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Derivation and Internal Validation of an Expanded Cardiovascular Risk Prediction Score for Rheumatoid Arthritis

A Consortium of Rheumatology Researchers of North America Registry Study

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Objective. **Cardiovascular disease (CVD) is the leading cause of mortality in rheumatoid arthritis (RA), but CV risk prediction scores derived from the general population do not accurately predict CV risk in RA patients. The goal of these analyses was to develop and internally validate an expanded CV risk prediction score for RA.**

Methods. **Study participants were patients with RA and no known CVD from the Consortium of Rheumatology Researchers of North America registry. Two-thirds of the cohort were used to derive the CV risk prediction score, and one-third for internal validation. Traditional CV risk factors were included in the base Cox regression model, and RA-related variables were assessed in an expanded model predicting confirmed CV events. Fit and utility of the expanded model were evaluated.**

Results. **The study cohort included 23,605 RA patients with 437 CV events over a median followup of 2.2 years. The RA variables found to be significant in the regression models and included in the expanded risk model were disease activity (Clinical Disease Activity Index >10 versus ≤10), disability (modified Health Assessment Questionnaire disability index >0.5 versus ≤0.5), daily prednisone use (any versus none), and disease duration (≥10 years versus <10 years). The expanded model had good fit (Hosmer-Lemeshow goodness of fit $P = 0.94$) and a lower Akaike's information criterion than the base model. In the internal validation cohort, the c-statistic for model discrimination was significantly improved from the base model to the expanded model (from 0.7261 to 0.7609; $P = 0.0104$). The net reclassification index of CV risk in models using a 4-category CV risk prediction tool was 40% (95% confidence interval 37–44%).**

Conclusion. **This newly developed, expanded risk score for CV outcomes in RA performs well and improves the classification of CV risk in comparison to a risk prediction score in which only traditional risk factors were included.**

The most common cause of mortality in rheumatoid arthritis (RA) is cardiovascular disease (CVD) (1,2). Patients with RA experience a 50–100% increase in the risk of CV events (3,4). Systemic inflammation likely contributes to this increased risk (5,6). However,

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the predictors of CVD in RA are incompletely understood. Beyond traditional CV risk factors, such as age, sex, diabetes, dyslipidemia, hypertension, and tobacco use, several RA-related factors appear to be associated with CVD and/or CV events based on prior epidemiologic studies. These factors include RA disease duration, functional status, RA disease activity, corticosteroid use, serologic status, extraarticular manifestations, and medications (7–13). Epidemiologic studies in which these risk factors have been assessed provide important insights, but they do not easily translate into improved clinical management of RA.

Risk prediction scores (or rules) provide an important tool for clinicians and patients to move epidemiologic observations into the clinic (14). Targeting interventions, such as the management of dyslipidemia, based on accurately predicted future risk allows interventions to be appropriately targeted to patients most likely to benefit. CV risk scores derived from the general population have been assessed in patients with RA, primarily using surrogates of CVD. Unfortunately, the results of these studies have suggested that both the Framingham Risk Score and the Reynolds Risk Score perform suboptimally in patients with RA, resulting in an underestimation of the CV risk (15–17). Although it has been suggested that applying a multiplier of 1.5 may help correct this underestimation (18), or that adding 10 years to the age of patients with RA would correct the risk prediction scores (13), the validity of these proposals has not been rigorously tested (18). Furthermore, the QRisk2 cardiovascular risk score incorporates RA, but not specific aspects of RA (19).

To improve CV risk prediction in RA requires a large cohort with prospectively collected risk factors and sufficient numbers of CV events. The Consortium of Rheumatology Researchers of North America (CORRONA) cohort is the largest US-based RA registry, compiling data from nearly 40,000 patients with rheumatic diseases. In this registry, CV event information has been collected and subjected to a confirmation process, and a complete set of CV risk factors has been compiled. We aimed to derive and internally validate an expanded CV risk score for patients with RA using prospectively collected data from the CORRONA registry, potentially facilitating more patient-tailored CV risk prediction.

PATIENTS AND METHODS

Study cohort and design. The CORRONA registry is a collection of data from 165 practices involving 610 rheumatologists in 35 US states and was initiated in 2001. Data are collected 3–4 times each year using structured case report forms that include medication use, RA disease activity and function, comorbid illnesses, and acute events, such as CV events, infections, and cancer. We assembled the study cohort from the CORRONA registry by requiring that patients have a record of at least 2 physician visits in which a diagnosis of RA was made, and by excluding those with diagnoses of other systemic rheumatic diseases. Subjects with prior known CVD at the time of enrollment were also excluded. Followup for new CV events began at the second registry visit. To allow for confirmation and adjudication of events, the last visit date used for this analysis was December 31, 2011.

