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

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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)

Key Indexing Terms:
RHEUMATOID ARTHRITIS
PSORIATIC ARTHRITIS
ANKYLOSING SPONDYLITIS
CARDIOVASCULAR DISEASE

Rheumatoid arthritis (RA), an autoimmune disorder affecting approximately 1% of the US population, is a costly and debilitating disease characterized by joint pain, stiffness, and impaired functionality. Progressive disability in joint function results from the inflammation and degradation of the synovial membrane[1]. With disease progression, patients often require invasive procedures and joint replacement. As a result, RA creates a large economic burden for patients, their families, and society. The estimated direct and indirect costs of RA-related care in the US total $19 billion annually[2].

Similarly, the spondyloarthropathies, psoriatic arthritis (PsA) and ankylosing spondylitis (AS), have a significant impact on patient functional status and quality of life. PsA is a chronic inflammatory arthropathy characterized by the association of arthritis and psoriasis. A substantial proportion of patients with PsA have persistent inflammation, and many patients develop progressive joint damage and disability, and have reduced life expectancy[3]. AS is a chronic inflammatory disease that causes severe back pain and damages the joints of the spine. Although AS is primarily a disease of the spine, many patients also experience inflammation in the shoulders, hips, ankles, and jaw. While researchers have only recently started to investigate the burden of this disease, comparisons with RA patients have shown similar degrees of pain and disability[4]. In addition, work disability is greater in patients with AS than in individuals without the disease[5].

The increased risk for cardiovascular disease in patients with RA has been well established. In a study of an inception cohort of 1010 patients with RA attending rheumatology clinics between 1981 and 1996, all-cause mortality, as assessed by standardized mortality ratios (SMR), was increased in men (SMR 1.45) and women (SMR 1.84), as was cardiovascular disease mortality in both men (SMR 1.36) and women (SMR

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1.93), when compared with that in the general population[6]. In a separate evaluation of the risks and predictors for mortality in a cohort of 152 consecutive outpatients with RA, the SMR was 1.61 for women, 1.52 for men, and 1.56 for both sexes combined. Cardiovascular disease comorbidity was a significant predictor of mortality in this study[7]. In addition, patients with RA were 30% to 60% more likely to suffer from a cardiovascular event[8].

In contrast to RA, only limited data are currently available regarding cardiovascular risk in patients with AS and PsA[9]. Our aim was to compare the prevalence of cardiovascular diseases and their risk factors between patients with RA, PsA, and AS and control subjects. The cardiovascular diseases/risk factors of interest were ischemic heart disease (IHD), atherosclerosis, peripheral vascular disease (PVD), congestive heart failure (CHF), cerebrovascular disease (CVD), type II diabetes, hyperlipidemia, and hypertension. We also assessed selected cardiovascular medication use in the patient and control groups.

MATERIALS AND METHODS

Data source. Patient data were obtained from the PharMetrics Patient-Centric Database, a database that contains fully adjudicated medical service and prescription drug claims from health plans across the US. To our knowledge, this is the largest integrated US health plan data set available for research purposes. Different types of managed care organizations, as well as benefit designs, are included in this predominantly working population. Inpatient and outpatient diagnoses [International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) format] and procedures (CPT-4 and HCPCS formats) are included in the data set. Additional data elements include demographic variables (e.g., age, sex, geographic region) and start and stop dates for plan enrollment. All patients who met the selection criteria specified below were included in the analyses.

Selection criteria. Data were selected for adults (age > 17 years) who were continuously enrolled from January 1, 2001, through December 31, 2002, in the PharMetrics integrated outcomes database with medical and drug benefits. Patients had to have had at least one interaction with the healthcare system to be included in the analysis. All diagnostic fields and levels of care with an appropriate ICD-9 code were used to identify disease populations and study events. Patients with RA (714.x), PsA (696.0), and AS (720.0) were matched at a 1:4 ratio to controls based on sex, age, geographic region, and previous length of time in plan. ICD-9 codes used to define the patient cohorts and cardiovascular diseases/risk factors were based on existing literature, expert opinion, and exploratory data analysis (Table 1)[10-14]. All patients had the same length of followup within the context of our data analysis.

