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Cardiovascular Risk Scores in Axial Spondyloarthritis Versus the General Population: A Cross-sectional Study

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ABSTRACT. ***Objective.*** Cardiovascular (CV) morbidity and mortality are increased in axial spondyloarthritis (axSpA). We conducted a cross-sectional study evaluating the 10-year atherosclerotic cardiovascular disease (ASCVD) risk in axSpA compared to the general US population.

Methods. We included 211 adults, 40–75 years old with ankylosing spondylitis (AS) or nonradiographic axSpA from 2 sites, who had available data on comorbidities, medication use, blood pressure measures, and laboratory cholesterol values. General population comparators from the 2009–2014 National Health and Examination Survey (NHANES) cycles were matched 4:1 to subjects, on age, sex, and race. We estimated the prevalence ratio for a 10-year ASCVD risk score ≥ 7.5% comparing axSpA and matched NHANES comparators using conditional Poisson regression.

Results. Overall, subjects were 53.9 ± 11.2 years old, 69% were male, and 74% were White. The mean 10-year ASCVD risk score was 6.7 ± 6.9% for those with axSpA, and 9.0 ± 10.5% for NHANES comparators. Compared to those with axSpA, the prevalence of current smoking and diabetes was higher among NHANES comparators. The estimated prevalence ratio for a 10-year ASCVD risk score ≥ 7.5% comparing those with axSpA and their age-, sex-, and race-matched comparators was 0.96 (95% CI 0.74–1.24).

Conclusion. The prevalence of a 10-year ASCVD risk score ≥ 7.5% was not significantly different comparing axSpA patients and those drawn from the general population who were similar in terms of age, sex, and race. Future studies should focus on improved CV risk prediction in axSpA, because underestimation by a general population risk score may potentially explain these results.

Key Indexing Terms: ankylosing spondylitis, axial spondyloarthritis, cardiovascular disease

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Cardiovascular disease (CVD) is the leading cause of death globally, and it is well established that individuals with ankylosing spondylitis (AS) have an increased risk of CVD and CVD-related morbidity and mortality compared to those of the same age and sex[1,2,3]. This increased cardiovascular (CV) risk in AS may be partially explained by an increased prevalence of CV risk factors such as hypertension compared to the general population[4,5,6]. Accelerated atherosclerosis related to the chronic systemic inflammation from AS disease activity may be another contributor to the overall CV risk[7,8,9,10].

In 2013, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines were revised to recommend lipid-lowering therapy with moderate- or high-intensity statins for primary prevention in individuals 40–75 years old with a 10-year atherosclerotic CV disease (ASCVD) risk score of ≥ 7.5%[11]. The guidelines were further updated in 2018 with a class I recommendation to consider initiating moderate-intensity statins in those with a 10-year risk of 7.5–20%[12]. The term *ASCVD* refers to acute coronary syndromes, angina, coronary revascularization, cerebrovascular disease, and peripheral vascular disease[11]. In 1 UK study, statin initiation in patients with AS was associated with a 37%

reduction in all-cause mortality compared to those who did not start statins[13]. Despite these data, individuals with spondyloarthritis (SpA) are currently undertreated in terms of dyslipidemia and other CV risk factors[14].

Few studies have been done in AS or in the broader axial SpA (axSpA) population addressing the CV risk profile, and only 1 small study has been performed using the ACC/AHA ASCVD risk score in a US sample population[15]. We performed a cross-sectional study to assess whether the 10-year ASCVD risk score differs between individuals with axSpA as compared to the general US adult population, with a hypothesis that axSpA would be associated with a higher risk score.

MATERIALS AND METHODS

AxSpA group. We initially included 795 adults from 2 prospective longitudinal cohorts. Of these, 606 were from the Prospective Study of Outcomes in Ankylosing Spondylitis (PSOAS) cohort, who met the modified New York criteria for AS [also known as radiographic axSpA (r-axSpA)][16], and who were followed at 2 sites: the University of California San Francisco (UCSF; n = 285) and the University of Texas Houston Health Science Center (n = 321). Institutional review board (IRB) approval was obtained for the PSOAS cohort study at each respective institution. The Human Subjects Division of the University of Washington determined that IRB review was not necessary for this study. Patient written informed consent was not obtained due to the retrospective nature of the current study. The PSOAS cohort has been described in detail elsewhere[17]. Briefly, clinical evaluation was performed using a standardized protocol at study entry and every 6 months by a study site investigator. At baseline, patient demographics and characteristics of AS disease status, including HLA-B27 status, date of symptom onset, patient-reported outcomes, extraarticular manifestations, comorbidities, and medication history were recorded. Comorbid conditions were then ascertained every 2 years by self-report; these included CV-related conditions and diabetes. On follow-up evaluations, vital signs including blood pressure were measured, and medications used in the preceding 6 months were taken by patient report.