The study cohort was split into risk score derivation and validation cohorts. The derivation cohort, a random sample of two-thirds of the total cohort, was used to identify variables for the expanded risk score in RA (referred to as the ERS-RA). The development of an expanded risk score started with traditional CV risk factors in a base model, which was then augmented by testing RA-related variables and other variables in an expanded model, in which the incremental value of each variable was assessed. We focused on adding variables that are easy to assess in a physician's office, as opposed to laboratory measures or biomarkers. The calibration and discrimination of the risk score was then tested in the remaining one-third of the internal validation cohort.

Cardiovascular outcomes. At each registry visit, physicians report whether adverse events have occurred in a patient between visits, including incident myocardial infarction (MI), stroke, or CV-related death. All physician-reported CV events prompt administration of a second questionnaire to the site, to confirm the CV event and to obtain additional details and verify that it was an incident event. We also request additional information to adjudicate the event, including medical records from the treating acute care hospital. All medical records were reviewed by an adjudication committee, comprising 2 cardiologists and a neurologist (for stroke), with use of adjudication methods established by the US Food and Drug Administraiton (20). Of the 437 rheumatologist-confirmed CV events, 170 (39%) had records available for adjudication; of these, 152 (89.4%) were adjudicated as definite or probable CV events, 9 (5.3%) as possible CV events, and 9 (5.3%) as non-events. The primary analysis used a composite end point of all confirmed MI, stroke, or CV death events. In addition, the sensitivity analysis examined the base and expanded risk models restricted to only the adjudicated events.

Potential predictors. All potential predictors were reported at baseline, defined as the time of enrollment in the CORRONA registry. The base model included traditional CV risk factors: age, sex, diabetes, hyperlipidemia, hypertension, and patient-reported tobacco use. The study database does not contain information on glycosylated hemoglobin levels, actual lipid levels, or blood pressure. Thus, diabetes, hyperlipidemia, and hypertension were each treated as a dichotomous variable, with presence or absence determined on the basis of the physician's report of diagnosis or the use of medications specific for one of these conditions.

RA-related variables included the level of disease activity, measured as the Clinical Disease Activity Index (CDAI) (21), the extent of disease disability, measured as the modified Health Assessment Questionnaire (M-HAQ) disability index (DI) (22), the duration of RA (in years), the presence of subcutaneous nodules, report of joint erosions on radiograph, serologic status (either rheumatoid factor– or anti–cyclic citrullinated peptide antibody–positive), and use of

typical RA medications with a putative association with CV events. These medications consisted of oral corticosteroids (measured as prednisone equivalents), methotrexate use, tumor necrosis factor antagonist use, and nonsteroidal anti-inflammatory drugs, including selective cyclooxygenase 2 inhibitors. If physician-reported data on corticosteroid use were missing (45% of subjects), patient-reported data were used instead, resulting in no missing values.

We also assessed other, non–RA-related variables as possible risk factors in the expanded model. These included educational attainment, race, physical activity, alcohol use, body mass index, family history of MI prior to age 50 years, and aspirin use. All of these variables can be relatively easily evaluated in the physician's office and have been linked with CV events in prior studies (23,24).

Similar to the Framingham Risk Score, covariates were not updated in a time-varying manner. Moreover, similar to the Framingham Risk Score, we dichotomized multilevel variables to simplify the potential use of a risk score for RA, with the CDAI dichotomized as remission or low disease activity versus moderate or high disease activity (21), the M-HAQ DI dichotomized as ≤ 0.5 versus >0.5, prednisone use dichotomized as any versus none, and RA disease duration dichotomized as <10 years versus ≥ 10 years.

Several variables had missing values. For composite variables (the CDAI and M-HAQ DI), if they had one missing component, we used the non-missing components to perform a multiple imputation using PROC MI (version 9.4; SAS Institute). The CDAI and M-HAQ DI could then be calculated using the observed components plus imputed components. If variables had missing data that were deemed likely to be informative, we created a missing category (e.g., M-HAQ DI, serologic status, and erosion status). Subjects with missing values for variables that were included in the expanded model were excluded (see Supplementary Figure 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39195/abstract).

Statistical analysis. After assembling the study cohort, we randomly assigned two-thirds of the patients to the derivation cohort and one-third to the internal validation cohort. The baseline characteristics of the 2 cohorts were compared. In addition, the incidence rates (IRs) of CV outcomes were compared across cohorts.

