Usefulness of Risk Scores to Estimate the Risk of Cardiovascular Disease in Patients With Rheumatoid Arthritis

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Patients with rheumatoid arthritis (RA) have an excess burden of cardiovascular (CV) disease (CVD). CV risk scores for the general population may not accurately predict CV risk for patients with RA. A population-based inception cohort of patients who fulfilled 1987 American College of Rheumatology criteria for RA from 1988 to 2007 was followed until death, migration, or December 31, 2008. CV risk factors and CVD (myocardial infarction, CV death, angina, stroke, intermittent claudication, and heart failure) were ascertained by medical record review. Ten-year predicted CVD risk was calculated using the general Framingham and the Reynolds risk scores. Standardized incidence ratios were calculated to compare observed and predicted CVD risks. The study included 525 patients with RA aged ≥30 years without previous CVD. The mean follow-up period was 8.4 years, during which 84 patients developed CVD. The observed CVD risk was 2-fold higher than the Framingham risk score predicted in women and 65% higher in men, and the Reynolds risk score revealed similar deficits. Patients aged ≥75 years had observed CVD risk >3 times the Framingham-predicted risk. Patients with positive rheumatoid factor or persistently elevated erythrocyte sedimentation rates also experienced more CVD events than predicted. In conclusion, the Framingham and Reynolds risk scores substantially underestimated CVD risk in patients with RA of both genders, especially in older ages and in patients with positive rheumatoid factor. These data underscore the need for more accurate tools to predict CVD risk in patients with RA. © 2012 Elsevier Inc. All rights reserved. (Am J Cardiol 2012;110:420–424)

Cardiovascular (CV) risk assessment tools designed for the general population, such as the Framingham risk score, may not predict the risk for CV disease (CVD) in patients with substantial co-morbidities, such as rheumatoid arthritis (RA).1 The profile of CV risk factors differs in patients with RA, who have a higher frequency of smoking and low body mass index compared to subjects without RA.5 In addition, many traditional CV risk factors, such as male gender, smoking, personal cardiac history, and lipids, have less impact or paradoxical effects on the development of CVD in patients with RA.2,5 Finally, although inflammation plays a pivotal role in the increased risk for CVD in patients with RA, it is not incorporated into many CV risk assessment tools.3,4 The Reynolds risk score includes C-reactive protein, so theoretically, it may perform better in patients with RA, but this has not been assessed.5 The objective of this study was to assess the accuracy of the Framingham and Reynolds risk scores for predicting CVD events in patients with RA.

Methods

This retrospective, population-based study was conducted using the resources of the Rochester Epidemiology Project, a medical records linkage system that allows ready access to the complete (inpatient and outpatient) medical records from all community medical providers.6 An incidence cohort of all residents of Olmsted County, Minnesota, aged ≥18 years who first fulfilled 1987 American College of Rheumatology classification criteria for RA from January 1, 1988, to December 31, 2007, was identified and followed until death, migration, or December 31, 2008.7,8 For each patient, the earliest date of fulfillment of ≥4 American College of Rheumatology criteria for RA was considered the RA incidence date. An Olmsted County resident of similar age and the same gender without RA was selected for each RA patient, and the RA incidence date was used as the index date for each of these non-RA subjects. The institutional review boards of the Mayo Clinic and the Olmsted Medical Center approved this study.

The presence of CV risk factors at RA incidence were ascertained by medical record review, including smoking status (never, current, or former), systolic and diastolic blood pressure measurements, use of antihypertensive medications, body mass index, and diabetes mellitus (defined as ≥2 measurements of fasting plasma glucose ≥126 mg/dl or a 2-hour plasma glucose level ≥200 mg/dl, physician diagnosis, or documented use of insulin and/or oral hypoglycemic agents). The results of all fasting serum lipid measurements, including total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides, were also ab-
Table 1
Characteristics and cardiovascular risk factors of patients with and without rheumatoid arthritis who had no previous cardiovascular disease

<table>
<thead>
<tr>
<th>Criterion for CV Risk Score</th>
<th>RA (n = 525)</th>
<th>Non-RA (n = 524)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>54.6 ± 13.7</td>
<td>54.5 ± 13.5</td>
</tr>
<tr>
<td>Rheumatoid factor positive</td>
<td>357 (68%)</td>
<td>—</td>
</tr>
<tr>
<td>Abnormal erythrocyte sedimentation rate at incidence (&gt;30 mm/hour)</td>
<td>203 (40%)</td>
<td>—</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>195.4 ± 35.7</td>
<td>205.8 ± 40.9</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>54.2 ± 16.1</td>
<td>55.5 ± 16.5</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>131.5 ± 18.3</td>
<td>129.1 ± 19.8</td>
</tr>
<tr>
<td>Blood pressure treatment</td>
<td>125 (24%)</td>
<td>109 (21%)</td>
</tr>
<tr>
<td>Current smoking</td>
<td>98 (19%)</td>
<td>91 (17%)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45 (9%)</td>
<td>38 (7%)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>28.3 ± 6.2</td>
<td>28.0 ± 6.1</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD or as number (percentage).

strated from the medical records. For blood pressure, lipids, and body mass index, the recorded value closest to RA incidence date within ±1 year was used to calculate the risk for CVD. Note that 80% of the values were obtained from 90 days before to 30 days after the RA incidence date. Data on RA characteristics (rheumatoid factor positivity, erythrocyte sedimentation rate, and C-reactive protein) were also collected. Persistently elevated erythrocyte sedimentation rate was defined as ≥3 measurements >40 mm/hour within the first year after RA incidence.

