Peters, M.J., Visman, I., Nielen, M.M.J., Dillen, N. van, Verheij, R.A., Horst-Bruinsma, I.E. van der, Dijkmans, B.A., Nurmohamed, M.T. Ankylosing spondylitis: a risk factor for myocardial infarction? Annals of the Rheumatic Diseases: 2010, 69(3), 579-581

Postprint Version	1.0
Journal website	http://ard.bmj.com/cgi/rapidpdf/ard.2009.110593v1
Pubmed link	http://preview.ncbi.nlm.nih.gov/pubmed/19403516
DOI	10.1136/ard.2009.110593

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

Ankylosing spondylitis; a risk factor for myocardial infarction?

M.J.L. PETERS[1], I. VISMAN[2], M.M.J. NIELEN[3], N. VAN DILLEN[2], R.A. VERHEIJ[3], I.E. VAN DER HORST-BRUINSMA[1], B.A.C. DIJKMANS[1,2], M.T.

Nurmohamed1,2,4 1Dept. of Rheumatology, VU University Medical Center, Amsterdam, the Netherlands 2Dept. of Rheumatology, Jan van Breemen Institute Amsterdam, the Netherlands 3NIVEL (Netherlands Institute for Health Services Research), Utrecht, the Netherlands 4Dept. of Internal Medicine VU University Medical Center, Amsterdam the Netherlands Corresponding author
Dr Michael T. Nurmohamed, rheumatologist VU University Medical Centre, departments of Internal Medicine and Rheumatology P.O. Box 7057, 1007 MB Amsterdam Email address: mt.nurmohamed@vumc.nl

ABSTRACT

Objectives: To ascertain the prevalence of myocardial infarction (MI) in ankylosing spondylitis (AS) relative to that in the general population.

Methods: A questionnaire was sent to 593 AS patients, aged between 50 and 75 years and registered at the Jan van Breemen Institute or VU University Medical Centre. A total of 383 (65%) AS patients returned their questionnaire that covered the primary outcome (non-fatal) MI. The prevalence for MI was calculated with data from the general population provided by Netherlands Information Network of General Practice databases as reference.

Results: The overall prevalence for MI was 4.4% in AS patients versus 1.2% in the general population, resulting in an age and gender adjusted odds ratio of 3.1 (95%CI: 1.9-5.1) for AS patients. When non-responders (35%) were considered as non-MI the odds ratio decreased to 1.9 (95%CI: 1.2-3.2).

Conclusions: Our observations indicate that the MI prevalence is increased in AS patients.

INTRODUCTION

An excessive risk of cardiovascular (CV) mortality and morbidity has been observed in patients with inflammatory arthritis (1;2). The inflammatory process appears to have an important role in causing this excess CV risk, since it resembles similar processes that contribute to all stages of atherosclerosis, from early atheroma formation to plaque instability and thrombus development responsible for CV events (3;4). Accordingly, the CV risk in ankylosing spondylitis (AS) might be increased as well. In an analysis with data from the integrated US health plan an increased CV disease prevalence was observed in AS patients as compared with age- and gender matched controls (5). Another study observed a higher prevalence of spondylarthropathies among patients who underwent coronary artery bypass grafting (CABG), and additionally demonstrated that spondylarthropathy was a stronger predictor of CABG than most traditional CV risk factors (6). However, despite these observations, literature regarding CV risk in AS is limited (7).

Hence, the aim of this paper is to 1] ascertain the prevalence of myocardial infarction (MI) in AS patients relative to the general population and 2] investigate differences in risk factors between AS patients with and without a history of MI.

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

METHODS

AS patients

Between June 1st and the end of September 2007, questionnaires covering the primary outcome MI were sent to all registered AS patients aged between 50 and 75 years from the Jan van Breemen Institute and VU University Medical Centre in Amsterdam, the Netherlands.

Patients not responding were sent a second and, if necessary, a third questionnaire with a two months interval.