Starting in the derivation cohort, a Cox proportional hazards regression model was fit with only the base variables: age, sex, diabetes, hyperlipidemia, hypertension, and tobacco use (base model). The RA-related and other variables were then tested, by adding each variable separately to the base model; the variables with *P* values less than 0.05 were included in a fully adjusted expanded risk model, forcing in all base model variables. The final base and expanded risk models were evaluated in the internal validation cohort. In addition, sensitivity analyses were performed to examine both models using only adjudicated CV outcomes.

Model fit statistics were calculated using the internal validation cohort. The Akaike's information criterion (AIC), a commonly used test of the relative quality of fit for models predicting the same outcome (25), the c-statistic (also known as the area under the receiver operating characteristic curve), which describes the performance of a binary classification variable at a variety of thresholds, and the Hosmer-Lemeshow goodness-of-fit test, which assesses whether the observed fit of a given model differs from the expected fit across subgroups of the population, were estimated. In the combined cohort, the net reclassification index (NRI) was calculated using a publically available SAS macro (available at http://ncook.bwh.harvard.edu/sas-macros.html), and the confidence interval (CI) was derived by bootstrapping 500 sample populations. The NRI was calculated for 2 sets of risk categories: one set corresponds to the original Adult Treatment Panel III (ATP III) risk categories used with the Framingham Risk Score (4 categories of 10-year predicted CV risk: $<5\%$, 5 to $<10\%$, 10 to $<20\%$, and $\geq 20\%$) (26), and the other set corresponds to the 2013 American College of Cardiology/American Heart Association (ACC/AHA) Task Force on Practice Guidelines recommendations for statin initiation (2 categories of 10-year predicted CV risk: $<7.5\%$ and $\geq 7.5\%$) (27). We used these 2 risk tools to explicitly assess reclassification of CV risk in RA patients in the CORRONA registry from the base to the expanded risk models.

All programming was conducted using SAS statistical software (version 9.3; SAS Institute).

RESULTS

From the 38,955 patients in the CORRONA registry, we identified 31,282 patients (80.3%) with >1 visit, and then excluded all those without RA (n = 4,685) or those with another systemic rheumatic disease (n = 555) (see Supplementary Figure 1). From the 26,042 patients with RA remaining in the cohort, we excluded 1,986 (7.6%) with known CVD and 451 (1.7%) with missing data that could not be imputed. The remaining cohort of 23,605 patients was followed up for a mean of 2.9 years (median 2.2 years, interquartile range 0.9–4.4 years).

The final cohort was randomly split by assigning two-thirds of the patients to the derivation cohort and one-third to the internal validation cohort. The characteristics of the patients in the 2 cohorts were similar (Table 1). The mean age was 57 years, and 22% of patients were men, reflecting the typical demographics of RA. The prevalence rates of diabetes (7%), hyperlipidemia (15%), hypertension (29%), and tobacco use (15%) were similar across cohorts. The characteristics of RA were also comparable across cohorts.

The IRs (per 1,000 person-years of followup) of CV events in the total cohort were as follows: for MI, IR 2.5 (95% CI 1.9–3.1), for stroke, IR 3.0 (95% CI 2.3–3.7), and for CV-related death, IR 1.0 (95% CI 0.6–1.4). These values reflect typical IRs for CV outcomes in patients with RA (4,28). The rates and confidence intervals in the derivation and internal validation cohorts overlapped (see Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39195/abstract).

The traditional CV risk factors were tested in the base model among patients in the derivation cohort (see Supplementary Table 2, available on the *Arthritis &*

