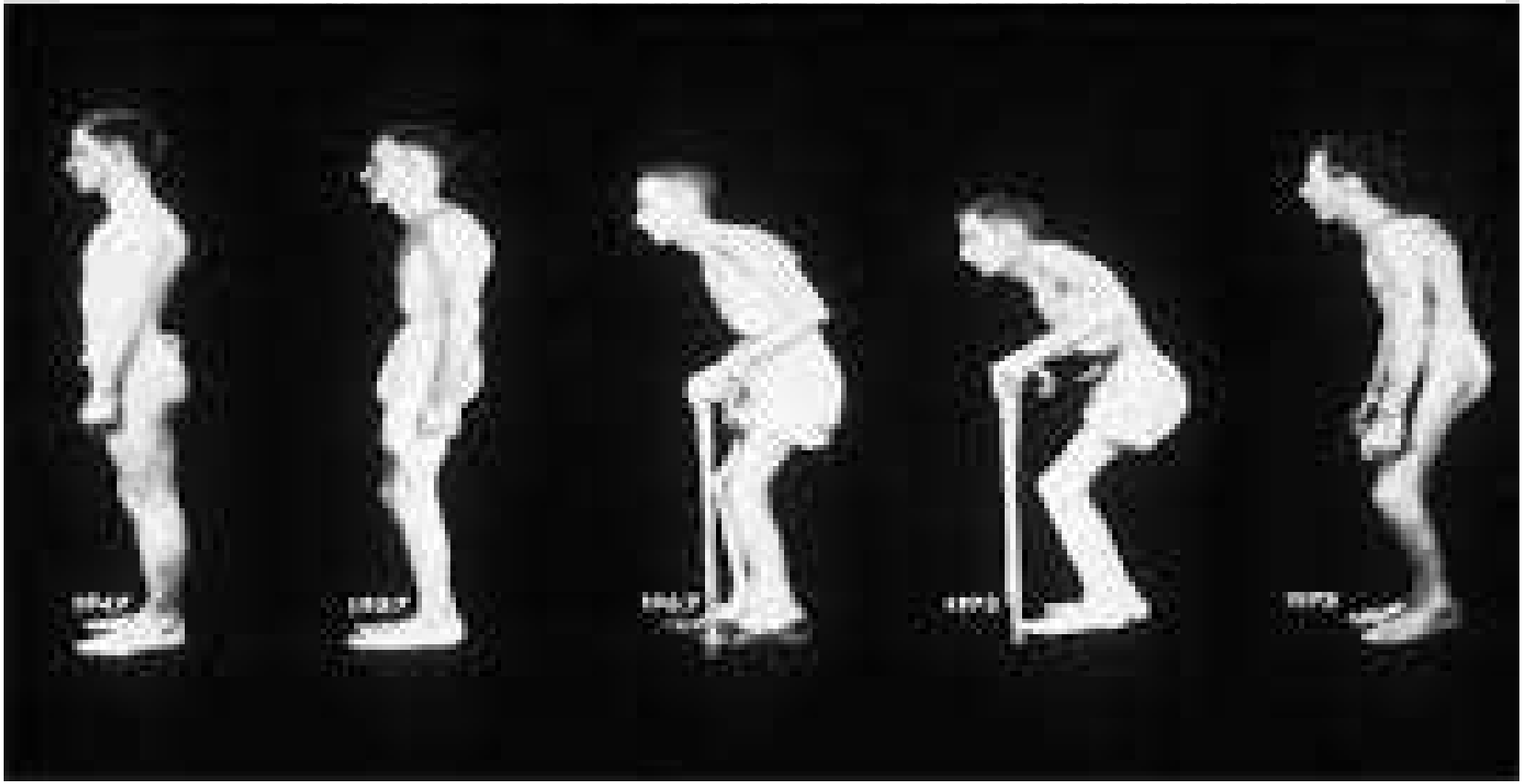
Rheumatology Department of Lucania
S. Carlo Hospital of Potenza and Madonna delle Grazie Hospital of Matera

Spondilite anchilosante e malattie cardiovascolari

Pietro Leccese



Patients with ankylosing spondylitis (AS) suffer from an increased cardiovascular (CV) risk.

- ✓ Inflammation
- ✓ AS related cardiovascular manifestations

- ✓ **Inflammation**

Accelerates atherosclerosis directly and via effects on CV risk factors (lipid levels, blood pressure and insulin resistance)

- ✓ Associated cardiovascular manifestations

- ✓ Mortality
- ✓ Cardiovascular comorbidity
- ✓ Preclinical atherosclerosis
- ✓ Cardiovascular risk factors

- ✓**Mortality**
- ✓Cardiovascular comorbidity
- ✓Preclinical atherosclerosis
- ✓Cardiovascular risk factors

Table 1 Mortality in ankylosing spondylitis

Study	Study design	Comparison group	Number of patients	Time period	Findings
Bakland et al. 2011 [2]	Hospital-based	General population Norway	677	1977–2009	SMR: 1.61 (1.29–1.93)
Mok et al. 2011 [3]	Hospital -based	General Population Hong Kong	2,332	1999–2008	SMR: 1.87 (1.61–2.13)

SMR: standardized mortality ratio

Increased mortality in ankylosing spondylitis is related to disease activity

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ABSTRACT

Background The onset of disease in ankylosing spondylitis (AS) is generally earlier than in other joint diseases, exposing patients to a prolonged burden of disease. Whether this is associated with excess mortality is still uncertain. Radiation therapy for AS has previously been shown to increase mortality. The present study investigated standardised mortality ratios, causes of death and survival predictors in a large regional cohort of patients with AS.

Method A total of 677 patients with AS followed at our hospital since 1977 were matched by gender, age and postal area to three controls from the general population and standardised mortality rates (SMRs) were calculated. Cause of death was established using patients' hospital records. In a subset of 360 patients, clinical and demographic data collected during an earlier research visit (1998–2000) were used in a prospective multivariate analysis of predictors for mortality in AS.

Results The crude mortality among patients with AS in this study was 14.5% (98 patients); SMR was only significantly increased among male patients compared with female patients (1.63 vs 1.38, $p<0.001$). Circulatory disease was the most frequent cause of death (40.0%), followed by malignant (26.8%) and infectious (23.2%) diseases. Factors independently associated with reduced survival were diagnostic delay (OR 1.05), increasing levels of C-reactive protein (OR 2.68), work disability (OR 3.65) and not using any non-steroidal anti-inflammatory drugs (OR 4.35).

Conclusions Mortality is increased in patients with AS and circulatory disease is the most frequent cause of death. Parameters reflecting the duration and intensity of inflammation are associated with reduced survival. These results indicate that, to improve long-term survival in AS, there is a need for early detection and anti-inflammatory treatment as well as a vigilant approach for cardiovascular risk factors.

Ann Rheum Dis 2011;**70**:1921–1925.

the potential for comorbidity development is present for several decades.[8] While malignant diseases occurred more frequently in patients with AS who received radiation therapy, circulatory diseases have been identified as a significant cause of mortality in AS in cohort studies.[3 5] Also, an increase in alcohol-related deaths in AS has been observed in a selected group of non-surviving patients with AS in Finland.[4] Given the limited amount of data on AS mortality in the literature and the fact that most of these studies were based on retrospectively collected data from the middle of the last century, it has been difficult to identify the risk factors associated with premature death in AS. In this study we present data on standardised mortality, long-term survival, cause of death and prospectively collected risk factors for premature death in a large cohort of patients with AS.