General population

Data for comparison were used from the Netherlands Information Network of General Practice. Data include information on consultations, morbidity, prescriptions and referrals to other health care professionals from general practices. The patients as well as general practices are representative for the Dutch population (8;9). Only individuals between 50 and 75 years were included. Morbidity data were derived from consultations and all prescriptions issued by the participating practices were used. Diagnoses were recorded using the international classification of primary care (ICPC-1) coding system (10). When issuing a prescription, a diagnostic code was recorded, and the selected drug was automatically linked to the ATC coding system (www.whocc.no/atcddd. 2007). This means that patients were classified as "having a MI event" if they had a MI event and/or if they needed a prescription linked to a previous MI. Individuals were classified with MI when the diagnosis was recorded in 2006 or in previous years (up to 2004).

Definition of MI

In AS patients, the ICD-9 code 410 was used to classify MI (11). Reported MI's were verified by chart review, by contacting the patient's general practitioner and/or local hospitals for documentation of the event, and were only used, when confirmatory medical information was available. In the general population, the presence of MI was determined by using the ICPC-1 code K75, which can be converted to the ICD-9 code 410 (10).

Nested case-control analysis: comparison of AS patients with and without MI

Additional data on CV risk factors could not be obtained from 4 of the 17 AS patients reporting MI due to withheld consent, leaving 13 AS MI patients for further investigation.

Thirty-nine age- and gender matched AS patients were selected to serve as controls. The following AS related variables were assessed: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), and a history of orthopaedic surgery. A further (physical) examination was performed that included the AS mobility score (Bath Ankylosing Spondylitis Metrology Index (BASMI)), cardiovascular risk factors (smoking (pack years), blood pressure, body mass index, waist to hip ratio, diabetes), and fasting blood samples (glucose, lipids, and C-reactive protein) as described elsewhere (12). Hypertension was defined as a systolic blood pressure over 140 mmHg and/or a diastolic blood pressure over 90 mmHg and/or the current use of antihypertensives. Diabetes was defined as a documented medical history of diabetes, glucose lowering agents usage or fasting glucose levels ≥7.0 mmol/l (13), and dyslipidemia as a TC/HDLc ratio above 4.0 and/or statin usage.

Statistical analyses

Logistic regression analyses were used to calculate odds ratios and 95% confidence intervals 1] per stratum adjusted for age, and 2] overall adjusted for age and gender. First, analyses were done including only patients of whom we received the questionnaire. Second, to judge the effect of non-responders on the study results, best-case calculations were carried out, i.e.

including all non-responders and consider them as non-MI. To detect differences in risk factors between AS patients with MI (case) and those without MI (control) and to deal with matched case-control pairs (for age and gender) conditional logistic regression analyses were performed.

RESULTS

AS patients

At conclusion of the protocol, 383 out of 593 (65%) AS patients had responded. There was no difference in age between patients returning their questionnaire and those who did not, but male patients were less likely to respond than female patients ($p<0.05$).

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

MI prevalence in AS patients versus controls

Table 1 summarizes the prevalence rates for MI in AS and in the general population, in strata defined by age and gender. Odds ratios per stratum were higher in both male and female AS patients. The overall prevalence was 4.4% in AS and 1.2% in the general population.

Compared with controls, the odds ratio for a history of MI was approximately 3-fold higher in AS. Since the response rate of 65% could result in bias, we performed additional analyses including all non-responders considering them as non-MI. Then, in comparison with controls, the prevalence for MI decreased to 2.9%, resulting in an approximately 2-fold higher age and gender adjusted odds ratio.

Differences between AS patients with and without prevalent MI

The prevalence of hypertension and dyslipidemia was higher in AS patients with MI (85% versus 54%, p = 0.07 and 92% versus 38%, p = 0.02). AS patients with MI had a less favourable body mass index and waist to hip ratio (31 kg/m^2 versus 28 kg/m^2, p = 0.08 and 1.00 versus 0.95, p = 0.05), and tended to have a higher prevalence of diabetes (23% versus 10%, p = 0.24). With regard to smoking, no difference was found in the number of pack years. Additionally, although most disease activity- and severity markers were higher in patients reporting MI, these markers were not significantly different. Finally, we did not find a significant difference in the use of antirheumatic treatment, i.e. disease modifying antirheumatic drugs, non-steroidal anti-inflammatory drugs, or antiTNFα treatment, between AS with and without a history of MI. A table showing all results is available on the journal website as an online supplemental file.

