Cardiovascular outcomes and extra-articular manifestations in patients with spondyloarthritis

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To Axel and Ivar

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ABSTRACT

Background: Spondyloarthritis (SpA) is a cluster of rheumatic diseases with similar clinical features, including association with extra-articular manifestations such as anterior uveitis (AU), inflammatory bowel disease (IBD) and psoriasis. Ankylosing spondylitis (AS), psoriatic arthritis (PsA) and undifferentiated SpA (uSpA) are the major subtypes of SpA. Chronic inflammatory diseases are potential risk factors for cardiovascular disease (CVD). The risk of CVD events in the different SpA subtypes has not been analysed in the same setting in large populations. Further, SpA has been linked to specific cardiovascular manifestations such as aortic regurgitation and cardiac conduction disturbances (CCDs).

Objectives: The aims with this thesis were to: A) calculate the incidence of acute coronary syndrome (ACS), stroke, venous thromboembolism (VTE), cardiac rhythm disturbances, aortic regurgitation, AU, IBD and psoriasis in patients with AS, PsA and uSpA in comparison to each other and to controls from general population (GP), B) describe electrocardiographic (ECG) development in AS and to identify associations between baseline characteristics and CCDs at five-year follow-up.

Methods: A) Cohorts of patients and controls from GP were identified and followed prospectively through a nationwide and comprehensive linkage of the Swedish health care and population registers. Incidence rates (IRs), events per 1000 person-years at risk, were calculated and standardized to the age and sex distribution in GP. For comparison of the cohorts, Cox regression, with age/sex-adjusted hazard ratios (HRs), and Poisson regression, with incidence rate ratios (IRRs), analyses were performed. B) A longitudinal cohort study of 172 patients with AS examined with ECG in 2009 and after five year in 2014. Logistic regression analyses were performed to identify if baseline characteristics were associated with a CCD at five-year follow-up.

Results: A significantly increased risk of all studied cardiovascular outcomes was demonstrated in SpA in comparison to GP. For ACS, stroke and VTE, the age/sex-adjusted HR point estimates in the SpA subtypes ranged between 1.4 to 1.8, 1.2 to 1.3 and 1.5 to 1.5, respectively. The increased relative risk of ACS was especially

pronounced in women with PsA (age-adjusted HR 2.0). Regarding cardiac rhythm disturbances, the highest absolute risk (IRs) was noted for atrial fibrillation (5.5 to 7.4 events per 1000 person-years), whereas the highest relative risk vs GP was found for AV block II-III in men with uSpA (age-adjusted HR 4.2) and AS (age-adjusted HR 2.5). In patients with AS, uSpA and PsA vs matched controls, relative risks (IRRs) were significantly increased for AU (20.2, 13.6 and 2.5), IBD (6.2, 5.7 and 2.3) and psoriasis (2.5, 3.8 and not applicable). In the ECG study, 13% had a CCD at follow-up. In age/sex-adjusted analyses; CCD at baseline, male sex, history of AU, higher AS disease activity score based on CRP, greater waist circumference, medication with anti-platelets and beta-blockers were associated with a CCD at five-year follow-up. Higher age/longer AS symptom duration was also associated with a CCD.

Conclusions: Patients with SpA have an increased risk of different manifestations of CVD including ACS and stroke in comparison to general population. These results underscore the need to implement strategies to improve CVD risk factors management in clinical practice for patients with SpA irrespective of subtype. Further, AS characteristics as well as markers of CVD were associated with the presence of CCD. Last, a strong association for AU and IBD was noted in AS, closely followed by uSpA, whereas the association for these manifestations was considerably weaker in PsA.

Keywords: Spondyloarthritis, cardiovascular disease, extra-articular manifestations

Sammanfattning på svenska

Bakgrund: Spondylartrit (SpA) är ett samlingsnamn för en grupp av reumatologiska tillstånd som har en likartad sjukdomsbild. Ankyloserande spondylit (AS), psoriasis med ledsjukdom (psoriasisartrit, PsA) och odifferentierad SpA ingår i begreppet. Inflammation av rygg- och bäckenleder, ledsvullnad som oftast drabbar ett fåtal leder samt sen- och muskelfästesinflammation hör till sjukdomsbilden. SpA är också kopplat till en ökad förekomst av regnbågshinneinflammation, psoriasis och inflammatorisk tarmsjukdom. Reumatologisk sjukdom har bedömts kunna vara en riskfaktor för att insjukna i kardiovaskulär sjukdom såsom stroke och hjärtinfarkt. I befolkningsstudier är dock detta samband studerat i mindre omfattning för SpA och framför allt saknas studier då AS, PsA och odifferentierad SpA undersöks samtidigt. Dessutom har en påverkan på hjärtats klaff- och retledningssystem kunnat ses vid SpA. Hjärtats aktivitet samordnas med hjälp av elektriska impulser som fortleds i banor mellan de olika delarna av hjärtat, detta utgör hjärtats retledningssystem och kan undersökas med EKG.

Syfte: För att ge oss ett underlag beträffande såväl skillnader som likheter mellan de olika SpA typerna var syftet med denna avhandling att undersöka och jämföra risken vid AS, PsA, odifferentierad SpA och befolkningskontroller för A) kardiovaskulära händelser såsom akut koronart syndrom (hjärtinfarkt/instabil kärlkramp), stroke, venös blodpropp, rytmrubbningar inklusive förmaksflimmer, och aortaklaffläckage, B) regnbågshinneinflammation, psoriasis och inflammatorisk tarmsjukdom.
Ytterligare syfte var att undersöka hur EKG hos patienter med AS ändrades under en femårsperiod och om det fanns några kännetecken vid första undersökningen som var kopplade till en framtida rubbning i retledningssystemet.

Metoder: Patienter och kontroller från övrig befolkning utsöktes via en omfattande länkning av det svenska patient- och befolkningsregistret. I patientregistret registreras sjukdomar/diagnoser kopplade till läkarbesök inom specialiserade öppenvårds-mottagningar (det vill säga inte primärvården) eller inneliggande vårdtid på sjukhus. Från patientregistret utsöktes sedan de händelserna som var avsedda att studeras. Antalet av respektive inträffad händelse delades med den sammanlagda uppföljningstiden per sjukdomsgrupp och jämfördes sinsemellan och mot övrig befolkning.
Dessutom EKG-undersöktes 172 patienter med AS under 2009 samt på nytt 2014. Patienterna var rekryterade från tre av reumatologenheterna i Västra Götaland (Alingsås, Borås, Göteborg) och fyllde också i formulär om sitt hälsotillstånd, undersöktes av reumatolog samt lämnade blodprover i samband med de två besöken.

Resultat: Patienter med SpA hade en 40-80% ökad risk för akut koronart syndrom, 20-30% ökad risk för stroke, 30-50% ökad risk för förmaksflimmer och 50% ökad risk för venös blodpropp i jämförelse med övrig befolkning. För akut koronart syndrom var risken jämfört med övrig befolkning högst hos kvinnor med PsA. Andra rytmrubbningar och aortaklaffläckage var mer sällsynt förekommande men också för dessa sågs en ökad risk hos SpA i jämförelse med övrig befolkning. För hjärtblock, som är en grav rubbning av retledningssystemet, var risken jämfört med övrig befolkning högst hos män med AS eller odifferentierad SpA.

AS och odifferentierad SpA var mycket starkt kopplat till framtida regnbågshinne-inflammation och starkt kopplat till inflammatorisk tarmsjukdom, medan PsA hade en betydligt svagare koppling till dessa sjukdomar.

I EKG-studien sågs rubbningar i retledningssystemet, varav de flesta av mildare typ, hos 18% vid något av de två undersökningstillfällena och hos 13% vid femårsuppföljningen. Manligt kön, hög ålder, tidigare regnbågshinneinflammation, aktiv AS sjukdom, större midjeomfång och läkemedel talande för kardiovaskulär sjukdom vid första undersökningstillfället var kopplat till rubbning i retledningssystemet vid femårsuppföljningen.

Slutsats: Patienter med SpA har på gruppnivå en ökad risk för kardiovaskulär sjukdom såsom hjärtinfarkt och stroke jämfört med övrig befolkning. Detta poängterar vikten av att eftersöka och behandla påverkbara kardiovaskulära riskfaktorer i denna patientgrupp för att på så sätt förbättra omhändertagandet av patienterna och minska risken för framtida kardiovaskulär sjukdom.

List of papers

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I.   **Bengtsson K**, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Are ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis associated with an increased risk of cardiovascular events? A prospective nationwide population-based cohort study. *Arthritis Research and Therapy 2017; 19:102.*

II.   **Bengtsson K**, Forsblad-d'Elia H, Lie E, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Risk of cardiac rhythm disturbances and aortic regurgitation in different spondyloarthritis subtypes in comparison with general population: a register-based study from Sweden. *Annals of the Rheumatic Diseases 2018; 77: 541-8.*

III. **Bengtsson K**, Klingberg E, Deminger A, Wallberg H, Jacobsson LTH, Bergfeldt L, Forsblad-d'Elia H. Cardiac conduction disturbances in patients with ankylosing spondylitis: results from a 5-year follow-up cohort study. *RMD Open 2019; 5(2):e001053.*

IV.   **Bengtsson K**, Forsblad-d'Elia H, Deminger A, Klingberg E, Dehlin M, Exarchou S, Lindström U, Askling J, Jacobsson LTH. Incidence of extra-articular manifestations in ankylosing spondylitis, psoriatic arthritis and undifferentiated spondyloarthritis – results from a national register-based cohort study. *Manuscript.*

Content

Abbreviations

AaIBD	Arthritis associated with inflammatory bowel disease
ACR	American college of Rheumatology
ACS	Acute coronary syndrome
AF	Atrial fibrillation
AIx	Augmentation index
AS	Ankylosing spondylitis
ASDAS	Ankylosing spondylitis disease activity score
ASDAS-CRP	Ankylosing spondylitis disease activity score based on CRP
ASAS	Assessment of Spondyloarthritis international Society
ATC	Anatomical Therapeutic Chemical Classification
AV	Atrioventricular
AU	Anterior uveitis
BASDAI	Bath Ankylosing spondylitis disease activity index
BASFI	Bath ankylosing spondylitis functional index
BASMI	Bath ankylosing spondylitis metrology index
BBB	Bundle branch block
bDMARD/s	Biological disease-modifying anti-rheumatic drug/s
BMI	Body mass index
CASPAR	Classification for Psoriatic Arthritis
CCD/s	Cardiac conduction disturbance/s
CD	Crohn's disease
CI	Confidence interval
cIMT	Carotid intima media thickness
CRP	C-reactive protein
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CVD	Cardiovascular disease
CT	Computed tomography
DMARD	Disease-modifying anti-rheumatic drug
EAMs	Extra-articular manifestations
ECG	Electrocardiogram/electrocardiographic
ESR	Erythrocyte sedimentation rate
ESSG	European Spondyloarthropathy Study Group
EULAR	European league against Rheumatism
GP	General population
HLA	Human leukocyte antigen
HR/s	Hazard ratio/s
Hs-CRP	High-sensitivity C-reactive protein
IBD	Inflammatory bowel disease
IBP	Inflammatory back pain
ICD	International Classification of Diseases
IHD	Ischemic heart disease
IL	Interleukin
IR/s	Incidence rate/s

IRR/s	Incidence rate ratio/s
LAFB	Left anterior fascicular block
LBBB	Left bundle branch block
MACE	Major adverse cardiovascular event
MHC	Major histocompatibility complex
MI	Myocardial infarction
mNY	Modified New York
MRI	Magnetic resonance imaging
mSASSS	Modified Stoke Ankylosing Spondylitis Spinal Score
NPR	National Patient Register
nr-axSpA	Non-radiographic axial spondyloarthritis
NSAIDs	Nonsteroidal anti-inflammatory drugs
OR/s	Odds ratio/s
PARs	Population attributable risks
PCI	Percutaneous coronary intervention
PDR	Prescribed Drug Register
PPVs	Positive predictive values
PROMs	Patient reported outcome measurements
PR/s	Prevalence ratio/s
PsA	Psoriatic arthritis
PWV	Pulse wave velocity
RA	Rheumatoid arthritis
r-axSpA	Radiographic axial spondyloarthritis
ReA	Reactive arthritis
RBBB	Right bundle branch block
SCORE	Systematic coronary risk evaluation
SD	Standard deviation
SMR/s	Standardized morbidity-rate ratio/s
SpA	Spondyloarthritis
SRQ	Swedish Rheumatology Quality Register
TIA	Transient ischemic attack
TNF	Tumour necrosis factor
UC	Ulcerative colitis
UK	United Kingdom
US	United States
uSpA	Undifferentiated spondyloarthritis
VTE	Venous thromboembolism

1 Spondyloarthritis

1.1 INTRODUCTION

Spondyloarthritis (SpA) is a cluster of rheumatic diseases with shared clinical features, comprising inflammation of the spine and sacroiliac joints, peripheral arthritis and enthesitis likewise an association with anterior uveitis (AU), inflammatory bowel disease (IBD) and psoriasis (1). The diseases have overlapping genetic predisposition, which includes association with human leukocyte antigen (HLA)-B27 (2). The concept of SpA, initially referred to as seronegative spondarthritides, was acknowledged in the 1970s and nowadays encompasses ankylosing spondylitis (AS), psoriatic arthritis (PsA), arthritis associated with IBD (AaIBD), reactive arthritis (ReA) and undifferentiated SpA (uSpA) (3). Lately, a growing approach has been to categorize the patients based on the predominant symptoms: axial SpA (which refers to the involvement of spine and sacroiliac joints) and peripheral SpA. The axial SpA is further grouped into radiographic axial SpA (r-axSpA), which has radiographic signs of typical structural changes in the sacroiliac joints and comprises patients with AS, and non-radiographic axial SpA (nr-axSpA) (4). Of note, the SpA subtypes AaIBD and ReA will not be specifically covered in this thesis.

1.2 EPIDEMIOLOGY

The prevalence of SpA in Europe has been estimated to 0.54% and the corresponding prevalence for AS was 0.25% and for PsA 0.19% (5). The prevalence of SpA varies geographically and partly correlates with the proportion of HLA-B27 in the studied population (5, 6). In Sweden, the prevalence of AS in the ages 16 to 64 years was 0.18% and with higher estimates in the northern part of Sweden, which population has a higher proportion of HLA-B27 than the southern part (7). In another study from the southern part of Sweden, the estimated prevalence of AS, PsA, uSpA and AaIBD was 0.12%, 0.25%, 0.10% and 0.015%, respectively (8).

In AS, there is a male predominance with a male-to-female ratio of 2-3:1 (5, 7, 9). The broader concept of axial SpA has a more equal sex distribution given that nr-axSpA encompasses more women than r-axSpA do (10). According to a recent meta-analysis, the pooled prevalence of men in nr-axSpA and r-axSpA were 54% and 70%, respectively (11). In PsA, the sex distribution seems to be rather equal without strong dominance of either sex (5, 12). A recent Danish incidence study of PsA and the Swedish prevalence study of PsA both described a slight female predominance (8, 13). For the uSpA diagnosis, limited data is available, but the Swedish prevalence study also here described a slight female predominance (8).

AS typically starts in the third decade of life and in the majority before 40 years of age, whereas patients with PsA often have a somewhat later onset of disease and commonly described to occur between the ages 30 to 50 years of age (9, 14-17). The mean age for PsA diagnosis was 47 to 50 years according to the Danish incidence study of PsA (13). In nr-axSpA and r-axSpA, the pooled mean age of symptom onset were 28 years and 26 years, respectively (11).