Measures and analyses. Direct adjustment methodology was used to calculate age- and sex-adjusted prevalences of comorbidities over a 2-year period[15]. Comorbidities assessed included IHD, atherosclerosis, PVD, CHF, CVD, type II diabetes, hyperlipidemia, and hypertension. The differences in the prevalence of comorbidities were compared between patient and control groups using the chi-square test[16]. From the database it is not possible to identify whether the comorbidities existed at baseline, or were incident during the followup period. Given the relatively short followup period, it is reasonable to assume that most of the comorbidities were present at baseline. Hence, we use the term prevalence ratio to denote the ratio of the proportion of patients with cardiovascular diseases and risk factors in the RA, AS, and PsA populations, compared with the control populations. The prevalence ratio was estimated using Cochran-Mantel Haenszel methodology[16] to examine the prevalence of cardiovascular diseases/risk factors in each patient group compared with the control group. The use of angiotensin-converting enzyme (ACE) inhibitors, beta blockers, calcium channel blockers, diuretics, nitrates/vasodilators, anticoagulants, and antihyperlipidemia agents was also assessed in the patient and control groups.

Table 1. ICD-9 codes for identifying patients.

Cardiovascular Diseases/Risk Factors	ICD-9 Codes
Rheumatoid arthritis	714.x
Psoriatic arthritis	696.0
Ankylosing spondylitis	720.0
Ischemic heart disease	410–414
Atherosclerosis	440.x
Peripheral vascular disease	440.x, 441.x, 443.x, 447.1, 557.1, 557.9, V43.4
Congestive heart failure	428.x
Cerebrovascular disease	430.x–438.x
Hyperlipidemia	272.0–4
Type II diabetes	250.x0, 250.x2
Hypertension	401.x

Statistical analyses were performed using the SAS® system (SAS Institute, Cary, NC, USA). All statistical tests were 2-sided and were performed at $\alpha = 0.05$.

RESULTS

Patient characteristics. Of the 2,769,935 individuals continuously enrolled in the PharMetrics database from January 1, 2001, through December 31, 2002, with medical and drug benefits and at least one medical claim, 28,208 (1.02%) had RA, 3066 (0.11%) had PsA, and 1843 (0.07%) had AS (Table 2). The patients with RA, PsA, and AS had mean ages of 51.9, 49.7, and 47.3 years, respectively. Among the patients with RA, PsA, and AS, 72.5%, 50.9%, and 40.4%, respectively, were women (Table 3). The average time in plan before the study period (2001) was approximately 12–13 months for cases and controls. With regard to geographic region in the US, 19% of patients were from the East, 34% from the Midwest, 41% from the South, and 7% from the West.

Prevalence and prevalence ratio of comorbidities. The prevalences of IHD, atherosclerosis, PVD, CHF, CVD, type II diabetes, hyperlipidemia, and hypertension were significantly higher in patients with RA than in controls ($p < 0.01$; Figure 1). Similar findings were observed in patients with PsA ($p < 0.05$), with the exception of atherosclerosis (Figure 2), and in patients with AS ($p < 0.05$), with the exception of atherosclerosis and type II diabetes (Figure 3). As indicated by the calculated prevalence ratio for these conditions, patients with RA, PsA, and AS had an increased risk for cardiovascular diseases and their risk factors than did controls (Figure 4). The prevalence ratio of cardiovascular diseases/risk factors was similar across the 3 diseases.

Concomitant medication use. In patients with RA, PsA, and AS, use of ACE inhibitors, calcium channel blockers, diuretics, nitrates/vasodilators, anticoagulants, and antihyperlipidemia agents was significantly higher in patient than control groups (Table 4).

Table 2. Patient disposition.

Adults enrolled from January 1, 2001, to December 31, 2002	n = 10,897,605 (%)
Adults continuously enrolled from January 1, 2001, to December 31, 2002	2,872,333 (26.4)
Medical and drug benefits and at least one medical claim	2,769,935 (25.4)
Patients with RA	28,208 (1.02)
Patients with PsA	3066 (0.11)
Patients with AS	1843 (0.07)

DISCUSSION

Results of previous studies have suggested a strong relationship between RA and cardiovascular diseases. Specifically, increased mortality and cardiovascular disease-specific deaths have been observed among these patients, and the risk can be related to disease severity or inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate[17-19]. However, literature regarding cardiovascular morbidity in patients with AS and PsA is limited[9].

We analyzed the prevalence of selected cardiovascular diseases and their risk factors between patients with RA, PsA, and AS and control subjects. The RA prevalence (1.0%) in our study population matched that of the general US population, and the demographic distributions of patient groups were similar to those of patients in the general population; for example, the majority (72.5%) of RA patients were women, while only 40.4% of AS patients were women[1].