METHODS

The AS cohort in this study has been described in detail previously.[9] In brief, it includes all patients fulfilling the modified New York criteria for AS[10] seen in this region over the last three decades. The year of onset of symptoms consistent with AS was considered as the time of onset of the disease, and the time of diagnosis as the time of definite radiographic changes in the SI joints. For this analysis, each patient was assigned three controls from the general population who were matched for gender, age and postal area of residence. Thus, if the patient experienced his or her first symptoms at the age of 25 years in 1980, three controls would be selected, matched for age, gender and area of residence, and followed retrospectively from 1980 onwards. The follow-up period was defined as the time from symptom onset to 1 May 2009 or until the date of death. The assignment of cause of death was based on data obtained from patients'

Table 1 Standardised mortality rate (SMR) and 95% CI in ankylosing spondylitis specified by time of symptom onset

	Overall mortality			
	1.61		1.29–1.93	
	Male		Female	
Time of symptom onset				
–1969	1.34	0.74 to 1.94	2.00	0.04 to 3.96
1970–9	1.89	1.15 to 2.63	1.33	–0.52 to 3.18
1980–9	1.51	0.99 to 2.03	1.20	–0.16 to 2.56
1990–	2.16	0.95 to 3.41	0	
Overall mortality, gender-specified	1.63	1.29 to 1.97	1.38	0.48 to 2.28

Table 2 Causes of death in ankylosing spondylitis

Cause of death	Ascertained	Contributory	Total	(%)*
Circulatory	16	17	33	40.2
Malignancy	22	–	22	26.8
Infection	18	1	19	23.2
Other causes	6	2	8	9.8
Unknown	–	–	16	NA

*Not including unknown causes of death.

Bakland G et al. Ann Rheum Dis 2011;70:1921-5.

Table 4 Variables independently associated with increased mortality in ankylosing spondylitis

	OR	p Value	95% CI for OR
CRP, increasing levels	2.68	<0.001	1.774 to 4.048
NSAIDs, infrequent use	4.35	0.002	1.753 to 10.771
Diagnostic delay	1.05	0.026	1.006 to 1.101
Work disability	3.65	0.008	1.400 to 9.506

AS, ankylosing spondylitis; CRP, C-reactive protein; NSAIDs, non-steroidal anti-inflammatory drugs.

Bakland G et al. Ann Rheum Dis 2011;70:1921-5.

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Life Expectancy, Standardized Mortality Ratios, and Causes of Death in Six Rheumatic Diseases in Hong Kong, China

C. C. Mok,[1] C. L. Kwok,[2] L. Y. Ho,[1] P. T. Chan,[1] and S. F. Yip[2]

Objective. **To examine the life expectancy, standardized mortality ratios (SMRs), and causes of death in 6 groups of patients from Hong Kong with different rheumatic diseases.**

Methods. **Patients with a diagnosis of systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), systemic vasculitis (SV), or systemic sclerosis (SSc) registered in 37 public hospitals between 1999 and 2008 were identified in the hospital registry. SMRs were calculated by comparing the mortality rate in patients with each disease with that in the general population. Life expectancy was calculated by abridged life-table analysis, and the causes of death were compared.**

Conclusion. **Our findings indicate that patients with SLE, RA, AS, PsA, SV, and SSc have increased mortality rates and reduced life expectancy. SLE has the highest adjusted SMR, and female SSc patients have the greatest loss in life expectancy. Infection is the leading cause of death, followed by cardiovascular complications and malignancies.**

Rheumatic diseases are chronic multisystemic medical illnesses that are associated with significant mortality and morbidity. Organ dysfunction as a result of disease involvement is a major cause of reduced survival. Examples are renal failure in patients with systemic lupus erythematosus (SLE) and systemic vasc-

Table 3. Causes of death in the patients with rheumatic diseases (January 1999 to December 2008)*

Cause of death	SLE (n = 514)	RA (n = 1,289)	AS (n = 197)	PsA (n = 51)	SSc (n = 110)	SV (n = 325)	Total (n = 2,486)
Infection	114 (22)	442 (34)	57 (29)	17 (33)	19 (17)	58 (18)	707 (28)
Septicemia	25 (5)	61 (5)	4 (2)	1 (2)	2 (2)	9 (3)	–
Pneumonia	72 (14)	324 (25)	43 (22)	12 (24)	12 (11)	44 (14)	–
Soft tissue	3 (0.6)	3 (0.2)	0 (0)	0 (0)	0 (0)	0 (0)	–
Tuberculosis	9 (1.8)	10 (0.8)	2 (1)	1 (2)	1 (1)	1 (0.3)	–
Other	5 (1)	44 (3)	8 (4)	3 (6)	4 (4)	4 (1)	–
Cancer	61 (12)	175 (14)	34 (17)	10 (20)	11 (10)	108 (33)	399 (16)
Cardiovascular	53 (10)	160 (12)	23 (12)	10 (20)	18 (16)	34 (10)	298 (12)
Coronary heart disease	29 (6)	89 (7)	9 (4.6)	5 (10)	8 (7)	15 (5)	–
Heart failure	7 (1.4)	45 (3.5)	11 (5.6)	5 (10)	4 (4)	14 (4)	–
Arrhythmia	4 (0.8)	10 (0.8)	1 (0.5)	0 (0)	0 (0)	3 (1)	–
Pulmonary embolism	2 (0.4)	3 (0.2)	1 (0.5)	0 (0)	0 (0)	0 (0)	–
Pulmonary hypertension	5 (1)	0 (0)	0 (0)	0 (0)	3 (3)	0 (0)	–
Other	6 (1.2)	13 (1)	1 (0.5)	0 (0)	3 (3)	2 (0.6)	–
Cerebrovascular	33 (6.4)	85 (6.6)	9 (4.6)	2 (4)	3 (3)	16 (5)	148 (6)
Gastrointestinal	24 (4.7)	44 (3.4)	7 (3.6)	1 (2)	2 (2)	8 (2.5)	86 (3)
Hepatic	7 (1.4)	16 (1.2)	2 (1)	2 (4)	2 (2)	4 (1)	33 (1)
Respiratory system	9 (1.8)	84 (6.5)	28 (14)	1 (2)	10 (9)	19 (6)	151 (6)
Obstructive airway disease	3 (0.6)	37 (3)	19 (10)	1 (2)	0 (0)	8 (2.5)	–
Bronchiectasis	0 (0)	15 (1.2)	2 (1)	0 (0)	0 (0)	4 (1)	–
Pulmonary fibrosis	4 (0.8)	21 (1.6)	1 (0.5)	0 (0)	8 (7)	3 (1)	–
Other	2 (0.4)	11 (0.9)	6 (3)	0 (0)	2 (2)	4 (1)	–
Renal failure	44 (9)	75 (6)	9 (4.6)	1 (2)	5 (4.5)	16 (5)	150 (6)
Poisoning/injury	7 (1.4)	7 (0.5)	1 (0.5)	2 (4)	0 (0)	0 (0)	17 (0.7)
Disease activity	110 (21)	28 (2.2)	3 (2)	0 (0)	26 (24)	5 (1.5)	172 (7)
Other	13 (2.5)	49 (4)	8 (4)	3 (6)	5 (4.5)	23 (7)	101 (4)
Unknown (missing data)	39 (8)	124 (10)	16 (8)	2 (4)	9 (8)	34 (10)	224 (9)

* Values are the number (%) of patients. See Table 1 for definitions.

Mok CC et al. Arthritis Rheum 2011;63:1182-9.

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Inflammation

- ✓ Mortality
- ✓ **Cardiovascular comorbidity**
- ✓ Preclinical atherosclerosis
- ✓ Cardiovascular risk factors

Comorbidity profiles among patients with ankylosing spondylitis: a nationwide population-based study

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► Additional data are published online only. To view these files please visit the journal online (http://ard.bmj.com).

