

CARDIOVASCULAR MORBIDITY IN PSORIATIC ARTHRITIS (PsA)

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Abstract

Background. Increasing evidence for cardiovascular mortality among patients with psoriasis and psoriatic arthritis (PsA) has accumulated, together with evidence for increased frequency of risk factors for cardiovascular disease.

Objectives. To describe cardiovascular morbidity in PsA, determine its prevalence, and identify risk factors for its development.

Methods. At the University of Toronto, patients have been followed prospectively according to a standard protocol including disease related features as well as co-morbidities. Patients with cardiovascular disease (CVD) including myocardial infarction (MI), angina, hypertension (HTN), and cerebrovascular accident (CVA) were identified. The prevalences of CVD morbidities in these patients were compared to data from the Canadian Community Health Survey (CCHS) through Standardized Prevalence Ratios (SPRs). Risk factor analyses are undertaken through use of Cox relative risk regression analysis

Results. At the time of analysis, 648 patients were registered in the database. After clinic entry, 122 developed hypertension, 38 had an MI, and 5, 21 and 11 had CVA, angina and congestive heart failure (CHF) respectively. A total of 155 patients had at least one of these conditions observed. The SPRs for MI [2.57; 95% CI: (1.73, 3.80)], angina [1.97; : (1.24, 3.12)] and hypertension [1.90; (1.59, 2.27)], were statistically significant, whereas the SPRs for CHF [1.19; : (0.50, 2.86)] and CVA [0.91; : (0.34, 2.43)] were not. Factors associated with CVD included diabetes, hyperlipidemia and high PASI scores.

Conclusion. Patients with PsA are at increased risk of cardiovascular morbidities compared to the general population. In addition to known risk factor for CVD, severe psoriasis is an important predictor in patients with PsA.

Psoriatic arthritis (PsA) is a chronic inflammatory arthritis associated with psoriasis that occurs in 0.3–1% of the population.[1] PsA is usually seronegative for rheumatoid factor, and is classified among the spondyloarthropathies. [2,3] The prototype of inflammatory arthritis, RA has been extensively researched, and multiple studies reiterate the increased cardiovascular morbidity and mortality rates, with standardized mortality ratios ranging from 0.87 to 3.0.[3-12] Psoriasis patients are also at significantly higher risk for cardiovascular deaths.[13-15] We have previously demonstrated an increased mortality risk in patients with PsA, and notably, the leading cause of death was cardiovascular disease (CVD).[16] Others have recently noted the increased cardiovascular risk among patients with spondyloarthritis.[17] Psoriasis was found to be an independent risk factor for myocardial infarction.[18] These findings indicate the possibility of increased risk of cardiovascular morbidities in PsA.

It has been suggested that the chronic inflammatory nature of RA and other inflammatory rheumatic diseases is very similar to that causing atherosclerosis.[19-21] Among risk factors for coronary heart disease (CHD) are modifiable factors such as smoking, diabetes, hypertension, increased total LDL and decreased HDL cholesterol levels, obesity, sedentary lifestyle and fixed factors such as age and gender.[19] However, additional risk factors, such as apoprotein B, Lp(a) lipoprotein, fibrinogen, C-reactive protein (CRP), soluble ICAM-1, homocysteine, PAI-1 plasminogen inhibitor, and MMP3 metalloproteinase, may play a role in chronic inflammatory diseases.[22] Treatments such as disease modifying anti-rheumatic drugs (DMARDs), or some non-steroidal anti-inflammatory drugs (NSAIDs) such as COX-2 inhibitors may also exacerbate heart disease.[21] While studies on the direct risk of CVD in psoriatic arthritis are few, the indirect evidence of a potential link is significant, and suggests benefit in further exploration of this topic.

The aim of the present investigation was threefold: we sought to describe CVD in our PsA cohort, to determine the prevalence of CVD in comparison to the general population, and to examine the risk factors of CVD relative to disease severity in PsA.