Patients with radiographic and nonradiographic axSpA meeting the Assessment of Spondyloarthritis international Society (ASAS) classification criteria (n = 189) from a longitudinal natural history cohort at UCSF were also included in our study. These patients were followed every 6 months, with collection of axSpA disease activity, physical function, and spinal mobility measures, along with medication use, vital signs, and comorbidity history. The inclusion of study subjects is illustrated in Figure 1.

We then excluded individuals aged < 40 years and > 75 years and with a history of ASCVD, since the 10-year ASCVD risk score calculator was developed for use among individuals within the age range of 40–75 years without clinical ASCVD. Laboratory data for cholesterol measures proximate to a study visit ± 36 months were added to the dataset utilizing chart review through the electronic health record at the 2 respective sites. Individuals without any available cholesterol or blood pressure measurements necessary for the calculation of the 10-year ASCVD risk score with the pooled cohort equation were excluded, leaving 211 individuals available for the main analysis. We used demographic information from the most recently available study visit for our cross-sectional analysis. The other variables of interest for our analysis (smoking status, diabetes, and antihypertensive treatment) were singly imputed using the last observation carried forward.

General population comparator group. The National Health and Nutrition Examination Survey (NHANES) is an annual survey of noninstitutionalized, civilian US residents. NHANES is a cross-sectional, continuous survey conducted in 2-year cycles using stratified, multistage probability sampling. Certain race/ethnicity, income status, and age categories are oversampled to increase the reliability and precision of estimates for these groups.

We included individuals from 3 cycles of NHANES from 2009 to 2014. Datasets for each NHANES cycle were merged and appended. Individuals with missing data for any of the ASCVD risk score variables were excluded. General population comparators from NHANES were frequency-matched 4:1 to subjects with axSpA, on sex, race, and age within 5 years.

Variables. For the NHANES subjects, we extracted basic demographic variables (age, sex, race) and variables necessary for the calculation of the 10-year ASCVD risk score. Race/ethnicity was reported categorically (Hispanic, non-Hispanic White, non-Hispanic Black, and other) for all NHANES cycles included in our study; thus, matching was performed based on this categorization. Current hypertensive medication use was determined from 2 patient-reported variables ("Because of your high blood pressure, have you ever been told to take prescribed medicine?" and "Are you now taking prescribed medicine for high blood pressure?"). Current smoking status was determined from 2 patient-reported variables ("Have you smoked at least 100 cigarettes in your entire life?" and "Do you now smoke cigarettes?"). Diabetes was determined by patient-report ("Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?"). High-density lipoprotein (HDL) and total cholesterol were laboratory values taken during the NHANES survey encounter. Systolic blood