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ABSTRACT

Objective Ankylosing spondylitis (AS) is a systemic inflammatory disease that can result in chronic pain and disability. This study aimed to analyse the prevalence and risk of medical comorbidities in patients with AS compared with the general population.

Methods 11 701 patients with AS and 58 505 matching controls were selected for analysis from the National Health Insurance Research Dataset (NHIRD) in Taiwan. The Elixhauser comorbidity index was used for selecting medical comorbidities. Pearson χ^2 tests and conditional logistic regression a nalyses were performed to examine the prevalence and risk of comorbidities between these two groups.

Results Patients with AS were at increased risk for multiple systemic comorbidities including cardiovascular, neurological, pulmonary, gastrointestinal, endocrine, haematological and mental illness. The most prevalent comorbidities in patients with AS were hypertension (16.4%), peptic ulcers (13.9%) and headaches (10.2%).

Conclusion The results show that patients with AS have a higher prevalence of multiple comorbidities than the general population in Taiwan. These findings are consistent with previous studies done in Western populations. The results could be useful for both the clinical management of patients with AS and for researching the underlying pathological mechanisms.

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in a Chinese population. AS is a heterogeneous disease and ethnic differences in its presentation have been noted in previous studies.[10] Exploring the comorbidity profiles of AS in a Chinese population would therefore be useful for documenting possible ethnic effects. We conducted a nationwide population-based study to clarify the issues above, aiming to explore the prevalence of comorbidities among patients with AS in Taiwan.

METHODS

Database

We used the National Health Insurance Research Dataset (NHIRD), which includes all medical claims for inpatient and ambulatory care services as well as a registry of beneficiaries including all enrollees. Since the NHIRD consists of de-identified secondary data released to the public for research purposes, this study was exempt from full review by the institutional review board.

Study sample

The study cohort comprised all patients who sought ambulatory care during 2007 and received a diagnosis of AS (ICD-9-CM codes 720 or 720.0; n=30 058). In order to ensure diagnostic validity and patient homogeneity, we selected only patients who had at least two consensus AS diag-

Table 2 Prevalence of medical comorbidities among patients with ankylosing spondylitis compared with controls (n=70 206)

Variable	Patients with ankylosing spondylitis (n=11 701)	Patients without ankylosing spondylitis (n=58 505)	p Value
Cardiovascular			
Hypertension	1920 (16.4)	6224 (10.6)	<0.001
Ischaemic heart disease	102 (0.9)	190 (0.3)	<0.001
Hyperlipidaemia	1009 (8.6)	3641 (6.2)	<0.001
Congestive heart failure	132 (1.1)	470 (0.8)	<0.001
Cardiac arrhythmias	279 (2.4)	784 (1.3)	<0.001
Peripheral vascular disorder	88 (0.8)	322 (0.6)	<0.001
Stroke	226 (1.9)	1123 (1.9)	0.931

Kang JH et al. Ann Rheum Dis 2010;69:1165-8.

Table 2 Cardiovascular comorbidities in patients with ankylosing spondylitis

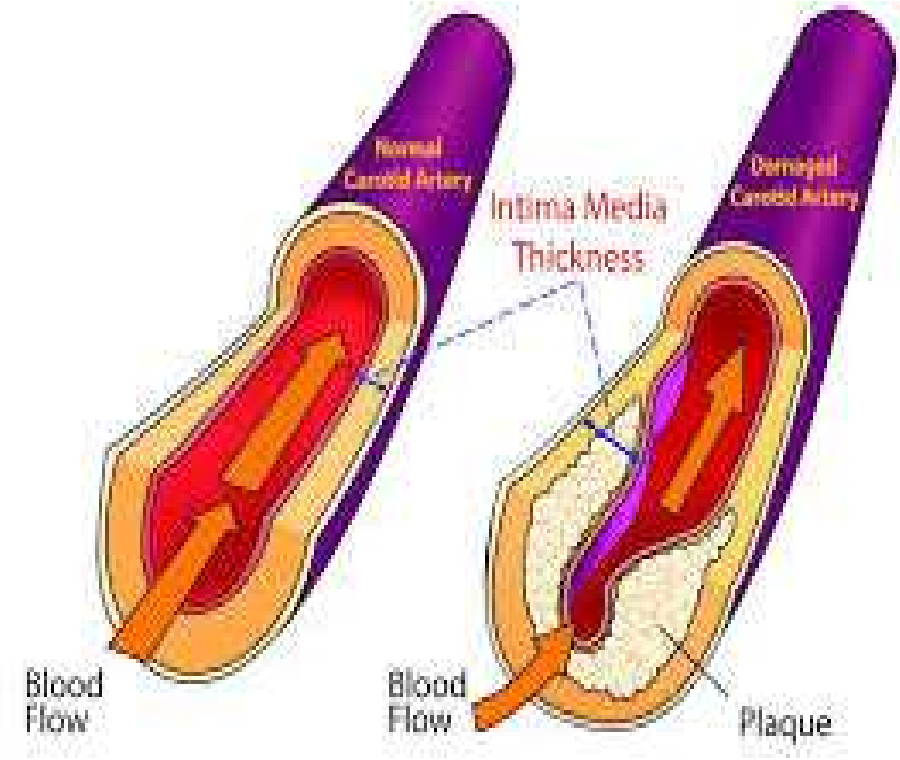
Study	Population studied	Study design	Number of AS patients	Outcome measures and findings
Symmons et al. 2004 [6•]	U.K.	Community-based AS cohort vs. general population	5,392	First myocardial infarction, hazard ratio: 1.4 (95 % CI: 1.2–1.8)
Han et al. 2006 [7]	U.S.	PharMetrics patient- centric database (U.S.) Cross-sectional vs. 4 matched controls	1,843	Prevalence ratio: - ischemic heart disease: 1.2 (95 % CI 1.0–1.5) - peripheral vascular disease: 1.6 (95 % CI 1.2–2.2) - congestive heart failure 1.8 (95 % CI 1.2–2.6) - cerebrovascular disease: 1.7 (95 % CI 1.3–2.3)
Peters et al. 2010 [9]	Netherlands	Referral based two-center study vs. general population	383	Odds ratio: 3.1 (95 % CI 1.9–5.1)
Szabo et al. 2011 [8••]	Canada	Population-based cohort compared with general population	8,616	Prevalence ratio: - ischemic heart disease: 1.37 (95 % CI 1.31–1.91) - peripheral vascular disease: 1.6 (95 % CI 1.2–2.2) - cerebrovascular disease: 1.25 (95 % CI 1.15–1.35)
Bremander et al. 2011 [10]	Sweden	Population-based cohort study	935	Ischemic heart disease SMR: 2.20 (95 % CI 1.77–2.70)