1.3 CLINICAL PRESENTATION

1.3.1 Axial Involvement

Inflammatory back or buttock pain is the major symptom in patients with axial SpA and involvement of the spine and sacroiliac joints (18). The inflammatory back pain (IBP) usually starts insidiously and involves the lower part of the back as a result of the inflammatory process in the sacroiliac joints. Classically, the pain improve with exercise but not with rest. The latest criteria for IBP was developed by the Assessment of SpondyloArthritis international Society (ASAS), with slight modifications from the preceding Calin and Berlin criteria, and has an estimated sensitivity of 80% and specificity of 72% (19-21). The different criteria for IBP are summarized in Table 1.

Table 1. ASAS, Berlin and Calin criteria for IBP.

ASAS criteria[§]	Berlin criteria[§]	Calin criteria
IBP if ≥ 4 parameters present	IBP if ≥2 parameters present	IBP if ≥4 parameters present
1. Age at onset < 40 years	1. Alternating buttock pain	1. Age at onset < 40 years
2. Insidious onset	2. Morning stiffness > 30 minutes	2. Insidious onset
3. Improvement with exercise	3. Improvement with exercise, but not with rest	3. Improvement with exercise
4. No improvement with rest	4. Awakening in the second half of the night because of back pain	4. Back pain > 3 months
5. Pain at night (with improvement upon getting up)		5. Associated with morning stiffness

[§]*To be applied in patients with chronic back pain > 3 month and, for Berlin criteria, in ages < 50 years.*

Axial involvement is mandatory in AS and exists in varying degree in the other SpA subtypes (18). In PsA, the axial involvement is poorly defined and rarely seen in isolated forms, whereas up to 40% may have signs of axial involvement such as IBP or imaging suggestive of axial disease accompanied with the peripheral involvement (22-24). In a Swedish validation study of uSpA, 45% of 186 patients reported IBP (25). Structural, but not inflammatory, changes such as erosions and signs of new bone formation in the sacroiliac joints and spine can be visualized by plain radiographs/computed tomography (CT) whereas inflammatory lesions can be detected by magnetic resonance imaging (MRI) (26). Depending on presence or absence of typical structural changes in the sacroiliac joints, the patients are characterized as r-axSpA or nr-axSpA (4, 10). Characteristically for AS is structural

changes with an excessive bone formation, which ultimately can cause a total ankylosed spine and sacroiliac joints in some of the patients (27). Structural changes and disease activity/spinal inflammation both contribute to an impaired physical function and spinal mobility in the patients (28, 29).

1.3.2 Peripheral involvement

Peripheral manifestations include peripheral arthritis, dactylitis and enthesitis. Peripheral arthritis typically, but not exclusively, presents as an asymmetric oligoarthritis with preference for large joints in the lower limbs (10). Approximately one third of the patients with AS and nr-axSpA have peripheral arthritis in addition to the axial involvement (11, 30). Opposite to AS, patients with PsA predominately have a peripheral involvement, which usually presents as an oligo- or polyarthritis and sometimes includes the distal interphalangeal joints (31, 32). Another characteristic feature of peripheral SpA, and especially PsA and ReA, is dactylitis or so-called sausage-shaped finger/toe, where several structures are inflamed and cause the entire swelling of the digit (33). Enthesitis, which is an inflammation at the insertion of tendon or ligament into bone, is often present and suggested as the primary focus for inflammation in SpA (34).

1.3.3 Extra-articular manifestations

Extra-articular manifestations (EAMs) such as AU, IBD and psoriasis are frequently present in SpA and particularly incorporated as part of the concept in PsA and AaIBD. Psoriasis affects approximately 2% of the population and according to a recent meta-analysis, 23% of European patients with psoriasis had concomitant PsA (35, 36). The rheumatic disease precede the onset of psoriasis in up to 15% of the patients (14, 37). In IBD, two studies reported SpA in 18-22% of the patients and 3-4% were diagnosed with AS (38, 39). Another study demonstrated axial or peripheral joint involvement in 44% of 2353 patients with IBD, but included self-reported inflammatory pain in the definition (40). Predictors were Crohn's disease (CD), female sex, higher age and active IBD (40). Previous studies have repeatedly demonstrated a large proportion of undiagnosed SpA among patients with acute AU (41-43). In a recent study, the prevalence of axial SpA in acute AU was at least 20% of which 23% were undiagnosed (44).

In AS, the pooled prevalence of uveitis, IBD and psoriasis were 26%, 7% and 9% according to a meta-analysis (45). Two additional meta-analyses have focused on the comparison between AS/r-axSpA and nr-axSpA and found similar pooled prevalence of IBD (4.1-6.5% in AS/r-axSpA and 5.6-6.4% in nr-axSpA) and psoriasis (8.5-10.2% in AS/r-axSpA and 9.3-10.9% in nr-axSpA) in the two groups, whereas the pooled prevalence of uveitis was higher in AS/r-axSpA (18.0-23.0%) than in nr-axSpA (14.3-15.9%) (11, 30). The prevalence of uveitis in PsA has shown conflicting results. In a

systematic literature review, 25% of the patients with PsA had a history of uveitis, whereas a large register-based cohort study found a history of uveitis in 1.5% of the patients with incident PsA (46, 47).

The studies on risk of EAMs in patients with SpA in comparison to general population are summarized in Table 2. In short, all studies show a clear association of the EAMs with AS and PsA, whereas no data are available for uSpA. One additional study of women with psoriasis in United States (US), demonstrated a particularly increased risk of CD in the patients with concomitant PsA (48). However, the analyses were based on only 3 events and should be interpreted with caution. In our AS cohort study in the Region of Västra Götaland, 3 of 204 (1.5%) patients with AS developed CD over a five-year period (49).

Table 2. Risk of EAMs in AS and PsA in comparison to controls.

Ref	Country	Pop.	N patients (men, mean age)	Outcome	N events	Metric	Effect
(50)	Sweden	AS	935 (67%, 52)	Uveitis	123	SMR	34.4 (28.6-41.0)
				IBD	59		9.3 (7.1-12.0)
				Psoriasis	36		2.9 (2.1-4.1)
(51)	UK	AS	4101 (71%, 44)	Uveitis	203	HR	20.9 (16.2-27.1)
				IBD	62		5.5 (3.9-7.6)
				Psoriasis	90		1.9 (1.5-2.4)
(52)	US	AS	6679 (61%, 51)	Uveitis	469	HR	22.7 (16.9-30.6)
				IBD	209		6.7 (4.9-9.0)
				CD	127		9.4 (6.2-14.3)
				UC	136		4.4 (2.9-6.7)
				Psoriasis	202		2.2 (1.6-2.9)
(53)	Denmark	PsA	6735 (44%, 40)	Uveitis	16	IRR	2.69 (1.65-4.39)
(54)	Denmark	PsA	8109 (43%, 40)	CD	28	IRR	3.40 (2.35-4.93)
				UC	54		2.42 (1.85-3.16)
(46)	UK	PsA	6783(49%, -)	Uveitis	42	RR	3.83 (2.45-5.99)
				IBD	30		1.95 (1.28-2.98)
				CD	16		3.08 (1.64-5.80)
				UC	11		1.30 (0.68-2.46)
(55)	Taiwan	PsA	10107 (62%, 43)	Uveitis	116	HR	1.8 (1.5-2.2)

Pop, population. HR, hazard ratio. SMR, standardized morbidity-rate ratio. IRR, incidence rate ratio. RR, relative risk. IBD, inflammatory bowel disease. CD, Crohn's disease. UC, ulcerative colitis. UK, United Kingdom. US, United States.

1.3.4 Extra-articular cardiac manifestation

AS, and also ReA, have since long been associated with some specific cardiac manifestations suggested to be part of the inflammatory process, namely aortic regurgitation and cardiac conduction disturbances (CCDs) (56-59). Two studies published already in the 1950s investigated cardiac manifestations in patients with AS. Bernstein et al reported clinically manifest cardiac disease in 5% of 352 patients with AS, including 6 cases of aortic regurgitation and 2 cases of total heart block (60). ECG

changes, mostly prolonged conduction time, were observed in 25% of 190 patients. Graham et al reported aortic insufficiency in 5% of 519 patients with AS, often accompanied by CCDs (61). Further, Bergfeldt et al retrospectively studied all available ECG after diagnosis in 68 patients with AS and observed CCD at least once in 22 (32%) of the patients of which six had total heart block (62). The study also demonstrated that CCDs could be intermittent, which is in line with another study and a recent case report (62-64). From the other perspective, 15 of 223 (7%) pacemaker-treated men was shown to fulfil the modified New York (mNY) criteria for AS and additional 13 patients had signs within the SpA concept in a study from the 1980s (65). Also in lone aortic regurgitation, 7 patients of 100 evaluated were found to have SpA (4 with AS and 3 with ReA) (66). Moreover, men, but not women, with pacemaker had an increased frequency of HLA-B27 compared to general population (67, 68). However, a more recent study could not demonstrate an increased frequency of HLA-B27 in patients with pacemaker compared to controls (69).

With regard to more contemporary investigations, four echocardiography studies (including our AS cohort) observed aortic regurgitation in 5-18% of patients with AS (70-73). Two of the studies compared against population data and one (70) found the prevalence higher than expected whereas the other (71) could not demonstrate a significant difference. Further, atrioventricular (AV) block was observed in 5-9% of patients with AS and incomplete or complete bundle branch block (BBB) in 9-19% (71, 73, 74). In our AS cohort, 10-33% of the 210 patients examined with ECG at baseline had a CCD depending on the definition applied and the proportion with AV block was higher than expected in comparison to population data (75). None of the presented ECG studies had a comparison group from the general population. AS has also been associated with diastolic left ventricular dysfunction, however the authors of a meta-analysis expressed concerns about the different methods to assess the outcome (76). In our AS cohort, mild diastolic dysfunction was found in 12% of the 187 patients examined with echocardiography at baseline (77).

Two studies based on administrative health care data have reported on the prevalence of aortic valve disease in patients with AS in comparison to controls, but neither of them discriminated between aortic regurgitation and aortic stenosis. Szabo et al demonstrated an increased prevalence (prevalence ratio (PR) 1.6, 95% confidence interval (CI) 1.3-1.9) in patients with AS compared to controls, and the PR was most prominent in men below 60 years of age (78). Ward et al studied patients with AS aged 65 years and older and found higher odds (Odds ratio (OR) 1.2-1.5 depending on age interval) of aortic valve disease compared to controls (79). The latter study also demonstrated slightly increased odds of having pacemaker in AS likewise an increased incidence (relative risk 1.1-1.3 depending on age interval) of pacemaker implantation in comparison to controls. In addition, a Swedish register-based study described a fourfold increased standardized morbidity-rate ratio (SMR) for AV block in patients

with AS compared to general population (50). Of note, no AV block were reported in the women with AS.
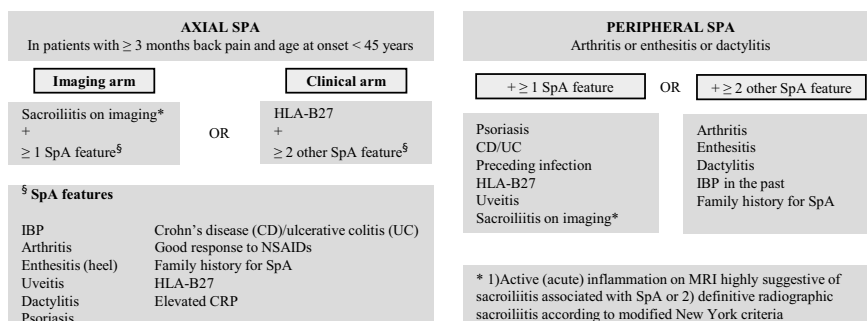
In PsA, these manifestations are scarcely explored. An ECG investigation of 92 patients with PsA observed a significantly longer PR interval in comparison to age- and sex-matched controls, and 2 patients had a prolonged PR interval and 6 had BBB (80). Mild aortic regurgitation was detected in 5 (10%) of patients with PsA (n=50, mean age 50 (13) years) examined with echocardiography, and neither the prevalence of aortic regurgitation nor left ventricular diastolic dysfunction were increased in comparison to controls (81). In a study that investigated comorbidities in SpA (n=1472), including all SpA subtypes, cardiac manifestations were detected in 44 (3%) of the patients of which 30 had AS and 11 had PsA and the majority had an axial component (n=37) (82).

1.4 CLASSIFICATION CRITERIA

1.4.1 Spondyloarthritis

Classification criteria facilitates categorization of patients in studies but are not primary for use in clinical practice. Different attempts have been made to classify the broader concept of SpA, first in the Amor criteria in 1990 and shortly thereafter in the European Spondyloarthropathy Study Group (ESSG) criteria (83, 84), see Appendix. To enable early detection of SpA and to integrate MRI as a diagnostic tool, ASAS developed new criteria for axial SpA in 2009 and peripheral SpA in 2011 (Figure 1) (85, 86).

Figure 1. ASAS classification criteria for axial and peripheral SpA (85, 86).

The classification criteria for peripheral SpA should be used in patients with peripheral manifestations only. Observe the different weighting of SpA features in the classification criteria for peripheral SpA.

1.4.2 Ankylosing spondylitis

The first criteria for AS was developed in Rome 1961, further improved in New York in 1966 and last in the mNY criteria from 1984, which is still in use in studies and clinical trials (Table 3) (87, 88). It was recently demonstrated that nearly all patients with axial SpA with radiographic sacroiliitis fulfilled both ASAS axial criteria and mNY criteria (89).

Table 3. Modified New York criteria.

Modified New York criteria for AS from 1984
Definitive AS if the radiologic criterion is associated with ≥1 clinical criterion.   **Probable AS** if**:**   A.   Three clinical criteria are present   B.   The radiologic criterion is present without any signs or symptoms satisfying the clinical criteria
CLINICAL CRITERION   -   Low back pain and stiffness for > 3 months, which improves with exercise, but is not relieved by rest   -   Limitation of motion of the lumbar spine in both sagittal and frontal planes.   -   Limitation of chest expansion relative to normal values correlated for age and sex.   **RADIOLOGIC CRITERION**   -   Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3-4 unilaterally[§]

[§] grade 0: normal; grade 1: suspicious changes; grade 2: minimal abnormality (small localized areas with erosion or sclerosis, without alteration in the joint width; grade 3: unequivocal abnormality (moderate or advanced sacroiliitis with erosions, evidence of sclerosis, widening, narrowing or partial ankylosis); grade 4: severe abnormality (total ankylosis).

1.4.3 Psoriatic arthritis

Moll and Wright proposed in 1973 to define PsA as psoriasis associated with inflammatory arthritis (peripheral arthritis and/or spondylitis) and usually negative serologic test for rheumatoid factor (90). The criteria was shown to discriminate inadequately between PsA and rheumatoid arthritis (RA) and several efforts were made during the following years to develop new classification criteria (91). Not until 2006, the Classification criteria for PsA (CASPAR) (Table 4) was proposed and thereafter widely used in clinical trials to define PsA (92).

Table 4. CASPAR criteria.