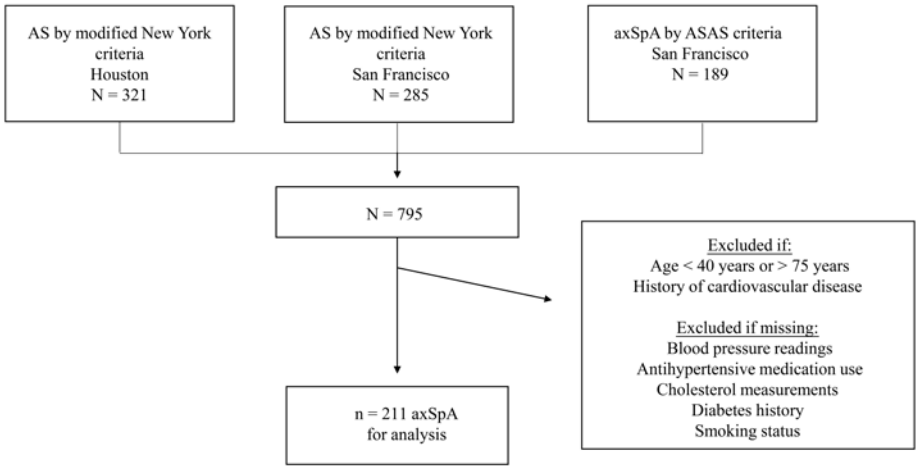

Figure 1. Algorithm for inclusion of individuals with axSpA into the main analysis. AS: ankylosing spondylitis; ASAS: Assessment of Spondyloarthritis International Society; axSpA: axial spondyloarthritis.

pressure (SBP) was the average of the last 2 measurements if 3 were taken during the encounter. If there were only 2 readings, then the SBP was the average of these.

Statistical analysis. The 10-year ASCVD risk score was calculated for both groups using the pooled cohort equation[18]. We performed descriptive statistics for the matched axSpA and NHANES groups, and estimated the prevalence ratio (PR) and 95% CI for a 10-year ASCVD risk score ≥ 7.5% comparing the 2 groups using Poisson regression, with adjustment for age in years, sex, and race. We performed a prespecified sensitivity analysis restricted to the subset of patients with AS (n = 161) and their matched comparators. In an exploratory analysis, we restricted the comparison of axSpA patients to NHANES comparators among nonsmokers. Analyses were conducted with a significance level of 0.05 and robust standard error estimates, and were performed in Stata version 15.0 (StataCorp).

RESULTS

Baseline characteristics for individuals with axSpA and age-, sex-, and race-matched comparators from NHANES are shown in Table 1. Overall, subjects had a mean age of 53.9 ± 11.2 years, 69% were male, and 74% were White. The mean 10-year ASCVD risk score was 8.5 ± 9.9%. Overall, 31% reported the use of antihypertensive medication, 17% were current smokers, and 12% reported a history of diabetes. The mean SBP was 123.2 ± 16.2 mmHg. The mean levels for HDL and total cholesterol were 51.5 ± 16.4 mg/dL and 195.4 ± 42.2 mg/dL, respectively. Compared to those with axSpA, there were more smokers and patient-reported diabetes among matched comparators. For those with axSpA, medication use included nonsteroidal antiinflammatory drugs in 135 (65%), biologics in 99 (48%), and glucocorticoids in 16 (8%; data not shown). Baseline characteristics for the subset with AS and their age-, sex-, and race-matched general population comparators are presented in Table 2. Compared to the overall axSpA group, the AS subset was slightly older with a greater proportion of males.

The PR for a 10-year ASCVD risk score ≥ 7.5% comparing those with axSpA and their age-, sex-, and race-matched comparators was 0.96 (95% CI 0.74–1.24). Among the subset of patients with AS, findings were similar with a PR of 1.01 (95% CI 0.77-1.34) for a 10-year ASCVD risk score ≥ 7.5%, compared to age-, sex-, and race-matched general population comparators. In the analysis restricted to nonsmokers, the PR for a high risk score was 0.91 (95% CI 0.70–1.19), comparing axSpA to the matched NHANES subjects.

DISCUSSION

In our study, we did not find a significant difference in the prevalence of 10-year ASCVD risk score ≥ 7.5% between individuals with axSpA and individuals drawn from the general population who were similar in terms of age, sex, and race. Results were similar among the subset of individuals with AS. These findings contrast with our hypothesis that individuals with axSpA would have higher ASCVD risk scores than general population comparators, as prior studies have indicated that CV risk is elevated among those with axSpA.

The 2013 ACC/AHA guidelines recommended the consideration of moderate- or high-intensity statin therapy for primary prevention in individuals whose 10-year ASCVD risk score is ≥ 7.5%[11]. Specific recommendations for those with inflammatory rheumatic diseases are not made by the ACC/AHA. The 2015/2016 European League Against Rheumatism recommendations do advise the use of risk prediction algorithms with a 1.5-fold multiplier for those with rheumatoid arthritis (RA), to help determine which individuals would benefit from

Table 1. Baseline characteristics, comparing axSpA patients with age-, sex-, and race-matched NHANES comparators.