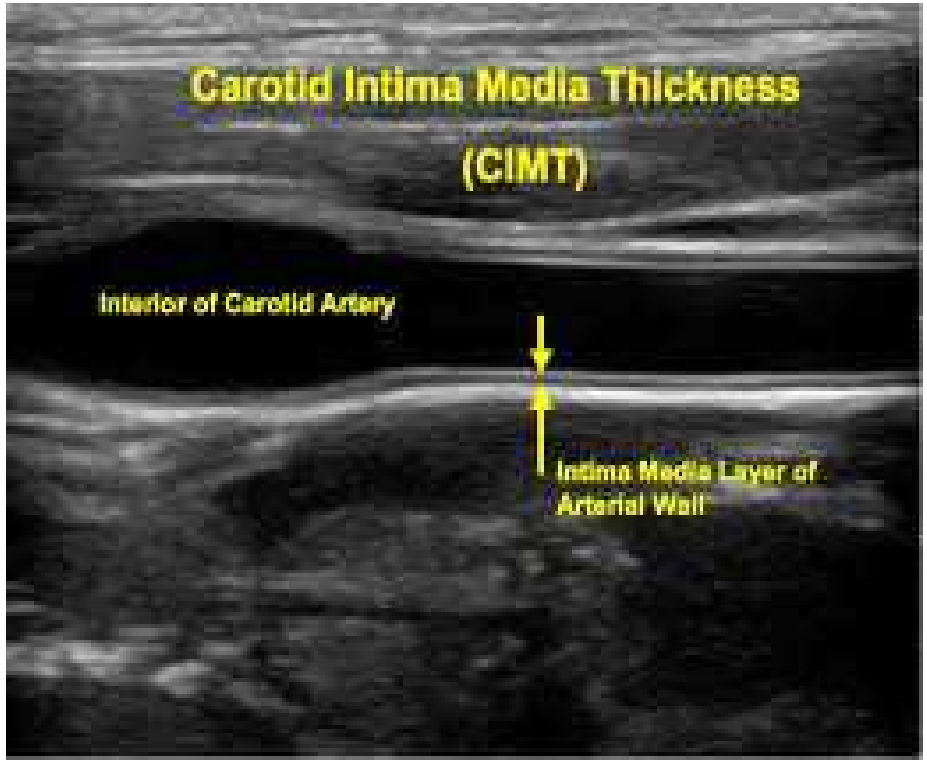
SMR: standardized morbidity ratio

Inflammation

- ✓ Mortality
- ✓ Cardiovascular comorbidity
- ✓ **Preclinical atherosclerosis**
- ✓ Cardiovascular risk factors

Carotid artery intima media thickness (cIMT)



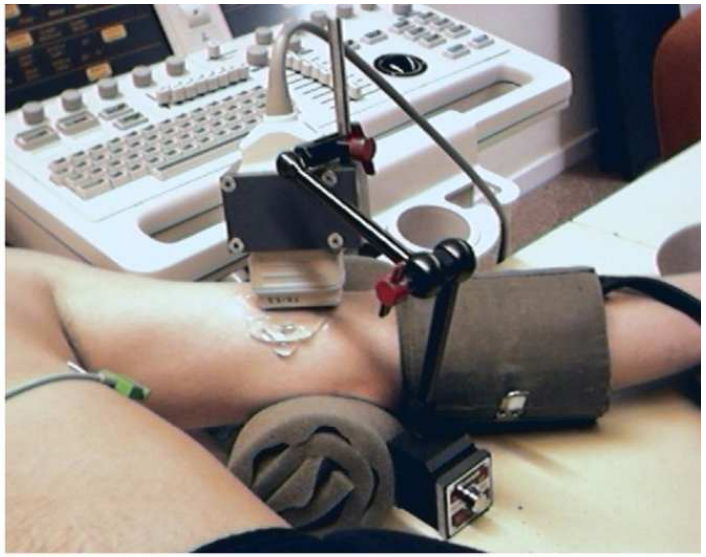


Valid instrument for quantifying early, preclinical atherosclerosis and as a predictor for future CV disease.

One of the pivotal studies in 5,000 persons from the general population showed that every 0.20-mm cIMT increase was associated with a 30 % increase of new CV events

Flow mediated dilatation (FMD) of the brachial artery

A



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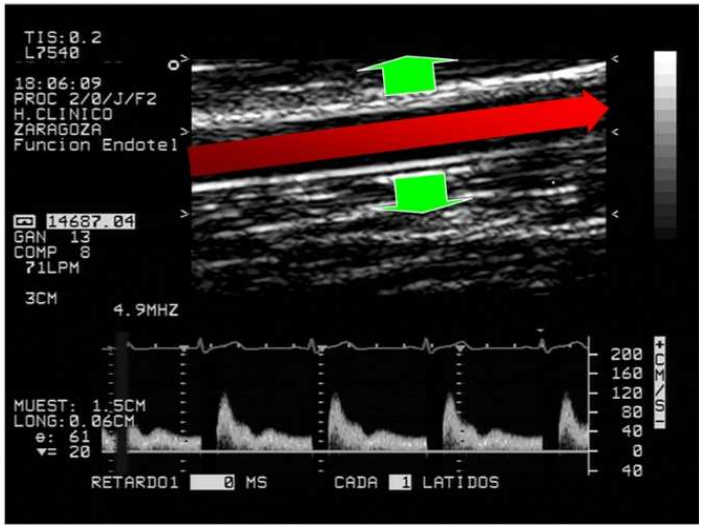
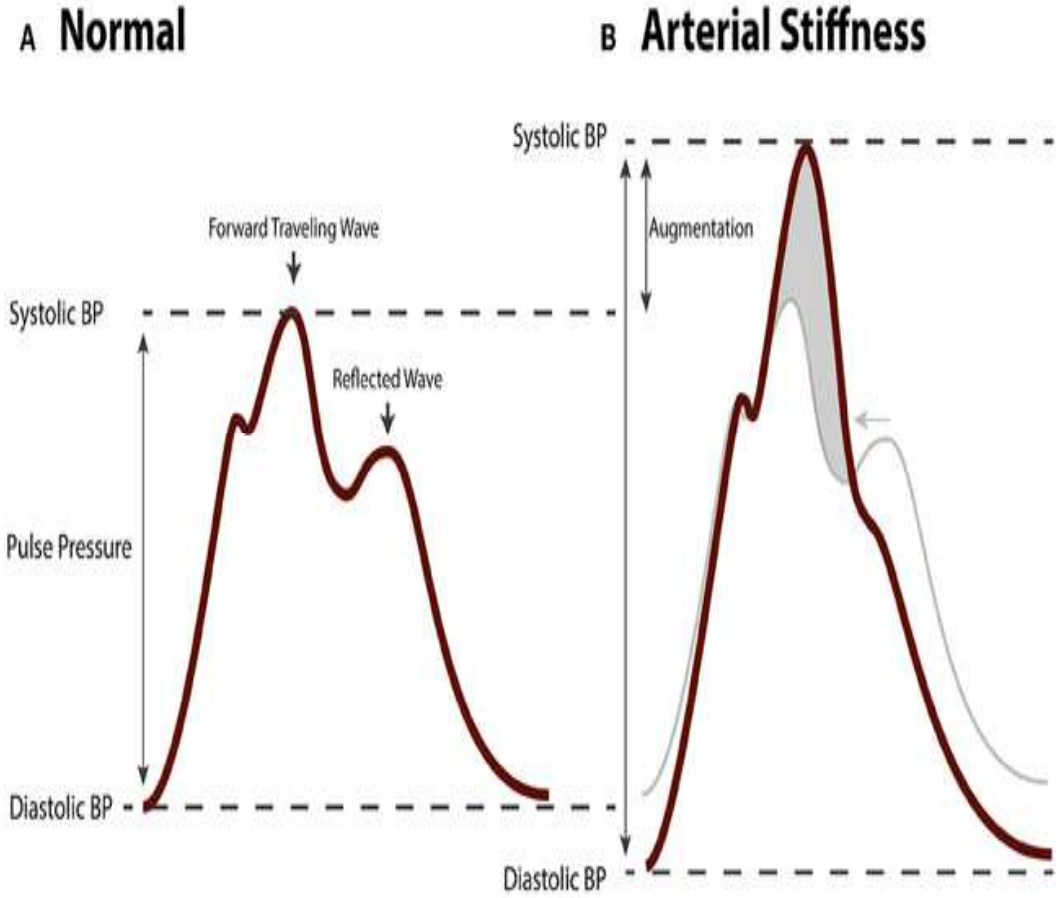


