Published in final edited form as:

Ann Rheum Dis. 2011 May ; 70(5): 719–721. doi:10.1136/ard.2010.145482.

Towards Improving Cardiovascular Risk Management in Patients with Rheumatoid Arthritis: the Need for Accurate Risk Assessment

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Keywords

rheumatoid arthritis; cardiovascular disease

Numerous reports of the increased incidence of cardiovascular disease (CVD) among patients with rheumatoid arthritis (RA) have been published during the past decade.[1, 2] In addition, the increased risk of CVD in RA patients cannot be explained by traditional cardiovascular (CV) risk factors alone.[3, 4] While these reports have increased awareness of CV morbidity and mortality among RA patients, the lack of CV risk assessment tools and evidence-based practice guidelines developed specifically for RA patients has slowed the translation of this knowledge into clinical decision-making. The following 2 case studies illustrate the need for accurate RA-specific CV risk assessment tools.

First, Ms. X was diagnosed with RA at age 40 with rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA) positivity and rheumatoid nodules present at diagnosis. She was a non-smoker and non-diabetic with total cholesterol of 6.7 mmol/L (258 mg/dL), HDL-c of 1.4 mmol/L (54 mg/dL) and a systolic blood pressure of 120 mm Hg. The SCORE risk assessment for populations at high CVD risk categorized her 10 year risk of fatal CVD as <1% and the general Framingham risk score (FRS) estimated her 10 year risk for any CVD event as 4%.[5, 6] Despite these low risk assessments, she experienced a myocardial infarction (MI) at age 45. Thus, the SCORE and FRS did not accurately predict CV risk for Ms. X.

Second, Mr. Y was diagnosed with RA at age 46 with RF/ACPA positivity and rheumatoid vasculitis present at diagnosis. He was a non-smoker and non-diabetic with total cholesterol of 8.8 mmol/L (341 mg/dL), HDL-c of 2.0 mmol/L (76 mg/dL), a systolic blood pressure of 140 mm Hg and normal body mass index (26 kg/m²). His SCORE risk was 2.6% and FRS was 9.2%. Despite these moderate risk assessments, he was started on anti-hypertensive

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medication and statins, but he still experienced a MI 6 months later. Thus, the SCORE and FRS did not accurately predict CV risk for Mr. Y.

The European League Against Rheumatism (EULAR) recommendations for CV risk management constitute the first attempt to provide recommendations to improve CVD management in RA patients.[7] A multiplier of 1.5, applied to a conventional CV risk assessment (e.g. SCORE or FRS), is recommended for RA patients with 2 of the following 3 criteria: disease duration >10 years, RF or ACPA positivity, and presence of severe extra-articular manifestations (ExRA). In the case studies, Ms. X would not meet these criteria. Mr. Y was RF positive and had a severe ExRA, so the multiplier would apply. This would increase his SCORE risk to 3.9% and his FRS to 13.8%, neither of which would meet recommended thresholds for intensified risk modification efforts of 10% for SCORE and 20% for FRS. Thus, application of these recommendations had little impact on the risk assessments for Ms. X and Mr. Y. Also, while these recommendations are evidence-based, some of the evidence is weak. Indeed, among patients with RA, the accuracy of CV risk assessment using tools for the general population and the ability of a simple multiplier to improve the accuracy of risk assessment are unknown. While the EULAR task force should be commended for addressing this important issue, the use of this multiplier and the choice of the criteria defining the patients with RA requiring the multiplier deserve a closer inspection.

First, the evidence of increased CVD risk associated with longer (>10 years) disease duration is lacking as neither of the 2 works cited in the recommendations support the inclusion of this criterion.[8, 9] Naz et al reported increased CVD mortality was present at RA symptom onset and throughout follow-up.[8] Gabriel et al showed the excess all-cause mortality among RA patients was not apparent until 8–10 years after RA diagnosis.[9] Neither of these reports examined the risk of CVD events, which could be increased earlier in the disease course than mortality. In contrast, several recent reports noted an increased CVD risk early in the RA disease course.[10–14] Maradit-Kremers et al found an increased risk of myocardial infarction (MI) prior to RA diagnosis.[10] In reports emerging after publication of the EULAR recommendations, Holmqvist et al reported an increased risk of MI within 1 year after RA diagnosis, Franklin et al reported an increased risk of hospital admissions for CVD within 7 years of RA diagnosis, and Södergren et al reported significant increases in intima media thickness among RA patients by 18 months after RA diagnosis.[12–14] Thus, most of the evidence now supports an increased risk of CVD early in the RA disease course.

