

Assessment of Cardiovascular Disease Risk in Rheumatoid Arthritis

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ABSTRACT

Objective: To review cardiovascular disease (CVD) risk assessment in patients with rheumatoid arthritis (RA).

Methods: Literature review of the assessment of CVD risk in RA.

Results: CVD is the leading cause of death among RA patients. Because of the increased risk of CVD events and CVD mortality in patients with RA, regular assessment of CVD risk and aggressive management of CVD risk in these patients is crucial. CVD risk estimation typically centers on the use of well-established CVD risk calculators. Most CVD risk scores from the general population do not contain RA-related factors predictive of CVD but have had more extensive performance testing, while novel RA-derived CVD risk scores that incorporate RA-related factors have had limited external validity testing. Neither set of risk scores incorporates novel imaging modalities or serum biomarkers, which are most likely to be helpful among individuals at intermediate risk.

Conclusion: Primary care and rheumatology providers must be aware of the increased risk of CVD in RA, a risk that approaches that of diabetic patients. Routine assessment of CVD risk is an essential first step in minimizing CVD risk in this population. Until the performance of RA-specific CVD risk scores can be better established, we recommend the use of nationally endorsed CVD risk scores, with the frequency of reassessment based on CVD risk.

Keywords: rheumatoid arthritis; cardiovascular disease; cardiovascular risk assessment.

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Rheumatoid arthritis (RA) is a chronic, autoimmune inflammatory arthritis affecting up to 1% of the US population that can lead to joint damage, functional disability, and reduced quality of life.¹ In addition to articular involvement, systemic inflammation accompanying RA may lead to extra-articular manifestations and increase the risk of premature death.² Cardiovascular disease (CVD), accounting for nearly half of all deaths among RA patients, is now recognized as a critical extra-articular manifestation of RA.^{2,3} As such, assessment and management of CVD risk is essential to the comprehensive care of the RA patient. This article reviews the approach to assessing CVD risk in patients with RA; the management of both traditional and RA-specific risk factors is discussed in a separate article.

Scope of the Problem

In a large meta-analysis of observational studies that included more than 111,000 patients with RA, CVD-related mortality rates were 1.5 times higher among RA patients than among general population controls.⁴ The risk of overall CVD, including nonfatal events, is similar; a separate meta-analysis of observational studies that included more than 41,000 patients with RA calculated a pooled relative risk for incident CVD of 1.48.⁵ Individual analyses identified heightened risk of acute coronary syndrome (ACS), cerebrovascular accident, and congestive heart failure (CHF).⁵ Perhaps more illustrative of the magnitude

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of the problem, the risk of CVD in RA approaches that observed among individuals with diabetes mellitus.^{6,7}

Coronary artery disease (CAD) accounts for a significant portion of the CVD risk in RA, but its presentation may be atypical in RA patients. RA patients are at higher risk of suffering unrecognized myocardial infarction (MI) and sudden cardiac death.⁸ The reasons for silent ischemia in RA are not fully known, but have been hypothesized to include imbalances of inflammatory cytokines, alterations in pain sensitization, or the female predominance of RA (with women more often presenting with atypical symptoms of myocardial ischemia).⁹ Alarmingly, a retrospective chart review study reported that RA patients admitted for an acute MI were less likely to receive appropriate reperfusion therapy as well as secondary prevention with beta-blockers and lipid-lowering agents.¹⁰ Even with appropriate therapy, long-term outcomes such as mortality and recurrent ischemic events are more likely to occur in RA patients after acute MI.¹¹⁻¹³

Independent of ischemic heart disease, RA patients are at increased risk of CHF.¹⁴⁻¹⁶ RA patients are at particular risk for CHF with preserved ejection fraction,¹⁷ which may be a result of systemic inflammation causing left ventricular stiffening.^{18,19} Similar to CAD, patients with RA are less likely to present with typical CHF symptoms, are less likely to receive guideline-concordant care, and have higher mortality rates following presentation with CHF.¹⁷