Pulse wave velocity (PWV)



Assessment of Subclinical Vascular Disease Associated with Ankylosing Spondylitis

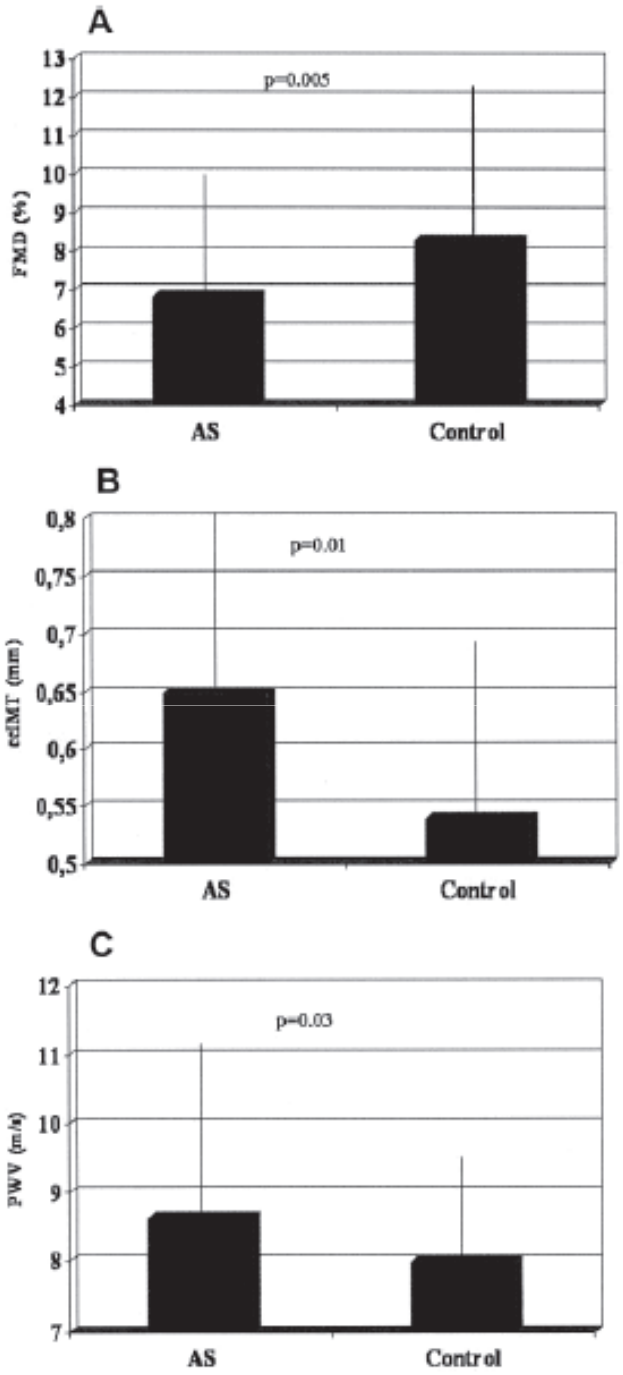
NÓRA BODNÁR, GYÖRGY KEREKES, ILDIKÓ SERES, GYÖRGY PARAGH, JÁNOS KAPPELMAYER, ZSUZSANNA GYURCSIK NÉMETHNÉ, GYULA SZEGEDI, YEHUDA SHOENFELD, SÁNDOR SIPKA, PÁL SOLTÉSZ, ZOLTÁN SZEKANECZ, and SÁNDOR SZÁNTÓ

ABSTRACT. ***Objective.*** Studies indicate that ankylosing spondylitis (AS), as well as rheumatoid arthritis, may be associated with accelerated atherosclerosis and vascular disease. We assessed endothelial dysfunction, carotid atherosclerosis, and aortic stiffness in AS in context with clinical and laboratory measurements.

Methods. Forty-three patients with AS and 40 matched healthy controls were studied. We assessed common carotid intima-media thickness (ccIMT), flow-mediated vasodilation (FMD), and pulse-wave velocity (PWV) in association with age, disease duration, smoking habits, body mass index, patient's assessment of pain and disease activity, Bath AS Disease Activity Index, Bath AS Functional Index (BASFI), metric measurements, erythrocyte sedimentation rate, C-reactive protein, and HLA-B27 status.

Results. We found impaired FMD (6.85 ± 2.98% vs 8.30 ± 3.96%; p = 0.005), increased ccIMT (0.65 ± 0.15 vs 0.54 ± 0.15 mm; p = 0.01), and higher PWV (8.64 ± 2.44 vs 8.00 ± 1.46 m/s; p = 0.03) in patients with AS compared to controls, respectively. We also found that ccIMT negatively correlated with FMD (r = –0.563; p = 0.0001) and positively correlated with PWV (r = 0.374; p = 0.018). Both ccIMT and PWV correlated with disease duration (r = 0.559; p = 0.013 and r = 0.520; p = 0.022, respectively), BASFI (r = 0.691; p = 0.003 and r = 0.654; p = 0.006), decreased lumbar spine mobility (r = –0.656; p = 0.006 and r = –0.604; p = 0.013), chest expansion (r = –0.502; p = 0.047 and r = –0.613; p = 0.012), and increased wall-occiput distance (r = 0.509; p = 0.044 and r = 0.614; p = 0.011).

Conclusion. In this well characterized AS population, impaired FMD and increased ccIMT and PWV indicate abnormal endothelial function and increased atherosclerosis and aortic stiffness, respectively. The value of noninvasive diagnostic tools needs to be further characterized. (First Release Jan 15 2011; J Rheumatol 2011;38:723–9; doi:10.3899/jrheum.100668)



Bodnár N et al. J Rheumatol 2011;38:723-9

Inflammation

- ✓ Mortality
- ✓ Cardiovascular comorbidity
- ✓ Preclinical atherosclerosis
- ✓ **Cardiovascular risk factors**

Cardiovascular Disease and Risk Factors in Patients with Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis

CHENGLONG HAN, DON W. ROBINSON Jr, MONICA V. HACKETT, L. CLARK PARAMORE, KATHY H. FRAEMAN, and MOHAN V. BALA

ABSTRACT. ***Objective.*** To compare the prevalence of cardiovascular diseases and their risk factors between patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA), and ankylosing spondylitis (AS) and control subjects.

Methods. Data for patients continuously enrolled in an integrated outcomes database between January 1, 2001, and December 31, 2002, with International Classification of Diseases, 9th Revision codes of 714.x (RA), 696.0 (PsA), or 720.0 (AS) were evaluated in this cross-sectional comparative study. Control groups were established for each patient group (1:4 ratio) by matching on the basis of age, sex, geographic region, and length of time in plan. Age- and sex-adjusted prevalence of cardiovascular comorbidities and risk factors were calculated; the prevalence ratio of the comorbidities and risk factors for the patient groups compared with the control population were estimated. Use of selected cardiovascular medications was also compared between patient and control groups.

Results. The RA, PsA, and AS cohorts comprised 28,208, 3066, and 1843 patients, respectively. The prevalence ratio of ischemic heart disease (1.5, 1.3, 1.2), atherosclerosis (1.9, 1.4, 1.5), peripheral vascular disease (2.4, 1.6, 1.6), congestive heart failure (2.0, 1.5, 1.8), cerebrovascular disease (1.6, 1.3, 1.7), type II diabetes (1.4, 1.5, 1.2), hyperlipidemia (1.2, 1.2, 1.2), and hypertension (1.3, 1.3, 1.3) were higher in patients than controls. For RA, PsA, and AS, use of angiotensin-converting enzyme inhibitors, calcium channel blockers, diuretics, nitrates/vasodilators, anticoagulants, and antihyperlipidemia agents was significantly higher in patients than controls.

