Editorial

When Is a Patient with Rheumatoid Arthritis at Risk for Cardiovascular Disease?

Over the past decade, a large number of investigations on cardiovascular disease (CVD) in rheumatoid arthritis (RA) have been reported. This followed the earlier seminal observations that subjects with RA experience markedly increased mortality rates and that this may be largely attributable to an excess of CVD\(^1\)\(^2\). Atherosclerosis is increasingly considered to be a dynamic and even reversible chronic inflammatory disease characterized by infiltration of activated monocytes/macrophages and T cells in the intima\(^3\). In the pathogenesis of CVD, the recognized sequential steps involve exposure to cardiovascular risk factors, endothelial dysfunction, atherosclerosis, and plaque rupture with atherothrombosis culminating in cardiovascular events. High grade systemic inflammation originating in inflamed joints is a hallmark of active RA. To date, relationships between markers of inflammation and endothelial dysfunction, atherosclerosis, and cardiovascular event rates have each been reported\(^4\)\(^-\)\(^7\). Further, inflammation was documented to adversely affect several traditional risk factors including insulin resistance and its related dyslipidemia (increased triglycerides and reduced HDL cholesterol concentrations)\(^8\).

Recent reports suggest that the evaluation and management of CVD in RA is challenging. Apart from the fact that several risk factors are involved (see below), the presenting features differ from those in the general population. RA patients may experience cardiovascular events in the presence of minimal atherosclerosis. Maradit-Kremers, et al\(^9\) recently reported that RA patients are at increased risk for coronary heart disease (CHD), not only from disease onset, but even prior to meeting the American College of Rheumatology criteria for RA. Yet, in early RA, the extent of coronary atherosclerosis is not increased\(^5\). These findings indicate that RA patients should be adequately monitored for CHD from disease onset\(^9\) and suggest that systemic inflammation and presumably other disease manifestations make relatively small atherosclerotic lesions vulnerable to rupture in RA.

Additionally, RA patients were found to experience angina less frequently and to sustain unrecognized myocardial infarction and sudden death more often than non-RA subjects\(^9\). Finally, the frequencies of multivessel coronary artery disease and recurrent ischemic events and death after an acute coronary syndrome are increased in RA\(^10\)\(^\)\(^-\)\(^11\).

In this issue of The Journal, Grover, et al\(^12\) report on ultrasonographically determined common carotid artery intima-media thickness (CCA IMT) in 57 RA patients and 45 controls. The population of India is now over one billion. Indians experience CHD at a younger age than Caucasians\(^13\). Up to 12.6% of the urban population and 7.4% of the rural population was reported to have CHD in India\(^13\). A genetically determined propensity for insulin resistance and its interplay with lifestyle changes secondary to urbanization are implicated and are expected to dramatically increase the future CHD prevalence in this population\(^13\).

Grover, et al\(^12\) found that the mean CCA IMT was 0.416 mm in controls and 0.558 mm in RA subjects (p < 0.0001). This difference of 0.142 mm is substantial. Whereas age is the most powerful predictor of atherosclerosis in the general population, the expected increase is only 0.010 mm per year in both women and men\(^14\). Of interest also, the mean age of the RA patients in the study by Grover, et al was only 42 years, a value that is much lower than in most other reported RA cohorts. The mean disease duration was 8 years. The age at RA onset may therefore be earlier in this population.

The investigators further report that age, disease duration, and tender joints were associated with atherosclerosis in RA. Of relevance in the present context, subjects with well known traditional risk factors including hypertension, smoking, diabetes, and prevalent CVD were excluded. Patients and controls were age and sex matched. This is a frequently used study design in investigations on CVD in RA. The aim is to avoid confounding and thus to facilitate providing evidence that RA itself is a risk factor for CVD and that the nontraditional risk factor, i.e., inflammation, is associated with CVD in this disease. These are important findings. However, since over 80% of RA patients have at least one modifiable traditional risk factor, the results cannot be generalized\(^15\)\(^\)\(^-\)\(^16\). Specifically, this study design pre-
cludes the determination of the relative contribution of traditional versus nontraditional risk factors to CVD in the RA population at large. To address this issue, cohorts of unselected patients are needed.

Cardiovascular risk factors that were reported to be associated with CVD in RA are shown in Table 1. This information was obtained through a Medline search under the terms rheumatoid arthritis, cardiovascular risk factors, endothelial dysfunction, arterial stiffness, atherosclerosis, cardiovascular events, and cardiovascular death. Risk factors identified by us in 74 largely unselected RA patients are shown in Figure 1. Only patients taking lipid lowering and antidiabetic agents were excluded.