Although accounting for a lower proportion of the excess CVD morbidity and mortality in RA, the risk of non-cardiac vascular disease is also increased in RA patients. Large meta-analyses have identified positive associations between RA with both ischemic (odds ratio [OR], 1.64 [95% confidence interval {CI}, 1.32-2.05]) and hemorrhagic (OR, 1.68 [95% CI, 1.11-2.53]) stroke.²⁰ Similarly, RA patients appear to have an approximately twofold higher risk of venous thromboembolic events.²¹ Less frequently studied than other forms of CVD, peripheral arterial disease may be increased in RA patients independent of other CVD and CVD risk factors.^{22,23}

Assessing CVD Risk in RA

CVD Risk Scores

In order to identify patients who may benefit from primary prevention interventions, such as lipid-lowering ther-

apy, CVD risk estimation typically centers on the use of well-established CVD risk calculators (**Table**). CVD risk scores such as the Framingham Risk Score (FRS), Systematic Coronary Risk Evaluation (SCORE), and American College of Cardiology/ American Heart Association (ACC/AHA) Pooled Cohort Equation incorporate traditional CVD risk factors, including age, sex, smoking status, blood pressure, lipid levels, and presence of diabetes mellitus.^{24,25} However, CVD risk in RA patients appears to be inadequately explained by traditional CVD risk factors,²⁶ with disease activity and inflammation being associated with higher CVD risk. Recognizing that inflammation may contribute to CVD risk even among non-RA patients, the Reynolds Risk Score includes high-sensitivity C-reactive protein (hsCRP) in its calculation.²⁷ In contrast to more robust performance in the general population, these well-established CVD risk scores have had variable predictive potential of incident CVD in RA patients.²⁸⁻³⁰

Several models, or adaptations to existing models, have been proposed to improve CVD risk assessment in RA populations (Table). In 2009, the European League Against Rheumatism (EULAR) task force suggested using a correction factor of 1.5 with traditional CVD risk models in RA patients with 2 of the following criteria: disease duration exceeding 10 years, rheumatoid factor or anti-cyclic citrullinated peptide (CCP) antibody positivity, or extra-articular manifestations of RA.³¹ An update to these recommendations in 2015 continued to propose the use of a 1.5 correction factor, but suggested applying this to all RA patients.³² QRISK2, a modification to QRISK1 which was developed to predict CVD in the UK general population, includes the diagnosis of RA as a risk factor, and in early validation efforts more accurately discriminated patients in the general population at increased risk of CVD compared to the FRS.³³ Additional disease-specific risk factors such as systemic lupus, steroid use, severe mental illness, and steroid and atypical antipsychotic use were incorporated in the QRISK3 algorithm, with model performance similar to the QRISK2.³⁴ The Expanded Cardiovascular Risk Prediction Score for RA (ERS-RA) was specifically developed to assess CVD risk in RA patients by including RA disease activity, level of physical disability, RA disease duration, and prednisone use.³⁵ Despite efforts to develop "RA-specific" risk scores, these have

Table. Comparison of the Components of General Population and Rheumatoid Arthritis-Specific Cardiovascular Disease Risk Calculators

Risk Calculator	Age	Sex	Race	BMI	Lipid Levels	HTN Rx	Sys BP	Smoking Status	Family History of CVD	hsCRP	Comorbid Conditions Included	RA-Specific Measures	Population Assessed
10-Year Framingham CVD Risk Score ²⁵	x	x			TC HDL	x	x	x			Diabetes		US general population
SCORE ²⁴	x	x			TC		x	x					European general population
Reynolds Risk Score ²⁷	x	x			TC HDL		x	x	x	x			Healthy US women
ACC/AHA Pooled Cohort Equation ⁶⁶	x	x	x		TC HDL	x	x	x			Diabetes		US general population
QRISK2 ^{a,33}	x	x	x	x	TC:HDL	x	x	x	x		Diabetes CKD IV-V AFib	RA diagnosis	UK general population
QRISK3 ^{a,34}	x	x	x	x	TC:HDL	x	x	x	x		Diabetes CKD III-V AFib Migraines SLE Psychiatric ^b Steroid use ED	RA diagnosis	UK general population
PROCAM Score ⁶⁷	x				LDL HDL TG		x	x	x		Diabetes		German general population
ERS-RA ³⁵	x	x						x			Hyper-lipidemia HTN Steroid use	CDAI mHAQ RA duration	US RA patients

