Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: A systematic review

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1. ABSTRACT

Objective: We performed a systematic review of the literature to describe current knowledge of cardiovascular risk prediction algorithms in rheumatic diseases.

Methods: A systematic search of MEDLINE, EMBASE, and Cochrane Central databases was performed. The search was restricted to original publications in English, had to include clinical cardiovascular events as study outcomes, assess the predictive properties of at least one cardiovascular risk prediction algorithm, and include patients with rheumatoid arthritis (RA), ankylosing spondylitis (AS), systemic lupus erythematosus (SLE), psoriatic arthritis (PsA) or psoriasis. By design, only cohort studies that followed participants for cardiovascular events were selected.

Results: Eleven of 146 identified manuscripts were included. Studies evaluated the predictive performance of the Framingham Risk Score, QRISK2, SCORE, Reynolds Risk Score, PCE, Expanded cardiovascular Risk Score for RA (ERS-RA), and the Italian Progetto CUORE score. Approaches to improve predictive performance of general risk algorithms in RA patients included the use of multipliers, biomarkers, disease-specific variables, or a combination of these to modify or develop an algorithm. In both SLE and PsA patients, multipliers were applied to general risk algorithms. In studies of RA and SLE patients, efforts to include non-traditional risk factors, disease-related variables, multipliers and biomarkers largely failed at substantially improving risk estimates.

Conclusion: Our study confirmed that general risk algorithms mostly underestimate and at times overestimate cardiovascular risk in rheumatic patients. We did not find studies that evaluated models for psoriasis or AS, which further demonstrates a need for research in these populations.

2. INTRODUCTION

Chronic inflammatory rheumatic diseases (IRDs) are associated with significant cardiovascular (CV) morbidity and mortality (1, 2). Patients with rheumatoid arthritis (RA) (3-5), systemic lupus erythematosus (SLE) (6-10), ankylosing spondylitis (AS) (11-14), psoriasis (15, 16) and psoriatic arthritis (PsA) (17-21) have an increased CV risk compared to the general population, which is attributed to a combination of systemic inflammation and high prevalence of traditional risk factors.

Cardiovascular risk prediction algorithms provide an important tool for clinicians to estimate patients' risk of developing future CV events. Based on the estimated risk, patients are stratified into risk groups, thereby allowing for preventive interventions to be appropriately targeted to those patients who are most likely to benefit. Therefore, precise estimates of CV risk are desirable and could lead to more effective health care delivery, ultimately resulting in decreased CV morbidity and mortality. Several CV risk prediction algorithms have been developed for use in the general population. These algorithms estimate the expected CV risk using various combinations of traditional CV risk factors. The Framingham Risk Score (FRS), one of the most widely used algorithms, was developed and validated in an American cohort to calculate the ten-year risk of CV disease and was most recently updated in 2008 (22, 23). The Systematic Coronary Risk Evaluation (SCORE) algorithm was developed and validated in twelve European cohorts to predict the ten-year risk of CV mortality (24). In 2013, the American College of Cardiology and American Heart Association released the Pooled Cohort Equations (PCE) (25). The PCE was derived from large racially and geographically diverse cohort studies to predict ten-year risk of atherosclerotic CV disease events. Unlike these scores, which are based solely on traditional risk factors, the QRISK2 algorithm includes RA as an independent risk factor(26).

Similarly, the Reynolds Risk Score (RRS) incorporates the inflammatory marker C-reactive protein (CRP) in addition to traditional risk factors (27, 28).

The performance of these algorithms in IRDs is suboptimal because traditional CV risk factors do not fully explain the increased CV risk in rheumatic patients, and current risk algorithms do not represent other contributing factors, thereby underestimating the actual CV risk (29). In an attempt to address these limitations, the 2016 European League Against Rheumatism (EULAR) recommendations for CV risk management proposed to apply a 1.5 multiplier to any calculated CV risk score to accommodate the risk (30).

The accuracy of these risk algorithms in predicting future CV events has not been summarized in IRDs. Therefore, the aims of this systematic review were (1) to describe current knowledge of CV risk prediction algorithms in patients with IRDs, and (2) to identify approaches to improve CV risk stratification. The results of this review could identify current knowledge gaps and inform the development of novel risk prediction algorithms.

3. METHODS

Study protocol

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to conduct our review and analysis. We searched OVID Medline (1946 to October 30, 2017), OVID Embase (1947 to October 30, 2017), and Cochrane Central Register databases using a search strategy developed by an experienced academic health sciences librarian (APA) with input from the study leads. The search strategy (Supplementary Data 1) was limited to English publications in humans.

