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Commentary: Evaluation of the Comorbidity Burden in Patients With Ankylosing Spondylitis Using a Large US Administrative Claims Data Set

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Abstract

Patients with chronic inflammatory rheumatic diseases, such as rheumatoid arthritis and spondyloarthritis, are at a higher risk of comorbidities, including cardiovascular disease. Although the prevalence of spondyloarthritis is estimated to be similar to that of rheumatoid arthritis, the risk of cardiovascular comorbidities in spondyloarthritis is not as well understood. Furthermore, the inflammatory rheumatic diseases differ in their pathogenic mechanisms, the populations affected, and treatment recommendations; therefore, it is important to examine these diseases separately. Ankylosing spondylitis (AS) is the prototype of spondyloarthritis; the onset of disease occurs at a relatively young age, and patients with AS are often undiagnosed for long periods of time. This increased duration of exposure to inflammation and use of nonsteroidal anti-inflammatory drugs may contribute to the higher risk of cardiovascular comorbidities in these patients.

Here we describe our recently published study (Walsh JA, et al. *Clin Rheumatol*. 2018;37[7]:1869-1878.), which used large national claims databases and showed that US patients with AS had significantly more comorbidities, including cardiovascular disease, than matched controls. We also review the current understanding of the risk of cardiovascular comorbidities in patients with AS. Knowledge of the frequency and risk of comorbidities can assist rheumatologists and primary care physicians with comorbidity screening and strategies for a holistic care approach for patients with AS, including the possibility of adapting the existing cardiovascular risk assessments for these patients. Counseling patients on additional lifestyle risk factors, early cardiovascular screening, and the necessity of further diagnostic testing will be important for optimizing patient care for AS.

Cardiovascular Disease in Patients With Inflammatory Rheumatic Diseases

Patients with chronic inflammatory rheumatic diseases, such as rheumatic arthritis, spondyloarthritis, and systemic lupus erythematosus, have an increased risk of cardiovascular disease[1-8]. The increased cardiovascular risk in patients with inflammatory rheumatic disease is likely related to systemic inflammation and traditional cardiovascular risk factors, such as hypertension, dyslipidemia, diabetes, smoking, and obesity, some of which are more prevalent in patients with rheumatic diseases. A link between inflammation and accelerated atherosclerosis has been identified in patients with inflammatory rheumatic disease[9-11]. Furthermore, endothelial dysfunction, oxidative stress, macrophage accumulation, toll-like receptor signaling, and proinflammatory cytokines have been implicated in atherogenesis[9,11,12]. Similar to the heterogeneity in

traditional cardiovascular risk factors, there are differences between the autoimmune and inflammatory risk factors of rheumatic diseases; therefore, cardiovascular risk assessment and treatment should be tailored for each rheumatic disease. In addition to traditional risk factors and systemic inflammation, the use of specific nonsteroidal anti-inflammatory drugs (NSAIDs), which are often used in the management of some inflammatory rheumatic diseases, may play a role in the risk of cardiovascular disease[13-16].

The Prototype of Spondyloarthritis: Ankylosing Spondylitis

Spondyloarthritis represents a group of inflammatory rheumatic disorders comprising ankylosing spondylitis (AS), nonradiographic axial spondyloarthritis, psoriatic arthritis, reactive arthritis, arthritis associated with inflammatory bowel disease, and undifferentiated spondyloarthropathies. With estimates of an overall prevalence of > 1% in the United States[17], spondyloarthritis is at least as common as rheumatoid arthritis among whites[18-21] and is one of the most common chronic inflammatory disorders. Spondyloarthritis is characterized by peripheral arthritis and enthesitis, axial inflammation (ie, sacroiliitis and spondylitis), and new bone formation leading to ankylosis. Because spondyloarthritis develops relatively early in life and has a chronic, progressive course, the impact of the disease on patients can be substantial.