EULAR modifier³²

Apply a multiplication factor of 1.5 to the criteria above utilized for CVD risk assessment

ACC/AHA, American College of Cardiology/American Heart Association; AFib, atrial fibrillation; BMI, body mass index; CDAI, clinical disease activity index; CKD, chronic kidney disease; ED, erectile dysfunction; ERS-RA, Expanded Cardiovascular Risk Prediction Score for RA; EULAR, European League Against Rheumatism; HDL, high-density lipoprotein; hsCRP, high-sensitivity C-reactive protein; HTN, hypertension; HTN rx, on antihypertensive therapy; LDL, low-density lipoprotein; mHAQ, modified Health Assessment Questionnaire; PROCAM, Prospective Cardiovascular Münster; RA, rheumatoid arthritis; SCORE, Systematic Coronary Risk Evaluation; SLE, systemic lupus erythematosus; Sys BP, systolic BP; TC, total cholesterol; TG, triglycerides.

^aTC:HDL, Systolic BP, and BMI are optional entries for the QRISK2 and QRISK3 algorithms.

^bIncludes history of "severe mental illness" to include: schizophrenia, bipolar disorder, and moderate/severe depression. Additionally, atypical antipsychotic use is included as a risk factor.

not consistently outperformed traditional CVD risk calculators.³⁶⁻³⁸ In one study involving more than 1700 RA patients, the ERS-RA performed similarly to the FRS and Reynolds Risk Score, with a net reclassification index of just 2.3% versus the FRS.³⁶

Imaging Modalities

Imaging modalities may assist in characterizing the increased risk of CVD in RA and the subclinical CVD manifestations that occur. For example, RA patients were shown to have more prevalent and unstable coronary plaque, higher carotid intima media thickness, and impaired myocardial function with computed tomography (CT) angiography and carotid ultrasound.^{39,40} However, studies harnessing noninvasive imaging to augment CVD risk assessment in RA patients are limited.

Until the performance of RA-specific CVD risk scores can be better established, we recommend the use of nationally endorsed CVD risk scores, with the frequency of reassessment based on CVD risk.

Carotid ultrasound has been the most extensively studied imaging modality for CVD risk assessment in RA. In a cohort of 599 RA patients with no history of ACS, rates of ACS were nearly 4 times higher in RA patients with bilateral carotid plaque on carotid ultrasound, and the association with ACS was independent of other traditional and RA-related risk factors.⁴¹ Presence of bilateral carotid plaques was similarly associated with an increased risk of overall CVD events (hazard ratio [HR], 3.34 [95% CI, 1.21-9.22]), ACS alone (HR, 6.31 [95% CI, 1.27-31.40]), and a lower mean CVD event-free survival (13.9 versus 15.2 years, $P = 0.01$) in a separate inception cohort of 105 RA patients with no prior history of CVD.⁴² The most useful application of carotid ultrasound may be in conjunction with clinical CVD risk models. Use of carotid ultrasound improved CVD risk stratification among RA patients who were considered at moderate risk by

the EULAR-modified SCORE calculator.⁴³ Beyond carotid ultrasound, measurement of arterial stiffness through ultrasound could also aid in CVD risk stratification. Aortic pulse wave velocity and augmentation index, measures of arterial stiffness, are predictive of CVD in the general population as well as RA patients and improve with reduction in RA disease activity.^{44,45} Peripheral arterial stiffness (brachial-ankle elasticity index) is impaired in RA patients and predictive of CVD morbidity and mortality in the general population.^{46,47}

