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Editorial

Inflammatory Joint Diseases and Risk of Cardiovascular Disease in Modern Rheumatology

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In this issue of *The Journal*, Liew, *et al* present a cross-sectional study comparing the 10-year atherosclerotic cardiovascular disease (ASCVD) risk score in patients with axial spondyloarthritis (axSpA) versus the general US population. Their hypothesis was that a diagnosis of axSpA would be associated with a higher risk score of ASCVD[1].

They studied patients with axSpA participating in 2 different cohort studies (followed at the University of California, San Francisco, and University of Texas Houston Health Science Center). Altogether, the cohorts included patients with both radiographic axSpA/ankylosing spondylitis (AS) and nonradiographic axSpA. Patients were followed prospectively with regular data collections. The 10-year ASCVD risk scores were calculated for patients aged 40–75 years without a history of ASCVD and with available measures of blood pressure and laboratory measures of cholesterol. Individuals from The National Health and Nutrition Examination Survey (NHANES) were used as a comparator group and were matched 4:1 to the axSpA patients according to age, sex, and race.

After calculating the 10-year ASCVD risk scores for both the axSpA group and the NHANES group, the authors subsequently compared the prevalence ratio for a 10-year ASCVD risk score ≥ 7.5% between the patients with axSpA and the comparator NHANES group, first for the whole axSpA group, and then for the patients with AS (sensitivity analyses).

The authors found that the prevalence ratio of the 10-year ASCVD risk score ≥ 7.5% was neither increased in patients with axSpA nor in patients with AS compared to the NHANES controls; this finding was in contrast to their hypothesis that patients with axSpA would have higher ASCVD risk scores. As an explanation of this finding, the authors suggest that the study may be underpowered to find a true difference in ASCVD risk. Alternatively, the results may reflect that the ASCVD risk score underestimates the risk of cardiovascular disease (CVD) in this patient group.

The baseline characteristics showed that there were more smokers and patients with diabetes among the comparators than among the axSpA patients, but analyses restricted to nonsmokers did not alter results. There were no obvious differences in the use of antihypertensives and lipid-lowering medication between the groups. Regarding the use of medication for axSpA, 48% of the patients used biologics and 65% used nonsteroidal antiinflammatory drugs (NSAID).

It has long been established that patients with radiographic axSpA have increased CV morbidity and mortality compared to the general population[2,3]. Similarly, patients with other inflammatory joint diseases (IJD), especially rheumatoid arthritis (RA) but also psoriatic arthritis (PsA), have been shown to have increased CVD morbidity and mortality[2,4,5].

The increased CV morbidity and mortality are most elucidated in RA, and is probably best explained by a complex interplay of several traditional and nontraditional risk factors of CVD[6,7]. Some traditional risk factors of CVD, such as hypertension (HTN) and obesity, are more frequent among patients with IJD than in the general population, thus enhancing the risk of CVD[2,6]. Hyperlipidemia, with elevated total cholesterol and low-density lipoprotein cholesterol, also contributes to CVD in patients with IJD, but the lipid levels in patients with IJD are not found to be elevated compared to the general population[5,8]. Interpreting the lipid levels is, however, complex in IJD, where there is an interaction between lipids and inflammation, resulting in lower lipids in patients with high-grade inflammation[5]. Moreover, in active RA, lower lipids have been found to be associated with increased risk of CVD. This phenomenon is referred to as the lipid paradox and is one of the mechanisms by which

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ASCVD risk score calculators may underestimate the risk of CVD in patients with inflammation[9].

Another important traditional risk factor of CVD is low level of physical activity[10]. Patients with RA and AS have reported less physical activity than population controls[6,11], even though exercise is recommended as basic treatment of AS. Important barriers for physical activity were pain, stiffness, reduced physical function, and fatigue[12].

Use of pain killers such as NSAID in the general population has been shown to be associated with increased risk of CVD[13], and the frequent use of NSAID in patients with IJD might also contribute to increased frequency of CVD[14]. Moreover, use of steroids, an alternative to NSAID in some cases, may also be associated with increased CVD[15].

Over the past decades, the pivotal role of inflammation in the development of atherosclerosis has become established[7]. In RA, inflammation and disease activity are found to be associated with CVD[7,16]. Although the inflammatory burden in patients with axSpA is probably less than in patients with RA, chronic inflammation is believed to enhance the atherosclerotic process, resulting in increased CVD morbidity and mortality[2,15].