Prevalence of AS in the United States has been estimated between 0.2% and 0.5%[17,22-24]. Although the age of onset is typically the late teens through 40 years of age, delays in diagnosis by as much as 8 to 11 years may lead to diagnoses at an older age[25-27]. In addition to inflammation of the spine, joints, and entheses, patients with AS often present with peripheral arthritis, uveitis, psoriasis, and inflammatory bowel diseases. Furthermore, studies have shown that compared with the general population, patients with AS are at a higher risk of developing comorbidities including cardiovascular disease, diabetes, malignancies, and depression[6,14,28-38].

Although previous studies of comorbidities in patients with AS have provided important information, most of these studies have been conducted outside of the United States. Because rates of comorbidities in the general population differ between the United States and other countries, there is a need to further understand comorbidities in US patients with AS. Here, we discuss the results of a recent real-world study, which examined the comorbidity burden of US patients with AS using a large national healthcare claims database. In addition, we review the current understanding of the risk of cardiovascular comorbidities in patients with AS.

Comorbidities in AS

Our recently published real-world study (Walsh JA, et al. *Clin Rheumatol*. 2018;37[7]:1869-1878.) compared the prevalence and incidence of comorbidities between patients with AS and matched controls using medical and pharmacy claims data from the MarketScan® Commercial and Medicare databases from 2012 through 2015. A total of 6679 patients with medical claims for AS were matched with 19,951 patients without AS at a ratio of up to 1:5 based on age, geographic location, index calendar year, and sex[39]. Patients with AS had a mean (SD) age of 50.8 (13.6) years, and 60.5% were men; matched controls had a mean age of 51.7 (13.4) years, and 60.8% were men[39]. The mean (SD) length of follow-up in patients with AS and in matched controls was 739 (139) days and 740 (139) days, respectively[39]. Patients with AS had a higher baseline comorbidity burden than matched controls (mean [SD] Deyo-Charlson Comorbidity Index score, 0.61 [1.15] vs 0.50 [1.14], $P < 0.001$) and were significantly more likely to have diagnoses of asthma, cardiovascular diseases, depression, dyslipidemia, gastrointestinal ulcers, malignancies, multiple sclerosis, osteoporosis, sleep apnea, spinal fracture, inflammatory bowel diseases, psoriasis, and uveitis (Table 1)[39].

Patients with AS had significantly higher incidence rates of all other comorbidities compared with matched controls, except for diabetes, dyslipidemia, and Parkinson disease (Table 2)[39]. In particular, for cardiovascular comorbidities, patients with AS had an approximately 1.25× higher incidence rate of angina, atherosclerosis, cerebrovascular disease/stroke, coronary artery disease, hypertension, myocardial infarction, and peripheral vascular disease and 2× higher incidence of venous thromboembolism compared with matched controls (Figure 1)[39]. The risk for cardiovascular disease persisted after statistical adjustments for baseline characteristics and comorbidities (including hypertension), as demonstrated in the published manuscript[39]. An important limitation of our study was the lack of body mass index data; therefore, obesity could not be evaluated as a comorbidity or be controlled for with related comorbidities such as cardiovascular disease and diabetes[39]. In addition, other risk factors that could have contributed to the development of comorbidities (eg, family history, smoking, alcohol consumption, and the use of over-the-counter NSAIDs) were not available in the data set[39].

Although our study did not examine the causality of cardiovascular comorbidities in patients with AS, the chronic inflammatory state of the disease may be linked to the development of these comorbidities[40], as seen in rheumatoid arthritis[41]. In addition, onset of disease begins

Table 1: Baseline clinical characteristics and comorbidities in patients with AS and their matched controls