The presence of CVD (myocardial infarction, CV death, angina, stroke, intermittent claudication, and heart failure) was ascertained throughout follow-up. Myocardial infarction was defined according to standardized criteria. CV death was defined using the underlying cause of death obtained from death certificates (International Classification of Diseases, Ninth Revision, codes 350.0 to 459.9, and International Classification of Diseases, Tenth Revision, codes 100 to 199). Angina was ascertained by physician diagnosis. Stroke and intermittent claudication were defined using physician diagnosis verified by imaging, cerebrospinal fluid analysis, or autopsy. Heart failure was defined using the Framingham criteria. Patients with CV outcomes before the RA incidence or index date were excluded from the analysis. Descriptive statistics were used to summarize the demographics of the RA and non-RA cohorts. Chi-square and rank-sum tests were used to examine differences in CV risk factors according to gender. The 10-year general Framingham risk score for CVD and the office-based 10-year Framingham risk score, which does not include laboratory values, were calculated according to published algorithms. In addition, the Reynolds risk score was calculated in patients with available C-reactive protein values. Observed follow-up was truncated at 10 years after RA incidence. For patients with <10 years of follow-up, the predicted risk for CVD was adjusted proportionately. Standardized incidence ratios, which are the ratios of the observed CVD in RA to the predicted CVD obtained from a risk score, were calculated assuming that the predicted rates are fixed and the observed CVD events follow a Poisson distribution.

The accuracy of predictions was assessed using calibration (i.e., agreement between the observed and predicted event rates) and discrimination (i.e., whether patients are correctly ranked from low to high risk). Calibration was assessed graphically comparing observed event rate for patients in each decile of predicted event rates. Discrimination was assessed using Harrell’s concordance (C) statistic. Analyses were conducted using R (R Project for Statistical Computing, Vienna, Austria) and SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

Results
The study included 525 patients with RA aged ≥30 years without previous CVD (mean age 57 years, 69% women) who were followed for a mean of 8.4 years and 524 patients without RA of similar age, gender, and follow-up duration. Table 1 lists the characteristics at the incidence or index date for patients with and without RA.

The general Framingham risk score and the office-based Framingham risk score were calculated. The 2 assessments were similar, but the office-based Framingham risk score yielded estimates that were on average 2.4% higher (median 0.9% higher) than the general Framingham risk score. Given this reasonably close agreement, the office-based Framingham risk score was used for 90 patients with RA without available lipid measurements. If the observed risk exceeds the predicted risk, using the office-based Framingham risk score would slightly diminish the differences between observed and predicted risk. The median Framingham risk score was 5.9% for women (range 0.6% to 67.8%) and 15.6% for men (range 1.2% to 90.5%). The actual observed 10-year risk for CVD in women was 18.3% (95% confidence interval [CI] 13.2% to 23.2%) and in men was 32.7% (95% CI 22.6% to 41.5%).

A total of 84 patients developed CVD during follow-up, but the Framingham risk score predicted only 45.7 CVD events in these patients (Table 2). The standardized incidence ratio was elevated overall and for both genders, indicating that the Framingham risk score significantly underestimated the CV risk in patients with RA in women (by 102%) and men (by 65%). Analysis of age groups revealed that the standardized incidence ratios were >1 for all age groups, with patients aged ≥75 years demonstrating substantially higher CV risk than predicted. Among the patients without RA aged 30 to 74 years, 47 developed CVD during follow-up; 40.0 events were predicted by the Framingham risk score. Thus, the risk score performed well in patients without RA from our community (standardized incidence ratio 1.18, 95% CI 0.88 to 1.56).

The discrepancies between observed and predicted CVD risk differed according to RA disease characteristics. No difference between observed and predicted CV risk was noted for rheumatoid factor–negative patients with RA. However, the observed CV risk was more than twofold greater than the predicted CV risk in patients with rheumatoid factor–positive RA. Also, the observed risk for CVD in patients with persistently elevated erythrocyte sedimentation rates was fourfold greater than expected, whereas the difference between the observed and predicted CVD risk for patients without persistently elevated erythrocyte sedimentation rates was less pronounced. C-reactive protein measures were available only in a subset of 167 patients, but the
results were similar to those for erythrocyte sedimentation rate. Patients with C-reactive protein $\geq 10$ mg/L had observed CVD risk greater than predicted (standardized incidence ratio 1.62, 95% CI 0.81 to 3.24), but this difference did not reach statistical significance ($p = 0.17$). There was no evidence of greater than expected CVD risk in patients with C-reactive protein $<10$ mg/L at RA incidence (standardized incidence ratio 0.81, 95% CI 0.26 to 2.50).