Conclusion. Cardiovascular diseases and their risk factors were more common in patients with RA, PsA, and AS than in matched controls. (First Release Sept 15 2006; J Rheumatol 2006;33:2167–72)

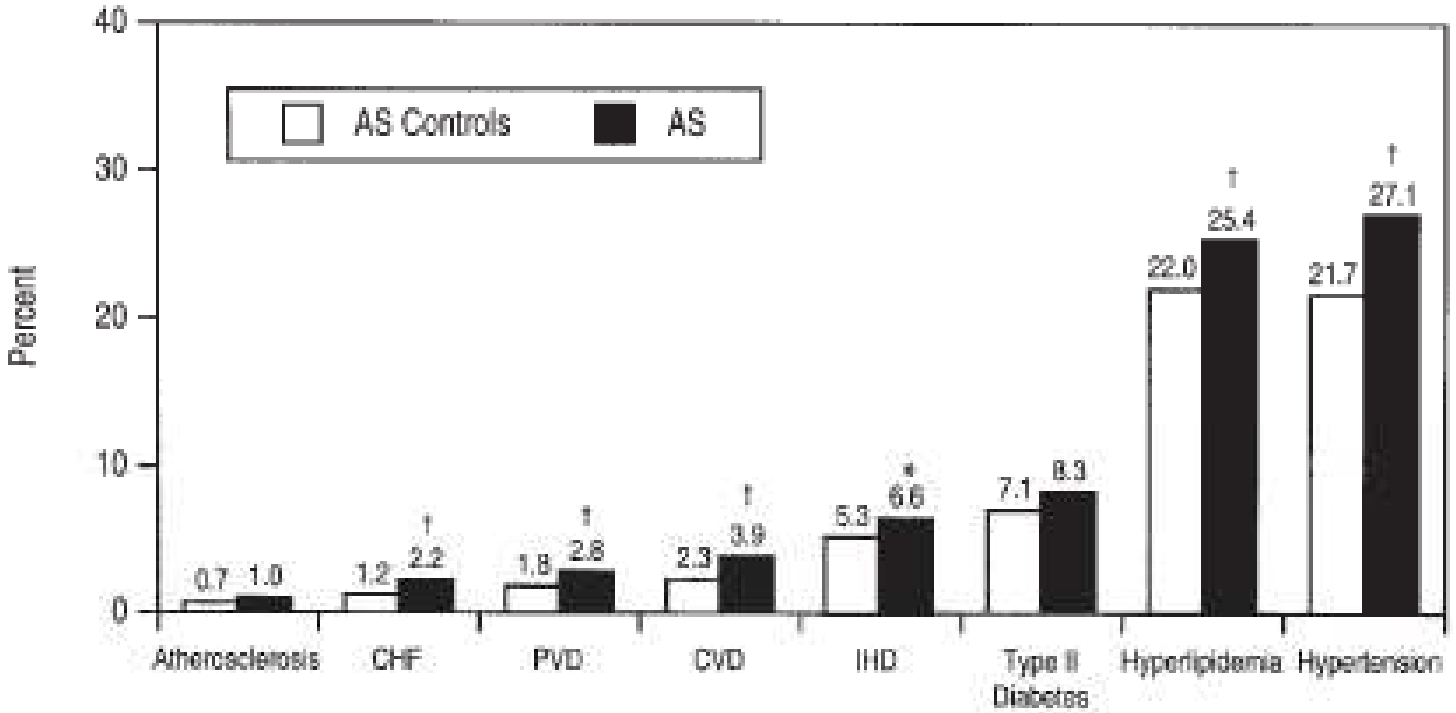


Figure 3. Age and sex-adjusted comorbidities of cardiovascular diseases/risk factors among patients with AS and controls. † $p < 0.01$ for patients with AS vs controls, * $p < 0.05$.

Han C et al. J Rheumatol 2006;33:2167-72.

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SPECIAL THEME ARTICLE: VASCULAR COMORBIDITY IN THE RHEUMATIC DISEASES

Cardiovascular Profile in Ankylosing Spondylitis: A Systematic Review and Meta-Analysis

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Objective. Rheumatoid arthritis is associated with increased cardiovascular risk. In ankylosing spondylitis (AS), there is a paucity of information concerning this risk. Our objective was to assess the incidence of myocardial infarction (MI) or strokes and the cardiovascular risk profile in AS patients.

Methods. We performed a systematic literature review using PubMed, EMBase, and the Cochrane Library up to August 2009. Incidence of MI or stroke was calculated by metaproportion. For cardiovascular risk factors, differences between AS patients and controls were expressed by standardized mean differences using inverse of variance method.

Results. For MI, 8 longitudinal studies were included. In controls (n = 82,745), 1,318 MI cases were observed (4.6%; 95% confidence interval [95% CI] 1.2%, 10.0%). In AS patients (n = 3,279), 224 MI cases were reported (incidence 7.4%; 95% CI 5.2%, 10.0%). The increase in MI cases in AS patients was not significant (risk ratio 1.88; 95% CI 0.83, 4.28). For stroke, 7 longitudinal studies reported 327 strokes in AS patients (n = 31,949), which is an incidence of 2.2% (95% CI 1.3%, 3.4%). In controls (n = 7,372), one study reported 170 strokes (2.3%; 95% CI 2.0%, 2.7%). For cardiovascular risk factors, 15 case–control studies and 9 abstracts were included (n = 1,214 for patients and n = 1,000 for controls). AS patients were characterized by a higher weighted mean intima-media thickness and higher risk of metabolic syndrome. In AS patients, there was a significant decrease in triglycerides, total cholesterol, and high-density lipoprotein (HDL) cholesterol.

Conclusion. AS patients appear to be at higher risk of MI, which could be due to low HDL cholesterol levels or to systemic inflammation. Management of cardiovascular risk factors and control of systemic inflammation should be taken into account in AS.