Comorbidities	Patients With AS (n = 6679)	Matched Controls (n = 19,951)	*P* Value
Deyo-Charlson Comorbidity Index, mean (SD)[a]	0.61 (1.15)	0.50 (1.14)	< 0.001
Comorbidities, n (%)			
Asthma	145 (2.2)	218 (1.1)	< 0.001
Cardiovascular disease	2295 (34.4)	5849 (29.3)	< 0.001
Angina	79 (1.2)	146 (0.7)	< 0.001
Atherosclerosis	482 (7.2)	1139 (5.7)	< 0.001
Cerebrovascular disease/stroke	110 (1.6)	260 (1.3)	0.038
Coronary artery disease	322 (4.8)	743 (3.7)	< 0.001
Hypertension	2053 (30.7)	5267 (26.4)	< 0.001
Myocardial infarction	84 (1.3)	177 (0.9)	0.009
Peripheral vascular disease	110 (1.6)	311 (1.6)	0.617
Venous thromboembolism	77 (1.2)	167 (0.8)	0.019
Depression	712 (10.7)	1152 (5.8)	< 0.001
Diabetes	656 (9.8)	2113 (10.6)	0.075
Dyslipidemia	1564 (23.4)	4439 (22.3)	0.048
Gastrointestinal ulcers	75 (1.1)	79 (0.4)	< 0.001
Malignancies	450 (6.7)	1094 (5.5)	< 0.001
Multiple sclerosis	31 (0.5)	51 (0.3)	0.008
Osteoporosis	259 (3.9)	191 (1.0)	< 0.001
Parkinson disease	17 (0.3)	43 (0.2)	0.561
Sleep apnea	585 (8.8)	1008 (5.1)	< 0.001
Spinal fracture	59 (0.9)	39 (0.2)	< 0.001
Extra-articular manifestations of AS, %			
Inflammatory bowel disease	439 (6.6)	128 (0.6)	< 0.001
Crohn disease	281 (4.2)	57 (0.3)	< 0.001
Ulcerative colitis	192 (2.9)	81 (0.4)	< 0.001
Psoriasis	138 (2.1)	171 (0.9)	< 0.001
Uveitis	654 (9.8)	45 (0.2)	< 0.001

AS, ankylosing spondylitis.

[a] Deyo-Charlson Comorbidity Index ranges from 0 to 33.

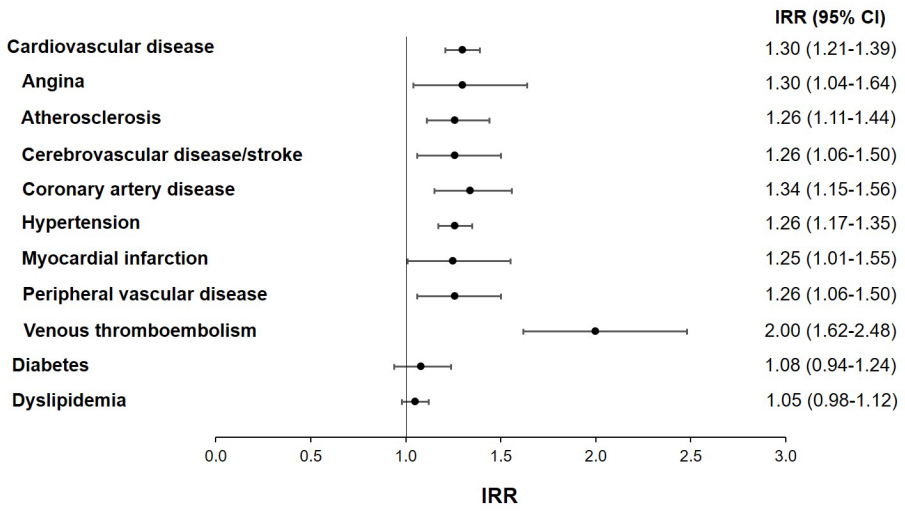

Figure 1: Incidence rate ratios of comorbidities in patients with ankylosing spondylitis vs their matched controls. IRR, incidence rate ratio.