Methods

Setting: The University of Toronto Psoriatic Arthritis Clinic in the Centre for Prognosis Studies in Rheumatic Diseases was founded in 1978 as a prospective longitudinal observational cohort of patients with PsA.[25] The cohort consists of patients with PsA who are referred to the clinic by family physicians and other medical specialists. Patients followed in the clinic may receive their primary rheumatological care at the clinic or may attend once or twice a year and continue to be followed by their community rheumatologists. The clinic thus includes the spectrum of PsA, from mild disease to very severe disease.

Clinical assessments: Each assessment consisted of a medical history, physical examination, and laboratory evaluation, including items related to PsA as well as co-morbidities and known risk factors. A standard protocol, completed at each clinic visit at 6-12 month intervals, has been entered into a computerized database.

Patient selection: Patients included in this study were registered at the clinic between January 1st 1978 and June 1st 2004. The database was used to identify the patients with cardiovascular

morbidity. Cardiovascular disease comprised hypertension (HTN), angina, myocardial infarction (MI), cerebrovascular accident (CVA), and congestive heart failure (CHF). Hypertension was defined as a blood pressure of greater than 140/90 on more than two consecutive occasions, or use of antihypertensive agents by the patients. Myocardial infarction was defined as one of: definite ECG abnormalities, typical symptoms with probable ECG abnormalities and abnormal enzymes (≥ 2 upper limit of normal); typical symptoms and abnormal enzymes.

Angina was defined as severe pain or discomfort over the upper or lower sternum or anterior left chest and left arm, of short duration relieved by rest or vasodilators. Cerebrovascular event was defined as an abrupt onset of neurological dysfunction resulting in neurological damage.

Additional information was sought from the patient charts to ensure accuracy and completeness of the database, since check up visits may occur between protocol visits. Moreover, documentation of the clinical events was obtained from hospital records and primary care physicians. Dates of diagnosis for each type of event were obtained. Deaths attributable to cardiovascular causes were recorded. The procedures used to identify causes of death have been previously described.[16]

Predictive factors: Known risk factors included age, gender, daily alcohol use, smoking, elevated triglycerides, elevated cholesterol, hyperuricemia, and diabetes. Other risk factors relating to PsA disease severity at first clinic visit were: age at onset (psoriasis and PsA), disease duration (psoriasis and PsA), actively inflamed joint count, clinically deformed joint count, Psoriasis Area and Severity Index (PASI) score, and erythrocyte sedimentation rate (ESR).

Comparison group: Comparative data on cardiovascular disease was obtained from the Canadian Community Health Survey (CCHS), a cross-sectional examination of health determinants, health status, and health system utilization, carried out by Statistics Canada in 2000-01.[24] This survey, conducted by telephone and computer-assisted personal interviews, took place at health region-level and provincial level; 39,278 individuals from Ontario aged 12 years and older were interviewed. The sample was weighted and results extrapolated to the Ontario population were used for analysis. Available summary tables are subdivided by age group and gender, subject to sample sizes meeting release guideline criteria of Statistics Canada. Otherwise, data are pooled to meet these guidelines.

Statistical analysis: The prevalence of CVD morbidities in patients under follow-up in the PsA cohort were compared to CCHS data through Standardized Prevalence Ratios (SPRs) calculated in the same fashion as the more familiar Standardized Mortality Ratios. The prevalence of CVD morbidities in the PsA cohort was estimated over the same time period (i.e. up to 2000-2001) with matched gender and age groups as was done for the cross-sectional CCHS. Specifically, all deaths before January 1, 2000 were excluded, and CVD events that occurred before December 31, 2001 were included for the SPR calculation. Additionally, where gender specific information was not available for particular age categories in the CCHS for particular morbidities, only the corresponding age categories in the PsA cohort were collapsed over gender when calculating the SPRs for those particular morbidities.