Eligibility criteria and study selection

To be included in the systematic review, original studies needed to fulfill the following inclusion criteria: **study design:** retrospective or prospective cohort; **population:** psoriasis, PsA, AS, RA or SLE; **study outcome:** myocardial infarction, stroke, transient ischemic attack, angina, ischemic heart disease, heart failure, cardiovascular death; **predictive ability:** evaluated predictive performance of a CV risk prediction algorithm using relevant statistics.

Titles and abstracts were initially screened by two reviewers (KC and VO) for potential inclusion. Selected publications were retrieved in full, and two reviewers (KC and VO) independently assessed them for eligibility; upon disagreement, a final decision was reached through discussion with a third reviewer (LE).

Data were independently extracted by two reviewers (KC and VO) according to a standardized form and summarized in tables. For each study, the following information was recorded: year of publication, disease, study location, study duration, mean age, sex, data source, sample size, incidence rate of CV events, evaluated predictors, type of CV outcomes, case definition, and performance of risk score.

Risk of bias in individual studies

For assessing methodological quality and risk of bias in cohort studies, the Newcastle-Ottawa Scale was used. This tool uses a star system to judge studies on three broad perspectives: the selection of study groups; the comparability of the groups; and the ascertainment of the outcome of interest. The highest quality studies are awarded up to nine stars. We decided to rate studies as low risk of bias if they received nine stars, moderate risk of bias if they received seven or eight stars, and high risk of bias if they received less, as no explicit guidance exists.

4. RESULTS

An initial search identified 12,099 entries, of which 146 articles were retrieved for review (Figure 1). After reviewing the manuscripts, 137 were excluded for the following reasons: 121 used at least one CV risk prediction algorithm but did not evaluate its predictive performance, 10 were the wrong study type (e.g. case-control, cross-sectional), and 6 did not report clinical CV events. During the preparation of the manuscript we identified two additional articles (31, 32) that met the inclusion criteria, however, since they were published in 2018 they were not included in the initial search results. We added these articles to the list of publications included in this review. Thus, a total of 11 studies (9 RA, 1 SLE, 1 PsA) were included in this review. The study characteristics and major findings are summarized in Tables 1 and 2.

Rheumatoid Arthritis

The performance of existing risk scores in predicting CV risk varies in different studies. Crowson et al. (33) found that the observed CV risk was 1.8 times higher than the predicted risk by FRS. The discrepancy was particularly high in women, seropositive patients and those with persistently elevated inflammatory markers. The RRS, which includes CRP in addition to traditional CV risk factors, showed similar deficits (33). In contrast, a recent publication from a large international cohort showed a tendency of existing risk scores, including FRS, and QRISK2 to overestimate CV risk, while the RRS underestimated CV risk (34). QRISK2 also overestimated risk in a Dutch cohort, whereas application of the FRS, RRS and SCORE led to underestimations (35).

Several approaches for improving CV risk prediction in patients with RA were assessed. The first approach included applying a multiplication factor to existing risk scores or recalibration of these scores by applying different weights to their components. This approach was evaluated in 3 studies (33, 34, 36). In a population-based study of the Rochester Epidemiology Project, a

multiplication factor of 1.8 was applied to the FRS in an attempt to improve model performance (33). Although this adjustment improved calibration (the agreement between observed and predicted CV risk) for patients with moderate CV risk, it had no effect on overall discrimination (correct classification of patients into the event and the non-event groups). The application of the EULAR multiplier to the FRS and PCE in an international multi-centre study resulted in overestimation of future CV risk and did not improve discrimination, as measured by c-statistics, compared to the existing risk scores (34). Arts et al. (36) evaluated the performance of a recalibrated version of SCORE by adjusting the weights of predictors originally included in SCORE. After the recalibrated SCORE was analyzed in their Dutch cohort, there was no improvement in discrimination. In fact, the reweighted traditional risk factors underestimated CV risk across all risk groups.

A second approach, performed in a Swiss cohort (37), included addition of autoantibodies and biomarkers of inflammation to the FRS. While the predictive ability of CRP, IgM-RF, anti-CCP, ox-LDL and NT-proBNP was modest, only anti-Apo A-I substantially enhanced the discrimination of the FRS. This led to a significant increase in AUC from 0.72 for FRS alone to 0.81 for the FRS and anti-Apo A-I combined, corresponding to a relative increase in integrated discrimination improvement (IDI) of 175%. Combining all biomarkers did not result in improvement, compared to the combination of FRS and anti-Apo A-I alone. However, it should be noted that the assessments of predictive ability of the combined models were not adjusted to the time at risk and that the duration of follow-up varied across study patients (interquartile range 5 to 15 years).