Table 1. Baseline characteristics of the study cohorts*

	Derivation cohort (n = 15,744)	Validation cohort (n = 7,861)	Total cohort (n = 23,605)
Traditional cardiovascular risk factors			
Age, mean ± SD years	57.2 ± 13.4	57.5 ± 13.5	57.3 ± 13.4
Male sex	3,392 (21.5)	1,720 (21.9)	5,112 (21.7)
Diabetes	1,087 (6.9)	538 (6.8)	1,625 (6.9)
Hyperlipidemia	2,291 (14.6)	1,163 (14.8)	3,454 (14.6)
Hypertension	4,507 (28.6)	2,293 (29.2)	6,800 (28.8)
Current tobacco use	2,387 (15.2)	1,201 (15.3)	3,588 (15.2)
RA-related variables			
CDAI, mean ± SD	13.8 ± 12.8	13.8 ± 12.6	13.8 ± 12.7
Remission	2,989 (19.0)	1,495 (19.0)	4,484 (19.0)
Low disease activity	4,933 (31.3)	2,393 (30.4)	7,326 (31.0)
Moderate disease activity	4,346 (27.6)	2,272 (28.9)	6,618 (28.0)
High disease activity	3,476 (22.1)	1,701 (21.6)	5,177 (21.9)
M-HAQ DI, mean ± SD	0.36 ± 0.45	0.36 ± 0.45	0.36 ± 0.45
Score <0.5	11,545 (73.3)	5,759 (73.3)	17,304 (73.3)
Score ≥0.5	4,183 (26.6)	2,084 (26.5)	6,267 (26.6)
Prednisone use	5,205 (33.1)	2,664 (33.9)	7,869 (33.3)
Disease duration, mean ± SD years	9.0 ± 9.5	9.1 ± 9.6	9.0 ± 9.5
<5 years	6,880 (43.9)	3,396 (43.5)	10,276 (43.8)
5–10 years	3,772 (24.1)	1,892 (24.2)	5,664 (24.1)
>10 years	5,007 (32.0)	2,524 (32.3)	7,531 (32.1)
Seropositivity for RF and/or ACPAs	7,663 (76.9)	3,848 (77.3)	11,511 (77.0)
Erosions	5,925 (50.3)	2,937 (50.3)	8,862 (50.3)
Subcutaneous nodules	4,581 (29.1)	2,300 (29.3)	6,881 (29.2)
Current NSAID use	9,882 (62.8)	5,006 (63.7)	14,888 (63.1)
Current MTX use	10,170 (64.6)	5,143 (65.4)	15,313 (64.9)
Current TNF antagonist use	5,495 (34.9)	2,762 (35.1)	8,257 (35.0)
Any DMARD use	14,411 (91.5)	7,218 (91.8)	21,629 (91.6)
Other variables			
Education, some college	8,301 (55.6)	4,124 (55.0)	12,425 (55.4)
Race			
White	14,000 (88.9)	7,070 (89.9)	21,070 (89.3)
Black	1,153 (7.3)	512 (6.5)	1,665 (7.1)
Other	591 (3.8)	279 (3.6)	870 (3.7)
Physical activity			
None	4,785 (31.4)	2,384 (31.5)	7,169 (31.4)
Any	10,450 (68.6)	5,190 (68.5)	15,640 (68.6)
Alcohol use, any	6,721 (45.1)	3,337 (45.0)	10,058 (45.1)
BMI, mean ± SD kg/m^2	29.08 ± 7.04	29.11 ± 7.08	29.09 ± 7.05
Family history of early MI	6,820 (43.3)	3,418 (43.5)	10,238 (43.4)
Aspirin use	2,498 (16.1)	1,246 (16.1)	3,744 (16.1)

* Except where indicated otherwise, values are the number (%) of patients. Several variables had subjects with missing data (the modified Health Assessment Questionnaire [M-HAQ] disability index [DI] n = 34, disease duration n = 134, serologic status n = 8,649, and erosions n = 5,972); "missing" was included as a category in further analyses. RA = rheumatoid arthritis; CDAI = Clinical Disease Activity Index; RF = rheumatoid factor; ACPAs = anti–citrullinated protein antibodies; NSAID = nonsteroidal antiinflammatory drug; MTX = methotrexate; TNF = tumor necrosis factor; DMARD = disease-modifying antirheumatic drug; BMI = body mass index; MI = myocardial infarction.

Rheumatology web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39195/abstract). As expected, traditional risk factors for CVD were predictive of CV events in the derivation cohort. We added each potential RA-related variable and other variables, separately, to the base model (see Supplementary Table 2). The variables identified for inclusion in the expanded model in both the derivation and internal validation cohorts were then tested in the total cohort (Table 2). These variables included RA disease activity as measured by the CDAI (HR 1.31, 95% CI 1.07–1.61 for moderate or high disease activity versus low disease activity or remission), disability as measured by the M-HAQ DI (HR 1.18, 95% CI 0.95–1.46 for moderate or high disability versus low disability or none), daily prednisone use (HR 1.61, 95% CI 1.33–1.95 for any versus none), and disease duration (HR 1.43, 95% CI 1.18–1.73 for ≥10 years versus <10 years). In addition, the base and expanded models were analyzed with inclusion of only those CV outcomes adjudicated to be definite or probable CV

Table 2. Cox regression models assessing baseline variables as predictors of cardiovascular events in the base and expanded risk models among patients in the total cohort*