Risk factor analyses were undertaken through use of Cox relative risk regression analysis with time-dependent explanatory variables and age as the chosen time scale.[25] Left truncation was incorporated into the Cox model. Data analyses include patients' records when information of the relevant potential risk factors is available from the previous clinic visit. However, if

laboratory tests measurements are not available at previous visit, the last recorded test measurements are used and the appropriate patients' records included. Due to PASI being recorded for patients only since 1991, missing values for this variable were handled by introducing an unknown PASI classification. This allowed more patients' records to be included in analyses but the qualitative findings were not sensitive to this decision. Additionally, to alleviate some of the problems that would result from missing information on medication information since last visit, in particular non-steroidal anti-inflammatory drugs, ever used medication variables were constructed. The logarithmic transformation of a laboratory measurement was chosen for assessing that covariate's effect on risk of having a CVD event if it either lessened the impact that a few extreme/outlying observations of the covariate may have on the results thus making them more robust or made the effect of the covariate approximately linear on the log hazard scale.

Results

Between January 1st 1978 and June 16th 2004, 648 patients were registered in the University of Toronto PsA clinic database; 364 (56.2%) were male and 284 (43.8%) were female. Mean age at first visit was 43.5 years and at last visit was 51.8 years. Average duration of follow up was 8.3 years. At first visit, duration of psoriasis and PsA were 14.6 years and 7.4 years; mean initial active joint count was 10, and mean initial Psoriasis Area and Severity Index (PASI) score was 5.5 for those enrolled since 1991 (Table 1).

Table 1: Patient characteristics at first visit

Total number of patients	648
Mean age at onset Psoriasis in years (SD)	28.9 (14.4)
Mean age at onset PsA in years (SD)	36.0 (13.2)
Mean psoriasis duration in years (SD)	14.6 (11.9)
Mean PsA duration in years (SD)	7.4 (8.3)
Mean number of actively inflamed joint count (SD)	10 (9.5)
Mean number of clinically deformed joint count (SD)	3.2 (7.6)
Mean PASI score (SD)	5.5 (7.9)
Mean ESR in mm/h (SD)	27.6 (21.7)
Current smoker (%)	18.4%
Daily alcohol use (%)	10.1%
Hyperuricemia (%) for males (uric acid in $\mu\text{mol/L}$ >480)	8.8%
Hyperuricemia (%) for females (uric acid in $\mu\text{mol/L}$ >400)	7.1%
Hypertriglyceridemia (%) (triglycerides in mmol/L >2.3)	19.2%
Hypercholesterolemia (%) (cholesterol in mmol/L >5.2)	44.8%

The number of cardiovascular morbidities observed at any time (including events before entry) in patients from the PsA cohort was as follows: hypertension - 206, MI - 50, angina - 33, CVA - 8 and CHF - 12. Overall, 227 individuals had at least one of these conditions, corresponding to a prevalence of 35.0%. Elevated prevalences were observed for hypertension, MI and angina with overall gender and age-adjusted SPRs of 1.9, 2.6 and 2.0 respectively (Table 2), where the corresponding numbers of observed hypertension, MI and angina up to 2001 were 122, 25 and 18 respectively.

Table 2. Standardized prevalence ratio of CVD events

	Standardized Prevalence Ratio*	LCL	UCL	p-value
Hypertension	1.90	1.59	2.27	<0.01
Cerebrovascular accident	0.91	0.34	2.43	0.85
Myocardial infarction	2.57	1.73	3.80	<0.01
Angina	1.97	1.24	3.12	<0.01
Congestive heart failure	1.19	0.50	2.86	0.69

*time range: Jan 1, 2000- Dec 31, 2001; reference rates calculated for Ontario, 2000/2001 CCHS, separately by gender and age where relevant

Unfortunately, for the youngest age group (i.e. for MI and angina: age 12-44; and for CHF: age 12-54), gender specific information on MI, angina and CHF was not available in the CCHS data. Therefore gender specific SPRs could be calculated only for hypertension and CVA. For males and females, the SPRs for CVA were 1.0 (95% CI [0.3,4.1]) and 0.8 (95% CI [0.2,3.3]) respectively, whilst the gender specific SPRs for hypertension were 2.1 (95% CI [1.7,2.6]) and 1.7 (95% CI [1.3,2.2]) for males and females respectively.