DISCUSSION

Although the increased CV risk in inflammatory arthritis patients is increasingly acknowledged, information about the magnitude of CV morbidity in AS is scarce. In this paper, we demonstrate that the prevalence rate for MI is approximately 2-3 fold increased as compared with the general population. This observation indicates that AS, as rheumatoid arthritis and psoriatic arthritis, should be considered as an important CV risk factor (1;14).

The key feature explaining the increased CV risk in inflammatory arthritis patients is thought to be inflammation, as it is an intrinsic element of atherogenesis in all stages of its development (15). However, although a non-significant trend was observed which may indicate that AS patients with a history of MI have a more severe disease, we observed no significant associations between disease activity- or severity markers and a history of MI.

This might be due to the small number of cases limiting statistical power or the crosssectional nature of the present study. Additionally, an increased CV risk in AS patients may be due to an unfavorable pattern of CV risk factors. Indeed, several risk factors, i.e. hypertension, dyslipidemia, and obesity were highly prevalent in AS and even more in patients with a history of MI. Untreated CV co morbidity is another potential explanation for our observations, and cannot be ruled out as a factor (partially) contributing to the increased CV risk in AS, since we observed a relatively high frequency of uncontrolled hypertension and dyslipidemia (data not shown). In terms of clinical implications, our findings substantiate the importance of proper CV risk assessment in AS, in particular CV risk screening and management.

Like all surveys, ours was subject to potential problems of response bias, since cases might be more interested in participating, which eventually may have led to an overestimation of actual MI rates. However, it should be emphasized that, when non-responders were considered as non-MI, the odds ratio for MI in AS decreased, but remained approximately 2-fold higher, as compared with controls. Unfortunately, no information was available regarding CV risk factors, physical activity, and social class from the general population, which prevents us from adjusting for these potential confounders. In conclusion, although our observations must be interpreted with caution, as the number of cases was low, particularly among females, they strengthen the need for larger well-controlled cohort studies to quantify the precise CV risk in AS patients and to identify those at elevated risk.

[TABLE 1]

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

REFERENCES

(1) Solomon DH, Karlson EW, Rimm EB, Cannuscio CC, Mandl LA, Manson JE et al.
Cardiovascular morbidity and mortality in women diagnosed with rheumatoid arthritis. Circulation 2003; 107(9):1303-1307.
(2) Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman AJ, Symmons DP. Mortality in early inflammatory polyarthritis: cardiovascular mortality is increased in seropositive patients. Arthritis Rheum 2002; 46(8):2010-2019.
(3) Libby P. Role of inflammation in atherosclerosis associated with rheumatoid arthritis.
Am J Med 2008; 121(10 Suppl 1):S21-S31.
(4) Goodson NJ, Symmons DP, Scott DG, Bunn D, Lunt M, Silman AJ. Baseline levels of C-reactive protein and prediction of death from cardiovascular disease in patients with inflammatory polyarthritis: a ten-year followup study of a primary care-based inception cohort. Arthritis Rheum 2005; 52(8):2293-2299.
(5) Han C, Robinson DW, Jr., Hackett MV, Paramore LC, Fraeman KH, Bala MV.
Cardiovascular disease and risk factors in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. J Rheumatol 2006; 33(11):2167-2172.
(6) Hollan I, Saatvedt K, Almdahl SM, Mikkelsen K, Moer R, Halvorsen P et al.
Spondyloarthritis: a strong predictor of early coronary artery bypass grafting. Scand J Rheumatol 2008; 37(1):18-22.
(7) Peters MJ, van der Horst-Bruinsma IE, Dijkmans BA, Nurmohamed MT.
Cardiovascular risk profile of patients with spondylarthropathies, particularly ankylosing spondylitis and psoriatic arthritis. Semin Arthritis Rheum 2004; 34(3):585-592.
(8) Verheij RA, Te Brake JHM, Abrahamse H, van den Hoogen H, Braspenning J, Jabaaij L et al. Landelijk Informatienetwerk Huisartsenzorg. Feiten en cijfers over huisartsenzorg in Nederland. http://www.linh.nl . 2006.
(9) Verheij RA, van der Zee J. Collecting information in general practice: just by pressing a single button? Morbidity, performance and quality in primary care. Dutch general practice on stage. 2006: 265-272.
(10) Lamberts H, Wood M. ICPC - International Classification of Primary Care. Oxford University Press: Oxford. 1987.
(11) World Health Organization: International Classification of Diseases, Ninth Edition.
Geneva 1977; Vols. 1 and 2.
(12) van Halm VP, Peters MJ, Voskuyl AE, Boers M, Lems WF, Visser M et al.
Rheumatoid arthritis versus diabetes as a risk factor for cardiovascular disease, a cross sectional study. The CARRE Investigation. Ann Rheum Dis 2008.
(13) Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998; 15(7):539-553.
(14) Gladman DD, Ang M, Su L, Tom BD, Schentag CP, Farewell VT. Cardiovascular morbidity in psoriatic arthritis (PsA). Ann Rheum Dis 2008.
(15) Sattar N, McCarey DW, Capell H, McInnes IB. Explaining how "high-grade" systemic inflammation accelerates vascular risk in rheumatoid arthritis. Circulation 2003; 108(24):2957-2963.