	Overall, n = 1055	axSpA, n = 211	NHANES, n = 844
Age, yrs	53.9 ± 11.2	53.9 ± 10.0	53.9 ± 11.5
Male sex	69	69	69
Race/ethnicity			
Non-Hispanic White	74	74	74
Non-Hispanic Black	3	3	3
Hispanic	1	1	1
Other	22	22[a]	22
10-year ASCVD risk score, %	8.5 ± 9.9	6.7 ± 6.9	9.0 ± 10.5
SBP, mmHg	123.2 ± 16.2	126.6 ± 16.0	122.3 ± 16.1
Taking antihypertensive medication	31	34	31
HDL, mg/dl	51.5 ± 16.4	54.8 ± 16.8	50.7 ± 16.2
Total cholesterol, mg/dl	195.4 ± 42.2	189.7 ± 43.5	196.7 ± 41.8
Taking lipid-lowering medication	23	20	23
ASCVD risk score ≥ 7.5%	38	34	40
Diabetes	12	7	14
Current smoker	17	5	20
BMI, kg/m^2 [b]	29.1 ± 8.3	28.0 ± 9.5	30.0 ± 7.1

Values are % or mean ± SD. [a] This category includes Asian, n = 29 (14%). [b] BMI available for n = 209 in axSpA and n = 258 in NHANES. ASCVD: atherosclerotic cardiovascular disease; axSpA: axial spondyloarthritis; HDL: high-density lipoprotein; NHANES: National Health and Examination Survey; SBP: systolic blood pressure.

Table 2. Baseline characteristics, comparing AS patients with age-, sex-, and race-matched NHANES comparators.

	Overall, n = 805	AS, n = 161	NHANES, n = 644
Age, yrs	55.2 ± 11.3	55.1 ± 10.0	55.2 ± 11.6
Male sex	78	78	78
Race/ethnicity			
White	74	74	74
Black	2	2	2
Hispanic	1	1	1
Other	23	23[a]	23
10-year ASCVD risk score, %	9.4 ± 10.1	7.7 ± 7.3	9.9 ± 10.7
SBP, mmHg	123.7 ± 15.4	128.4 ± 16.1	122.6 ± 15.0
Taking antihypertensive medication	33	39	31
HDL, mg/dl	50.2 ± 14.9	52.8 ± 15.4	49.6 ± 16.7
Total cholesterol, mg/dl	195.2 ± 42.4	188.0 ± 40.2	197.0 ± 42.8
Taking lipid-lowering medication	24	21	25
ASCVD risk score ≥ 7.5%	42	39	43
Diabetes	11	7	12
Current smoker	18	4	21
BMI, kg/m^2 [b]	29.3 ± 8.4	28.3 ± 10.4	30.2 ± 6.0

Values are % or mean ± SD. [a] This category includes Asian, n = 21 (13%). [b] BMI available for n = 160 in AS and n = 185 in NHANES. AS: ankylosing spondylitis; ASCVD: atherosclerotic cardiovascular disease; HDL: high-density lipoprotein; NHANES: National Health and Examination Survey; SBP: systolic blood pressure.

lipid-lowering treatment[19]. The available evidence to motivate developing similar risk score adjustments for axSpA and psoriatic arthritis (PsA) remains scarce.

Multiple population-level studies have shown that the incidence of CV outcomes like myocardial infarction and the prevalence of established CV risk factors such as hypertension, is elevated among people with AS versus age- and sex-matched comparators[1,2,3,4,5,6]. However, CV risk factors are underscreened and undertreated among those with axSpA. In a multinational cross-sectional study, a complete CV evaluation of blood pressure, glycemic control, and cholesterol levels had only been undertaken in 50.5% of SpA patients in the previous year, per chart review[14]. Blood pressure screening occurred in 81%, but only 56% had had lipid evaluation. A Dutch study of 254 patients with AS noted that although 37% had an indication for CV risk treatment, these patients were being undertreated in terms of CV risk prevention[20]. In another multinational study, underdiagnosis and undertreatment were associated with younger age and male sex[21].