CASPAR criteria for PsA from 2006
PsA is defined in the presence of inflammatory articular disease (joint, spine, or entheseal) with ≥3 points from the following categories below.
CATEGORIES (points) - Current psoriasis observed on current physical examination (2 points), personal or family history of psoriasis (1 point) - Typical psoriatic nail dystrophy including onycholysis, pitting and hyperkeratosis observed on current physical examination (1 point) - A negative test result for the presence of rheumatoid factor (1 point) - Either current dactylitis, defined as a swelling of an entire digit, or a history of dactylitis recorded by a rheumatologist (1 point) - Radiographic evidence of juxtaarticular new bone formation appearing as ill-defined ossification near joint margins (but excluding osteophyte formation) on plain radiographs of the hand and foot (1 point)

1.5 PATHOGENESIS

There is an overlap in genetic susceptibility both within SpA and with the EAMs (2, 57, 93-95). AS and PsA have a high heritability and genetic risk factors in AS contribute to over 90% of the susceptibility to develop the disease (95, 96). The major known genetic risk factor in AS is HLA-B27, which together with small contribution from other major histocompatibility complex (MHC) variants explains approximately 20% of the 28% so far recognized genetic heritability of AS (94). The strong association between HLA-B27 and AS was detected in 1973 by two independent research groups and shortly thereafter an association between HLA-B27 and ReA likewise AU were reported (97-100). HLA-B27 is associated with the other SpA subtypes but to a weaker degree than in AS (14, 95). However, the pooled prevalence of HLA-B27 was reasonable similar in nr-axSpA (72-77%) and in AS/r-axSpA (77-78%) according to previous meta-analyses (11, 30). The exact mechanisms how HLA-B27 contributes to the pathogenesis of SpA has not yet been fully understood (10). Additional overlap of genetic associations, such as ERAP1/2 and genes involved in the interleukin (IL)-23 pathway, such as IL-12B and IL-23R, have been confirmed through genome-wide association studies (94, 101). Moreover, suggested pathophysiological explanatory models for development of disease in genetically predisposed individuals are similar in the SpA subtypes and include mechanical stress and local micro-damage in the enthesis as well as disturbed gut barrier function and altered microbiota (10, 12, 96, 102). The close connection between SpA and EAMs is further demonstrated in animal models of SpA where HLA-B27/hβ_2m-transgenic rats developed inflammatory

lesions in the gut, skin, eyes and heart in addition to the musculoskeletal system (103). In another animal model overexpressing IL-23, entheseal γ/δ T-cells important in IL-23-induced inflammation were found to be accumulated also in the aortic root and near the ciliary body in the eyes (104).

1.6 MANAGEMENT

The European league against rheumatism (EULAR) and American college of Rheumatology (ACR) provide treatment recommendations for axial SpA and PsA (105-108). Also, in Sweden there are national treatment guidelines updated yearly (www.svenskreumatologi.se/srfs-riktlinjer). The management of SpA differs partly depending on the involvement, peripheral and/or axial, and the presence of EAMs. The corner stone for treatment of axial SpA is nonsteroidal anti-inflammatory drugs (NSAIDs) and exercise/physiotherapy. Tumour necrosis factor (TNF) and IL-17 inhibitors may be initiated if the first step is insufficient or contraindicated. For the peripheral joint involvement in axial SpA without PsA, a conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) such as sulfasalazine may be considered (105, 107). For PsA, specific recommendations are available where options for the axial involvement are similar as for other axial SpA. For peripheral joint involvement in PsA, csDMARDs such as methotrexate, leflunomide and sulfasalazine, biologic DMARDs (bDMARDs) such as TNF inhibitors, IL-17 inhibitors, IL-12/23 inhibitors and abatacept, and targeted synthetic DMARDs such as PDE4 inhibitors (apremilast) and JAK inhibitors (tofacitinib) are available options. Intra-articular glucocorticoid injections are alternatives in patients with mono- or oligoarthritis (106, 108, 109).

2 Cardiovascular disease

2.1 INTRODUCTION

Cardiovascular disease (CVD) is a wide concept and conditions taken into account in the thesis comprise acute coronary syndrome (ACS), stroke and transient ischemic attack (TIA), venous thromboembolism (VTE), atrial fibrillation (AF), AV block and other CCDs, and aortic regurgitation. CCDs and aortic regurgitation have been described in section 1.3.4 (Extra-articular cardiac manifestations).

2.1.1 Mortality

On the whole, CVD is the major cause of mortality in the world. Ischemic heart disease (IHD) and stroke are the main contributors and explains together 85% of the CVD related mortality (110). The actual death rates from CVD have declined the last decades, especially in high-income countries, and the higher burden of CVD is driven by the aging and growing population (111).

2.1.2 Atherosclerotic CVD

Acute coronary syndrome (ACS), which includes myocardial infarction (MI) and unstable angina, stroke and transient ischemic attack (TIA) are acute manifestations of IHD and cerebrovascular disease, respectively. These diseases are largely attributed to atherosclerosis, overall more frequent in men than women, rarely observed in ages below 40 years of age and become more prevalent with increasing age thereafter (112-114). In the INTERHEART study (described in the next section), women experienced their incident MI on average 9 years later than men (115). Stroke is further classified into ischemic stroke, which constitutes the great majority of all strokes, and intracranial or subarachnoid haemorrhage (116, 117).

In addition to non-modifiable risk factors such as age, sex and family history, several potentially modifiable risk factors have been recognized. In INTERHEART, a multi-nation study of incident MI, nine independent risk factors (smoking, history of hypertension and diabetes, abdominal obesity, diet, physical inactivity, consumption of alcohol, abnormal lipids and psychosocial factors) explained 90% and 94% of the population attributable risks (PARs) for MI in men and women, respectively (118). Abnormal lipids and smoking had the highest individual PARs and together contributed to 67% of the PARs for MI. INTERSTROKE, a study of incident stroke using the same approach, showed similar results in which ten potentially modifiable risk factors (the nine factors mentioned above and in addition cardiac causes) explained 91% of the PARs for stroke. The major risk factor overall was hypertension. Hypertension was more associated with haemorrhagic stroke than ischemic stroke, and

the opposite was shown for current smoking, diabetes, abnormal lipids and cardiac causes (119). With regard to cardiac causes, AF is a major risk factor for ischemic stroke (120). A meta-analysis demonstrated that 24% of the patients with ischemic stroke or TIA had a newly detected AF in the monitoring after the cerebrovascular event (121).

The importance of identifying and treat risk factors for CVD has been highlighted the last decades and risk scores have been developed for guidance. The European Society of Cardiology recommends the use of Systematic Coronary Risk Evaluation (SCORE) in European population (122). SCORE estimates the ten-year risk of a fatal (atherosclerotic) CVD. It can be applied in persons aged 40 to 65 years without manifest CVD and includes the parameters sex, age, systolic blood pressure, smoking status and total cholesterol level (123).

Further, it is now well-established that atherosclerosis is an inflammatory process where the immune system is highly involved in the development and progression of atherosclerosis (124, 125). Chronic systemic inflammation has been suggested as a risk factor for accelerating the atherosclerotic process (126, 127). Both the European and American guidelines on CVD prevention acknowledge chronic inflammatory conditions such as RA and psoriasis as potential risk enhancing factors (122, 128).

Clinical trials have studied the benefit of targeting the inflammation in IHD. Canakinumab, a monoclonal antibody targeting IL-1β, given to patients with a previous MI and high-sensitivity C-reactive protein (hs-CRP) ≥ 2 mg/l reduced the levels of hs-CRP and the rate of recurrent cardiovascular event in comparison to placebo. However, the treatment was associated with higher risk of fatal infections compared to placebo (129). Treatment with methotrexate in patients with a previous MI or multivessel coronary disease together with type 2 diabetes or metabolic syndrome did not show any reduction in cardiovascular events compared with placebo (130). Recently, a randomized controlled trial of colchicine in patients with a recent MI found that patients treated with colchicine had a significantly lower risk of the composite CVD endpoint including cardiovascular death, recurrent MI and stroke than placebo (131).

2.1.3 Venous thromboembolism

VTE, which incorporates deep vein thrombosis and pulmonary embolism, increases with advancing age and may overall occur slightly more frequent in men than women (132, 133). Risk factors for VTE include multiple trauma, major surgery, marked immobilization, cancer, pregnancy/puerperium and acquired or inherited thrombophilia (132, 134). According to several studies, higher BMI and other measures of adiposity are additional risk factors for VTE (135-138). In a recent meta-

analysis of traditional CVD risk factors and VTE, current smoking was a risk factor for VTE, whereas this neither was demonstrated for hypertension, diabetes nor hyperlipidaemia (139). Further, inflammation has been proposed to be involved also in the VTE process (140).

2.1.4 Atrial fibrillation

AF is the most common arrhythmia and the lifetime risks to develop AF in men and women at age 40 and older have been estimated to 26% and 23%, respectively (141). The prevalence of AF increases with advancing age and is more common in men than women. Additional risk factors are obesity, hypertension, diabetes and cardiac conditions such as congestive heart disease, ischemic heart disease and valve disorders (142-144). Further, AF is a risk factor for incident congestive heart disease and stroke (143).

2.2 CVD IN SPONDYLOARTHRITIS

2.2.1 Mortality

An increased mortality has been demonstrated in AS and, in accordance with the general population, CVD was the major cause of death (145-147). In PsA, studies have shown inconclusive results (148). A study from Sweden demonstrated an increased risk of CVD mortality, but not overall mortality, in 464 patients with PsA compared to general population (149). A large population-based study from UK found an increased overall mortality and risk of cardiovascular deaths in psoriasis but not in PsA in comparison to controls (150, 151). Still, the majority of deaths in PsA was from cardiovascular origin (152). In similarity, a Danish nationwide study did not find an increased overall or CVD mortality in PsA in comparison to controls from general population (153).

2.2.2 Cardiovascular outcomes

Population-based studies with primary aim to report risk of atherosclerotic and/or venous thromboembolic events in patients with SpA in comparison to general population are summarized in Table 5. The results from Paper I is presented in the section 5.1.2 (Paper I – main results) and not included in Table 5 (154). Additionally, a US study based on administrative data demonstrated a 41% increased risk of a composite CVD outcome in AS compared to controls (52). A twofold increased prevalence of MI and angina and a similar prevalence of stroke was demonstrated in a longitudinal cohort study of PsA (n=648) in comparison to standard population (155). An increased self-reported prevalence of angina and percutaneous coronary intervention (PCI), however not MI and stroke, was observed in a Norwegian study of PsA (n=338) in comparison to controls (156). However, a Swedish longitudinal study

of PsA (n=464) demonstrated decreased standardized incidence ratio for both stroke and acute MI compared to general population (149).

The risk of CVD events in SpA has also been compared to other rheumatic diseases and related conditions. We have previously described the risk of ACS, VTE and stroke in AS and RA and found similar risk estimates for stroke in comparison to general population, whereas RA had higher risk estimates for ACS and VTE than AS (157). Ogdie et al described a higher relative risk of cardiovascular deaths in RA, but not in PsA, in comparison to general population and overall higher risk estimates for MI and VTE in RA than in PsA (151, 158). In comparison to psoriasis, an increased relative risk of cerebrovascular and cardiovascular events was demonstrated in PsA in one study, while another study did not find any significant difference in risk for these events in PsA and psoriasis (159, 160). A Swiss study investigated incidence of major adverse cardiovascular events (MACE), defined as MI, TIA, stroke or cardiovascular death, in patients with axial SpA, PsA and RA identified in the Swiss Clinical Quality Management registry (161). After adjustment for age, sex, disease duration and traditional risk factors, no significant difference could be demonstrated in neither axial SpA (IRR 0.9, 95% CI 0.5-1.7) nor PsA (IRR 0.6, 95% CI 0.3-1.1) in comparison to patients with RA. However, the patients with axial SpA and PsA had a young median age (29 and 39 years, respectively) and the low number of reported MACE identified in these patient cohorts may have hampered the results. Last, a Spanish longitudinal cohort study of CVD in patients with AS, PsA and RA recently reported data from their 2.5 years follow-up where AS diagnosis was a risk factor for an incident CVE (162).

Table 5. Risk of CVD outcomes in SpA in comparison to general population.

Ref	Country	Population	Study period	N patients (men, mean age)	Outcome	N events	Metric	Effect	Adjusted effect[§]
(163)	US	AS	2001-2002	1843 (60%, 47)	IHD	-	PR	1.2 (1.0-1.5)	
					Cerebrovascular			1.7 (1.3-2.3)	
		PsA		3066 (49%, 50)	IHD			1.3 (1.1-1.5)	
					Cerebrovascular			1.3 (1.1-1.7)	
(164)	Taiwan	AS	2007	11701 (79%, -)	IHD	102	OR	2.7 (2.15-3.5)	
(50)	Sweden	AS	2004-2007	935 (67%, 52)	Stroke	226	SMR	1.0 (0.9-1.2)	
					IHD	91		2.2 (1.8-2.7)	
(78)	Canada	AS	1996-2006	8616 (56%, -)	Acute MI	20	PR	1.3 (0.9-2.0)	
					IHD	-		1.37 (1.31-1.44)	
(165)	UK	AS	1999-2010	1686 (76%, 46)	Cerebrovascular	40	HR	1.25 (1.15-1.35)	
					Acute MI	37		1.3 (0.9-1.7)	
(166)	Taiwan	AS	2000-2009	6262 (48%, -)	Stroke	221	IRR	1.0 (0.7-1.4)	
					ACS	102		1.5 (1.3-1.75)	1.4 (1.2-1.6)
(167)	Taiwan	AS	2001-2005	1479 (-, -)	Stroke	38	HR	2.4 (2.0-2.8)	2.3 (1.9-2.8)
(168)	UK	AS	1987-2012	3809 (71%, -)	IHD	53	HR	1.20 (0.97-1.48)	1.00 (0.80-1.25)
(151)	UK	PsA, DMARD	1994-2010	4532 (51%, 50)	Acute MI	46	HR	0.91 (0.65-1.28)	0.76 (0.53-1.09)
					MI	70		1.35 (1.03-1.79)	1.36 (1.01-1.84)
					Stroke	73		1.12 (0.83-1.50)	1.13 (0.83-1.55)
		PsA, no DMARD		4174 (51%, 52)	MI			1.46 (1.14-1.86)	1.36 (1.04-1.77)
					Stroke			1.36 (1.08-1.73)	1.33 (1.03-1.71)
(169)	UK	PsA	1988-2012	7982 (49%, 46)	CVD	732	IRR	1.33 (1.23-1.44)	
(157)	Sweden	AS	2006-2012	8454 (49%, 47)	MACE	288	HR	1.30 (1.15-1.47)	
				5358 (68%, 49)	ACS	69		1.3 (1.0-1.7)	
					Stroke	65		1.5 (1.1-2.0)	
(158)	UK	PsA, DMARD	1994-2014	6396 (51%, 49)	VTE	68	HR	1.4 (1.1-1.9)	1.10 (0.92-1.31)
		PsA, no DMARD		5688 (51%, 51)	VTE	158		1.27 (1.09-1.49)	1.07 (0.88-1.29)
(170)	Denmark	PsA	2008-2012	8149 (44%, 55)	MI	159	HR	1.23 (1.05-1.44)	1.23 (1.04-1.47)
(171)	UK	PsA	1999-2013	2128 (47%, 50)	MACE	128	HR	-	1.5 (0.9-2.5)
(172)	South	AS	2010-2015	12988 (73%, 40)	Acute MI	43	HR	2.0 (1.5-2.7)	1.8 (1.3-2.4)
(173)	Korea	AS	1996-2012	7190 (51%, 46)	Ischemic stroke	62	HR	1.5 (1.1-1.9)	1.35 (1.04-1.75)
(174)	Canada	AS			VTE	73	HR	2.1 (1.6-2.7)	1.5 (1.2-2.0)
(160)	UK	PsA	1998-2014	6783 (49%, -)	IHD	167	RR	1.41 (1.18-1.69)	1.27 (1.05-1.54)
					Cerebrovascular	128		1.40 (1.14-1.73)	1.24 (0.99-1.56)

[§] Adjustment for at least one more factor than age and sex. ACS, acute coronary syndrome. CVD, cardiovascular disease. HR, hazard ratio. IHD, ischemic heart disease. IRR, incidence rate ratio. MACE, major adverse cardiovascular event. MI, myocardial infarction. OR, odds ratio. PR, prevalence ratio. RR, relative risk. SMR, standardized morbidity-rate ratio. UK, United Kingdom.

