aortic regurgitation, likewise the presumed association with the other SpA subtypes, especially uSpA and to a lesser extent PsA. In similarity to our result, Szabo et al found an increased standardised PR (1.6 (1.3 to 1.9)) for aortic valvular heart disease in patients with AS compared with GP.[22] Very limited data are available regarding PsA. One previous study identified subtle involvement of the AV node, measured by prolonged PR interval, in patients with PsA compared with controls.[23]

In the sex-stratified analyses, the risk of AV block was elevated in male but not female patients compared with GP and especially elevated in male patients with AS or uSpA. Our findings could be seen in the context of other recognised sex differences in AS, such as more radiographic alterations in male contra female patients.[24 25] In a study of extra-articular manifestations in patients with AS compared with controls, men with AS had higher risk estimates than the women, especially for uveitis.[26] In addition, Bergfeldt and Möller have

previously demonstrated a sex difference in pacemaker-treated AV block, where male but not female patients had a significantly increased frequency of HLA-B27.[27] Male sex is a risk factor for AV block in the GP, resulting in low numbers of AV block in the female cohorts, which may have hampered the statistical power.[28]

The increased risk of AF may partly explain the increased risk of stroke shown in patients with SpA.[22 29–31] AF is therefore an important risk factor to identify and treat in these patients, and intervention could possibly reduce the occurrence of stroke.[32] In patients with psoriasis, three previous studies have found an increased risk of AF with risk levels that are in agreement with our result, although results are not entirely consistent.[33–36]

According to a previous Swedish study, the most common aetiology for PM in the GP was conduction system fibrosis, followed by ischaemic heart disease. Electrocardiographical indications for PM were related to AV conduction disorders and AF in 38% and 15%, respectively.[37] Another study demonstrated that first-degree AV block was associated with a threefold increased risk of future PM and also with an increased risk of AF.[38] Based on these results, the increased risk of PM in SpA is likely to be attributable largely to the increased incidence of AV block and AF. This is in accordance with our own results, which show a considerable co-occurrence between PM and AV block/AF (online supplementary table S7).

In the present study, the low incidence rates and absolute risk differences between groups, especially for AV block and aortic regurgitation, may suggest limited clinical importance. On the other hand, the method used for detecting these outcomes in the present study by registered diagnoses is likely, except for PM, to underestimate the true occurrence. The increased HRs demonstrated for all the studied cardiac outcomes in the different SpA subtypes highlight the need of awareness in case of symptoms, both obvious and vague, that may be related to these cardiac manifestations.

Some limitations of the study need to be acknowledged. First, we cannot exclude misclassifications of the SpA diagnoses or the outcomes. However, the ICD codes used for identification of AS, PsA and uSpA as well as AF are validated before with high validity/PPVs.[20 21 39] Second, patients with SpA who were solely followed in primary care, and presumably have less severe disease, were not included, and this may have influenced the generalisability of our results. In Sweden, patients with SpA without DMARDs may be monitored in primary care but are predominantly diagnosed in rheumatology or internal medicine outpatient care and would thus have been identified in our study. Furthermore, outcomes diagnosed only in primary care are not identified. Third, we cannot exclude the possibility for a detection bias based on more thorough search for AV block and aortic regurgitation in patients with SpA. Fourth, due to the register-based design, we lack detailed information on an individual level (smoking habits, body mass index, SpA activity measurements, etc). We have deliberately avoided adjustments in the main analyses for other factors than age/sex, and the aim was to assess rather than try to explain what causes the increased risks of the studied outcomes. Finally, the association between conduction disturbances and the different SpA types should preferably been related to HLA-B27 status, which unfortunately was not available.

The present study also have several strengths. First, it is the first study to our knowledge that compares the risk of cardiac rhythm disturbances and aortic regurgitation in different

subtypes of SpA in the same setting simultaneously. Second, the large study population made it possible to study also rare events. Third, it is a population-based study of healthcare registers, minimising problems with selection bias and with negligible loss of follow-up.

To conclude, patients with SpA are at increased risk of aortic regurgitation, cardiac rhythm disturbances and, as a probable consequence, also PM. Particularly for AF, the most common arrhythmia, increased caution is warranted, whereas AV block should be looked for especially in men with AS or uSpA.