To our knowledge, our study is the largest US-based study that also compares risk scores with a group drawn from the general population. Few prior studies have measured 10-year ASCVD risk scores in an axSpA or AS population. Only 1 study was US-based and used the ACC/AHA ASCVD risk score in a SpA population of 43 individuals (which included both peripheral and axial subtypes)[22]. Compared to our study, Ahmad, *et al* found a higher median 10-year risk score of 13.1%[22]. However, these patients had a higher prevalence of CV risk factors overall, with a median age of 56 years, 97.7% male, and the prevalence of diabetes, hypertension, and smoking was 33%, 19%, 47%, respectively. Further interpretation of this study was limited by its small sample size and lack of a comparator group. In a Danish cross-sectional study, in which 10-year ASCVD risk was calculated using the Systemic Coronary Risk Evaluation (SCORE), Nissen, *et al* showed that those with AS had a lower risk score compared to individuals with RA, but their study did not include a comparison with individuals who did not have inflammatory arthritis[23]. Berg, *et al* studied 159 AS patients and 134 non-AS controls from Norway. The 2 groups had similar frequencies of traditional CV risk factors and overall, similar scores on 3 CV risk scores (Reynolds Risk Score, Framingham, European Heart Score)[24]. Only those with higher disease activity, compared to controls, had statistically significant age- and sex-adjusted Reynolds Risk Scores. In a Spanish cross-sectional study of 73 patients with AS, 80.8% were stratified as low-risk for 10-year CV death per the SCORE, 19.2% as intermediate risk, and none as high risk[25]. Several studies in PsA using carotid ultrasonography as the gold standard measurement of subclinical atherosclerosis have demonstrated that currently available methods of determining ASCVD risk score tend to underestimate the true CV risk in this population[26,27,28]. Other studies in PsA, performed in the US, have shown that the previously widely used Framingham Risk Score underestimated the CV risk[21,29]. While one potential explanation for our findings is that there is truly no difference in CV risk between axSpA patients and general population comparators, another possibility is that our results reflect the underestimation of true CV risk in this disease group.

A strength of our study is that it is the first to examine 10-year ASCVD risk in axSpA compared to the US general population, to our knowledge. Limitations of this study include its cross-sectional design, from which we were only able to assess relationships at 1 point in time. Our study may have been underpowered to detect a statistically significant difference between the groups; alternatively, a statistically and clinically significant difference may not truly exist. Generalizability may be limited

because the axSpA patients in our study were derived from cohorts in 2 US sites (San Francisco and Houston), and our patient population may have a different distribution of CV risk factors compared to other parts of the country. The differences in the prevalence of diabetes noted in prior AS studies (8–11%)[5,30] compared to the prevalence of diabetes in the cohort from which our AS patients were sampled (5%)[31] must also be considered. There is possible selection bias: The majority of patients from our cohorts who were excluded from this analysis had missing cholesterol or blood pressure measures, which precluded risk score calculation. Patients who were lost to cohort follow-up are more likely to have missing variables, and they may have a different CV risk compared to the patients included in our study. AxSpA patients with available data for risk score calculation may also have had better access to medical care than general population comparators. Being treated with antiinflammatory therapy for axSpA may also have attenuated the CV risk factors that can be captured by the risk score, as prior cohort studies have shown that CV mortality in patients with AS tends to be associated with persistent disease activity. We included axSpA patients with and without radiographic damage, and those without radiographic damage may have a lower burden of CV risk factors. We accounted for this possible heterogeneity in our study population by performing an analysis restricted to those with AS. Diabetes, hypertension, and smoking status were determined by patient-report in both the axSpA group and in NHANES, but due to the differences in questionnaire wording between PSOAS and NHANES, there may have been a degree of differential misclassification. Finally, there were likely unmeasured confounders that we could not account for in our analysis.

In a cross-sectional, multisite US study, we did not detect significantly different 10-year ASCVD risk scores using the ACC/AHA calculator comparing individuals with axSpA and US adults who were matched on age, sex, and race. Although our study may have been underpowered to detect a true difference, these findings may alternatively reflect an underestimation of the true CV risk among those with axSpA, a population that is known to have increased CV risk. The previously demonstrated increased risk of CVD and CVD-related mortality among individuals with axSpA should motivate clinicians to screen for CV risk factors, such as hypertension and hyperlipidemia based on the currently available guidelines. The development of a prediction score that better reflects the CV risk in axSpA should be considered.

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