We performed sensitivity analyses to examine the results for SPRs. For hypertension, after redefining the 39 cases that were solely identified by consecutive high blood pressure measurements in the PsA cohort after the first visit to be non-hypertensive, the estimated SPR was reduced to 1.29 (95% CI [1.04, 1.60]). These 39 excluded patients in the PsA clinic represent those patients who might be identified as having hypertension through the more regular follow-up that takes place in the Toronto PsA clinic. For MI and angina, less likely to be over-reported due to regular follow-up, we examined the potential effect of reclassification on reported significance tests. The observation of just 16 or more of the 25 MI cases and 15 or more of the 18 angina cases would provide statistical evidence for elevated prevalences in 0.05 significance level tests.

After clinic entry, 122 PsA clinic patients developed hypertension, 38 had an MI, and 5, 21 and 11 had CVA, angina and CHF respectively. A total of 155 patients had at least one of these conditions observed after clinic entry.

Table 3 presents single risk factor time to event analyses for hypertension, MI and any CVD conditions. Small numbers of events precluded informative analyses of the other specific cardiovascular conditions. Effects for diabetes, triglycerides, and PASI are evident for the

hypertension and first CVD event analyses. With smaller numbers the only risk factor found for MI were smoking and triglycerides

Table 3. Cox regression analyses with individual disease-related variables, controlled for gender and age at onset of psoriasis.

Disease-related variables	Hypertension		MI		First CVD event	
	HR	P	HR	P	HR	P
Gender	1.29	0.19	2.48	0.01	1.55	0.01
Age at onset of PS	1.01	0.08	1.00	0.74	1.00	0.73
Age at onset of PSA	0.98	0.13	1.00	0.86	0.99	0.14
No. of actively inflamed joints	1.01	0.61	1.02	0.41	1.00	0.98
No. of clinically deformed joints	1.00	0.99	1.00	0.85	1.00	0.80
NSAIDS ever used	1.57	0.30	2.53	0.37	1.27	0.50
Intra-articular steroid ever used	1.20	0.34	1.24	0.56	1.23	0.23
DMARDS ever used	1.21	0.31	0.86	0.64	1.11	0.51
Methotrexate ever used	1.39	0.08	0.75	0.40	1.17	0.34
Biologics ever used	0.62	0.63			0.41	0.38
Steroids ever used	1.37	0.15	1.48	0.29	1.30	0.18
Immunosuppressive drugs ever used	1.31	0.14	0.79	0.47	1.15	0.40
Diabetes	3.40	<0.01	1.79	0.36	2.49	0.01
Daily alcohol use	1.55	0.38	0.88	0.91	1.62	0.31
Current smoker	0.46	0.29	15.89	0.01	1.03	0.96
Logarithm of uric acid	1.47	0.15	2.48	0.09	1.49	0.08
Logarithm of Triglycerides	1.44	<0.01	1.52	0.03	1.47	<0.01
Logarithm of Cholesterol	1.26	0.22	1.40	0.25	1.31	0.10
ESR	1.00	1.00	1.01	0.34	1.00	0.69
Interaction of ESR and gender	1.01	0.14	1.01	0.58	1.01	0.15
PASI score (base category=0)		0.02		0.19		<0.01
0< PASI <=10	0.85	0.67	1.84	0.56	0.91	0.79
10<PASI <=20	0.72	0.51	1.23	0.87	0.68	0.42
PASI>20	2.27	0.08	5.59	0.13	2.70	0.02

Due to long follow-up period in the PsA cohort, we also investigated the possible differential effects of risk factors over calendar time. Interactions terms between calendar time and risk factors were examined individually. In addition to medication variables defined as ever used only, we also checked the medication variables defined as whether used since last visit, when possible. For hypertension, age at onset of PS and steroids since last visit were found to have possible interactions with calendar time that disappear after multiplicity adjustment. Similarly, ESR and gender for MI, as well as age at onset of psoriasis, steroids since last visit and PASI for first CVD event have inconclusive evidence for differential effects over calendar time.