REFERENCES

1. Palazzi C, Salvarani C, D'Angelo S, *et al*. Aortitis and periaortitis in ankylosing spondylitis. *Joint Bone Spine* 2011;78:451–5.
2. Nurmohamed MT, van der Horst-Bruinsma I, Maksymowych WP. Cardiovascular and cerebrovascular diseases in ankylosing spondylitis: current insights. *Curr Rheumatol Rep* 2012;14:415–21.
3. Bergfeldt L, Edhag O, Vallin H. Cardiac conduction disturbances, an underestimated manifestation in ankylosing spondylitis. A 25-year follow-up study of 68 patients. *Acta Med Scand* 1982;212:217–23.
4. O'Neill TW, King G, Graham IM, *et al*. Echocardiographic abnormalities in ankylosing spondylitis. *Ann Rheum Dis* 1992;51:652–4.
5. Brunner F, Kunz A, Weber U, *et al*. Ankylosing spondylitis and heart abnormalities: do cardiac conduction disorders, valve regurgitation and diastolic dysfunction occur more often in male patients with diagnosed ankylosing spondylitis for over 15 years than in the normal population? *Clin Rheumatol* 2006;25:24–9.
6. Forsblad-d'Elia H, Wallberg H, Klingberg E, *et al*. Cardiac conduction system abnormalities in ankylosing spondylitis: a cross-sectional study. *BMC Musculoskelet Disord* 2013;14:237.
7. Klingberg E, Sveälv BG, Täng MS, *et al*. Aortic regurgitation is common in ankylosing spondylitis: time for routine echocardiography evaluation? *Am J Med* 2015;128:1244–50.
8. Dik VK, Peters MJ, Dijkmans PA, *et al*. The relationship between disease-related characteristics and conduction disturbances in ankylosing spondylitis. *Scand J Rheumatol* 2010;39:38–41.
9. Roldan CA, Chavez J, Wiest PW, *et al*. Aortic root disease and valve disease associated with ankylosing spondylitis. *J Am Coll Cardiol* 1998;32:1397–404.
10. Thomsen NH, Hørslev-Petersen K, Beyer JM. Ambulatory 24-hour continuous electrocardiographic monitoring in 54 patients with ankylosing spondylitis. *Eur Heart J* 1986;7:240–6.
11. Khan MA. Update on spondyloarthropathies. *Ann Intern Med* 2002;136:896–907.
12. Sieper J, Rudwaleit M, Khan MA, *et al*. Concepts and epidemiology of spondyloarthritis. *Best Pract Res Clin Rheumatol* 2006;20:401–17.
13. Qaiyumi S, Hassan ZU, Toone E. Seronegative spondyloarthropathies in lone aortic insufficiency. *Arch Intern Med* 1985;145:822–4.
14. Rossen RM, Goodman DJ, Harrison DC. A-V conduction disturbances in reiter's syndrome. *Am J Med* 1975;58:280–4.
15. Haverman JF, Van Albada-Kuipers GA, Dohmen HJ, *et al*. Atrioventricular conduction disturbance as an early feature of reiter's syndrome. *Ann Rheum Dis* 1988;47:1017–20.
16. Bergfeldt L. HLA-B27-associated cardiac disease. *Ann Intern Med* 1997;127:621–9.
17. Peeters AJ, ten Wolde S, Sedney MI, *et al*. Heart conduction disturbance: an HLA-B27 associated disease. *Ann Rheum Dis* 1991;50:348–50.
18. Lloyd-Jones DM, Wang TJ, Leip EP, *et al*. Lifetime risk for development of atrial fibrillation: the framingham heart study. *Circulation* 2004;110:1042–6.
19. Wadström H, Eriksson JK, Neovius M, *et al*. How good is the coverage and how accurate are exposure data in the Swedish biologics register (ARTIS)? *Scand J Rheumatol* 2015;44:22–8.
20. Lindström U, Exarchou S, Sigurdardottir V, *et al*. Validity of ankylosing spondylitis and undifferentiated spondyloarthritis diagnoses in the Swedish national patient register. *Scand J Rheumatol* 2015;44:369–76.
21. Löfvendahl S, Theander E, Svensson Å, *et al*. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in southern Sweden--a population-based register study. *PLoS One* 2014;9:e98024.
22. Szabo SM, Levy AR, Rao SR, *et al*. Increased risk of cardiovascular and cerebrovascular diseases in individuals with ankylosing spondylitis: a population-based study. *Arthritis Rheum* 2011;63:3294–304.
23. Feld J, Weiss G, Rosner I, *et al*. Electrocardiographic findings in psoriatic arthritis: a case-controlled study. *J Rheumatol* 2008;35:2379.
24. Lee W, Reveille JD, Davis JC, *et al*. Are there gender differences in severity of ankylosing spondylitis? Results from the PSOAS cohort. *Ann Rheum Dis* 2007;66:633–8.
25. Webers C, Essers I, Ramiro S, *et al*. Gender-attributable differences in outcome of ankylosing spondylitis: long-term results from the outcome in ankylosing spondylitis international study. *Rheumatology* 2016;55:419–28.
26. Stolwijk C, Essers I, van Tubergen A, *et al*. The epidemiology of extra-articular manifestations in ankylosing spondylitis: a population-based matched cohort study. *Ann Rheum Dis* 2015;74:1373–8.
27. Bergfeldt L, Möller E. Pacemaker treated women with heart block have no increase in the frequency of HLA-B27 and associated rheumatic disorders in contrast to men--a sex linked difference in disease susceptibility. *J Rheumatol* 1986;13:941–3.
28. Nowak B, Misselwitz B, Erdogan A, *et al*. Do gender differences exist in pacemaker implantation? Results of an obligatory external quality control program. *Europace* 2010;12:210–5.
29. Polachek A, Touma Z, Anderson M, *et al*. Risk of cardiovascular morbidity in patients with psoriatic arthritis: a meta-analysis of observational studies. *Arthritis Care Res* 2017;69:67–74.
30. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the framingham study. *Stroke* 1991;22:983–8.
31. Bengtsson K, Forsblad-d'Elia H, Lie E, *et al*. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Res Ther* 2017;19:102.
32. Freedman B, Potpara TS, Lip GY. Stroke prevention in atrial fibrillation. *Lancet* 2016;388:806–17.
33. Armstrong AW, Azizi S, Wu J, *et al*. Psoriasis, electrocardiographic characteristics, and incidence of atrial fibrillation. *Arch Dermatol Res* 2013;305:891–7.
34. Ahlehoff O, Gislason GH, Jørgensen CH, *et al*. Psoriasis and risk of atrial fibrillation and ischaemic stroke: a Danish nationwide cohort study. *Eur Heart J* 2012;33:2054–64.
35. Chiu HY, Chang WL, Huang WF, *et al*. Increased risk of arrhythmia in patients with psoriatic disease: a nationwide population-based matched cohort study. *J Am Acad Dermatol* 2015;73:429–38.
36. Bang CN, Okin PM, Køber L, *et al*. Psoriasis is associated with subsequent atrial fibrillation in hypertensive patients with left ventricular hypertrophy: the losartan intervention for endpoint study. *J Hypertens* 2014;32:667–72.