	Base model	Expanded model
FRS variable		
Age, years		
40–44	1.37 (0.46–4.07)	1.36 (0.46–4.04)
45–49	2.34 (0.93–5.86)	2.23 (0.93–5.59)
50–54	2.65 (1.55–8.61)	3.35 (1.55–7.92)
55–59	3.99 (1.71–9.33)	3.66 (1.71–8.56)
60–64	5.36 (2.31–12.48)	4.91 (2.31–11.45)
65–69	8.94 (3.88–20.62)	8.07 (3.88–18.64)
70–74	10.24 (4.41–23.77)	9.20 (4.41–21.39)
75+	17.71 (7.74–40.49)	15.80 (7.74–36.20)
Male sex	1.67 (1.37–2.04)	1.74 (1.42–2.12)
Diabetes	1.54 (1.14–2.09)	1.52 (1.14–2.06)
Hyperlipidemia	1.31 (1.02–1.69)	1.38 (1.02–1.78)
Hypertension	1.26 (1.03–1.54)	1.23 (1.03–1.50)
Current tobacco use	2.47 (1.96–3.10)	2.38 (1.96–3.01)
RA-related variable	–	1.31 (1.07–1.61)
CDAI, moderate or high		
M-HAQ DI >0.5	–	1.18 (0.95–1.46)
Prednisone use	–	1.61 (1.33–1.95)
Disease duration ≥10 years	–	1.43 (1.18–1.73)

* Values are the hazard ratio (95% confidence interval). Reference categories were ages 20–39 years, female sex, no diabetes, no hyperlipidemia, no hypertension, no current tobacco use, Clinical Disease Activity Index (CDAI)–defined remission or low disease activity, modified Health Assessment Questionnaire (M-HAQ) disability index (DI) ≤0.5, no prednisone use, and rheumatoid arthritis (RA) disease duration <10 years. FRS = Framingham Risk Score.

events, and the results remained similar (see Supplementary Table 3, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.39195/abstract).

Model fit metrics were calculated to compare the base risk model with the expanded risk model, using the internal validation cohort. Model discrimination, as measured by the c-statistic, improved significantly from the base model (c = 0.7261) to the expanded model (c = 0.7609; $P = 0.0104$) (Figure 1). In addition, the AIC estimate of model fit improved (from 1,383 to 1,358), and the Hosmer-Lemeshow goodness-of-fit tests also yielded favorable results ($P = 0.45$ in the base risk model and $P = 0.94$ in the expanded risk model), indicating adequate model calibration.

The total study cohort was used to derive a risk score based on the expanded model for the 10-year predicted probability of a CV event (Figure 2). Tables 3 and 4 show the 10-year predicted probabilities of CV risk compared with the observed event rates in each patient, with the 10-year predicted risk stratified using a 4-category risk tool (0 to <5%, 5% to <10%, 10% to <20%, and ≥20%) and a 2-category risk tool (0 to <7.5% and ≥7.5%), corresponding to the original Framingham Risk Score categories and the new ACC/AHA risk categories, respectively (27). When the 4-category and 2-category risk prediction tools were used to stratify patients into CV risk categories, the expanded risk score demonstrated significant improvement from the base model risk score in predicting the 10-year risk of CV events (NRI 40%, 95% CI 37–44% with the 4-category risk tool, and NRI 7%, 95% CI 6–8% with the 2-category risk tool) (Tables 3 and 4). Overall, in models using the 4 risk prediction categories, the CV risk was correctly classified in 17% more RA patients with the expanded model risk score as compared with the base model risk score. In models with 2 risk prediction categories, the risk of CV events was correctly classified in 10% more RA patients with the expanded model risk score compared with the base model risk score.

DISCUSSION

We have derived and validated an expanded risk score for CVD in RA (the ERS-RA). This newly developed expanded risk score is based on standard methods for improving risk models and mirrors what has been done in the general population for improving the Framingham Risk Score (29). In addition to the traditional CV risk factors (age, sex, presence of diabetes, presence of hypertension, presence of hyperlipidemia,