Healthcare claims databases have been used in a number of large cardiovascular epidemiological studies that assessed disease prevalence and healthcare costs. These sources have been considered reliable enough for use in the US to track the quality of cardiovascular care in health plans and hospitals[15,20-22]. The identification of cardiovascular diseases and their risk factors through ICD-9 codes in healthcare claims data have been verified through medical chart reviews, which have shown reasonably good positive predictive values for most cardiovascular events, especially for conditions like acute myocardial infarction and stroke[23-25]. The evidence for using ICD-9 codes to identify CHF is not as clear[25,26].

As indicated by the calculated prevalence ratios, patients with RA, PsA, and AS in our study had a higher prevalence of cardiovascular diseases and their risk factors, especially IHD,

Table 3. Demographic characteristics of the study population.

Study Group	N	Female, %	Age, mean (SD)	Pre-2001 Time in Plan, mean (SD) mo
RA				
Patients	28,208	72.6	51.9 (12.5)	13.2 (12.63)
Controls	112,832	72.6	51.9 (12.6)	13.2 (12.54)
PsA				
Patients	3066	50.9	49.7 (11.2)	13.6 (13.2)
Controls	12,264	50.9	49.7 (11.2)	13.5 (13.2)
AS				
Patients	1843	40.4	47.3 (12.0)	12.1 (12.88)
Controls	7372	40.4	47.3 (12.0)	13.2 (13.08)

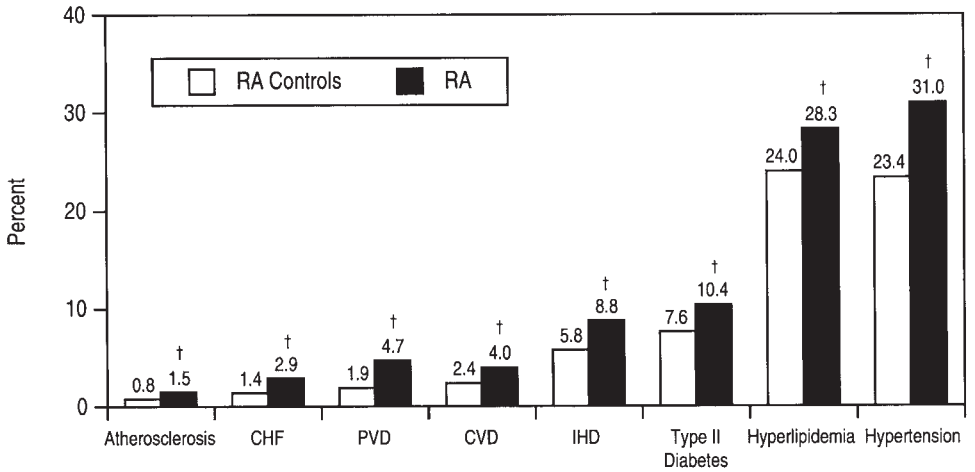

Figure 1. Age and sex-adjusted comorbidities of cardiovascular diseases/risk factors among patients with RA and controls. † $p < 0.01$ for patients with RA vs controls.

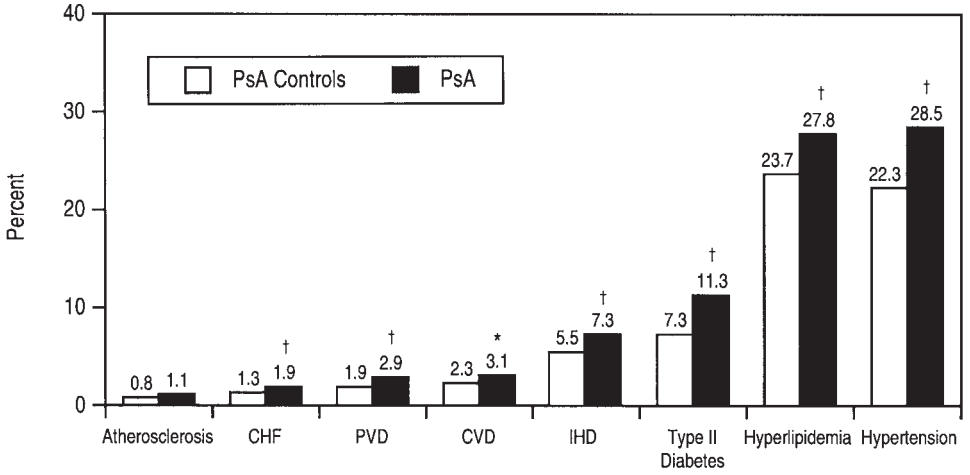

Figure 2. Age and sex-adjusted comorbidities of cardiovascular diseases/risk factors among patients with PsA and controls. † $p < 0.01$; * $p < 0.05$ for patients with PsA vs controls.