37 Gadler F, Valzania C, Linde C. Current use of implantable electrical devices in Sweden: data from the Swedish pacemaker and implantable cardioverter-defibrillator registry. *Europace* 2015;17:69–77.

38 Cheng S, Keyes MJ, Larson MG, *et al*. Long-term outcomes in individuals with prolonged PR interval or first-degree atrioventricular block. *JAMA* 2009;301:2571–7.

39 Smith JG, Platonov PG, Hedblad B, *et al*. Atrial fibrillation in the Malmö diet and cancer study: a study of occurrence, risk factors and diagnostic validity. *Eur J Epidemiol* 2010;25:95–102.

40 Bengtsson K, Forsblad-d'Elia H, Lie E, *et al*. Increased risk of atrioventricular block, atrial fibrillation and pacemaker implantation in ankylosing spondylitis, undifferentiated spondylarthritis and psoriatic arthritis compared to general population. *Arthritis Rheumatol* 2015;67(suppl 10):1059.

41 Bengtsson K, Forsblad-d'Elia H, Lie E, *et al*. Increased risk of atrioventricular block, atrial fibrillation and pacemaker implantation in ankylosing spondylitis, undifferentiated spondylarthritis and psoriatic arthritis compared to general population. *Reumabulletinen* 2016;4:15–16.