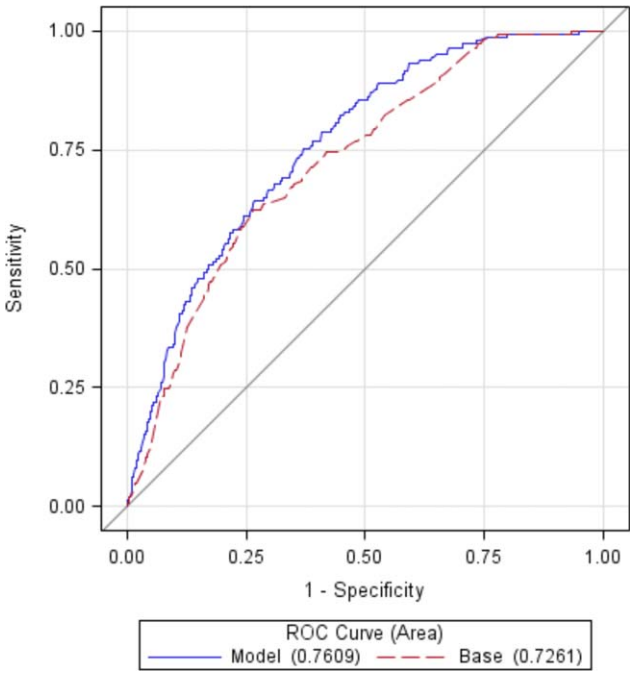

Figure 1. Area under the receiver operating characteristic (ROC) curves for predicting the risk of cardiovascular events in the internal validation cohort. The ROC curves demonstrate an improved discrimination of the expanded risk model (c-statistic 0.7609) compared with the base model (c-statistic 0.7261) ($P < 0.0001$).

Risk Factor	Acceptable Range	Current Profile	Comparative Profile
Age	20-80	55	55
Gender	M=Male, F=Female	F	F
Diabetes	Y=Yes; N=No	N	N
Hyperlipidemia	Y=Yes; N=No	N	N
Hypertension	Y=Yes; N=No	Y	Y
Current tobacco use	Y=Yes; N=No	N	N
CDAI	Y if CDAI>10; N if CDAI≤10	Y	N
M-HAQ DI > 0.5	Y if M-HAQ DI>0.50; N if M-HAQ DI≤0.5	Y	Y
Prednisone use	Y=Current Use; N=No Current Use	Y	N
RA Disease duration ≥ 10 y	Y if duration>10 yrs; N if duration≤10 yrs	Y	Y

Current Profile	The 10-Year ERS-RA risk score.	9.3
Comparative Profile	10-Year ERS-RA risk for a person with slightly different characteristics as the Current Profile.	4.5

Calculation of ERS-RA Risk Score

$$\text{10-yr cardiovascular risk (\%)} = \left[1 - 0.99395^{exp(B)}\right] * 100\%$$

where

B = 0.0343 (if Age ≥40 & Age≤44) +0.0801 (if Age ≥45 & Age≤49)
+ 1.2099 (if Age ≥50 & Age≤54) + 1.2977 (if Age ≥55 & Age≤59)
+ 1.5922 (if Age ≥60 & Age≤64) + 2.0880 (if Age ≥64 & Age≤69)
+ 2.2187 (if Age ≥70 & Age≤74) + 2.7600 (if Age ≥75)
+ 0.5525 (if Male) + 0.8686 (if Smoking)
+ 0.4207 (if Diabetic) + 0.3229 (if Dx hyperlipidemia)
+ 0.2056 (if Dx hypertension) + 0.3563 (if RA Duration>10 yrs)
+ 0.2776 (if CDAI>10) + 0.1644 (if mHAQ-DI>0.5)
+ 0.4758 (if using Prednisone)

Figure 2. The expanded risk model was used to estimate an expanded risk score in patients with rheumatoid arthritis (ERS-RA) based on the equation noted. In the ERS-RA Risk Score Calculator, risk factors refer to the variables used in the risk score, acceptable range refers to the acceptable values of the risk factors, current profile refers to the input values for a given patient, and the comparative profile refers to the input values for a patient with slightly different characteristics (to compare with the current profile). The ERS-RA Risk Score Calculator (http://www.brighamandwomens.org/Research/depts/Medicine/Rheumatology/Sect_Clinical_Sciences/ResearchFocus/ClinicalResearchTools.aspx?sub=0#cvd) is not intended to provide treatment recommendations; treatment decisions should be made by the relevant clinician and the patient. CDAI = Clinical Disease Activity Index; M-HAQ = modified Health Assessment Questionnaire; DI = disability index; Dx = diagnosis.

and tobacco use), we found that RA disease activity (moderate or high disease activity versus low disease activity or remission), disability (moderate or high disability versus low disability or none), daily prednisone use (any versus none), and disease duration (at least 10 years versus <10 years) contributed to a significantly improved model for the prediction of CV events. A risk score based on this expanded model demonstrated excellent model fit metrics and significantly improved the net reclassification of patients using either a 4-category or 2-category risk prediction tool at commonly used CV risk thresholds.