(50, 78, 151, 157, 158, 160, 163-174)

2.2.3 Risk factors

In comparison to general population
Overall, the traditional risk factor profile for CVD appears to be unfavourable in SpA (148, 175).

In AS, several studies have reported an increased prevalence of hypertension and some of them an increased prevalence of diabetes mellitus and hyperlipidaemia in comparison to controls (52, 163-167, 176-178). Smoking was more prevalent in AS than controls according to two studies (176, 177). An increased risk of incident hypertension and diabetes mellitus in comparison to general population have also been described (50, 52, 179). On the contrary, a Swedish study found no significant differences in patients with AS (n=88) compared to controls with regard to hypertension, BMI, smoking status and physical activity (180).

In PsA, studies relatively consistent report an increased prevalence of hypertension, dyslipidaemia, diabetes mellitus, obesity and the composite outcome metabolic syndrome in comparison to general population (155, 156, 163, 178, 181-185). Prior studies, based on questionnaire with comparison to controls/general population, have demonstrated higher prevalence of current smoking in PsA and ever smoking in women with PsA, respectively (156, 181). Patients with PsA also confer an increased risk of incident diabetes mellitus (160, 186, 187).

In comparison to each other or related conditions
Several studies have also compared the risk profile in different rheumatic or related conditions. In comparison to psoriasis, patients with PsA were more likely to have hypertension, obesity and higher BMI and also more likely to acquire hypertension, diabetes, hyperlipidaemia and obesity (184, 188, 189). Compared to RA, studies have demonstrated an increased prevalence of metabolic syndrome, diabetes mellitus and dyslipidaemia in PsA (182, 190). A Danish study investigated the CVD risk profile in AS, PsA and RA (191). In comparison to RA, patients with AS had higher odds of hypertension, patients with PsA and AS had significantly higher levels of cholesterol, women with AS and PsA had greater waist circumference and women with PsA also higher BMI (191). The patients with RA were more frequently smokers than patients with PsA. Moreover, metabolic syndrome was also more frequently present in PsA, whereas not in AS and RA, in comparison to controls (182). A Belgian study demonstrated that PsA in comparison to other SpA subtypes more frequently had coronary artery disease, diabetes mellitus, hyperlipidaemia, hypertension and metabolic syndrome (192). Likewise, a Spanish study observed more CVD risk factors in PsA than in RA and AS, whereas current smoking was more prevalent in patients with AS (193). In a multi-nation study of SpA, patients with axial SpA had lower prevalence of hypertension, dyslipidaemia, obesity and diabetes mellitus but higher prevalence of smoking than patients with peripheral SpA (194). However, the patients with peripheral SpA were on average 9 years older than the patients with axial SpA.

Taken all studies together, PsA seem to have an overall more aggravated traditional risk profile (except for smoking) than both psoriasis, RA and the other SpA subtypes.

Interference with rheumatic disease

As described in the next sections, traditional risk factors can interfere with the rheumatic disease per se and are not always easily disentangled. In AS and axial SpA, cigarette smoking has been associated with earlier symptom onset, higher disease activity, decreased physical mobility, worse functional status, poorer quality of life and more structural changes (195-197). Further, smoking is a risk factor in axial SpA for radiographic progression (198-200). In the SpA subtypes, smoking has been associated with shorter adherence and poorer response to treatment with TNF inhibitors (201-203). However, a recent study did not reveal any association between smoking status and discontinuation of TNF inhibitors in axial SpA but in similarity with other studies observed worse patient reported outcome measurements (PROMs) in smokers compared to non-smokers before initiation of TNF inhibitors (204). Smoking was associated with future risk of PsA in one study, whereas another suggested an inverse association between smoking and risk of PsA in patients with psoriasis (205, 206). Nguyen et al found an increased risk of PsA in smokers compared to non-smokers in general population, but smoking was not a risk factor for PsA in the patients with psoriasis (207).

Obesity has been suggested as risk factor for PsA in patients with psoriasis (208, 209). Obese patients with PsA have a lower probability to achieve minimal disease activity (210, 211). Additionally, weight loss treatment in PsA resulted in lower disease activity (212). Overall, obesity has been associated with lower odds of response to TNF inhibitors in different rheumatic diseases and in PsA specifically (213-215). In our AS cohort, obesity predicted radiographic progression (200).

First line treatment in SpA frequently includes NSAIDs, which risk of vascular events and congestive heart disease are an often highlighted concern (216). In a longitudinal cohort study of patients with AS (n= 628), continuous NSAID therapy (vs non-continuous NSAID) was associated with higher risk of hypertension (217). In a register-based study, increased odds of MI were observed in patients with SpA and current treatment with diclofenac, but not naproxen, in comparison to controls with previous but not current such treatment (218). However, NSAIDs are not easily explored in observational studies given the obvious channelling of indication. As an example, in a Swedish register-based study of SpA and exposure to non-selective NSAIDs and coxibs, patients without exposure had overall more comorbidities and higher risk of incident congestive heart disease compared to non-selective NSAIDs (219). As a further illustration, Haroon et al noted lack of NSAID exposure as a risk factor for vascular mortality in patients with AS aged 66 years and older (147).

Subclinical atherosclerosis and disease characteristics
In both AS and PsA, studies of subclinical atherosclerosis have revealed an impaired endothelial function (early step in atherosclerosis), greater carotid intima media thickness (cIMT), and increased arterial stiffness compared to controls (220-224). Higher frequency of carotid plaques have been demonstrated in PsA, but not unanimously in AS (220, 222). Additionally, patients with axial SpA had higher frequency of carotid plaques compared to controls, while this was not found in sub-analysis of patients with nr-axSpA (225, 226). Coronary CT angiography has shown an increased prevalence, burden and severity of coronary plaques in patients with PsA without manifest CVD compared to controls (227, 228).

In PsA (n=235), higher erythrocyte sedimentation rate (ESR), white blood cells and disease activity score for PsA were associated with more severe atherosclerosis (measured with carotid total plaque area) (229). However, after adjustment for traditional CVD risk factors, the association were no longer significant and the authors reflected if the inflammatory burden was mediated by the traditional CVD risk factors. In similarity, a longitudinal study of arterial stiffness (measured with pulse wave velocity (PWV)) in PsA (n=72) demonstrated an association between a higher cumulative burden of inflammation (measured with the average ESR) and high PWV category (221). However, the same was not shown for average CRP during follow-up. Also, treatment with TNF inhibitors (vs no TNF inhibitors) has been associated with lower progression of total plaque area in the carotids in patients with PsA (n=34) (230). Sustained minimal disease activity in PsA was further shown to have a protective effect on plaque progression in patients with PsA (n=90) (231).

In a cross-sectional study of patients with AS (n=151), a trend of increased arterial stiffness (measured with augmentation index (AIx)) was found in the patients with AS disease activity score (ASDAS) $\geq$ 2.1 (224). Further, C-reactive protein (CRP) and ASDAS at baseline were associated with elevated arterial stiffness assessed after five years in 85 patients with AS (232). Interestingly, concomitant psoriasis was independently associated with the presence of carotid plaques in patients with axial SpA (225).

With further regard to disease characteristics, a history of AU was associated with increased odds of hypertension and atherosclerosis (defined as manifest CVD or presence of carotid plaques) in a cross-sectional study of 159 patients with AS (233). In a longitudinal study of 1091 patients with PsA, independent risk factors for MACE were in addition to hypertension and diabetes, also number of dactylitis digits and in women ESR (234).

2.3 CVD IN RELATED DISEASES

2.3.1 Rheumatoid arthritis

It is well-established that patients with RA suffer from an increased risk of both cardiovascular mortality and atherosclerotic cardiovascular events in comparison to general population (235-238). Furthermore, an approximately twofold increased risk of VTE have been observed (239-241). The inflammatory burden in addition to traditional risk factors have been proposed to explain the increased risk of CVD (242-245). Treatment with TNF inhibitors and methotrexate seem to decrease the risk of CVD (246). A multiplication factor of 1.5 in CVD risk prediction models such as SCORE is recommended in RA (247).

2.3.2 Psoriasis

Several studies have addressed the risk of CVD in psoriasis. An increased risk of cardiovascular death, MI, stroke and VTE have been shown (248-250). Moreover, some but not all studies have found an increased risk of AF in patients with psoriasis (251-253). With regard to traditional risk factors, an increased prevalence of metabolic syndrome, hypertension, diabetes, obesity and current or former smoking have been observed in psoriasis compared to controls without psoriasis and with greater odds of metabolic syndrome, hypertension, diabetes and obesity in patients with severe psoriasis than in mild forms (254-258). Additionally, an increased risk of future diabetes, obesity, hyperlipidaemia and hypertension have been noted in patients with psoriasis compared with controls without psoriasis (259, 260). Smoking has been proposed as a risk factor for development of psoriasis (261-263).

3 Aim

The overall aim of this thesis was to acquire a greater knowledge of cardiovascular outcomes and extra-articular manifestations in patients with different types of SpA examined in the same setting. Specific aims with each paper were:

I. To calculate the incidence of ACS, stroke and VTE in patients with AS, PsA and uSpA in comparison to each other and to the general population.

II. To calculate the incidence of AV block II-III, AF, pacemaker implantation and aortic regurgitation in patients with AS, PsA and uSpA in comparison to each other and to the general population.

III. To describe electrographic development from baseline to five-year follow-up in patients with AS and to identify associations between baseline characteristics and CCDs at five-year follow-up.

IV. To describe the incidence and strengths of association of AU, IBD and psoriasis in patients with AS, uSpA and PsA in comparison to general population.

4 Patients and Methods

4.1 DATA SOURCES

Study I, II and IV are register-based cohort studies with derived data from a nationwide linkage of the Swedish health care and population registers. The register linkage is possible due to the unique personal identification number each Swedish resident has. The utilized registers are introduced shortly in the section below.

National Patient Register (NPR) started to record data from inpatient care in the 1960s and reached full nationwide coverage in 1987. The registered data from inpatient care includes the reported primary and secondary discharge diagnoses, according to the year appropriate International Classification of Diseases (ICD) version, and surgical procedure codes. From 2001, NPR also records data from specialized outpatient care. All specialized outpatient caregivers are bound to report, but data from private caregivers are not complete (264). The National Board of Health and Welfare administers NPR.

The **Swedish Population Register** comprises demographic data such as migration, birth and death of all Swedish residents. The register is administered by Statistics Sweden.

Prescribed Drug Register (PDR) register all dispensed prescriptions according to the Anatomical Therapeutic Chemical Classification (ATC) system and on an individual level since July 2005. Importantly, PDR do not capture unutilized prescriptions and medications bought over the counter. The National Board of Health and Welfare administers PDR.

Register of Education holds information of the highest level of education for each Swedish resident. The register is administered by Statistics Sweden.

Swedish Rheumatology Quality Register (SRQ) is a national quality register which aims to improve the management and follow-up of patients with rheumatic diseases. The register gather information on disease characteristics, current and past treatment, PROMs and clinical parameters from the responsible caregiver (for example number of swollen and tender joints, laboratory measurements). In the present studies, SRQ was used to capture intravenously administered TNF inhibitors (infliximab) which is not registered in PDR. According to a previous study, the coverage in SRQ of patients with SpA and bDMARD was estimated to 86% (265).

4.2 PATIENTS AND CONTROLS

4.2.1 Paper I, II

The inclusion process of patients and controls are described in Figure 2. The patients were identified in the NPR and the controls were identified in the Population Register. In short, patients finally included in the AS, PsA and uSpA cohort had at least one registered diagnosis of AS (ICD 10: M45), PsA (ICD 10: L450.5, M07.0-3) and uSpA (ICD 10: M46.8-9) in outpatient rheumatology or internal medicine care during the period 2001 to 2009. Observe, patients with uSpA comprise both axial and peripheral SpA (25). To avoid case mixing, patients with mixture of diagnoses were analysed separately in a mixed SpA cohort (n=1931). We decided to add all eligible controls from the initial matching process and assemble them into one unmatched comparator cohort from the general population (GP).

Figure 2. Inclusion of patients with AS, PsA and uSpA and controls from GP.
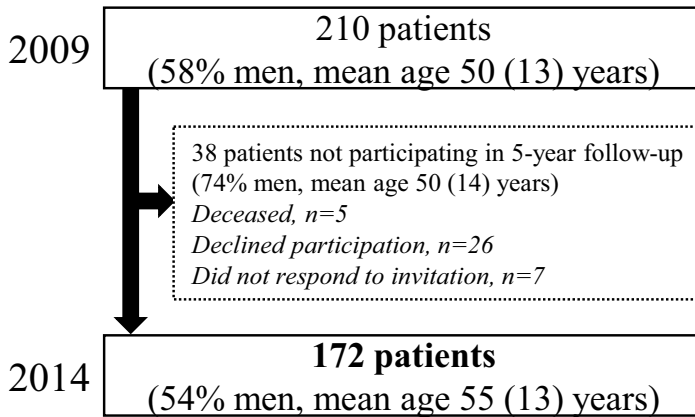

[§]*Patients and controls included in the final cohorts were 18 to 99 years of age, alive and lived in Sweden at start of follow-up. Exclusion criteria for the patients was a registered diagnosis of RA or SLE 2001 to 2009. Exclusion criteria for controls was a registered diagnosis of any of the SpA subtypes before start of follow-up. Patients with diagnostic codes for more than one SpA subtype before start of follow-up were analysed separately in a mixed SpA cohort.*

4.2.2 Paper III

Patients with AS according to mNY criteria and without exclusion criteria (psoriasis, IBD, pregnancy, malignancy, dementia, difficulties in understanding Swedish) were identified through medical records at three Rheumatology departments in Region Västra Götaland (Sahlgrenska University Hospital, Södra Älvsborgs Hospital and Alingsås Hospital) and invited in 2009 to participate in a longitudinal cohort study with a planned follow-up after five years. The initial enrolment process has been described thoroughly in a previous publication (75). Patients included in Paper III are the 172 patients of initial 210 patients participating in the five-year follow-up (Figure 3).
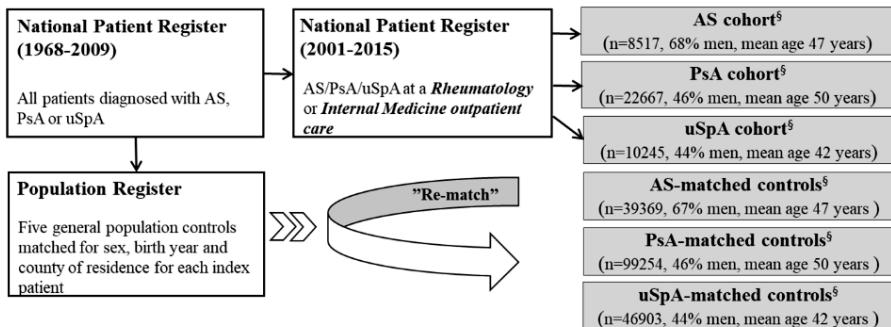
Figure 3. Flow-chart of the patients participating at inclusion 2009 (n=210) and at 5-year follow-up 2014 (n=172).