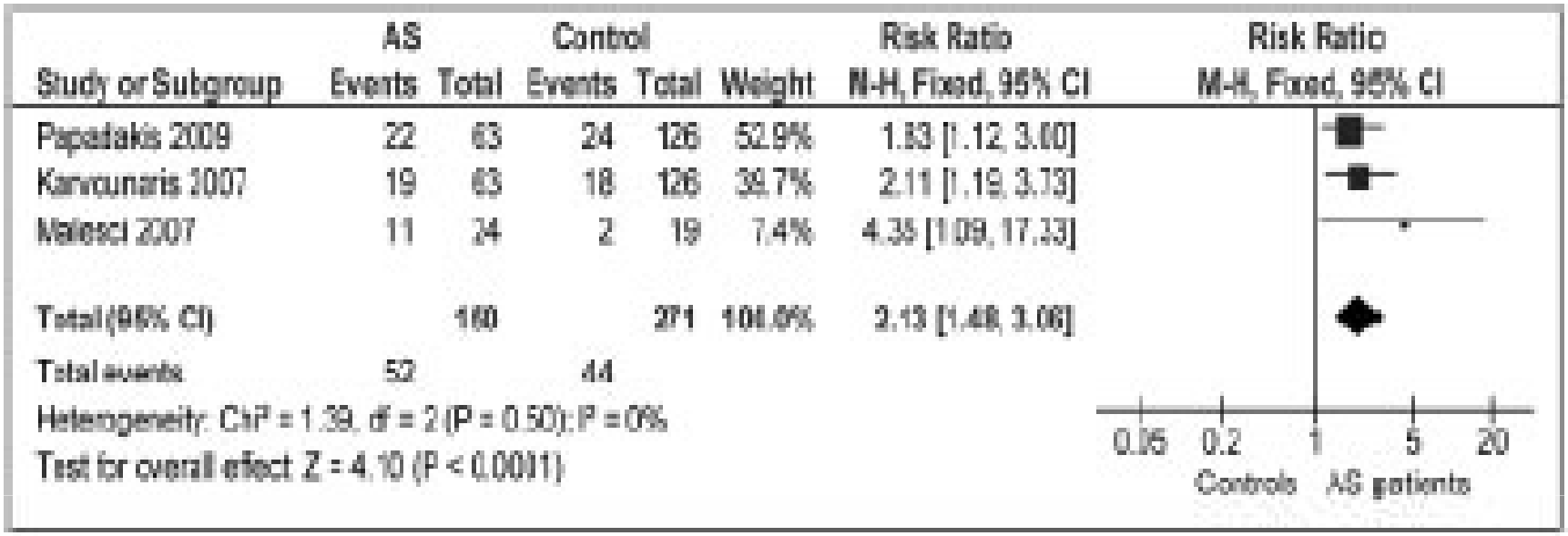


Figure 4. Comparison of prevalence of metabolic syndrome between ankylosing spondylitis (AS) patients and controls. M-H = Mantel-Haenszel procedure; 95% CI = 95% confidence interval.

Mathieu S et al. Arthritis Care Res 2011;63:557-63.

Table 1. Comparison of cardiovascular risk in case–control studies*

Characteristics	Studies, no.	AS patients, weighted mean ± SD	Controls, weighted mean ± SD	SMD (95% CI)†	*P*	I^2, %
Erythrocyte sedimentation rate, mm/hour	3	19.4 ± 18.1	5.2 ± 4.7	0.96 (0.51, 1.41)	< 0.001	65
C-reactive protein level, mg/dl	7	10.0 ± 9.8	1.9 ± 1.9	1.06 (0.79, 1.33)	< 0.001	53
Systolic blood pressure, mm Hg	10	120.4 ± 12.8	119.1 ± 13.1	0.08 (−0.25, 0.40)	0.65	79
Diastolic blood pressure, mm Hg	10	76.3 ± 7.8	74.4 ± 10.5	0.13 (−0.11, 0.37)	0.29	60
Glycemia, gm/liter	3	0.88 ± 0.16	0.89 ± 0.17	−0.02 (−0.36, 0.33)	0.92	74
Total cholesterol, gm/liter	10	1.77 ± 0.36	1.93 ± 0.36	−0.32 (−0.56, −0.07)	0.01	68
Low-density lipoprotein cholesterol, gm/liter	10	1.08 ± 0.35	1.14 ± 0.34	−0.10 (−0.23, 0.03)	0.14	36
High-density lipoprotein cholesterol, gm/liter	10	0.48 ± 0.14	0.55 ± 0.14	−0.45 (−0.78, −0.13)	0.007	82
Triglycerides, gm/liter	10	0.93 ± 0.49	0.98 ± 0.62	−0.15 (−0.28, −0.02)	0.03	4
Atherogenic index‡	3	3.69 ± 1.14	3.38 ± 1.16	0.35 (−0.20, 0.89)	0.21	87
Homocysteinemia, nmoles/liter	3	11.8 ± 9.9	10.4 ± 3.3	0.11 (−0.09, 0.31)	0.30	0
Body mass index, kg/m^2	11	25.0 ± 4.0	24.8 ± 3.8	0.03 (−0.10, 0.15)	0.69	39
Intima-media thickness, mm	6	0.61 ± 0.12	0.54 ± 0.10	0.45 (0.12, 0.78)	0.008	66

* AS = ankylosing spondylitis; SMD = standardized mean difference; 95% CI = 95% confidence interval.
† Fixed or random effects.
‡ Total cholesterol/high-density lipoprotein cholesterol.

Mathieu S et al. Arthritis Care Res 2011;63:557-63.

Dyslipidemia is related to disease activity in AS.

Lower HDL-cholesterol and total cholesterol levels in patients with active disease.

Patients with AS smoke twice in comparison with the general population.

Mathieu S et al. Arthritis Care Res 2011;63:557-63.
Divecha H et al. Clin Sci 2005;109:171-6.
Papadakis JA et al. Clin Exp Rheumatol 2009;27:292-8.

- ✓ Inflammation

  Accelerates atherosclerosis directly and via effects on CV risk factors (lipid levels, blood pressure and insulin resistance)

- ✓ **Associated cardiovascular manifestations**

Associated cardiovascular manifestations

- ✓ Aortic valve involvement
- ✓ Conduction Abnormalities
- ✓ Left ventricular dysfunction
- ✓ Coronaric, thoracic and abdominal aorta aneurisms

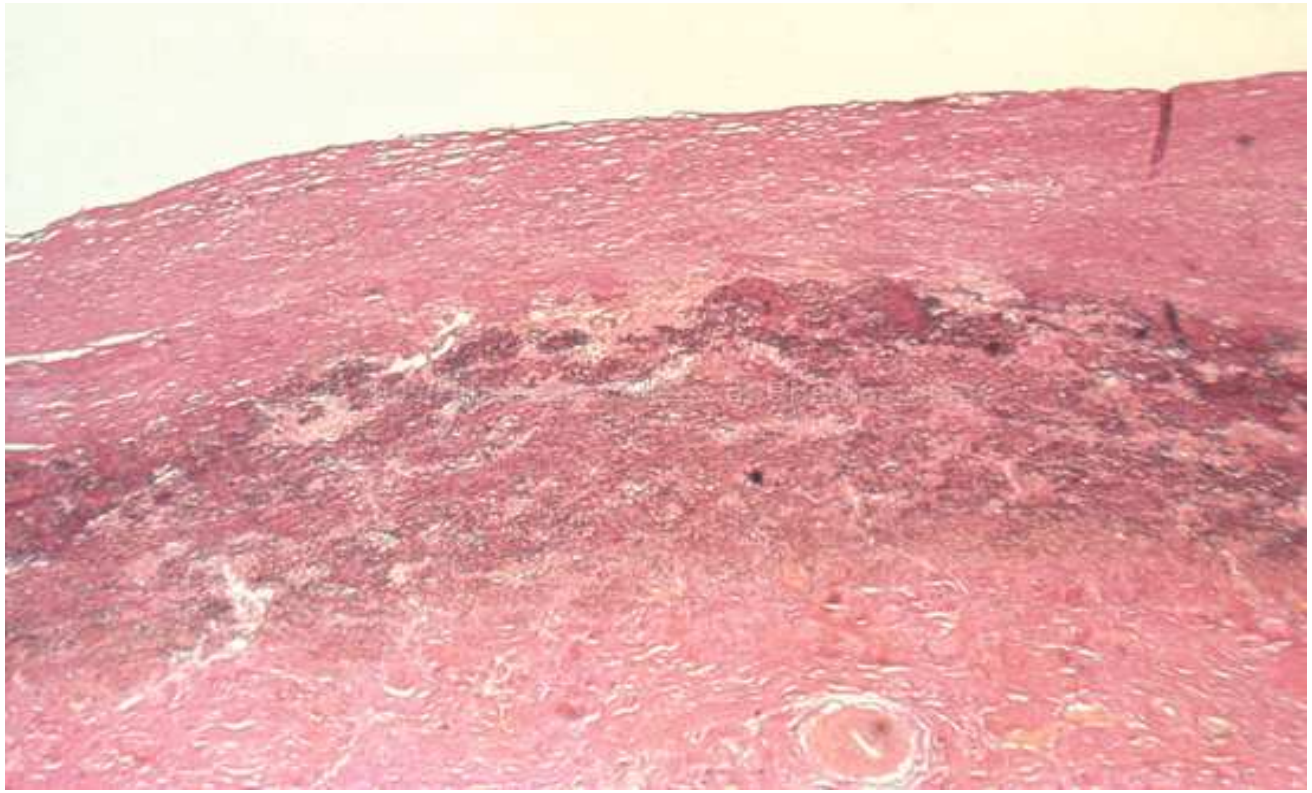
Associated cardiovascular manifestations