Table 4 presents multivariate time to event analyses. For hypertension and first CVD event, the interactions for age at onset of psoriasis and steroids since last visit with calendar time were not evident. However, for first CVD event, the interaction between PASI and calendar time is borderline significant ($p=0.05$), thus suggesting a possible changing effect of PASI over calendar time. An elevated effect of PASI on hypertension was seen for a PASI score greater than a threshold of 20. It can also be concluded that diabetes and triglycerides are significantly related to hypertension and the occurrence of any CVD event. If the interaction of steroid use since last visit and calendar time is excluded, then the main effects of steroid use since last visit are found not to be statistically significant in the models for hypertension and first CVD event ($p = 0.11$ and 0.18 respectively).

For MI, the differential effect of gender and ESR over calendar time is borderline statistically significant ($p=0.04$). Smoking and triglycerides were both found to be positively related to the risk of experiencing MI.

Table 4. Multivariate Cox regression analyses, controlled for gender and age at onset of PS and their interactions with calendar time.

Disease-related variables	Hazard ratio	LCL	UCL	p-value
Hypertension:				
Steroids used since last visit	1.98	1.01	3.88	0.05
Interaction of steroids and calendar time	1.69	0.86	3.31	0.13
Diabetes	2.42	1.01	5.83	0.05
Logarithm of triglycerides	1.43	1.11	1.86	0.01
PASI score (base category 0)				0.03
0< PASI <=10	0.83	0.41	1.71	
10<PASI <=20	0.73	0.27	1.94	
PASI>20	2.12	0.87	5.20	
Unknown PASI	0.65	0.25	1.71	
Myocardial infarction:				
ESR	1.01	0.99	1.04	0.29
Interaction of ESR and gender	1.01	0.97	1.04	0.74
Interaction of ESR and calendar time	1.02	1.00	1.04	0.05
Interaction of ESR, gender and calendar time	0.98	0.95	1.00	0.04
Current smoker				
Yes	9.09	1.93	42.76	0.01
Unknown	2.35	0.70	7.88	0.17
Logarithm of triglycerides	1.49	1.01	2.19	0.04
First CVD event:				
Steroids used since last visit	1.78	0.96	3.31	0.07
Interaction of steroids and calendar time	1.70	0.90	3.20	0.10
Diabetes	2.10	1.00	4.43	0.05
Logarithm of triglycerides	1.47	1.17	1.83	<0.01
PASI score (base category=0)				0.05
0< PASI <=10	1.28	0.61	2.69	
10<PASI <=20	0.88	0.35	2.24	
PASI>20	2.71	1.13	6.51	
Unknown PASI	1.45	0.50	4.19	
Interaction of PASI score and calendar time				0.05
0< PASI <=10	0.53	0.28	0.98	
10<PASI <=20	0.67	0.20	2.32	
PASI>20	0.97	0.32	2.94	
Unknown PASI	1.51	0.75	3.02	