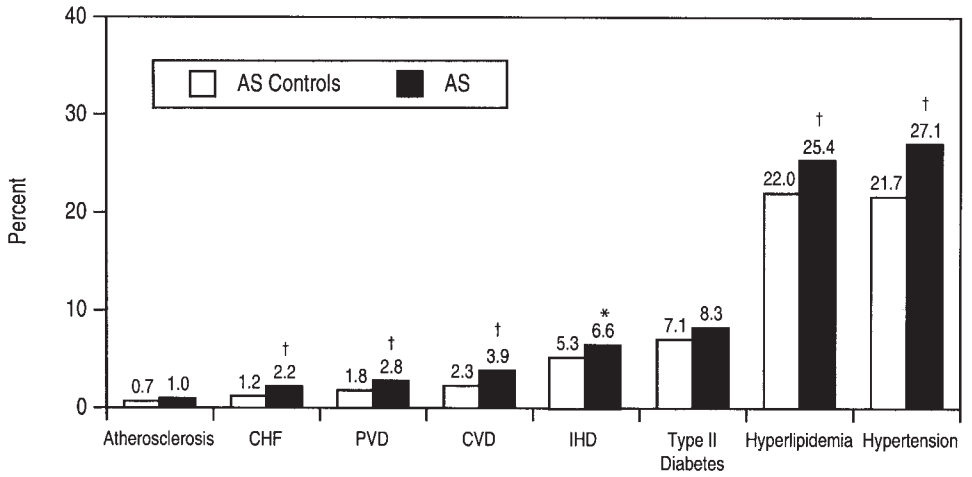

Figure 3. Age and sex-adjusted comorbidities of cardiovascular diseases/risk factors among patients with AS and controls. † $p < 0.01$ for patients with AS vs controls. * $p < 0.05$.

atherosclerosis, hyperlipidemia, hypertension, CVD, and PVD. These findings are in agreement with those of Dessein, *et al*[27], who conducted a cardiovascular risk assessment in 79 patients with RA and 39 age- and sex-matched patients with osteoarthritis (OA). In their study, patients with RA had a higher frequency of diabetes, and also had lower high-density lipoprotein levels, when compared with those of patients with OA. The CRP levels were also higher in patients with RA compared with OA. Inflammation, as reflected by the acute phase response, is implicated in cardiovascular disease both in the general population and in patients with RA, suggesting that RA and cardiovascular disease may share a common predisposition[27]. The significantly higher use of cardiovascular medications among patients with RA, PsA, and AS was in agreement with the prevalence ratio results we obtained.

The finding of an increased prevalence of hyperlipidemia in patients with RA compared with control subjects appears to be at odds with previous findings of low cholesterol levels in these patients[27,28]. However, serum lipid levels are affected by several factors, including diet and the use of disease modifying antirheumatic drugs[29], which we did not assess or control for in our analysis. Further work in this area should address these confounding factors.

There are several other limitations to our study. First, since it is a cross-sectional comparative study, the results do not have a causal association with the diseases studied and the cardiovascular diseases and their risk factors. Also, the limited information available to us in the claims database prevented us from controlling for other possible confounding factors such as family history, disease severity, smoking, etc. While the available data used represent final, adjudicated claims in a health plan setting, it is possible that the data elements used are subject to coding or misclassification error. However, if such errors exist, there is no reason to expect that coding