- ✓ **Aortic valve involvement**
- ✓ Conduction Abnormalities
- ✓ Left ventricular dysfunction
- ✓ Coronaric, thoracic and abdominal aorta aneurisms

Aortic valve involvement

Lone aortic insufficiency (without stenosis)

- The course is highly variable, ranging from chronic haemodynamically irrelevant fibrosis to acute aortic insufficiency



- Histology: proliferation of the cells of the intima, focal infiltration of monucleate cells in the media, fibrotic thickening of the adventitia

Aortic valve involvement

Prevalence

Transthoracic echocardiography

- Yildirir A *et al*. Clin Rheumatol 2002;21:129-34.

  4 with aortic regurgitation out of 88 patients with AS.

- Lange U *et al*. Eur J Med Res 2007;14:573-81.

  20 with aortic or mitral insufficiency out of 77 patients with AS.

- Brunner F *et al*. Clin Rheumatol 2006;25:24-9.

  No significant increase in the prevalence of aortic regurgitation in 100 AS patients in comparison with the normal population.

Aortic valve involvement

Prevalence

Transesophageal echocardiography

Roldan CA *et al.* J Am Coll Cardiol 1998;32:1397-404.

- 44 patients with AS and 30 controls.
- Aortic root disease and valve disease were more common in patients (82%) than in controls (27%) ($p<0.001$)
- During follow-up of 25 patients new aortic root and valve abnormalities developed in 24% and 12% existing valve abnormalities worsened significantly.
- 20% of patients developed heart failure, underwent valve replacement, had a stroke or died as compared with 3% of controls.

Park SH *et al.* J Cardiovasc Ultrasound 2012;20:30-6.

- 70 patients with AS and 25 controls
- The prevalence of aortic and mitral regurgitation was very low and similar in the two groups.
- The thickness of both aortic and mitral valve was more increased in AS patients than in controls.

Aortic valve involvement

Role of HLA-B27

Bergfeldt L *et al*. Am J Med 1988;85:12-8.

91 patients with lone aortic regurgitation

HLA-B27 associated disease was considered the probable cause of 15-20% of cases

Qaiyumi S *et al*. Arch Intern Med 1985;145:822-4.

100 consecutive patients with lone aortic insufficiency

7 HLA-B27 positive (4 with AS and 3 with reactive arthritis).

Johnsen K *et al*. Scand Cardiovasc J 2009;43:176-80.

In Sami population (Northern Norway) aortic regurgitation is strongly associated with AS but not with the HLA-B27 antigen

Associated cardiovascular manifestations

- ✓ Aortic valve involvement
- ✓ **Conduction Abnormalities**
- ✓ Left ventricular dysfunction
- ✓ Coronaric, thoracic and abdominal aorta aneurisms

Conduction abnormalities

- Extension of inflammation and fibrosis to the interventricular septum
- First, second and third degree atrioventricular blocks
- Intraventricular blocks and bradycardia/pauses caused by sinus node involvement
- First degree blocks can be asymptomatic, complete blocks may give Stokes-Adams's attacks
- Spontaneous remission is frequent

Conduction abnormalities

- Prevalence in older literature ranges from 1% to 33%

- A recent study revealed intraventricular disturbances in 30% of 131 consecutive patients

Dik VK et al. Scand J Rheumatol 2010;39:38-41.

- Some other recent studies did not reveal an increased rate in comparison with historical controls.

Yildirir A et al. Clin Rheumatol 2002;21:129-34.

Brumer F et al. Clin Rheumatol 2006;25:24-9.

- 12.6% of patients with permanent pacemaker had a HLA-B27 related SpA.

Bergfeldt L et al. Am J Med 1983;75:210-5.

Associated cardiovascular manifestations

- ✓ Aortic valve involvement
- ✓ Conduction Abnormalities
- ✓ **Left ventricular dysfunction**
- ✓ Coronaric, thoracic and abdominal aorta aneurisms

Left ventricular dysfunction

- Yildirir A et al. Clin Rheumatol 2002;21:129-34.

  Lower diastolic function due to compromised left ventricular activity, assessed with Doppler echocardiography, in 88 AS patients than in 31 healthy controls.

- Caliskan M et al. Atherosclerosis 2008;196:306-12.

  Decreased left ventricular function in 40 AS patients in comparison with 35 controls.

- Kiris A et al. Echocardiography 2012;29:661-7.

  Increased tissue synchronization imaging (TSI) in 77 AS patients in comparison with 40 controls.

- Yalcin H et al. Rev Esp Med Nucl 2011;30:292-6.

  SPECT (single photon emission computed tomography) study in 28 AS patients. Left ventricular wall motion abnormalities but normal myocardial perfusion.

- Acar G et al. Echocardiography 2009;26:549-57.

  Left ventricular dysfunction and delayed atrial electromechanical coupling intervals (40 AS patients and 42 controls examined)

- Gunes Y et al. Acta Cardiol 2009;64:385-92.

  No abnormal left ventricular function in 35 AS patients.

Associated cardiovascular manifestations

- ✓ Aortic valve involvement
- ✓ Conduction Abnormalities
- ✓ Left ventricular dysfunction
- ✓ **Coronaric, thoracic and abdominal aorta aneurisms**

Coronaric aneurysms, thoracic and abdominal aneurisms

Two cases of coronary aneurisms

Huffer LL &Furgerson JL. Tex Heart Inst J 2006;33:70-3.

Worthley MI & Curtis MJ. Int J Cardiol2006;106:422-3.

Some cases of thoracic aorta aneurisms.

Rasmussen TE *et al*. J Vasc Surg 1997;25:356-64.

Seo JW *et al*. J Korean Med Sci 1991;6:75-82.

Juan A *et al*. J Rheumatol 2008;35:713-6.

Foffa I *et al*. Cardiovasc Ultrasound 2009;7:34.

A case of inflammatory abdominal aortic aneurism. However, spine radiographs were suggestive of DISH.

Takagi H et al. Vasc Surg 2003;38:613-6.

Retroperitoneal fibrosis

Afeltra A et al. Retroperitoneal fibrosis and ankylosing spondylitis: which links? Semin Arthritis Rheum 2005;35:43-8.

Description of a case and review of the literature.

18 cases of concomitant retroperitoneal fibrosis and spondyloarthritis,

mainly AS.

Take home messages

CONCLUSIONS

- ✓ Patients with AS suffer from an increased cardiovascular (CV) risk.
- ✓ Inflammation accelerates atherosclerosis directly and via effects on CV risk factors (lipid levels, blood pressure and insulin resistance).
- ✓ Associated cardiovascular manifestations (aortic valve involvement, conduction abnormalities, left ventricular dysfunction).
- ✓ Patients with AS have 60-90% increased mortality in comparison with the general population.