Discussion

Much evidence has been accumulating surrounding the link between rheumatic diseases and cardiovascular disease. Studies have found increased rates of cardiovascular death in RA, systemic lupus erythematosus, ankylosing spondylitis, psoriasis, and psoriatic arthritis.[4,14,16,20,26] Cardiovascular disease is among the leading causes of death among patients with PsA²⁹. Recent evidence suggests that patients with PsA are at an increased risk for developing cardiovascular disease.[28-30] A study from the integrated outcomes database identified 3066 patients with PsA who were matched 1:4 with individuals in the database on the basis of age, sex, location and length in the plan. The prevalence ratio of peripheral vascular disease (1.6), congestive heart failure (1.5), atherosclerosis (1.4), ischemic heart disease (1.3), cerebrovascular disease (1.3), and hypertension (1.3) were higher in PsA patients than controls. They also found that risk factors for coronary artery disease such as hypertension, diabetes and hyperlipidemia produced higher prevalence ratios in patients with PsA (1.3, 1.5, 1.2 respectively) than controls.[29] We have now found indication of such effects in patients with PsA followed prospectively. For hypertension, myocardial infarction and angina, prevalences were significantly higher in the PsA cohort compared with data from the CCHS with standardized prevalence ratios of 1.9, 2.57 and 1.97 respectively. Higher prevalences of risk factors for coronary artery disease were also reported for patients with psoriasis compared to the general population, although it is not clear how many of those patients had PsA.[31] Similar observations were previously reported from our PsA cohort.[32] Also, two recent studies have shown an increased frequency of subclinical atherosclerosis, expressed by endothelial dysfunction and increased carotid artery intima-media thickness, in PsA patients without clinically evident cardiovascular disease or classic cardiovascular risk factors.[33,34] Interestingly, in keeping with our results, these authors did not find any association between the severity or the pattern of joint involvement and the development of subclinical atherosclerosis. No information about the severity of psoriasis skin involvement was given in these two studies. However, we did observe a role for high PASI scores representing more severe psoriasis. Severe psoriasis was found to be an independent risk factor for myocardial infarction in a population study of patients with psoriasis.[18] It is possible that the additive effect of PsA by itself as a chronic inflammatory disease along with a higher frequency of traditional cardiovascular risk factors in these patients may account for the increased incidence of cardiovascular events observed in PsA patients.

We have previously reported that ESR and radiological damage were associated with increased relative risk values for deaths related to the circulatory system.[27] However, no substantial evidence for a role for ESR emerged in our current analysis. Traditional Framingham factors, high triglyceride levels and presence of diabetes, were found to be prognostic for cardiovascular morbidity.

Chronic inflammation with perpetually raised levels of proinflammatory cytokines and immune cells can lead to endothelial dysfunction and formation of atherosclerotic plaque.[4,19] IL-6 and TNF can also induce hepatic synthesis of CRP, a serum marker of inflammation associated with heart disease.[4] Anti-inflammatory medications can also contribute to the development of cardiovascular disease.[35] Glucocorticoids, although anti-inflammatory, can lead to hypertension, hyperglycemia, and a negative lipid profile, and non-steroidal anti-inflammatory drugs (NSAIDs) similarly raise blood pressure and also may promote thrombosis

via COX-2 inhibition.[35] Elderly patients on rofecoxib were at increased risk of congestive heart failure.[36] Methotrexate affects homocysteine levels, which is a risk factor for atherosclerosis.[4,37] In patients with arthritis is limited movement and sedentary lifestyle may contribute, since regular exercise is a protective factor against heart disease.[4] In psoriasis, abnormalities of coagulation and fibrinolysis and elevated homocysteine levels have been documented.[38,39]

Many of these measures might be useful prognostic factors in predicting heart disease, but our data was primarily rheumatologic data and not cardiologic. As a result, we did not have data on body mass index or CRP. In addition, the true morbidity rate is difficult to measure, even with data from regular clinic visits, since it was found that up to half of ischemic heart disease in rheumatoid arthritis patients is clinically silent.[40] Events in our study were recorded from patient self-reporting at clinic visits, protocol physical examinations, and possible referrals for consultations on symptoms presenting at clinic visits. An appropriate control group is also important, which was the reason for using data from the CCHS in our study. The community cohort in the CCHS is comparable to our outpatient PsA clinic and these were compared over the same time period. Collection of data in the CCHS was systematic, and data specific to the province of Ontario was readily available. However, it should be noted that while the PsA patients were followed prospectively, the information on the controls was collected cross-sectionally.

It is possible that significance in the other outcomes was not detected due to low numbers of events (i.e. lack of power) although this PsA patient population is the largest group prospectively followed to date. Unlike RA, there is no national patient registry of psoriatic arthritis patients, however.