2009 | **210 patients**
(58% men, mean age 50 (13) years)

38 patients not participating in 5-year follow-up
(74% men, mean age 50 (14) years)
Deceased, n=5
Declined participation, n=26
Did not respond to invitation, n=7

2014 | **172 patients**
(54% men, mean age 55 (13) years)

4.2.3 Paper IV

Except for a longer inclusion period (2001 to 2015), adding of one ICD code to define uSpA (M46.1) and limiting the eligible patients to the ages 18 to 69 years of age, the inclusion and exclusion criteria for patients were identical as described in 4.2.1. In Paper IV we decided to keep a matched control design. A new matching (based on sex, birth year and county of residence the year before start of follow-up for each index patient) was performed on the controls who were alive, without diagnosis of SpA and lived in Sweden at start of follow-up.

Figure 4. Inclusion of patients with AS, PsA and uSpA and matched controls from GP.

National Patient Register (1968-2009)

All patients diagnosed with AS, PsA or uSpA

National Patient Register (2001-2015)

AS/PsA/uSpA at a *Rheumatology* or *Internal Medicine outpatient care*

AS cohort[§]
(n=8517, 68% men, mean age 47 years)

PsA cohort[§]
(n=22667, 46% men, mean age 50 years)

uSpA cohort[§]
(n=10245, 44% men, mean age 42 years)

Population Register

Five general population controls matched for sex, birth year and county of residence for each index patient

"Re-match"

AS-matched controls[§]
(n=39369, 67% men, mean age 47 years)

PsA-matched controls[§]
(n=99254, 46% men, mean age 50 years)

uSpA-matched controls[§]
(n=46903, 44% men, mean age 42 years)

[§]*Patients and controls included in the final cohorts were 18 to 69 years of age, alive and lived in Sweden at start of follow-up. Exclusion criteria for the patients was a registered diagnosis of RA or SLE 2001 to 2015. Patients with diagnostic codes for more than one SpA subtype before start of follow-up were analysed separately in a mixed SpA cohort.*

4.3 METHODS

Table 6. Summarized description of the used primary analyses for each Paper.

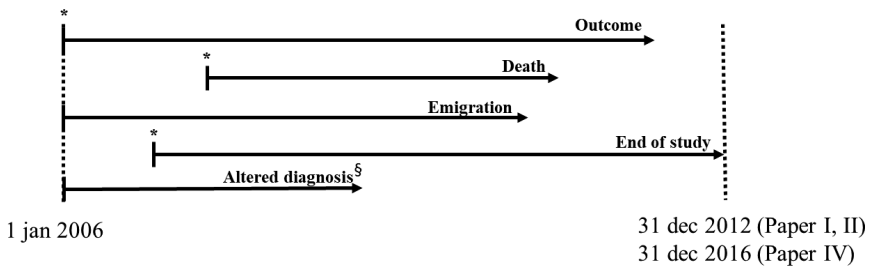| Paper	Primary analyses	Metrics
I, II	Cox regression analyses, age/sex adjusted	Hazard ratios (HRs)
III	Logistic regression analyses, age/sex adjusted	Odds ratios (ORs)
IV	Poisson regression analyses	Incidence rate ratios (IRRs)

4.3.1 Paper I, II, IV

Study design

Nationwide register-based prospective cohort studies which aimed to calculate incidence of first-time cardiovascular and extra-articular outcomes.

Follow-up period

In Paper I-II patients were included between 2001 and 2009 and in Paper IV between 2001 and 2015. The follow-up started 1 January 2006 or 6 months after the first SpA diagnosis, whichever came latest. We set the first possible date of follow-up to 1 January 2006 to get access of data from PDR for baseline characteristics. In Paper I-II the controls started 1 January 2006 (or at the time of immigration if this occurred later) and in Paper IV the controls started at the same date as their index case. The principles of start and end of follow-up are described in Figure 5. Censoring caused by death and emigration was identified in the Population Register.

Figure 5. Principles for start and end of follow-up.

1 jan 2006

31 dec 2012 (Paper I, II)
31 dec 2016 (Paper IV)

*Patients and controls were followed until the time of the first occurrence of an outcome or censored in case of death, emigration, altered diagnosis or end of study, whichever came first. * Latest date of 1 January 2006 or 6 months after the first registered SpA diagnosis for patients. §Altered diagnosis refers in patients to a registered second and different SpA subtype and in controls a registered first SpA diagnosis.*

Outcome of interest

Paper I focused on first-time atherosclerotic CVD outcomes (ACS and stroke) and VTE. Paper II studied cardiac rhythm disturbances (AF, AV block II-III, pacemaker implantation) and aortic regurgitation. Paper IV investigated EAMs (AU, IBD and psoriasis). All different outcomes were analysed separately and only patients and controls without a history of the respective outcome were eligible to enter the analysis. AU is rarely a chronic disease and exclusively for this outcome, we also analysed recurrent AU flares during follow-up. Consequently, patients and controls could contribute with more than one AU each during the follow-up period. Exclusion for the recurrent AU analysis was a registered diagnosis of chronic AU within a five-year period before start of follow-up. The outcomes were defined according to pre-specified ICD, procedure and/or ATC codes identified in NPR and/or PDR and for some of the outcomes further specification of inpatient/outpatient care, primary/secondary diagnosis and specified care were required (Table 7). For example, the outcome ACS was defined as a primary discharge diagnosis from inpatient care.

Table 7. Description of outcome definitions.

	O[§]	I[§]	Primary	Secondary	Source	Specified care
Paper I						
ACS		x	x		ICD	
Composite stroke[§§]		x	x	X	ICD	
VTE	x	x	x	X	ICD	
Paper II						
AV block II-III	x	x	x	X	ICD	
Atrial fibrillation	x	x	x	X	ICD	
Pacemaker	x	x	n.a	n.a	Procedure	
Aortic regurgitation	x	x	x	X	ICD	
Paper IV						
Anterior uveitis	x	x	x	X	ICD	Ophthalmology
IBD	x	x	x	X	ICD	Internal medicine / Surgery / Gastroent.
Psoriasis	x	x	x	X	ICD +ATC	

[§] O, outpatient care; I, inpatient care. [§§] Composite stroke comprises transient ischemic attack (TIA), ischemic, haemorrhagic and unspecified stroke. Gastroent, Gastroenterology.
Of note, the definitions refer to incident outcome during follow-up. Exclusion was based on any existing ICD/procedure/ATC code corresponding to the outcome of interest before start of follow-up.

Baseline characteristics

We obtained data from NPR, PDR, SRQ and Register of Education to describe the patients and GP controls at baseline with regard to CVD-related (Paper I, II) and SpA-related (Paper I, II, IV) comorbidity and pharmacological treatment likewise highest

level of education (Paper I, II). Pharmacological treatment was defined as ≥ 1 dispensed prescription with a pre-specified ATC code within a time frame of 6 months before start of follow-up. Specifically for intravenously administered TNF inhibitors (infliximab), the data was instead obtained from SRQ. The highest level of education was categorized into ≤ 9 years, 10-12 years and > 12 years, and used as an approximation of socioeconomic status.

Statistics

Paper I-II, IV are built on survival analyses where the time to each outcome of interest were studied. The number of outcomes and number of person-years at risk during the follow-up period were counted for each cohort and stratified by sex and age intervals (18 to 29 years, 30 to 39 years, 40 to 49 years, 50 to 59 years, 60 to 69 years, 70 to 79 years (Paper I, II) and ≥ 80 years (Paper I, II)). If an individual changed age interval during the follow-up, the individual was censored from the initial age interval by that time and started to contribute person-years at risk (and outcome of interest) to the new age interval. The incidence rates (IRs) were presented as number of outcomes per 1000 person-years at risk with 95% CI. We assumed a Poisson distribution except for the recurrent AU, where robust 95% CI were estimated. Due to the different age and sex distribution in the SpA subtypes and the unmatched GP cohort in Paper I-II, for each SpA subtype we calculated standardized IRs to the age (by the age intervals) and sex distribution in the GP cohort. Survival and cumulative incidence probability curves were plotted for visual assessment. In paper I-II, age- and sex-adjusted Cox regression analyses were performed for the comparison between the subtypes (PsA as reference) and for the comparison with the GP cohort. We planned to perform Cox regression analyses also in Paper IV, but the assumptions of proportionality was violated for some of the analyses. For the comparison (SpA subtype vs matched controls) we instead performed Poisson regression analyses and calculated incidence rate ratios (IRRs) with 95% CI.

In addition and exclusively for the thesis, I have also calculated standardized IRRs for the outcomes in Paper I stratified by age intervals.

Baseline characteristics was presented as mean (SD) or number (%).

The statistical analyses were performed by PASW Statistics version 19 (Paper I, II), SAS version 9.3 (Paper I, II) and SAS version 9.4 (Paper IV).

4.3.2 Paper III

Study design

Longitudinal cohort study of patients with AS which aimed to study ECG development and identify associations between characteristics at baseline and CCDs at five-year follow-up.

Physical examinations

All 172 patients were examined by one physician (Eva Klingberg) at baseline in 2009. The examination included 66/68 swollen/tender joints index, Bath AS Metrology Index (BASMI), systolic and diastolic blood pressure. At 5-year follow-up the patients were re-examined using the same protocol by another physician (Anna Deminger).

Questionnaires

The patients filled in questionnaires regarding their medical history, pharmacological treatment, life style habits and PROMs relevant for AS such as Bath AS patient global score (BAS-G), Bath AS Disease Activity Index (BASDAI) and Bath AS Functional Index (BASFI) (266).

ECG

Standard resting 12-lead ECG was recorded in immediate connection with the baseline and follow-up visits. At baseline, the ECG was interpreted by one physician (Hanna Wallberg) and then jointly with a specialist in cardiology (Lennart Bergfeldt). At the 5-year follow-up, I first interpreted the ECG after instructions from Lennart Bergfeldt and then jointly with him. At time of interpretation, we did not have knowledge of the ECG at baseline or any patient characteristics except for age and sex. We analysed the rhythm (sinus, AF, pacemaker rhythm, other) and presence of CCD (Table 8). In contrast to the baseline, the intervals (PR, QRS and QT) at 5-year follow-up were provided from the ECG machine and were not measured manually. QT were further corrected for heart rate using the Bassett's formula.

Table 8. Definition of a CCD.

CCD
1. AV block of first to third degree (AV block I-III)
a. AV block Ix (PR interval 200-219 ms)
b. AV block I (PR interval ≥ 220 ms)
2. Right bundle branch block (RBBB)
3. Left bundle branch block (LBBB)
4. Unspecified intraventricular conduction disturbance (QRS ≥ 120 ms without typical morphology)
5. Left anterior fascicular block (LAFB)
6. Left posterior fascicular block (LPFB)
7. Pacemaker rhythm

Other measures or examinations at baseline

Anthropometric (body weight, length, waist circumference) measurements and blood sampling with analyses including ESR, CRP and HLA-B27 status were carried out. Body mass index (BMI) was calculated from weight and length and further categorized into <25 kg/m^2 and ≥25 kg/m^2, the latter corresponding to overweight or obesity. CRP was further dichotomized in <5 mg/l and ≥ 5 mg. AS disease activity score based on CRP (ASDAS-CRP) was calculated and dichotomized into ASDAS-CRP < 2.1 (corresponding to low or inactive disease) and ASDAS-CRP ≥ 2.1 (corresponding to a high or very high disease activity) (267, 268).

All 172 patients were examined with lateral spine radiographs for evaluation of AS related changes. The AS related changes were graded with modified Stoke AS Spinal Score (mSASSS) and dichotomized into presence or not of at least one syndesmophyte. Further, 159 of the 172 patients (92%) were examined at baseline with echocardiography to identify presence and grading of aortic regurgitation.

Statistics

Descriptive statistics were reported as number (%), median (25th percentile (Q1), 75th percentile (Q3)) or mean (SD) and presented stratified by sex and median age. With regard to ECG measurements (heart rate, PR, QRS and QTcB), differences between baseline and follow-up were examined with Wilcoxon signed-rank test. Logistic regression analyses, univariate and age/sex-adjusted, were performed to identify associations between baseline characteristics (independent variables) and present CCD at five-year follow-up (dependent variable). Log transformation of mSASSS+1 was used due to skewed distribution. Correlation between the independent variables (age, sex and respective baseline characteristic) was tested. The regression model was not carried out in case of a Spearman's correlation coefficient <-0.6 or > 0.6 between the independent variables. Unbalanced data of the independent variables was looked for in scatter plots of the independent variables. All tests were two-tailed and p < 0.05 was considered statistically significant. The statistical analyses were performed by PASW Statistics version 19.

We had planned to perform a linear regression analysis with PR interval at five-year follow-up as dependent variable, but the assumptions of linearity were not fulfilled.

4.4 ETHICAL CONSIDERATIONS

The comprehensive register-linkage used in Paper I, II and IV was approved by the Regional Ethics committee in Stockholm. Due to the register-based approach no written informed consent was needed. The longitudinal cohort study of patients with AS (Paper III) was approved by the Regional Ethics Committee in Gothenburg both at baseline and at five-year follow-up. The participating patients gave their written informed consent at both occasions. The research was performed in compliance with the Helsinki declaration.
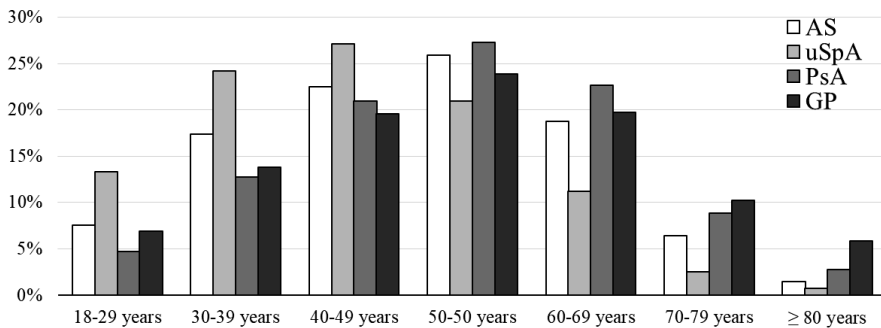
5 Results

5.1 PAPER I, II

5.1.1 Cohorts

Three separate cohorts of patients with AS (n=6448, 32% women, mean age 50 (14) years), uSpA (n=5190, 55% women, mean age 45 (13)) and PsA (n=16063, 55% women, mean age 53 (14)) and one GP cohort (n=266435, 51% women, mean age 53 (16)) were included in Paper I-II. The age distribution at start of follow-up are described in Figure 6.

Figure 6. Age distribution at start of follow-up in the AS, uSpA, PsA and GP cohort.

5.1.2 Paper I – main results

Incidence rates
Overall, the standardized IR point estimates for ACS, composite stroke and VTE ranged between 4.3 to 5.4 incident ACS events, 5.4 to 5.9 incident composite stroke events, and 3.2 to 3.6 incident VTE events per 1000 person-years at risk in the SpA subtypes compared to 3.2, 4.7 and 2.2 in the GP cohort. The standardized IRs stratified by sex are presented in Figure 7.

The standardized IRs and corresponding IRRs (SpA subtype vs GP) stratified by age intervals are presented in Figure 8 and Table 9. As shown, the IRs and IRRs in the oldest age interval (≥80 years) are based on few events in AS and uSpA and should be interpreted with caution.

