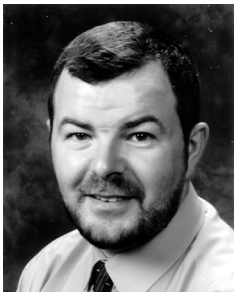
Editorial

Cardiovascular Risk in Inflammatory Rheumatic Diseases: Loose Ends and Common Threads



It is well established that rheumatoid arthritis (RA) is associated with reduced life expectancy[1-3]. While the absolute increase in mortality risk varies between studies[4], most found that the majority of these excess deaths result from cardiovascular disease (CVD)[3,5,6], in particular, atherosclerotic CVD[7,8].

The risk of myocardial infarction in RA patients is, for example, increased by a factor of 2 to 3[6-8]. Premature CVD mortality and morbidity in RA has been the subject of much investigation, and both traditional and nontraditional CVD risk factors have been implicated[9-12]. Traditional CVD risk factors found to be associated with atherosclerosis in RA include age, smoking, hypertension, and dyslipidemia[10-12]. However, traditional risk factors alone do not fully explain the excess CVD risk in RA. Other nontraditional factors are hypothesized to play a role, in particular the burden of inflammation as indicated by the C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)[9,13,14]. In a community-based cohort of patients with inflammatory polyarthritis, Goodson, *et al* also noted that excess CVD mortality was confined to patients who were rheumatoid factor-positive[5]. These markers of inflammation and inflammatory burden confer additional risk of CVD death in those with RA after adjusting for traditional CVD risk factors and comorbidities[15].

If RA is associated with increased CVD risk compared to the general population and this is in part due to chronic inflammation, then other inflammatory rheumatic diseases, such as ankylosing spondylitis (AS) and psoriatic arthritis (PsA) might also be hypothesized to have increased CVD risk. There are, however, a limited number of studies that have examined these conditions in relation to both mortality and the contribution of CVD to any observed excess deaths. In a community-based cohort of patients with PsA, for example, no excess mortality was noted[16]. In contrast, Wong, *et al* found in a hospital-based PsA cohort that mortality was increased, principally due to respiratory rather than cardiovascular deaths[17]. More recently, Peters, *et al* reviewed studies that investigated CVD mortality and morbidity and/or CVD risk factors in AS and PsA. They concluded that while there were a limited number of studies, there was evidence of increased CVD risk in AS and PsA[18]. CVD mortality in both conditions was associated with disease duration and severity, as well as traditional CVD risk factors, e.g., smoking, lipid profile, and hypertension. In addition, there was evidence that HLA-B27 status, increased platelet count, and fibrinogen may also play a role. It is clear, however, that compared to RA, the evidence base to support the hypothesis of increased CVD risk in PsA and AS is much less definitive, and many questions remain unresolved.

Han and colleagues' cross-sectional comparison of cardiovascular diseases and risk factors in RA, PsA, and AS patients, presented in this issue of *The Journal*, is an interesting contribution to this debate[19]. From a large health plan database in the US, the prevalence ratios of CVD diagnoses and risk factors in these 3 conditions were compared with unaffected population-matched controls (1:4 ratio). From almost 3 million individuals in the analysis, prevalence ratios of the cardiovascular diagnoses (ischemic heart disease, atherosclerosis, peripheral vascular disease, congestive heart failure, and cerebrovascular disease) and cardiovascular risk factors (type II diabetes, hyperlipidemia, and hypertension) were higher in the patients with RA, PsA, and AS. In addition, the use of cardiovascular drugs was also higher in all 3 patient groups.

There are, however, issues relating to these types of data and subsequent analyses that may limit their generalizability to the population as a whole. Health plan data do not necessarily represent the population within which they are based, due to the selection criteria of the particular plan[20]. In addition, selection criteria for the study may further

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restrict the population studied. In the data used by Han, *et al*, while the analysis uses a large dataset with impressive numbers, in fact only 25% of all adults enrolled to the health plan in the selected timeframe were eligible for inclusion[19]. It is unlikely that this proportion of people would be fully representative of all those in the health plan, and more important, it is therefore likely to be an unrepresentative sample of the general population.

The data presented are largely based on a working population, and only those continuously enrolled in the plan for a 2-year period and who had at least one interaction with the health plan were included. Therefore, for example, subjects who died during this 2-year period would automatically be excluded. Such restrictions will presumably reduce the numbers with chronic inflammatory conditions or cardiovascular comorbidities, and would serve to minimize any differences observed. The prevalence ratios for all conditions mentioned may therefore be significant underestimates of the true risk in the population. Conversely, only those that made a claim or had an interaction with the health plan were included, which may serve to bias estimates in the opposite direction, since those with preexisting conditions are more likely to utilize the health plan. It is by no means clear in the analysis which is the dominant source of confounding, and therefore the prevalence ratios reported may be much higher or lower than the true CVD risk status of the 3 populations.

The use of cross-sectional studies to assess if RA, PsA, or AS patients are at risk of CVD also has the disadvantage that information on the temporal relationship of these conditions is lacking; in particular, this means that from this study we cannot determine whether inflammatory rheumatic conditions increase the risk of CVD or whether CVD predisposes to inflammatory rheumatic disease[21,22]. In the current study this problem is further compounded by the inclusion of both prevalent and incident cases. Further, no adjustment for potential confounders was carried out, either of those factors compared between the patient groups (type II diabetes, hyperlipidemia, and hypertension), or of other traditional CVD risk factors (e.g., smoking, family history, weight, and comorbidities).

A potential explanation for increased prevalence ratios of CVD and risk factors in the 3 patient groups is that of diagnostic suspicion bias. Subjects with a chronic condition such as RA, PsA, or AS are more likely to be screened and investigated to explain symptoms such as chest pain or ankle swelling. Having contact with the healthcare system will also increase opportunities to participate in a planned or opportunistic cardiovascular risk screening program. Therefore much of the increase in CVD and risk factors reported may simply reflect this bias. One clue to this is the increased prevalence of hyperlipidemia noted among RA patients[19]. Previous work has found that total and/or LDL-cholesterol concentrations in patients with RA are lower than in controls[23,24]. Therefore, in the US, where LDL-cholesterol is the key lipid target on which intervention guidelines are based[25], one would expect a lower or comparable prevalence of hyperlipidemia in patients with RA. The finding of more hyperlipidemia in RA strongly suggests that this population is systematically different from those reported previously and casts some doubt on the other conclusions and estimates reported by the authors.

Ideally, to further study CVD risk in AS or PsA, large-scale prospective studies are required. Such studies should have predetermined definitions for each risk factor and outcome, all of which should be ascertained by the same approaches in both cases and controls. Prevalent and incident cases can also be distinguished in such a study design, which would help determine the direction of any association seen. Such studies will enable us to begin to understand for each condition the true magnitude of CVD risk, as well as the relative importance and contribution of traditional cardiovascular risk factors, inflammation, and therapeutic agents of relevance to this risk.

We know that atherosclerotic cardiovascular disease is a major problem in both systemic lupus erythematosus and RA. If, as we suspect, inflammation has a key role in the genesis of atherosclerosis, then studying the seronegative arthropathies, where different inflammatory mechanisms are likely to be dominant, may have a lot to teach us. The study by Han, *et al* adds to the evidence that CVD may well be a significant problem in AS and PsA. Well designed prospective studies are now needed to confirm these observations and to help determine whether increased risk of CVD in PsA and AS is primarily driven by traditional risk factors, chronic inflammation, or the consequences of treatment.

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