Our clinic serves as both a primary, secondary and tertiary referral centre and includes the whole spectrum of PsA, from mild to severe disease, thus it is representative of patients with PsA who see rheumatologists. Moreover, our cohort is similar in demography and disease characteristics to others reported in the literature.[1] This is the first study to examine cardiovascular morbidity among patients with PsA followed prospectively. Our findings show significantly increased risk of hypertension, MI, and angina in psoriatic arthritis. However, our analyses were exploratory and multiple testing may inflate Type I error rates. Even so, our results are in accord with findings from studies in other rheumatic diseases suggesting that the inflammatory process in PsA also predisposes these patients to these co-morbidities.[5,6,10,24] These findings need to be confirmed with other large cohorts of patients with PsA followed prospectively. Moreover, attempts should be made to record and address the risk factors identified in this study in all patients with PsA.

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References

1. Gladman DD: Psoriatic arthritis. Oxford Textbook of Rheumatology. 3rd Edition. Edited by Maddison PJ, Isenberg DA, Woo P, Glass DN, Breedveld F. Oxford University Press, 2004; pp 766-78.
2. Gladman DG. Psoriatic arthritis. *Rheum Dis Clin North Am* 1998;24:829-44.
3. Prior P, Symmons DP, Scott DL, Brown R, Hawkins CF. Cause of death in rheumatoid arthritis. *Br J Rheumatol.* 1984;23:92-9.
4. del Rincon I, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular events in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;44:2737-45.
5. Mikuls TR, Saag KG. Comorbidity in rheumatoid arthritis. *Rheum Dis Clin North Am* 2001;27: 283-303.
6. Jonsson SW, Backman C, Johnson O, Karp K, Lundstrom E, Sundqvist KG, Dahlqvist SR. Increased prevalence of atherosclerosis in patients with medium term rheumatoid arthritis. *J Rheumatol.* 2001;28:2597-602.
7. Wolfe F, Freundlich B, Straus WL. Increase in cardiovascular and cerebrovascular disease in rheumatoid arthritis. *J Rheumatol* 2003; 30:36-40.
8. Wolfe F, Michaud K. Heart failure in rheumatoid arthritis: rates, predictors, and the effect of anti-tumor necrosis factor therapy. *Am J Med* 2004;116:305-11.
9. Turesson C, Jaraenros A, Jacobsson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. *Ann Rheum Dis* 2004;63: 952-5.
10. Gonzalez-Gay MA, Gonzalez-Juanatey C, Martin J. Rheumatoid arthritis: a disease associated with accelerated atherogenesis. *Semin Arthritis Rheum* 2005; 35:8-17.
11. Nicola PJ, Crowson CS, Maradit-Kremers H, Ballman KV, Roger VL, Jacobsen SJ et al. Contribution of congestive heart failure and ischemic heart disease to excess mortality in rheumatoid arthritis. *Arthritis Rheum* 2006; 54:60-7.
12. Wolfe F, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994; 37:481-494.
13. Lindegard B. Mortality and causes of death among psoriatics. *Dermatologica* 1989; 179: 91-2.
14. Poikolainen K, Karvonen J, Pukkala E. Excess mortality related to alcohol and smoking among hospital-treated patients with psoriasis. *Arch Dermatol* 1989;135:1490-3.