The ERS-RA builds on a large body of epidemiologic studies assessing clinical risk factors associated with CVD or CV events in RA (5,7–9). None of the RA-related variables found to be predictors were surprising, and they all added to the risk prediction of the expanded model. These variables are all simple to measure in the office setting. A web-based ERS-RA Risk Score Calculator (as shown in Figure 2) has been developed to facilitate use of the ERS-RA. Other CV risk scores have been proposed for RA cohorts, but none has been tested so rigorously or in such a large cohort with RA (18,19).

The ERS-RA should allow for more accurate risk stratification among patients with RA. The following implications of this strategy should be considered. First, more aggressive CV risk prevention strategies could be targeted to patients at moderate-to-high risk of CV events. Statin use has been suggested for patients with a 10-year predicted probability of a CV event of >7.5% in the new ACC/AHA recommendations (27). Alternatively, the 4-category risk tool used by the ATP III suggests the need for lipid-lowering treatment for patients with a 10-year predicted probability of CV events of 10% or higher (26).

Second, several of the risk factors in the ERS-RA are potentially modifiable targets for CVD prevention programs. These include tobacco cessation, lowering RA

Table 3. Reclassification of the predicted 10-year cardiovascular (CV) risk in patients with rheumatoid arthritis, stratified with the 4-category risk tool*

Predicted CV risk category in base model	Predicted CV risk category in expanded model				Total no. of patients with predicted events	No. (%) of patients with CV risk reclassified by expanded model
	<5% risk	5% to <10% risk	10% to <20% risk	≥20% risk		
<5% risk						
No. of patients with predicted events	4,628	340	0	0	4,968	340 (6.84)
Actual event rate†	2.16	8.82	0	0		
5% to <10% risk						
No. of patients with predicted events	1,942	3,703	938	0	6,583	2,880 (47.72)
Actual event rate†	2.06	12.15	20.26	0		
10% to <20% risk						
No. of patients with predicted events	0	1,484	3,648	863	5,995	2,347 (39.85)
Actual event rate†	0	7.41	13.35	46.35		
≥20% risk						
No. of patients with predicted events	0	0	1,532	4,493	6,025	1,532 (24.94)
Actual event rate†	0	0	28.72	45.63		

* Analyses compared the numbers of observed events with numbers of predicted events ascertained in the base model versus expanded model. Thirty-four patients with missing values for the modified Health Assessment Questionnaire disability index were not included in these analyses.
† Event rates are number of observed events per 1,000 person-years of followup, calculated by dividing the number of events by (participants × 10 years × 100 person-years).

disease activity, mitigation of RA disability, and cessation of corticosteroid use whenever possible. Although these are not new recommendations, the ERS-RA illustrates their importance.

Since the ERS-RA patient variables were assessed at baseline, several examples of RA case profiles could illustrate how the ERS-RA might be useful in managing clinical cases. Example 1 is a 55-year-old female RA patient having a disease duration of >10 years and receiving ongoing treatment with corticosteroids, with a history of hypertension, moderate disease activity, an M-HAQ DI >0.5, no diabetes, no hyperlipidemia, and no tobacco use. Running these characteristics through the ERS-RA (Figure 2) would give her a 10-year probability of a CV outcome of 9.3%. This exceeds the current ACC/AHA recommended threshold for starting a statin, which is a 10-year CV risk probability of 7.5%. However, if she did not take corticosteroids and/or had reduced disease activity (i.e., low disease activity or remission), her 10-year probability of a CV event would be 4.5%, below the threshold for statin consideration.

Table 4. Reclassification of the predicted 10-year cardiovascular (CV) risk in patients with rheumatoid arthritis, stratified with the 2-category risk tool*

Predicted CV risk category in base model	Predicted CV risk category in expanded model		Total no. of patients with predicted events	No. (%) of patients with CV risk reclassified by expanded model
	<7.5% risk	≥7.5% risk		
<7.5% risk				
No. of patients with predicted events	8,175	783	8,958	783 (8.74)
Actual event rate†	3.79	17.88		
≥7.5% risk				
No. of patients with predicted events	1,573	13,040	14,613	1,573 (10.76)
Actual event rate†	6.36	29.06		

* Analyses compared the numbers of observed events with numbers of predicted events ascertained in the base model versus expanded model. Thirty-four patients with missing values for the modified Health Assessment Questionnaire disability index were not included in these analyses.
† Event rates are number of observed events per 1,000 person-years of followup, calculated by dividing the number of events by (participants × 10 years × 100 person-years).