To reduce CV morbidity and mortality in patients with IJD and in the general population, it is important to identify patients with increased risk of CVD. Identifying risk can be performed by evaluating traditional CVD risk factors like HTN, hyperlipidemia, obesity, and additional use of CVD risk scores for the general population[10,15]. There are several calculators of CVD risk score, both nationally developed calculators and calculators developed based on data from several countries. In Europe, the European Heart Score is frequently used, whereas in the United States, the Framingham Risk Score calculator was previously used but has since been replaced by the ASCVD Risk Estimator[10,17]. The latter calculates the 10-year risk of ASCVD, and for a risk score of ≥ 7.5% to 20% (intermediate risk of ASCVD), initiation of treatment with statins should be considered[18]. Additional calculators that take into account nontraditional risk factors such as inflammation in the Reynolds Score, or ethnicity and presence of RA in the QRISK score, have also been developed[5,10].

Although we have not found studies comparing the validity of CVD risk scores in an axSpA population, established risk calculators have been found to underestimate the risk in populations of patients with RA and PsA, while the QRISK was found to overestimate risk in RA[19,20]. Due to the underestimation by several CVD risk calculators in IJD, The European League Against Rheumatism (EULAR) recommendations for CVD risk management has suggested multiplying the calculated risk by 1.5 to get a more accurate risk[15]. Efforts have been made to develop RA-specific CVD risk calculators; however, the performance of these calculators have not been superior to the calculators for the general population[5]. Liew, *et al* suggest in their study that development of a prediction score that better reflects axSpA should be considered[1]. Although we see the value of validating the risk score in each IJD population, we believe that these costly and expansive studies may cause unnecessary delays. We know enough to act now.

EULAR has recommended that patients with IJD should be evaluated every fifth year, and that treatment of risk factors should be initiated when indicated as in the general population[15]. Still, several studies have indicated that there are many patients with IJD who are not evaluated for CVD risk and that there is an undertreatment of the CVD risk factors[5,21].

Since inflammation is believed to be an important cause of enhanced atherosclerosis[7], reducing inflammation and disease activity is important when aiming to reduce risk of CVD in these patients[15]. With increased focus on treat-to-target strategies and more availability of biologic treatments, especially in the last 10 years, it is likely that the degree of systemic inflammation of patients with IJD has been reduced. The risk of CVD in IJD may be accordingly reduced through decreased disease activity and inflammation[5,22,23]. Moreover, if inflammation is the main cause of increased CVD risk in IJD, one would expect that the increased risk of CVD may be ameliorated in modern rheumatology, where patients receive more effective inflammation-lowering treatment. In this case, there may not be a true increased frequency of CVD morbidity and mortality in patients with IJD in modern rheumatology[23].

As mentioned above, in the results of the study by Liew, *et al,* the lack of significant differences in the CVD risk scores can indicate that CVD risk in patients with axSpA is underestimated by using CVD risk scores for the general population, given that there is an increased frequency of CVD in patients with axSpA in modern rheumatology[1]. Conversely, finding no significant difference in ASCVD risk score may indicate that with the availability of effective antiinflammatory treatment, there is no increased risk of CVD among patients with axSpA. In the Liew, *et al*'s study, 48% of the axSpA patients were on biologics, which indicates a well-treated patient group using modern strategies[1].

Still, CVD is a health problem both among patients with IJD and in the general population, and is one of the leading causes of death[10]. Both patients with rheumatic diseases and those in the general population should be evaluated for CVD risk regularly, and treatment should be initiated when indicated. Some earlier studies have, as mentioned above, indicated that there is undertreatment of HTN and hyperlipidemia in patients with IJD. However, in the study by Liew, *et al*, the blood pressure and cholesterol levels, as well as the proportion taking antihypertensive or lipid-lowering medications, seem to be similar between patients and controls, suggesting that there is no obvious undertreatment of CVD risk factors[1]. This is a possible result of greater focus on CVD in IJD in recent years.

In summary, it has been found previously that increased CV morbidity and mortality are caused by insufficiently targeting patients with IJD, which are diseases related to enhanced atherosclerosis caused by systemic inflammation, and by underestimating or not identifying traditional CVD risk factors through ASCVD risk calculators. To reduce CV morbidity and mortality in patients with IJD, it is important to follow both of these strategies in the future to reduce CVD: optimal antiinflammatory treatment, and regular evaluations for CVD risk factors as well as initiation of treatment of CVD risk factors when indicated.

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