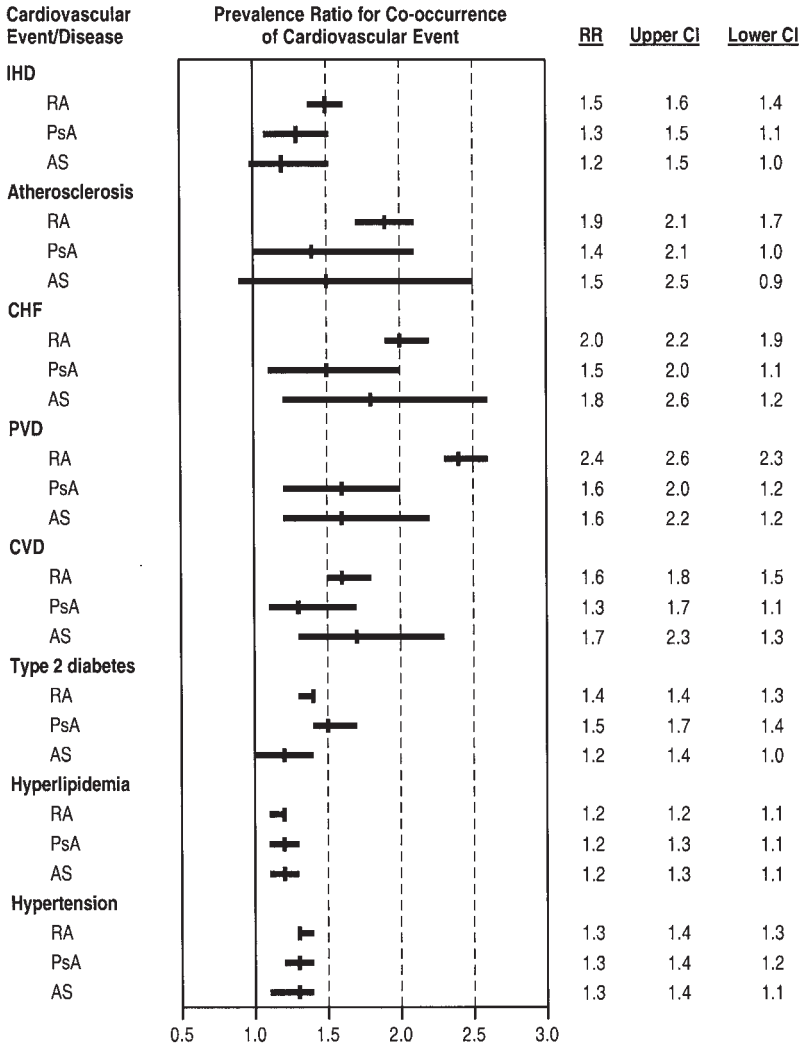

Figure 4. The prevalence ratios for co-occurrence of cardiovascular diseases/risk factors: comparisons between patient and control groups.

Table 4. Summary of selected medications prescribed for patient and control groups.

Agent	AS		PsA		RA	
	Patients, % (n = 1843)	Controls, % (n = 7372)	Patients, % (n = 3066)	Controls, % (n = 12,264)	Patients, % (n = 28,208)	Controls, % (n = 112,832)
ACE inhibitor	13.2**	10.5	14.2**	11.2	15.5**	12.8
Beta-blocker	0.3	0.2	0.1	0.2	0.3	0.3
Calcium channel blocker	8.8**	6.6	10.0**	8.0	12.9**	9.5
Diuretic	13.7**	9.3	16.1**	11.3	20.7**	14.1
Nitrate/vasodilator	3.6*	2.7	4.0**	2.7	4.8**	3.2
Anticoagulant	3.9**	1.6	3.3**	1.7	4.5**	2.2
Antihyperlipidemia agent	15.6*	13.6	17.8**	15.7	17.8**	17.0

Compared with control groups: * $p < 0.05$, ** $p < 0.01$. ACE: angiotensin-converting enzyme.

errors would disproportionately affect the patients with RA and PsA relative to controls in our study. This analysis is also limited by the fact that we assessed data for patients with nonfatal cardiovascular disease rather than that for patients whose cardiovascular disease(s) resulted in mortality during the study period. However, while this approach may exclude data for higher-risk patients who died, we believe that exclusion of data for these patients would produce a bias against our find-

ings since it is documented that patients with RA are at higher risk of mortality than the general population, and that cardiovascular disease does lead to death.

Another limitation, noted earlier, was that we were not able to distinguish between prevalent and incident cases of cardiovascular disease. A prospective study with a longterm followup period is needed to clearly address the relative risk in these populations for the incidence of cardiovascular disease. Finally, there are difficulties inherent in working with such a large database in that coding depends on a diagnosis being made and that patients with one chronic condition such as RA, PsA, or AS are more likely to take part in screening and to have additional tests performed to delineate the disease process involved. As such, some of the differences we observed may reflect more adequate screening of these patients.

In conclusion, there was an increased prevalence of cardiovascular diseases and their risk factors in patients with RA, PsA, and AS. This finding has obvious implications for health assessment and treatment planning by rheumatologists in these populations.

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