Figure 1 shows the observed and predicted 10-year risk for CVD according to deciles of the predicted risk obtained from the Framingham risk score. The observed risk (solid bars) was obtained using Kaplan-Meier methods.

higher than the predicted CVD risk in 6 of the 10 deciles. This indicates that the Framingham risk score is poorly calibrated for patients with RA. In addition, the widely varying levels of observed CVD risk in deciles 1 to 4 indicate that the Framingham risk score did not properly rank the patients with RA from lowest to highest CVD risk. Although overall, the discrimination was good (C-statistic $= 0.786$, 95% CI 0.721 to 0.851), discrimination in the lowest 4 deciles was much poorer (C-
The Reynolds risk score for CVD risk in patients with RA of both genders, especially in older ages and in patients with positive rheumatoid factor and those with persistently elevated erythrocyte sedimentation rates. This indicates that RA disease severity and inflammation play a role in CVD risk that is not accounted for in the Framingham risk score. In addition, the Reynolds risk score underestimated CVD risk in women with RA, despite its inclusion of C-reactive protein.

Despite numerous assessments in patients with high risk for CVD, such as those with diabetes, chronic kidney disease, and systemic lupus erythematosus, the accuracy of Framingham risk score predictions in patients with RA has not been previously examined. The poor discrimination and calibration of the Framingham risk score in patients with RA could result in missed opportunities for preventive interventions and may provide a false sense of security regarding CVD risk for patients and their physicians.

The National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood cholesterol in Adults (Adult Treatment Panel III) and other commonly used guidelines recommend that preventive strategies should be initiated for patients with risks >20% and should not be considered for patients with risks <10%. However, patients with RA with predicted risks as low as 11.1% actually have risks 1.8 times higher than predicted (i.e., 11.1% × 1.8 = 20%), which would classify them as high-risk (≥20%) patients warranting initiation of more aggressive intervention. To address this, it has been suggested that a simple multiplier could be used as a means to improve CVD risk prediction in patients with RA. This would improve calibration on average, but discrimination would not improve.

The differences between observed and predicted CVD risk in patients with RA may be due to differential effects of traditional CV risk factors in patients with RA. Despite the increased prevalence of smoking in patients with RA, smoking seems to have less effect on CVD in patients with RA. In addition, total cholesterol and low-density lipoprotein levels may not be considered for high-risk patients with RA.

An additional analysis was performed using erythrocyte sedimentation rate values to impute C-reactive protein values, allowing examination of the utility of the Reynolds risk score in a larger sample of patients with RA. A linear regression model was used to model the association between erythrocyte sedimentation rate and log-transformed C-reactive protein (R² = 0.42, p <0.001). The standardized incidence ratio was 2.00 (95% CI 1.44 to 2.78, p <0.001), indicating that the Reynolds risk score underestimated the risk for CVD in women with RA.

In a sensitivity analysis, all women with RA were assumed to have C-reactive protein of 50 mg/L. This high value, which is at about the 90th percentile of the available C-reactive protein values, was chosen to examine the potential of the Reynolds score to accurately assess risk for CVD in women with RA. The standardized incidence ratio was 1.48 (95% CI 1.07 to 2.06, p = 0.02), indicating that the Reynolds risk score cannot adequately predict the risk for CVD in women with RA. The Reynolds risk score for men was not assessed, because of the small number of men with available C-reactive protein values in this study.

Discussion

The Framingham risk score substantially underestimated CVD risk in patients with RA of both genders, especially in older ages and in patients with positive rheumatoid factor and those with persistently elevated erythrocyte sedimentation rates. This indicates that RA disease severity and inflammation play a role in CVD risk that is not accounted for in the Framingham risk score.

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C-reactive protein is included in the Reynolds risk score, and it did not perform any better in patients with RA than the Framingham risk score did.

Other factors that may influence CVD risk in patients with RA include the loss of function and muscle mass that commonly occurs after diagnosis of RA. Furthermore, therapies used to treat patients with RA, such as corticosteroids, disease-modifying antirheumatic medications, and biologic response modifiers, may have disparate impacts on CVD risk because there is likely considerable confounding of these factors, randomized clinical trials are needed to help disentangle the drivers of CVD risk and the most effective interventions to improve CVD outcomes in patients with RA.

Strengths of this study include its population-based cohort of patients who meet objective criteria for RA and the complete ascertainment of clinically identified CVD events obtained from comprehensive (inpatient and outpatient) medical records. Potential study limitations include the predominately white population of Olmsted County, which may limit the generalizability of these results to more diverse populations. In addition, the retrospective study design is a limitation, and lipid measurements were not available for some patients. For these patients, the office-based Framingham risk score was used, which may slightly diminish the differences between observed and predicted risks, because the office-based Framingham risk score was slightly higher than the general Framingham risk score in patients for whom both could be assessed.