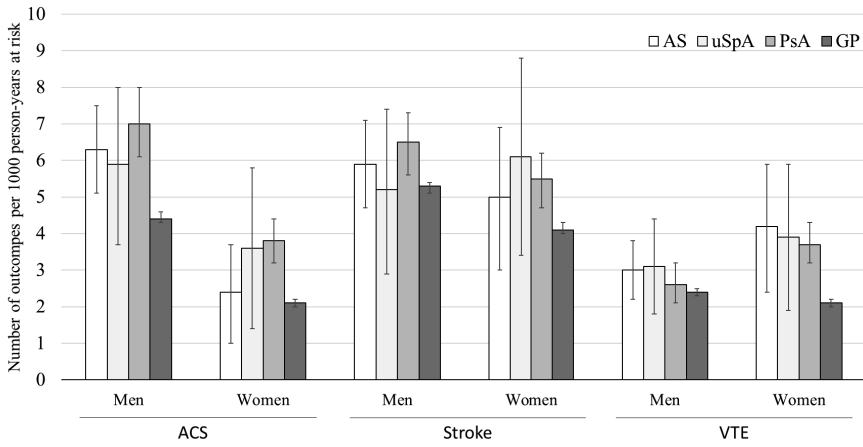*Figure 7. Standardized IRs with 95% CI for ACS, stroke and VTE, stratified by sex.*

Figure 8. Standardized IRs with 95% CI for ACS, stroke and VTE, stratified by age intervals.
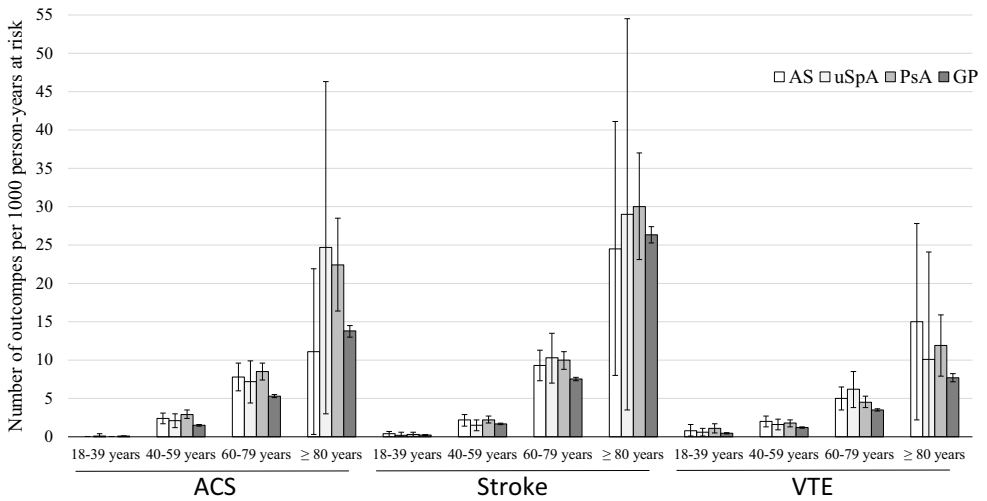
Table 9. Number (N) of outcomes during follow-up and age/sex-standardized IRRs (SpA subtype vs GP) with 95% CI per age interval.
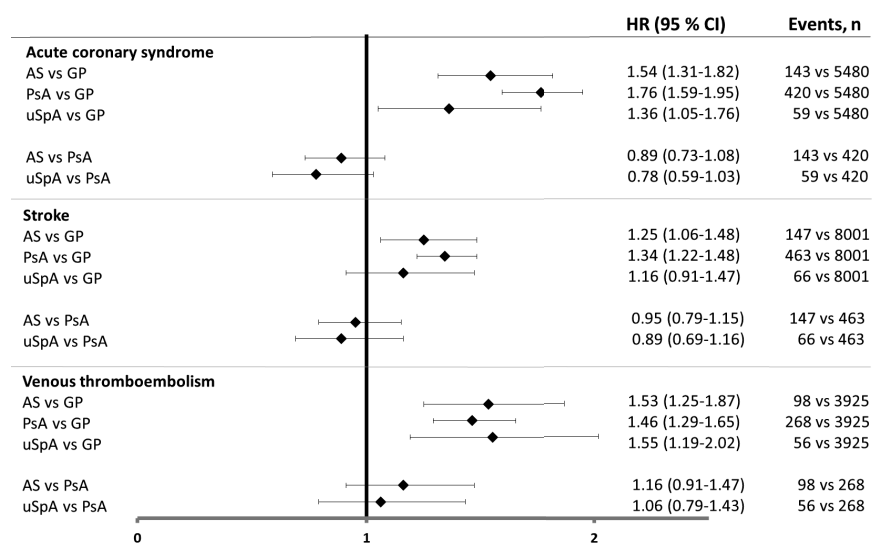
	GP	AS		uSpA		PsA	
	N	N	IRR (95%CI)	N	IRR (95% CI)	N	IRR (95%CI)
ACS							
18-39 years	27	0	0	1	1.4 (0.2-9.7)	0	0
40-59 years	1119	50	1.6 (1.2-2.2)	24	1.4 (0.97-2.0)	122	2.0 (1.6-2.4)
60-79 years	3046	88	1.5 (1.2-1.8)	29	1.4 (0.96-1.9)	244	1.6 (1.4-1.8)
≥ 80 years	1288	5	0.8 (0.3-1.9)	5	1.8 (0.8-4.3)	54	1.6 (1.3-2.1)
Stroke							
18-39 years	69	4	1.6 (0.5-5.6)	2	1.0 (0.2-4.2)	4	1.3 (0.5-3.6)
40-59 years	1246	38	1.3 (0.9-1.8)	17	0.9 (0.6-1.4)	94	1.3 (1.1-1.6)
60-79 years	4316	95	1.2 (1.0-1.5)	42	1.4 (1.0-1.8)	292	1.3 (1.2-1.5)
≥ 80 years	2370	10	0.9 (0.5-1.7)	5	1.1 (0.5-2.7)	73	1.1 (0.9-1.4)
VTE							
18-39 years	137	6	1.8 (0.8-4.2)	5	1.3 (0.5-3.1)	15	2.4 (1.4-4.2)
40-59 years	900	35	1.6 (1.2-2.3)	20	1.3 (0.9-2.0)	73	1.4 (1.1-1.8)
60-79 years	2088	51	1.4 (1.1-1.9)	29	1.8 (1.2-2.5)	145	1.3 (1.1-1.5)
≥ 80 years	800	6	2.0 (0.98-3.9)	2	1.3 (0.3-5.1)	35	1.5 (1.1-2.2)

Cox regression analyses

The age/sex-adjusted HRs for ACS, stroke and VTE were significantly increased in all SpA cohorts (vs GP) except for stroke in patients with uSpA (Figure 9). In sub-analyses, overall similar results were shown for ischemic stroke, whereas no increased HR for haemorrhagic stroke was observed in any of the SpA cohorts. In the sex stratified results, significantly increased age-adjusted HRs for ACS were noted in all men (vs GP) and in women with PsA (vs GP). The highest HR point estimate was noted in women with PsA vs GP (age-adjusted HR 2.0). For stroke, significantly increased age-adjusted HRs were noted in men with AS (vs GP) and in men and women with PsA (vs GP). In sex stratified results for VTE, significantly increased age-adjusted HRs were noted in all SpA cohorts (vs GP) except for men with PsA.

In comparison to PsA, no significant differences were demonstrated in AS and uSpA overall (Figure 9). In sex stratified analyses, women with AS (vs women with PsA) had significantly lower HRs for incident ACS.

Figure 9. Hazard ratios with 95% CI for ACS, stroke and VTE in the SpA subtypes (vs GP and vs PsA, respectively).
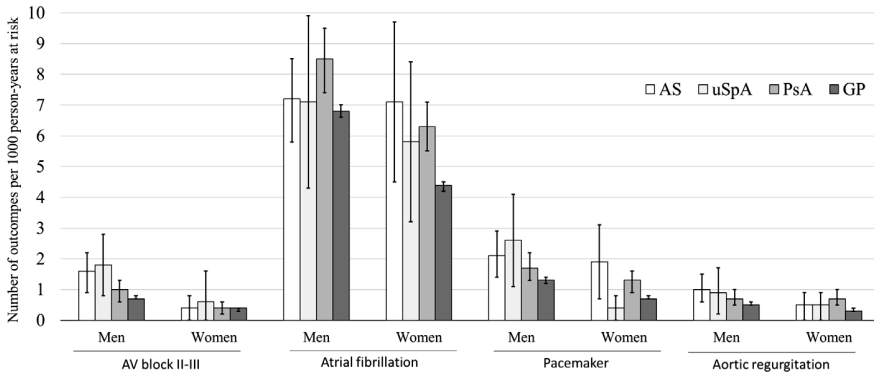
	HR (95 % CI)	Events, n
Acute coronary syndrome		
AS vs GP	1.54 (1.31-1.82)	143 vs 5480
PsA vs GP	1.76 (1.59-1.95)	420 vs 5480
uSpA vs GP	1.36 (1.05-1.76)	59 vs 5480
AS vs PsA	0.89 (0.73-1.08)	143 vs 420
uSpA vs PsA	0.78 (0.59-1.03)	59 vs 420
Stroke		
AS vs GP	1.25 (1.06-1.48)	147 vs 8001
PsA vs GP	1.34 (1.22-1.48)	463 vs 8001
uSpA vs GP	1.16 (0.91-1.47)	66 vs 8001
AS vs PsA	0.95 (0.79-1.15)	147 vs 463
uSpA vs PsA	0.89 (0.69-1.16)	66 vs 463
Venous thromboembolism		
AS vs GP	1.53 (1.25-1.87)	98 vs 3925
PsA vs GP	1.46 (1.29-1.65)	268 vs 3925
uSpA vs GP	1.55 (1.19-2.02)	56 vs 3925
AS vs PsA	1.16 (0.91-1.47)	98 vs 268
uSpA vs PsA	1.06 (0.79-1.43)	56 vs 268

5.1.3 Paper II – main results

Incidence rates

Overall, the standardized IR point estimates for AV block II-III, AF and aortic regurgitation ranged between 0.7 to 1.2 AV block II-III, 6.4 to 7.4 AF, and 0.7 to 0.7 aortic regurgitation per 1000 person-years at risk in the SpA subtypes compared to 0.5, 5.5 and 0.4 in the GP cohort. The corresponding standardized IR point estimates for pacemaker implantation ranged between 1.5 to 2.0 pacemaker implantation per 1000 person-years at risk in the SpA subtypes compared to 1.0 in the GP cohort.

The standardized IRs stratified by sex are presented in Figure 10. Of note, low number of outcomes were noted for pacemaker implantation in women with uSpA (n=3), AV block II-III in women with AS (n=3) and uSpA (n=2), and aortic regurgitation in uSpA (n=7 in men, n=6 in women) and in women with AS (n=4).
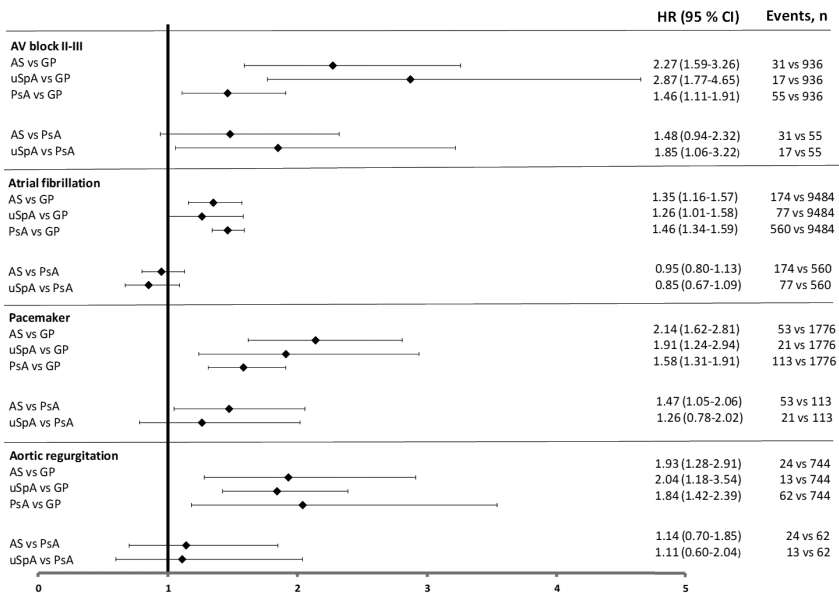
Figure 10. Standardized IRs with 95% CI for AV block II-III, AF, pacemaker implantation and aortic regurgitation, , stratified by sex

Cox regression analyses

Overall, the age/sex-adjusted HRs were significantly increased for all studied outcomes in AS, uSpA and PsA in comparison to GP cohort (Figure 11). The highest HR point estimates were observed for AV block II-III in AS and uSpA. In the sex stratified results significantly increased HRs for AV block II-III were seen in men with SpA, especially in AS (age-adjusted HR 2.5) and uSpA (age-adjusted HR 4.2), whereas no significantly increased HR was noted in women with SpA vs GP. In comparison to PsA, significantly increased HRs for pacemaker were noted in patients with AS and for AV block II-III in patients with uSpA.

Figure 11. HRs with 95% CI for AV block II-III, AF, pacemaker and aortic regurgitation in the SpA subtypes (vs GP and vs PsA, respectively)
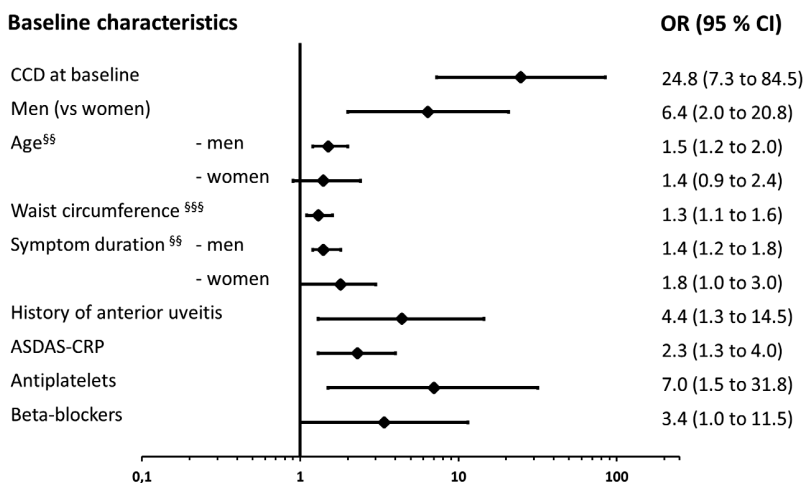
5.2 PAPER III

ECG development from baseline to five-year follow-up

The majority (n=156, 91%) had normal sinus rhythm at follow-up, whereas three had pacemaker rhythm, two had AF and the remaining 11 patients had either sinus bradycardia or tachycardia. The PR interval increased significantly from baseline to five-year follow-up in both sexes and QRS interval increased in men. In total, 23 patients (13%) had a CCD according to the definition (Table 8). Of these 23 CCD, 14 were lone AV block of first degree, three were LAFB (one combined with AV block Ix), three were bundle branch block (one RBBB combined with AV block I) and three had pacemaker rhythm. Eight CCDs were developed from baseline (six AV block of first degree and two pacemakers) and eight ECG (six AV block of first degree and two LAFB) were normalized. With regard to sex and age, 19 of 23 were men and 18 were older than the median age 49 years at baseline.

Logistic regression analyses

In the age/sex-adjusted logistic regression analyses, CCD at baseline, history of AU, higher ASDAS-CRP, greater waist-circumference and treatment with platelets and beta-blockers at baseline were significantly associated with CCD at follow-up (Figure 12). Higher age and longer symptom duration (highly correlated with age) likewise male sex (adjusted for age only) were significantly associated with CCD at follow-up (Figure 12).