Markers of inflammation were found to be associated with CVD in RA by many investigators. However, the role of traditional risk factors and the interaction between inflammation and traditional risk factors seem to be equally important. Risk prediction models based on traditional risk factors such as the Framingham equation predict CHD in up to 75% of cases in the general population. Although the Framingham equation may underestimate atherosclerosis in RA, evidence was reported that each of the well known traditional risk factors predicts CVD in RA. This applies to age, gender, hypertension, dyslipidemia, diabetes, smoking, and a parental history of fatal CVD. Other established cardiovascular risk factors in the general population include insulin resistance, chronic kidney disease, and subclinical hypothyroidism. In our experience, over 70% of RA patients demonstrate insulin resistance, whereas the prevalence of both chronic kidney disease and hypothyroidism (overt or subclinical) is over 20% in RA.

Evidence was also reported to suggest a role for these 3 risk factors in RA

Table 1. Traditional and nontraditional risk factors for cardiovascular disease in rheumatoid arthritis.

<table>
<thead>
<tr>
<th>Traditional</th>
<th>Nontraditional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Systemic inflammation: C-reactive protein,</td>
</tr>
<tr>
<td>Gender</td>
<td>erythrocyte sedimentation rate, leukocyte and</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>polymorphonuclear cell counts, interleukin-6</td>
</tr>
<tr>
<td>Smoking</td>
<td>Disease severity: Joint deformities, radiographic</td>
</tr>
<tr>
<td>Diabetes</td>
<td>scores, extraarticular manifestations</td>
</tr>
<tr>
<td>Family history of CHD</td>
<td>Disease duration</td>
</tr>
<tr>
<td>Metabolic syndrome features</td>
<td>Disability: HAQ-DI</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>Humoral immunity: Rheumatoid factor</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>Antirheumatic agents: No use of methotrexate or/and TNF-alpha blockade, use of glucocorticoids</td>
</tr>
<tr>
<td></td>
<td>Other: Hypofibrinolysis, CD4+CD28null T lymphocytes,</td>
</tr>
<tr>
<td></td>
<td>HLA-DRB1*0404, reduced number and impaired function of endothelial progenitor cells</td>
</tr>
</tbody>
</table>

CHD: coronary heart disease; RA: rheumatoid arthritis; HAQ-DI: Health Assessment Questionnaire-Disability Index; TNF: tumor necrosis factor

Figure 1. Associations between risk factors and cardiovascular disease in 74 largely unselected RA patients. Endothelial function was assessed by circulating biomarkers (vascular cell adhesion molecule-1, intercellular adhesion molecule-1, and endothelial leukocyte adhesion molecule-1). Atherosclerosis was determined ultrasonographically in the common carotid arteries (intima-media thickness and plaque). Vascular cell adhesion molecule-1 concentrations were also associated with atherosclerosis. *Traditional risk factors.
atherosclerosis in 631 RA patients, traditional risk factors and RA characteristics explained similar proportions of the variance in carotid artery atherosclerosis, with RA characteristics contributing more in younger patients and traditional risk factors contributing more in elderly patients. Moreover, a significant interaction between the number of traditional cardiovascular risk factors and the erythrocyte sedimentation rate (ESR) was found. An elevated ESR was associated with an increased carotid artery intima-media thickness only in patients who had one or more traditional cardiovascular risk factors.

Last but not least, antirheumatic agents markedly influence CVD in RA. Chronic glucocorticoid therapy increases not only insulin resistance and the occurrence of diabetes, but also cardiovascular event rates. Methotrexate use and anti-tumor necrosis factor-α therapy were reported to protect against CVD, thereby further supporting a role of inflammation in RA atherogenesis. The use of the now withdrawn agent rofecoxib was associated with a 2.2 fold increased risk for CVD.

In conclusion, whereas CVD is a complex disease in the general population, it is even more so in RA. Traditional risk factors, a range of nontraditional risk factors that are RA characteristics, as well as risk factor interactions, are all likely to be involved. Most risk factors identified so far can be easily assessed, and some are modifiable (Table 1). Under-treatment of cardiovascular comorbidity in RA may contribute to increased cardiovascular mortality in this disease. Until optimal preventative strategies can be defined on the basis of results from longitudinal studies, we suggest that comprehensive assessment and treatment of traditional and nontraditional cardiovascular risk factors should form part of the routine care of the RA patient.

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REFERENCES