CT coronary angiography and coronary artery calcium (CAC) scores are reliable measures of coronary artery atherosclerosis and have been validated for CVD risk assessment in the general population.⁴⁸⁻⁵² While the association between RA and CT-related findings of atherosclerosis is well established, assessment of CT-mediated evaluation as a prognostic tool for CVD in RA is limited. In one cohort study, CAC predicted higher rates of CVD events in Chinese patients with RA and systemic lupus erythematosus in a pooled analysis, although results were limited by low event rates and the absence of RA-only subanalyses.⁵³

While the aforementioned imaging modalities have focused on enhancing the identification of atherosclerosis, echocardiography or cardiac magnetic resonance imaging (MRI) may be useful for detecting subclinical structural and/or functional abnormalities that predispose to CHF. Structural abnormalities including increased left ventricular mass and hypertrophy are more prevalent in RA patients and predict incident CHF in the general population.⁵⁴⁻⁵⁶ MRI measures of myocardial inflammation, including T1 mapping and extracellular volume, are associated with higher mortality rates and also appear to be elevated in RA patients.^{57,58} Whether identification of these imaging findings influences the cost-effective clinical management of RA patients needs further study.

Biomarkers

Serum biomarkers, such as the anti-CCP antibody, have become crucial to the evaluation of patients suspected to have RA. With the growing understanding of the role pro-inflammatory mediators play in CVD pathogenesis and the relative ease with which they can be measured, serum biomarkers have potential to inform CVD risk assessment. In

the general population, hsCRP concentrations are predictive of CVD and are included in the Reynolds Risk Score.²⁷ In RA, CRP concentrations are typically much higher than those observed among individuals in the general population solely at increased CVD risk, yet elevated levels remain predictive of CVD death independent of RA disease activity and traditional CVD risk factors.⁵⁹ Several additional cytokines, chemokines, and adhesion molecules have been associated with surrogate markers of CVD in RA patients, although further study is needed to elucidate thresholds that signify increased CVD risk in a population characterized by the presence of systemic inflammation.⁶⁰

Cardiac biomarkers used frequently in the general population may be useful to assess CVD risk in RA patients. N-terminal-pro brain natriuretic peptide (NT-pro BNP) is a biomarker typically used to evaluate CHF severity, but it may also predict long-term mortality in patients with coronary heart disease.^{61,62} Circulating NT-pro BNP concentrations are elevated in RA independent of prevalent CHF and may serve as a useful tool to identify subclinical cardiac disease in RA patients.⁶³ High-sensitivity cardiac troponin I (HS-cTnI) assays are capable of detecting levels of cardiac troponin below the threshold typically used to diagnose ACS. HS-cTnI levels are increased in RA patients independent of additional CVD risk factors, and elevated levels (> 1.5 pg/mL) were associated with more severe CT angiography findings of coronary plaque as well as increased risk of CVD events.^{64,65}

Clinical Application

A fully validated algorithm for CVD risk assessment in RA is lacking. Most CVD risk scores from the general population do not contain RA-related factors predictive of CVD but have had more extensive performance testing. In contrast, novel RA-derived CVD risk scores incorporate RA-related factors, but have had limited external validity testing. Additionally, RA-derived risk scores are less likely to be utilized and adopted by primary care providers and cardiologists involved in RA patients' care. Neither set of risk scores incorporates novel imaging modalities or serum biomarkers, which are most likely to be helpful among individuals at intermediate risk. Therefore, until the performance of RA-specific CVD risk scores can be better established, we recommend the use of nationally

endorsed CVD risk scores, with the frequency of reassessment based on CVD risk.

Conclusion

RA patients are at increased risk of CVD and CVD-related mortality relative to the general population. The disproportionate CVD burden seen in RA appears to be multifactorial, owing to the complex effects of systemic inflammation, endothelial dysfunction, and pro-atherogenic lipoprotein modifications. Additionally, many traditional CVD risk factors are more prevalent and suboptimally managed in RA patients. To mitigate the increased risk of CVD in RA, primary care and subspecialty providers alike must be aware of this heightened risk in RA, perform frequent assessment of CVD risk, and aggressively manage both traditional and nontraditional CVD risk factors. The management of CVD risk factors is discussed in detail in the second part of this article.

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