Figure 12. Age/sex-adjusted[§] logistic regression analyses (each baseline characteristic analysed separately) with CCD at follow-up as the dependent variable.
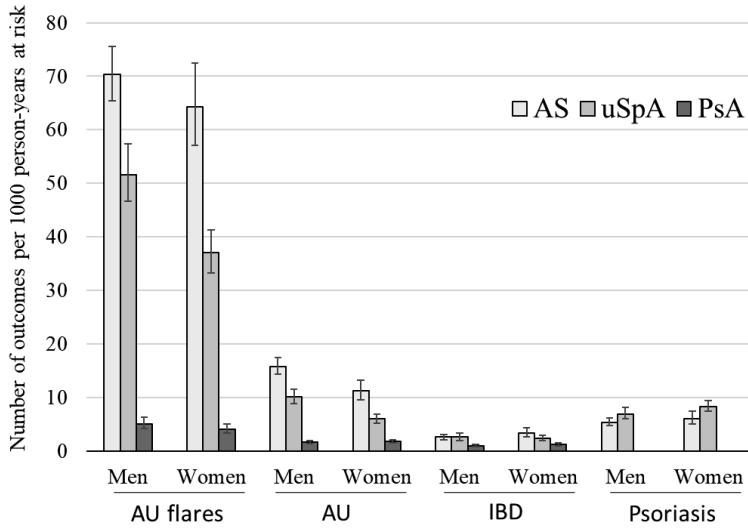

Baseline characteristics		OR (95 % CI)
CCD at baseline		24.8 (7.3 to 84.5)
Men (vs women)		6.4 (2.0 to 20.8)
Age[§§] - men		1.5 (1.2 to 2.0)
- women		1.4 (0.9 to 2.4)
Waist circumference [§§§]		1.3 (1.1 to 1.6)
Symptom duration [§§] - men		1.4 (1.2 to 1.8)
- women		1.8 (1.0 to 3.0)
History of anterior uveitis		4.4 (1.3 to 14.5)
ASDAS-CRP		2.3 (1.3 to 4.0)
Antiplatelets		7.0 (1.5 to 31.8)
Beta-blockers		3.4 (1.0 to 11.5)

[§]Age and symptom duration is stratified by sex and not further adjusted. Sex (men vs women) is adjusted for age only. [§§] Per five years. [§§§] Per five cm.

5.3 PAPER IV

Incidence rates

The IRs for the studied EAMs in AS, uSpA and PsA are presented in Figure 13. The highest IRs were noted for AU in all SpA subtypes (psoriasis in PsA not taken into account). In AS and uSpA, women had lower IRs for incident AU than men.
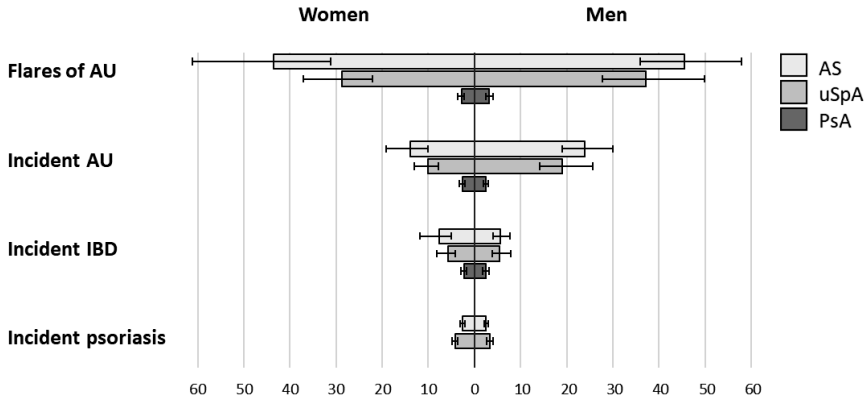
Figure 13. IRs with 95% CI for the studied EAMs in patients with AS, uSpA and PsA.

Poisson regression analyses

The IRRs for the different EAMs are shown in Figure 14. Overall, the highest IRRs (SpA subtype vs matched controls) were noted for AU in patients with AS.

Figure 14. IRRs with 95% CI for the studied EAMs in patients with AS, uSpA and PsA.

6 Discussion

This thesis reports on the risk of CVD outcomes and extra-articular manifestations in SpA in comparison to general population, and includes results for uSpA where previous research is especially lacking. Importantly, uSpA constituted a large proportion of the patients with diagnosed SpA included in Paper I-II, IV.

6.1 MAIN FINDINGS AND PREVIOUS RESEARCH

6.1.1 ACS and stroke

In paper I, we demonstrated an increased risk (36-76%) of ACS in all studied SpA subtypes in comparison to general population and an increased risk of the composite stroke outcome (25-34%) in AS and PsA. In PsA, the increased relative risk of ACS was consistent in both sexes, especially pronounced in women, and in all ages above 40 years of age. For AS and uSpA, the increased relative risk of ACS was significantly increased in men, but not in women. The absolute risks (IRs) for the composite stroke outcome were slightly higher than the absolute risks (IRs) for ACS in all cohorts, whereas the relative risk for the composite stroke outcome was lower than for ACS in all SpA subtypes vs general population.

With regard to other previous studies of PsA (Table 5), the current results are in concordance with the Danish and UK studies on MI/IHD and cerebrovascular disease, albeit their relative risk estimates for acute MI and IHD were lower than ours (for ACS) and with regard to stroke, Ogdie et al demonstrated an increased risk only in PsA without csDMARD at baseline (151, 160, 170). Of note, none of these studies provided sex stratified results and Ogdie et al did not reveal an increased relative risk of cardiovascular death in PsA. To my knowledge, other published, population-based studies specifically on incidence on MI/ACS or stroke in PsA have not been performed. Though, the current results are also in accordance with a cross-sectional US study who demonstrated increased prevalence of IHD and cerebrovascular disease in PsA compared to controls and with a British study who reported an increased incidence of the composite outcome MACE compared to controls (163, 169). Also, Gladman et al found a twofold increased prevalence of MI and angina in patients with PsA followed at a specialist rheumatology unit compared with standard population in Ontario and Gulati et al found an increased self-reported prevalence of angina and PCI, however not MI, in 338 patients with PsA compared to controls (155, 156). Neither of these two studies found an increased prevalence of stroke. Also contrary to our results, a Swedish study of 464 patients with PsA found decreased standardized incidence ratio for both stroke and acute MI compared to general population (149). On the other hand and contrary to Ogdie et al, the latter study found an increased SMR for cardiovascular death. Last, our preliminary data presented as an abstract have been part of a meta-

analysis of CVD in PsA which demonstrated an increased risk of MI (pooled OR 1.7) and cerebrovascular events (pooled OR 1.2) (269).

In AS, studies of atherosclerotic CVDs have drawn diverging conclusions (Table 5). However, in similarity with our results the majority of studies did report an increased relative risk of ACS/MI/IHD outcomes, although neither Bremander et al nor Brophy et al could demonstrate significantly increased risk for acute MI (50, 163-166, 172). Of note, slightly more women than men with AS were included in the study by Chou et al and an equally increased relative risk of ACS in men and women was demonstrated (166). In contrast to the other studies, Essers et al did not reveal an increased risk of acute MI in patients with AS in comparison to controls (age/sex-adjusted HR 0.9) (168). Yet, the study demonstrated an increased risk of IHD in women with AS (age-adjusted HR 1.9 (1.2 to 2.9)), but after adjustment for recent NSAID the relative risk became non-significantly increased (adjusted HR 1.6 (0.99-2.5)) and further attenuated when the analysis was adjusted for other CVD risk factors (adjusted HR 1.3 (0.8 to 2.1)). For stroke, the relative risk estimates span from no increased risk (UK, Taiwan) to a more than twofold increased risk (Taiwan) (78, 163-165, 173).

In conclusion, the increased relative risk for ACS found in the present thesis is mainly supported by others, whereas the overall result for stroke is less elucidative and also in the present thesis consistent with lower relative risk estimates than for ACS.

6.1.2 VTE

With regard to venous thromboembolic outcomes, we demonstrated an increased risk (46-55%) of VTE in all studied SpA subtypes in comparison to general population (Paper I). In accordance, a study from UK found an increased risk of VTE in patients with PsA compared to controls from general population (158). However, the increased risk was diminished after further adjustment of potential VTE risk factors at baseline. After the publication of Paper I, one additional study have reported on VTE risk in AS and found an twofold increased relative risk in the age/sex-adjusted analyses and still increased after further adjustment for baseline characteristics (174).

6.1.3 AF

In paper II, we revealed an increased overall risk of AF (26-46%) in all SpA subtypes in comparison to general population and the increased relative risk was especially pronounced in women with SpA. After the publication of Paper II, one additional study has reported an increased relative risk of AF in patients with AS (unadjusted HR 1.5 (1.2-1.8), adjusted HR 1.3 (1.0-1.6)) (270). There are no other studies investigating risk of AF specifically in PsA, however some studies of psoriasis have found an increased risk (251, 253). Also, one study found increased risk of arrhythmia, which

comprised AF, in PsA compared to controls (271). As stated previously, underlying cardiac disease increases the risk of AF and presence of AF increases the risk of stroke and TIA. Thus, AF is an important factor to consider in the context.

6.1.4 Other cardiac manifestations

Concerning the other cardiac, and possible extra-articular, manifestations, an increased risk of AV block II-III and aortic regurgitation were shown in all SpA subtypes in comparison to general population. Of importance when interpreting the relative risks, the IRs were substantially higher for AF in all cohorts than for AV block II-III and aortic regurgitation. The result is in line with the beforehand acknowledged association with AS described more thoroughly in section 1.3.4 (Extra-articular cardiac manifestations). Interestingly, patients with uSpA had increased relative risk of AV block II-III in comparison to PsA, and the same was shown for the pacemaker outcome in AS in comparison to PsA. Further, we demonstrated a clear sex difference for AV block II-III which concerned AS and uSpA, but not PsA. Men, but not women, with AS and uSpA had an increased relative risk, more than twofold, for AV block II-III in comparison to general population. In similarity, Bremander et al found a fourfold increased SMR in AS for AV block, but did not register any AV block in women with AS (50). In further accordance with the current observed sex difference, men but not women with pacemaker-treated heart block had an increased frequency of HLA-B27 and associated rheumatic disorders (67). Also in the general population, a sex difference with regard to indication for pacemaker implantation is acknowledged. Men are more likely to have heart block as the primary indication for pacemaker implantation, while women are more likely to have sinus node disease or AF (272). In a Swedish study, AV conduction disturbance, sick sinus syndrome and AF were the ECG indications in 38%, 34% and 15%, respectively, of the pacemaker implantations (273). Hence, the increased risk of pacemaker implantation in all SpA subtypes in comparison to general population is most likely, at least in part, a result of the increased risk of AF and AV block II-III. Ward et al found only a slightly higher relative risk of pacemaker implantation in AS aged 65 years and older in comparison to general population (79). In the present study, 85% of patients with AS were younger than 65 years at start of follow-up which make comparison difficult.

6.1.5 Characteristics associated with CCDs

In Paper III, 23 (13%) had a CCD at five-year follow-up, the majority consisted of AV block of first degree or LAFB and would consequently not be captured by Paper II. In addition to higher age/longer symptom duration and male sex, CCD at baseline, history of AU, higher ASDAS-CRP, greater waist circumference and treatment with platelets and beta-blockers at baseline were significantly associated with CCD at follow-up.

First of all, some of the observed associations with CCDs, such as male sex, age and markers of CVD are not unique for AS but also found in the general population (274). AS characteristics associated with CCDs are very little explored in contemporary cohorts and no study to my knowledge have investigated CCDs prospectively in patients with AS. Lange et al compared characteristics in a cross-sectional study of AS (n=77) and found higher CRP and ESR in the patients with ECG abnormalities (n=12) compared with the patients without (73). The study did not demonstrate any significant difference in age and sex between the groups, however the mean age was 6 years older in the group with ECG abnormalities and all were men. Clinical characteristics such as AU and disease activity scores were not analysed. Dik et al investigated AS characteristics, however not AU, in relation to the PR and QRS intervals in 131 patients with AS (74). Age, disease duration and BMI were associated with the PR interval and male sex, disease duration and BASMI were associated with the QRS interval. No association with ESR, CRP, BASDAI and BASFI were shown. HLA-B27 has been proposed as a genetic risk factor for cardiac manifestations per se (57). Neither we, Dik et al nor Lange et al, could find a significant association with HLA-B27, but all three studied cohorts had an overall high prevalence of HLA-B27. According to some historical cohorts, peripheral arthritis was observed more frequently in patients with vs without cardiac involvement, however not found in the present cohort (61-63). Of note, history of AU was also independently associated with aortic regurgitation in the baseline investigation of the AS cohort studied in Paper III (70).

6.1.6 Extra-articular manifestations

Extra-articular manifestations such as AU, IBD and psoriasis are closely linked to the SpA diagnoses but as shown in Paper IV with considerably different strengths depending on the diagnosis. AS and uSpA were strongly associated with AU and IBD, whereas a considerably weaker association were demonstrated in PsA for these two EAMs. The overall results with regard to relative risk estimates in comparison to general population are in reasonable agreement with existing studies of incident EAMs in AS and PsA (Table 2) and provide robustness to the results especially in PsA, both with regard to prevalence of EAMs at baseline and incidence during follow-up, given the inconclusive results for AU and UC in previous studies (46, 47, 50-55). In similarity with the results for AV block II-III (Paper II), a sex difference was observed also in Paper IV for AS and uSpA. Men with AS and uSpA had higher absolute risk (IRs) for incident AU than women with AS and uSpA. This is in line with Stolwijk et al, who also observed higher HR point estimates (sex stratified IRs not provided) for men with AS vs controls than for the women with AS vs controls (51). On the contrary, a previous Swedish study demonstrated higher SMR (and slightly higher morbidity rates) for AU in women with AS than in men with AS, however not statistically different (50). Importantly, other sex differences, such as more structural changes in men than women with axial SpA, are well recognized (275).

6.2 METHODOLOGICAL LIMITATIONS

6.2.1 Study design

Paper I, II, IV are population-based observational cohort studies. The Swedish health care and population registers enable a unique and cost-effective possibility to study rare events with minimal loss of follow-up. The main disadvantages are the risk of misclassifications and the lack of details (further described in the next sections).

Paper III is a prospective, longitudinal cohort study with investigations at two occasions five years apart. The patients are thoroughly described and examined at both occasions. Repeated examinations and ECG during the follow-up could have strengthen the study. Dropouts are an overall concern in longitudinal cohort studies.

6.2.2 Selection of patients and controls

Paper I, II, IV

Selection bias secondary to non-representative sampling is a minor concern since all patients in Sweden who fulfilled the inclusion criteria and without exclusion criteria were included.

Misclassifications (information bias) are a potential risk since the patients were selected based on ICD codes. The ICD codes for AS and uSpA have been validated in a previous study (25). In AS, the PPVs for fulfilling mNY criteria, ASAS-axial or any set of SpA criteria (mNY, ASAS-axial/peripheral, ESSG or Amor) was 70%, 79% and 89%, respectively. For the AS patients with available imaging and/or HLA-B27, the PPVs increased to 80%, 86% and 97%, respectively. In uSpA, corresponding PPVs for mNY criteria, ASAS-axial/peripheral or any set of SpA criteria were 20%, 73% and 79%. Likewise, for the patients with available imaging and/or HLA-B27 the PPVs increased to 26%, 82% and 89%. In PsA, a validation study including both primary and specialized care showed overall PPVs within the range of 63% to 92%, the difference secondary to insufficient information for diagnosis verification (276). The highest PPVs (89% to 95%) were demonstrated in case of registered ICD codes at least on two occasions in any specialized care. The PPVs for ICD codes specifically in rheumatology or internal medicine care were not determined.