Example 2 is a 50-year-old male RA patient with a disease duration of ≤10 years and no corticosteroid use, having a history of hypertension, low disease activity, an M-HAQ DI >0.5, no diabetes, no hyperlipidemia, and no tobacco use. His 10-year probability of a CV outcome is 5% according to the ERS-RA (Figure 2). With a 10-year probability of <7.5%, he would not meet the ACC/AHA recommendations for use of a statin. Even if his disease duration was >10 years, his 10-year probability of a CV event outcome would still be 7%, below the threshold for statin initiation.

Third, patients at moderate–to-high risk of a CV event might be considered for enrollment into intervention trials, testing lifestyle modification or pharmacologic treatments. Intensive physical training to reduce disabilities may be useful in these groups. Although we did not find that baseline use of specific immunomodulatory agents was associated with CV risk, it is possible that ongoing treatment strategies (e.g., treat to target) might be useful to consider in targeted groups of patients with RA. Moreover, CV imaging tests (such as carotid ultrasound, coronary computed tomography or magnetic resonance imaging, or coronary flow reserve) or biomarker panels may help more precisely define an at-risk group of RA patients.

The current set of analyses has several strengths. The study is based on a large, prospectively collected cohort consisting of typical RA patients from across the US. Risk factors for CVD are routinely collected as part of the CORRONA registry. We included easy-to-collect variables as potential predictors, facilitating widespread use of the ERS-RA. The registry also prospectively collects CV outcome information and routinely confirms the events with each site. In approximately one-third of the cases, medical records were made available and a formal adjudication validated the events. The size of the cohort permitted us to derive and internally validate the expanded risk model. We also used standardized methods for deriving, validating, and testing the ERS-RA to allow for comparison with other CV risk scores (29,30,31). Finally, the inclusion of a marker of disease activity, the CDAI, corresponds to the current understanding that systemic inflammation underpins the excess CV risk observed in RA.

Several important limitations are worth noting. First, not all CV outcomes could be adjudicated, because of a lack of medical records. As we noted above, when records were available, 89.4% were definite or probable cases of a CV event.

Second, the data set did not contain information on actual lipid levels or blood pressure measurements, restricting our ability to calculate a Framingham Risk Score. We used dichotomous variables for noting whether hypertension or hyperlipidemia were present. This has been used successfully in other analyses (32). Although simplifying these parameters will likely reduce the ability of any prediction model to accurately predict observed events, it nevertheless provides easier application of such a model in a clinical setting.

Third, the validation of the ERS-RA occurred using the same data set as that used for its development. We followed standard methods for derivation and internal validation in a separate, randomly chosen subgroup, but further testing of the score in external data sets is imperative.

Fourth, we did not test novel serum biomarkers to improve prediction of CV risk in RA. Instead, the focus of this exercise was on risk factors that would be easy to collect in a physician's office, not requiring laboratory testing.

Fifth, these data may not extrapolate well to populations with different racial and ethnic backgrounds, or to health care systems with different RA treatment practices. However, we do show the importance of including RA risk factors for CV risk prediction, and this research lays the foundation of evaluating these risk factors in RA populations with different demographics.

Sixth, it may be that risk factors (or their weights) for CV events in RA may differ between patients with early disease and those with established disease. We did not explicitly test this issue, because there were relatively few events in subjects with early disease, but it would be worth examining in larger data sets.

Finally, because the majority of our population was followed up for ≤5 years, we had to make assumptions about the 10-year risk estimates. Other CVD risk scores have employed similar extrapolation (33), but it would be important to test these assumptions in populations with longer periods of followup.

In conclusion, we derived and validated an expanded risk score for CV events in RA. The ERS-RA had good model fit characteristics, and it improved risk prediction significantly over a base model with only traditional risk factors. This improvement was evident with the use of both the 4-category and 2-category risk prediction tools. If further validated, we anticipate that the ERS-RA may provide a system for targeted management of CVD in RA, an approach that may be more aggressive in some and perhaps less aggressive in others. It may also facilitate targeted intervention and diagnostic trials to continue to improve outcomes in RA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Solomon had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Solomon, Greenberg, Curtis, Farkouh, Tsao, Etzel.
Acquisition of data. Greenberg, Kremer, Etzel.
Analysis and interpretation of data. Solomon, Greenberg, Curtis, Liu, Farkouh, Tsao, Kremer, Etzel.

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