15. Mallbris L, Akre O, Granath F, Yin L, Lindelof B, Ekbom A et al. Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. *Eur J Epidemiol* 2004; 19:225-230.
16. Wong D, Gladman DD, Husted J, Long JA, Farewell VT. Mortality studies in psoriatic arthritis: results from a single outpatient clinic. I. Causes and risk of death. *Arthritis Rheum* 1997;40:1868-72.
17. 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; 34:585-592.
18. Gelfand JM, Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB. Risk of myocardial infarction in patients with psoriasis. *JAMA* 2006;296:1735-41.
19. Ross R. Atherosclerosis - an inflammatory disease. *N Engl J Med* 1999;340:115–26.
20. van Doornum S, McColl G, Wicks IP. Accelerated atherosclerosis. An extra-articular feature of rheumatoid arthritis? *Arthritis Rheum* 2003;46:862–73.
21. Kitas GD, Erb N. Tackling ischaemic heart disease in rheumatoid arthritis. *Rheumatology (Oxford)* 2003; 42:607–13.
22. Meyer O. Atherosclerosis and connective tissue diseases. *Joint, Bone, Spine: Revue du Rhumatisme* 2001 ;68:564-75.
23. Gladman DD, Shuckett R, Russell ML, Thorne JC, Schachter RK. Psoriatic arthritis (PsA)—an analysis of 220 patients. *QJM*. 1987;62:127-41.
24. Statistics Canada. Canadian Community Health Survey. 2002.
25. Cox DR. Regression Models and Life-Tables. *Journal of the Royal Statistical Society. Series B (Methodological)*, 1972, 34: 187-220
26. Bjornadal L, Yin L, Granath F, Klareskog L, Ekbom A. Cardiovascular disease a hazard despite improved prognosis in patients with systemic lupus erythematosus: results from a Swedish population based study 1964-95. *J Rheumatol* 2004;31: 713-9.
27. Gladman DD, Farewell VT, Wong K, Husted J. Mortality studies in psoriatic arthritis: results from a single outpatient center. II. Prognostic indicators for death. *Arthritis Rheum* 1998;41:1103-10.
28. 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; 34:585-592.

29. 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; 33:2167-2172.
30. Kimhi O, Caspi D, Bornstein NM, Maharshak N, Gur A, Arbel Y et al. Prevalence and risk factors of atherosclerosis in patients with psoriatic arthritis. *Semin Arthritis Rheum* 2007; 36:203-209.
31. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. *J Am Acad Dermatol* 2006;55:829-35.
32. Bruce IN, Schentag C, Gladman DD. Hyperuricemia in psoriatic arthritis (PsA) does not reflect the extent of skin involvement. *J Clin Rheumatol* 2000;6:6-9.
33. Gonzalez-Juanatey C, Llorca J, Miranda-Filloo JA, Amigo-Diaz E, Testa A, Garcia-Porrua C, et al. Endothelial dysfunction in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57:287-93.
34. Gonzalez-Juanatey C, Llorca J, Amigo-Diaz E, Dierssen T, Martin J, Gonzalez-Gay MA. High prevalence of subclinical atherosclerosis in psoriatic arthritis patients without clinically evident cardiovascular disease or classic atherosclerosis risk factors. *Arthritis Rheum* 2007; 57:1074-80.
35. Mikuls TR. Co-morbidity in rheumatoid arthritis. *Best Practice & Research in Clinical Rheumatology* 2003;17:729-52.
36. Mamdani M, Juurlink DN, Lee DS, Rochon PA, Kopp A, Naglie G, Austin PC, Laupacis A, Stukel TA. Cyclo-oxygenase-2 inhibitors versus non-selective non-steroidal anti-inflammatory drugs and congestive heart failure outcomes in elderly patients: a population-based cohort study. *Lancet* 2004;363:1751-6.
37. Clarke R, Daly L, Robinson K, Naughten E, Cahalane S, Fowler B, et al. Hyperhomocysteinemia: an independent risk factor for vascular disease. *N Engl J Med*. 1991;324: 1149-55.
38. Marongiu F, Sorano GG, Bibbo C, Pistis MP, Conti M, Mulas P et al. Abnormalities of blood coagulation and fibrinolysis in psoriasis. *Dermatology* 1994; 189:32-37.
39. Vanizor KB, Orem A, Cimsit G, Uydu HA, Yandi YE, Alver A. Plasma homocysteine and its relationships with atherothrombotic markers in psoriatic patients. *Clin Chim Acta* 2003; 332:23-30.
40. Wislowska M, Sypula S, Kowalik I. Echocardiographic findings, 24-hour electrocardiographic Holter monitoring in patients with rheumatoid arthritis according to

Steinbrocker's criteria, functional index, value of Waaler-Rose titre and duration of disease. *Clin Rheumatol* 1998;17:369-77.