To avoid mixing of the SpA diagnoses, we analysed those with more than two diagnoses in a mixed SpA cohort. One alternative could have been to keep the patients with mix diagnoses of uSpA and AS/PsA in the more specified cohort (AS and PsA, respectively). The validation study of AS and uSpA demonstrated that patients with an overlap had similar PPVs for fulfilling mNY criteria as patients with AS which would have supported such strategy (25). Furthermore, in Paper IV and in contrast to Paper I-II, the number of patients with uSpA exceeded the number of patients with AS. In

Paper IV we added one more possible ICD code for uSpA which understandably will explain some of this difference. This difference was explored in two steps. First, the patients with uSpA from Paper I, II were compared with their counterparts in Paper IV (without the age restriction) included 2001 to 2009. The age and sex distribution was similar and also the proportion with a history of AU, IBD and psoriasis. Second, in Paper IV, the patients who started the follow-up 2006 to 2009 consisted of 22% AS, 23% uSpA and 55% PsA. Corresponding proportions for the last study period 2013 to 2016 were 18% AS, 28% uSpA and 54% PsA. This shift in diagnoses probably mirrors the increased awareness of the broader SpA concept and coincide with the publication of the new criteria for axial and peripheral SpA (85, 86). Clearly and also demonstrated by the validity study described above, some remaining overlapping between the SpA cohorts are unavoidable despite our efforts to avoid case mixing.

Left censoring secondary to the inclusion of prevalent and not incident patients is another possible limitation. The patients who already have experienced an outcome after their SpA symptom onset but before the start of follow-up are not taken into account in the primary analyses. The NPR can unfortunately not discriminate between incident and prevalent patients (25). Diagnostic delays are still an issue for patients with SpA (277).

External validity is the ability to generalize the study findings to patients outside the target population. Patients with SpA not eligible to enter the studies were, among others, those only followed in primary health care and undiagnosed patients with SpA. These are patients with a presumably less severe disease which may have influenced the generalizability of the results.

For the controls, different strategies were used for the selection in Paper I-II and Paper IV. Originally, the controls were matched on birth year, sex and county of residence at the date of the first SpA diagnosis in NPR for each index patient, irrespective of health care level and year of diagnosis. The controls were identified from a Population register of all Swedish residents, thus with low risk of selection bias. In Paper I-II all available controls that fulfilled the inclusion but not the exclusion criteria were used as one single comparator group. As a consequence, all analyses needed adjustment or standardization for age and sex. In Paper IV we instead decided to keep a matched strategy but made a contemporary re-match on birth year, sex and county of residence.

Paper III
Selection biases are potential limitations in Paper III. The patients were identified from medical records at three Rheumatology departments in Region Västra Götaland and all eligible patients (n=361) were invited to participate in the study at baseline. However, some of the patients (n=132) declined participation or did not respond to the invitation. These patients had a lower mean age, but the sex distribution was not statistically

different (75). During follow-up, additionally 38 patients (mean age 50 (14) years, 74% men) dropped out from the study, five had died and the remaining 33 patients did not respond or declined further participation. In comparison to the participating patients, the mean age was similar, however significantly more men than women dropped out. Dropouts may have introduced a selection bias and may have affected the internal validity.

6.2.3 Outcomes

Paper I, II, IV

First, misclassifications are a major concern for the outcome definitions based on ICD, procedure or ATC codes in the registers. Some of the outcomes (MI, angina, stroke, AF, VTE, psoriasis, IBD with subcategories) have been validated in NPR with PPVs ranging between 68% (CD) to 98% (MI) (264, 278-282). One possibility to strengthen the VTE outcome, which was not done in Paper I, could have been to demand a prescription of anticoagulation treatment in close connection to the registered ICD code.

Second, for outcomes such as AF and psoriasis there is a risk of underestimation based on potential management solely in primary health care. We tried to overcome this partially for psoriasis by adding ATC codes to the definition. Further, neither CVD events resulting in sudden deaths nor ACS and stroke managed outside of inpatient care are detected. The restriction to inpatient care was on the other hand done to ensure high validity of these outcomes.

Third, diagnoses made in specialized outpatient care before 2001 are not captured in NPR. This was an issue only for prior outcomes and not the outcomes identified during follow-up, but might have misclassified some truly prevalent outcomes as incident.

Fourth, surveillance bias might be an issue particularly for the EAMs, including aortic regurgitation and psoriasis, based on more thorough search or alertness for these manifestations in patients with SpA compared to controls.

Paper III

Inter-rater variability is a possible limitation in Paper III. Different methods were used for the specific measurements of the ECG intervals, at baseline this was done manually and at follow-up the measurements were provided from the ECG machine. The ECG interpretation was performed by two different investigators at baseline and follow-up, although thereafter jointly with the same specialist in cardiology at both occasions. We cannot categorically exclude that some variation of the intervals and ECG interpretation are explained by an inter-rater variability.

Recall bias is another potential limitation since some of the baseline characteristics used as independent variables, such as symptom duration, are based on questionnaires.

6.2.4 Analyses

In Paper I, analyses stratified by age intervals should preferable have been presented in the publication.

In Paper II, except for AF the number of outcomes were relatively few in the SpA cohorts and especially scarce in some of the stratified data (for example AV block in women with AS and uSpA). This may have resulted in type II errors, which is the inability to reject a null hypothesis which is not true.

In Paper I-II, potential confounding factors beyond age and sex were not accounted for. We could have adjusted for some CVD related medications and risk factors through data from the PDR and NPR (and also did in supplementary material for Paper II). However, residual confounding would have been unavoidable secondary to incomplete CVD risk factor profile including smoking, hereditary factors, psychosocial deprivation, physical activity and adiposity measurements and lack of SpA disease-activity measurements, clinical appearance (axial/peripheral involvement) and HLA-B27 status. Further, the patients had a prevalent SpA and baseline characteristics can have been affected by prior SpA manifestations. Of importance, we were well aware of this limitation in beforehand and the aim was to assess, and not explain, the risk of CVD outcomes in the different SpA subtypes. Also in Paper IV, the SpA related disease characteristics would have been of great value.

In Paper III, the analyses were constrained by the low number of CCDs (the dependent variable) which inhibited adjustment beyond age and sex and extensive check of interactions. There were also signs of unbalanced data for some of the CVD related medical treatments with regard to age, and the outcome was also rarely seen in the ages below 50 years. Thus, the results may not be valid for patients below 50 years of age.

6.3   IMPLICATIONS AND FUTURE PERSPECTIVE

The report from this thesis clearly point towards an increased risk of ACS in SpA, particularly in the PsA subtype, and a probable increased risk of stroke at least in AS and PsA. The findings reinforce that the EULAR recommendations and Swedish Rheumatology Guidelines (www.svenskreumatologi.se/srfs-riktlinjer) for CVD prevention should be applied in all SpA (247). EULAR recommendations, which is in accordance with European Society of Cardiology guidelines on CVD prevention, recommend CVD risk assessment at least once every fifth year and to use SCORE if no other national guideline is available. A recent study revealed that patients with psoriatic disease were both underdiagnosed and undertreated with regard to cardiovascular risk factors (283). Another contemporary study from Norway showed that a great proportion of patients with axial SpA and PsA were left untreated despite indication for antihypertensive and lipid-lowering treatment or were insufficiently treated with regard to treatment targets (284). Also in AS, treatment targets for

hypertension and hyperlipidaemia were not reached according to another study (176). Hence, it is of great importance to implement strategies in the clinic to identify and improve CVD risk factors in patients with SpA. Moreover, identification of lifestyle factors such as smoking, physical inactivity and obesity should be assessed continuously and as part of the regular rheumatology follow-up.

Apart from AF, we did not address possible causes of the detected increased risk of ACS, stroke and VTE. As discussed in the previous section 2.2.3 (Risk factors) several other studies have focused on the CVD risk profile and often found the traditional risk profile more unfavourable than in general population/controls and especially in PsA, whereas the inflammatory contribution is less conclusive. Remarkably, the results with regard to cardiovascular mortality in PsA has not been consistent (148). Of note, obesity is considered as an inflammatory state per se and an appealing factor to target, given the possible link between risk of atherosclerotic and venous thromboembolic events likewise disease-activity at least in PsA (136, 285, 286). Previous studies have recognized an underestimation of CVD risk scores in SpA and some have suggested to include subclinical atherosclerosis markers likewise in PsA the use of multiplication factor of 1.5 in CVD risk scores (287-292). These suggestions can accordingly not be answered by this thesis. Disentangling the traditional risk factors from the inflammatory component is not an easy-forward task. Investigations on markers of subclinical atherosclerosis might give rise to new tools how the CVD risk assessment in SpA can be improved. With current knowledge, carotid ultrasound for atherosclerotic plaque detection and ankle-brachial index may be considered as a risk modifier in CV risk assessment, whereas cIMT is not recommended according to the European guideline on CVD prevention (122). Additionally, future studies will enlighten if target inflammation in atherosclerosis will improve outcome also in the general population.

Except for the confirmation of its existence and need of an enhanced awareness, the immediate implication in clinical practice of the increased risk of aortic regurgitation and AV block II-III in SpA in comparison to general population is less straight forward. The explanatory factors that contribute to the increased risk of these manifestations may differ between the SpA subtypes, which the difference between AS/uSpA and PsA might imply, and the absolute risks were considerably lower than the absolute risks of for example AF. Inevitably, the methods used to detect these manifestations in Paper II will underestimate the true incidence. Indeed, a larger proportion, 18% of the 172 patients, had a CCD at baseline and/or at follow-up in the longitudinal AS cohort study (Paper III). The clinical characteristics found to be associated with CCD in Paper III could be used to identify patients particularly prone (or not) to present with CCDs. The associations with AU and disease activity measured with ASDAS-CRP are also intriguing. However, the majority of CCDs was AV block of first degree or LAFB and the clinical relevance is less clear even if AV block of first

degree also in the general population have suggested unfavourable prognosis (293). Hence, there are several important questions to address in future research which includes: Are these cardiac manifestations modifiable by anti-rheumatic treatment? Can early detection and follow-up in asymptomatic stages affect treatment decision and long-term prognosis? Until these future questions are clarified, systematic screening of patients with SpA is hard to support in ordinary clinical practice.

The last main finding from the thesis involves the pattern of the EAMs in AS, uSpA and PsA. Based on the comparable strengths of association of the different EAMs in AS and uSpA and also a similar sex difference with regard to incident AU and AV block II-III, the results suggest a substantial shared aetiology between AS and uSpA. On the contrary, the considerably weaker association found in PsA points toward a more diverse and less shared aetiology between (or within) PsA and the other two subtypes. The SpA has moved towards a concept built on subdividing the diseases in the phenotypic expression in peripheral and axial SpA and grouping of the AS/r-axSpA and nr-axSpA into one entity. Several research questions of disease evolvement and progression likewise the observed phenotypical and sex differences remain to study. More specifically, it would be of interest to further study the women with AS/uSpA and AU with regard to other disease characteristics and recurrence rate of AU.

7 Conclusion

✓ Patients with SpA are at increased risk of ACS, stroke, VTE and AF compared to general population. The increased relative risk of ACS was especially pronounced in women with PsA.

✓ Patients with SpA are at increased risk of diagnosed aortic regurgitation and AV block II-III, cardiovascular outcomes also considered as potential EAMs, in comparison to general population, although the absolute risks were low. The increased relative risk of AV block II-III was especially pronounced in men with AS and uSpA.

✓ An increased relative risk of pacemaker implantation was observed in all SpA subtypes in comparison to general population, and likely as a result of the increased risk for AF and AV block II-III.

✓ CCD was found in 18% of 172 patients with AS, either at baseline and/or at five-year follow-up, and infrequently in women and in ages below 50 years at baseline. In addition to male sex and higher age/longer AS symptom duration, characteristics at baseline such as CCD, higher AS disease activity, history of AU and markers of CVD were associated with presence of CCD at five-year follow-up.

✓ As expected, the extra-articular manifestations (AU, IBD and psoriasis) were significantly associated with SpA, but with considerably different strengths depending on the specific SpA subtype. Hence, a strong association for AU and IBD was noted in AS, closely followed by uSpA, whereas the association for these manifestations was considerably weaker in PsA.

✓ Overall, the results underscore the need to implement strategies in clinical practice to improve CVD risk factors management in patients with SpA irrespective of subtype. The patients would plausible benefit both with regard to improvement of future CVD risk and with regard to the rheumatic disease per se.

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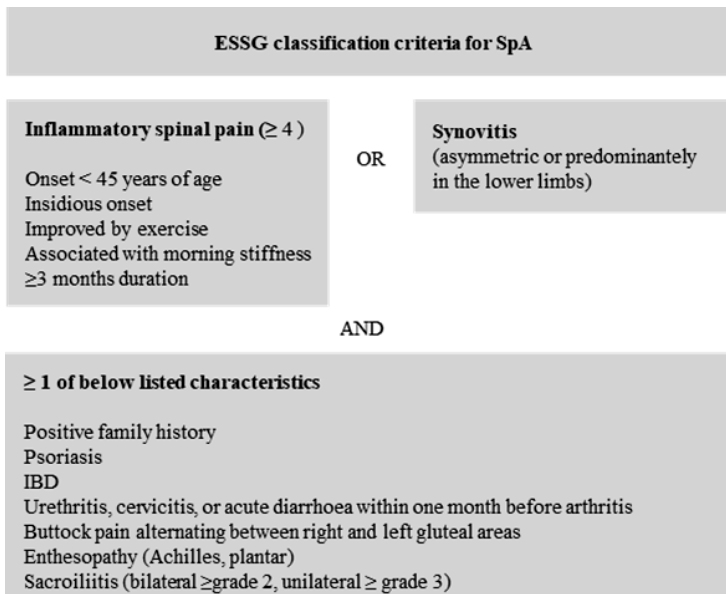
Appendix

Table 10. Amor criteria for SpA (83, 266)

Amor criteria for SpA
Definitive SpA if ≥ 6 points, probable SpA if ≥ 5 points
Clinical symptoms or past history - Lumbar or dorsal pain during the night, or morning stiffness of lumbar or dorsal spine (1 point) - Asymmetric oligoarthritis (2 points) - Buttock pain (1 point), if affecting alternately the right or the left buttock (2 points) - Sausage-like toe or digit (dactylitis) (2 points) - Heel pain or any other well defined enthesiopathy (enthesitis) (2 points) - Iritis (2 points) - Non-gonococcal urethritis or cervicitis accompanying, or within 1 month before, the onset of arthritis (1 point) - Acute diarrhea accompanying, or within 1 month before, the onset of arthritis (1 point) - Presence of psoriasis, balanitis or IBD (2 points) **Radiological findings** - Sacroiliitis grade ≥2 bilaterally or sacroiliitis grade 3-4 unilaterally (3 points) **Genetic background** - Presence of HLA-B27, or familial history of AS, Reiters syndrome, uveitis, psoriasis or IBD (2 points) **Response to treatment** - Good respons to NSAIDs in less than 48 hours, or relapse of pain in less than 48 hours if NSAID discontinued (2 points)

Figure 15. ESSG criteria for SpA(84)

ESSG classification criteria for SpA

Inflammatory spinal pain (≥ 4)

Onset < 45 years of age
Insidious onset
Improved by exercise
Associated with morning stiffness
≥3 months duration

OR

Synovitis
(asymmetric or predominantely in the lower limbs)

AND

≥ 1 of below listed characteristics

Positive family history
Psoriasis
IBD
Urethritis, cervicitis, or acute diarrhoea within one month before arthritis
Buttock pain alternating between right and left gluteal areas
Enthesopathy (Achilles, plantar)
Sacroiliitis (bilateral ≥grade 2, unilateral ≥ grade 3)

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