[TABLE 2]

This is a NIVEL certified Post Print, more info at http://www.nivel.eu

TABLES

Table 1.

	Patients			Controls				
	MI's	*Total number of patients*	*Prevalence*	*MI's*	*Total number of persons*	*Prevalence*	Only responders OR (95%CI)	Including non-responders OR (95%CI)
Male								
50-65	8	200 (329)	4.0 (2.4)	409	28078	1.5	2.85 (1.40-5.83)	1.71 (0.84-3.48)
66-75	5	82 (123)	6.1 (4.1)	281	9521	3.0	2.28 (0.91-5.68)	1.47 (0.60-3.63)
Total	13	282 (451)	4.6 (2.9)	690	37599	1.8	2.60 (1.48-4.56)	1.60 (0.92-2.80)
Female								
50-65	3	83 (118)	3.6 (2.5)	103	27085	0.4	9.73 (3.02-31.36)	6.94 (2.17-22.21)
66-75	1	18 (23)	5.6 (4.3)	129	10647	1.2	4.80 (0.63-36.31)	3.80 (0.51-28.45)
Total	4	101 (141)	3.9 (2.8)	232	37732	0.6	7.91 (2.86-21.85)	5.75 (2.10-15.78)
Total	17	383 (593)	4.4 (2.9)	922	75333	1.2	3.10 (1.89 to 5.09)	1.94 (1.19-3.17)

MI = myocardial infarction; OR = Odds Ratio; The numbers and percentages corresponding with the best-case calculations are added in brackets. Conditional logistic regression analyses were performed to calculate the odds ratios.

Table 2 (online supplemental file)

Differences between AS patients with and without CVD

	AS patients with MI (n = 13)	*AS patients without MI (n = 39)*	*P-Value*
Demographic			
Age, years	63 (4)	63 (5)	-
Men, %	77	77	-
AS related factors			
Disease duration, years	32 (19-38)	25 (19-36)	0.88
BASDAI (range 0-10)	3.1 (1.3-5.7)	2.5 (1.5-4.5)	0.59
BASFI (range 0-10)	3.5 (2.4-4.8)	2.9 (1.6-5.0)	0.96
BASMI (range 0-10)	4 (3-6)	4 (2-6)	0.61
Orthopadic surgery, %	31	13	0.16
CRP (mg/L)	6 (3-7)	7 (3-16)	0.93
Cardiovascular factors			
Smoking, years	24 (16-33)	20 (15-30)	0.96
Hypertension, %	85	54	0.07
Dyslipidemia, %	92	38	0.02
Diabetes, %	23	10	0.24
BMI (kg/m2)	31 (6)	28 (6)	0.08
Waist to hip ratio	1.00 (0.07)	0.95 (0.09)	0.05
Medication			
Current NSAIDs, %	38	54	0.34
Past NSAIDs, %	77	74	0.85
Current DMARDs, %	0	5	0.27
Past DMARDs, %	23	18	0.62
Current TNFa blockers, %	15	16	1

Continuous variables are presented as means with standard deviations (SD) in case of a normal distribution or as medians with interquartile ranges (IQR) in case of a non-normal distribution. Dichotomous variables are presented as number of cases and percentage of total.

This is a NIVEL certified Post Print, more info at http://www.nivel.eu