Table 2: Proportions of patients with new comorbidities and the incidence rates per 100 patient-years

	Patients With AS N = 6679		Matched Controls N = 19,951		*P* Value
	n (%)	Incidence rate	n (%)	Incidence rate	
Comorbidities					
Asthma	178 (2.7)	1.37	302 (1.5)	0.76	< 0.001
Cardiovascular disease	1080 (16.2)	14.36	2795 (14.0)	11.06	< 0.001
Angina	104 (1.6)	0.79	240 (1.2)	0.60	0.027
Atherosclerosis	328 (4.9)	2.69	794 (4.0)	2.13	0.001
Cerebrovascular disease/stroke	185 (2.8)	1.41	442 (2.2)	1.12	0.010
Coronary artery disease	233 (3.5)	1.85	529 (2.7)	1.38	< 0.001
Hypertension	1044 (15.6)	12.98	2736 (13.7)	10.33	< 0.001
Myocardial infarction	118 (1.8)	0.89	284 (1.4)	0.71	0.046
Peripheral vascular disease	177 (2.70	1.35	422 (2.1)	1.07	0.011
Venous thromboembolism	142 (2.1)	1.07	214 (1.1)	0.54	< 0.001
Depression	686 (10.3)	6.05	1187 (6.0)	3.22	< 0.001
Diabetes	273 (4.1)	2.30	752 (3.8)	2.13	0.242
Dyslipidemia	1208 (18.1)	13.52	3544 (17.8)	12.90	0.551
Gastrointestinal ulcers	93 (1.4)	0.70	156 (0.8)	0.39	< 0.001
Malignancies	394 (5.9)	3.24	879 (4.4)	2.35	< 0.001
Multiple sclerosis	19 (0.3)	0.14	16 (0.1)	0.04	< 0.001
Osteoporosis	286 (4.3)	2.26	250 (1.3)	0.63	< 0.001
Parkinson disease	14 (0.2)	0.10	32 (0.2)	0.08	0.402
Sleep apnea	445 (6.7)	3.76	827 (4.1)	2.21	< 0.001
Spinal fracture	107 (1.6)	0.81	89 (0.4)	0.22	< 0.001
Extra-articular manifestations of AS					
Inflammatory bowel disease	209 (3.1)	1.69	85 (0.4)	0.21	< 0.001
Crohn disease	127 (1.9)	0.99	40 (0.2)	0.10	< 0.001
Ulcerative colitis	136 (2.0)	1.05	59 (0.3)	0.15	< 0.001
Psoriasis	202 (3.0)	1.55	180 (0.9)	0.45	< 0.001
Uveitis	469 (7.0)	4.04	60 (0.3)	0.15	< 0.001

AS, ankylosing spondylitis.

earlier in patients with AS compared with rheumatoid arthritis, and patients with AS are often undiagnosed for longer periods of time without having their underlying inflammation managed[25-27]; therefore, the increased duration of uncontrolled inflammation may contribute to the higher risk of cardiovascular comorbidities in patients with AS. Furthermore, in patients with AS, NSAIDs are recommended as first-line therapy[42-45] and may be used more commonly and persistently in patients with AS than in those with other inflammatory rheumatic diseases. Further research is needed to evaluate the potential cause and effect relationships between AS and comorbidities.

The elevated risk of cardiovascular disease in patients with AS shown in our study[39] supported evidence from published reports on the risk of developing new cardiovascular comorbidities in patients with AS[14,35,46]. A study from the Swedish National Patient Register showed a 50% higher risk of acute coronary syndrome and vascular thromboembolism and a 25% higher risk of stroke in patients with AS compared with the general population[46]. A meta-analysis of 18 studies of patients with AS and 12 studies of control patients reported a relative risk of myocardial infarction of 1.44 (95% CI, 1.25-1.67) in patients with AS compared with controls[6]. The same study also reported the results of a meta-analysis of 7 studies and reported a relative risk of stroke of 1.37 (95% CI, 1.08-1.73)[6]. Furthermore, an administrative claims study from the Taiwan National Health Insurance Database showed a > 2-fold increase in the risk of stroke in patients with AS compared with a comparison cohort without AS[35]. Notably, the increased risk of cardiovascular disease in patients with AS was demonstrated globally despite geographic differences in baseline cardiovascular disease risk in the general population.