Second, evidence for the association between CVD risk and RF or ACPA positivity is wanting. While the increased risk of CVD among RF positive RA patients is well established, the lack of an increased risk of CVD among RF negative RA patients is unclear. Previous reports showed no increased risk of all-cause and CVD mortality and of heart failure among RF negative RA patients compared to persons without RA.[2, 8, 15] However, Holmqvist et al recently reported similarly increased risks of hospitalization for MI among both RF positive and RF negative RA patients compared to persons without RA.[12] Also, few studies have examined CVD risk among ACPA positive and negative patients. Farragher et al reported a higher risk of all-cause and CVD mortality among ACPA positive compared to ACPA negative RA patients.[16] Since most ACPA positive RA patients are also RF positive, it seems likely that ACPA positive patients have an increased risk of CVD. However, whether ACPA negative RA patients have a higher risk of CVD than the general population is unknown. Hence, the possibility of an increased risk of CVD for either RF negative or ACPA negative RA patients requires more investigation.

Third, while the increased risk of CVD among patients with severe extra-articular manifestations (ExRA) of RA is substantial (e.g. > 3-fold increased risk), the rarity of these ExRA (e.g. the cumulative incidence at 10 years of RA disease duration is <10%) limits their clinical utility in the context of the EULAR recommendations, which require 2 of 3 criteria to be met.[17–19] For example, 30% of the prevalent cases of RA in Olmsted County, Minnesota on January 1, 2000 satisfied 2 of the 3 criteria, but only 4% used the presence of severe ExRA to fulfill the criteria. The other 3.5% with ExRA also had both >10 years duration of RA and RF positivity. In addition, the inclusion of other risk factors associated with increased risk of CVD in RA patients, such as rheumatoid nodules or abnormal C-reactive protein, should be considered.[8, 16]. Also, if each of the criteria is indicative of increased risk, why not apply the multiplier to RA patients with only one criterion?

Furthermore, the multiplier value of 1.5 was based on many reports of the increased risk of CVD among RA patients compared to those without RA, but the increased risk among the subset of RA patients that meet 2 of the 3 criteria is unknown. If these patients are at higher risk than other RA patients, their increased risk of CVD may be much higher than 1.5 times the general population risk. Conversely, if this subset of RA patients also have more CV risk factors, the general population risk assessment tools may already account for some of their increased risk, so the 1.5 multiplier could lead to overestimation of the risk of CVD. Another complexity is that traditional CV risk factors appear to have differing, even paradoxical, effects on the risk of CVD for RA patients.[3, 4, 20, 21] For example, Peters et al reported no association between total cholesterol and CVD events, and Myasoedova et al reported increased CVD risk for RA patients with low total cholesterol.[20, 22] Others have reported low body mass index was associated with increased risks of all-cause and CVD mortality in RA patients.[21, 23] These risk factors may require different weights than those used in the general population in order to accurately predict CV risk in RA patients.

In addition, both calibration and discrimination should be assessed to determine the accuracy of CVD risk prediction using the multiplier.[24] Calibration refers to the ability to predict the absolute risk level. While applying a multiplier may improve the average level of CVD risk estimated for RA patients, it is unclear whether the resulting risk estimates are accurate for individual RA patients. Perhaps the multiplier increases the estimated risk too much for some patients and not enough for others. Discrimination refers to the ability to accurately rank risk levels in order to distinguish low from high risk. The use of a multiplier would change their ranking relative to other RA patients, but it would have little impact on patients with low risk estimates (e.g. 1.5 times 1% yields 1.5%). Hence, if RA patients with high levels of systemic inflammation but few or no traditional CV risk factors have high risk for CVD, then the use of a multiplier would not substantially improve discrimination. Thus, while a simple multiplier applied to existing CV risk tools may improve average calibration, it may not be accurate for individual patients and it may not improve discrimination, raising questions regarding the clinical utility of this approach to accurately predict risk.

Instead, the incorporation of non-traditional risk factors, such as measures of inflammation and perhaps genetic markers extensively associated with cardiovascular risk, such as the presence of HLA-DRB1*-shared epitope, into a risk score would be needed in order to correctly rank the CV risk in RA patients.[16, 25, 26] In addition to single measures of inflammation, inflammatory burden may play a crucial role in CV risk, and suppression of inflammation may be a pivotal requirement for improving CV risk management.[20] In addition, non-invasive surrogate markers of subclinical cardiovascular disease, such as carotid intima-medial thickness, should be considered and possibly used in the assessment of the cardiovascular risk of patients with RA. [27, 28] However, careful consideration of the clinical utility, healthcare costs and recommended frequency of assessment should be done

before including these measures in a risk assessment tool for cardiovascular disease among patients with RA.

In conclusion, CV risk assessment tools designed for the general population may not accurately estimate CV risk for individual patients with RA, even if a multiplier is applied. In addition, while the EULAR recommendations aim to improve cardiovascular risk management in rheumatoid arthritis patients, rheumatologists should be cautioned to avoid over-interpreting them. Patients satisfying the criteria for use of the multiplier likely do have increased risk of CVD, but those who do not meet these criteria may also have increased risk. The disease duration criterion is particularly worrisome as the increased risk of CVD likely begins early, and the inclusion of this criterion may inadvertently lead clinicians to underestimate the early risk of CVD, perhaps leading to less diligence regarding CV risk assessment at RA diagnosis. Further research is needed to derive a tool for accurately assessing the risk of CVD in patients with RA.

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