Not all cardiac outcomes were assessed in our study. Valvular heart disease and conduction abnormalities are of interest in AS because they have been linked to aortitis and HLA-B27 positivity. In a study of Medicare beneficiaries over the age of 65 years, statistically higher risks were reported for mitral and aortic valve disease (OR, 1.06-1.51) in AS patients

(n = 42,327) vs controls (n = 19,211,703)[47]. Rates of aortic valve procedures were also statistically higher in AS patients than controls (OR, 1.22-1.46), but rates of mitral valve procedures were similar between groups[47]. In addition, pacemaker insertions were evaluated as an estimate of serious and symptomatic conduction abnormalities and were more frequent in patients with AS than controls (OR, 1.11-1.32), particularly in older age groups[47]. These small risk differences do not support routine screening for valvular heart disease or conduction abnormalities in asymptomatic AS patients.

The European League Against Rheumatism (EULAR) recommendations for cardiovascular disease risk management advise clinicians to be aware of the higher risk of cardiovascular disease in patients with inflammatory joint disease and screen patients for cardiovascular risk at least every 5 years and following changes in antirheumatic therapy[1]. Commonly used cardiovascular risk assessments in the general population are the Framingham Risk Score, the Systematic Coronary Risk Evaluation (SCORE), the Reynolds Risk Score, and the QRESEARCH Cardiovascular Risk Algorithm (QRisk) 2 score. However, these risk assessments may underestimate the cardiovascular disease risk in patients with AS because nontraditional cardiovascular risk factors are not included. The use of a relative risk chart has also been proposed as an alternative to the Systematic Coronary Risk Evaluation in patients aged < 50 years to determine the risk of cardiovascular disease[48]. Furthermore, the European League Against Rheumatism recommendations advise adapting cardiovascular risk assessments for patients with rheumatoid arthritis with a multiplication factor of 1.5[1]. Whether this multiplication factor should also apply to patients with AS remains unclear, but it may be an appropriate option in the absence of risk prediction models with proven accuracy and superiority in patients with inflammatory joint disease.

Screening for asymptomatic atherosclerotic plaques using carotid ultrasound is recommended in patients with rheumatoid arthrits[1] and may be appropriate for patients with AS, especially younger patients[48]. Patients with AS are generally younger than patients with rheumatoid arthritis, and as a result, they may not receive the same cardiovascular screening. Because of the increased risk of cardiovascular disease in patients with AS compared with the general population, monitoring for cardiovascular disease may be needed at an earlier age than what is traditionally recommended for patients without AS.

Prompt recognition and treatment of cardiovascular risk factors is important to decrease the morbidity and mortality associated with cardiovascular disease. Furthermore, the age and demographic characteristics of the individual patient must be considered. Patients with AS are diagnosed at a younger age than those with rheumatoid arthritis and are more likely to be male, which also increases their risk of cardiovascular disease. How age affects cardiovascular disease risk in patients with AS is unknown, although it has been explored in other inflammatory rheumatic diseases. Notably, younger women with systemic lupus erythematosus have a higher relative risk of cardiovascular disease compared with the general population than women with systemic lupus erythematosus who are > 60 years of age[7].

Conclusions

Our AS comorbidities study[39], which evaluated a large real-world sample of patients with AS, was among the first to evaluate comorbidities, including cardiovascular comorbidities, in US patients with AS compared with matched controls. Our study provides important information about the increased risks of comorbidities in US patients with AS, and research is needed to evaluate potential relationships between inflammation and comorbidities in patients with AS.

Knowledge of the frequency and risk of comorbidities can assist rheumatologists and primary care physicians with comorbidity screening and strategies for management in patients with AS. Importantly, in addition to lifestyle management and counseling related to the traditional risk factors of cardiovascular disease, patients with AS may need diagnostic screening for cardiovascular disease at an earlier age than patients without AS, as well as further modification of the standard cardiovascular risk assessments. Furthermore, tailoring recommendations and treatment based on studies in patients with AS instead of adapting existing recommendations based on studies in patients with other inflammatory rheumatic diseases may provide optimal care for patients with AS.

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