In a third approach, two studies added disease-specific variables to general risk scores (36, 38). Alemao et al (38) evaluated the addition of CRP to two existing risk scores, FRS and QRISK2,

in a population-based cohort of patients with RA from the UK. Although CRP was associated with an increased CV risk when added to the FRS (12% increase in hazard ratio), the addition of CRP as a predictor to both models resulted in subtle improvements in discrimination that were clinically insignificant. In addition, reclassification using the FRS was characterized by a non-significant improvement, and a worsening of reclassification by QRISK2. In the second study utilizing a Dutch cohort, the original SCORE was adapted with the addition of both traditional and disease-specific risk factors (36). The adapted SCORE showed a subtle improvement in discriminatory ability compared to the original SCORE which was not significant. Furthermore, it did not lead to a significant improvement in reclassification of patients into risk groups that better matched their actual CV risk. When the adapted SCORE was evaluated in external cohorts from the United Kingdom and Norway, the discriminatory ability of the adapted model was worse than the original SCORE.

Two studies attempted to derive new RA-specific risk algorithms using traditional CV risk factors and RA characteristics (39, 40). The ERS-RA was developed and internally validated using a large patient registry in the USA (39). The score was derived from a base model, which included only traditional CV risk factors and an expanded model which evaluated RA- and non-RA related variables. The addition of measures of RA disease activity (Clinical Disease Activity Index), disability (modified Health Assessment Questionnaire disability index), daily prednisone use, and disease duration (>10 years) contributed to a significantly improved model, demonstrating a significant improvement in discrimination with adequate model calibration (improvement in c-statistics from 0.73 in the base model to 0.76 in the expanded model). The ERS-RA significantly improved the net reclassification of patients using both the FRS and PCE with reclassification of 17% and 10% of the patients, respectively, reclassified to the correct risk

categories in the expanded model. However, in a recent study Crowson et al (34) found that the ERS-RA overestimated CV risk in a large international cohort and that its discriminatory ability was inferior to that of general risk scores including QRISK2, FRS, PCE and RRS. External validation of the ERS-RA in Swedish cohorts demonstrated good discriminatory capability, and overestimation of risk in the highest risk groups was observed. However, no comparisons were made to general risk scores (32).

The second study attempting to derive a RA-specific risk score included several international longitudinal cohorts. Crowson et al (40) assessed two models that included traditional risk factors along with either HAQ or DAS28. Neither of these models demonstrated improved discrimination compared to general risk scores including FRS, PCE, SCORE or QRISK2 (c-statistics ranged from 0.70 to 0.72). Although the RA-specific models showed better calibration than the general risk scores, this may be explained by the fact that calibration is expected to be better in the cohort used to develop the new risk score than the general scores developed in other models. The developed models also significantly overestimated CV events.

Systemic Lupus Erythematosus

In the study that followed patients seen at the University of Toronto Lupus Clinic since 1970, the FRS was compared to a modified FRS with four multiplication factors (range 1.5 to 4) (41). A multiplier of 2 predicted CV risk more accurately than the original FRS (20% vs. 2.9% risk, respectively), and most appropriately categorized patients with moderate/high risk with sufficient sensitivity and specificity. The sensitivity and specificity for FRS (moderate/high risk vs. low risk) to predict cardiovascular events were 6.8 and 98.1, respectively, whereas the sensitivity for the FRS with a multiplication factor of 2 increased to 34.5 with a modest reduction in specificity

to 84.4, respectively. The study did not compare global measures of model predictive ability between the models (e.g. AUC).

Psoriatic Arthritis

In a small Italian cohort of patients with PsA, five general risk scores (FRS, SCORE, QRISK2, RRS and CUORE) were adapted to EULAR recommendations by adding a 1.5 multiplier or including weight adaptation for RA in QRISK2 (31). The five algorithms underestimated CV risk, and the adaptation suggested by EULAR did not increase the discriminative ability or calibration of any of the evaluated algorithms. Overall, the original risk scores demonstrated relatively good discrimination between patients with or without CV events, with a range of AUC between 0.718 (for RRS) and 0.866 (for QRISK2).

Quality Assessment

One study had low risk of bias, six studies had moderate risk of bias, and two studies had high risk of bias (Table 3). In one study, it was unclear whether participants with a history of CV disease were excluded from analysis (38). There was limited information on how CV events were ascertained in three studies (34, 40, 41). Due to the limited number of studies included in this review, those with lower scores were not excluded from the quality assessment.

5. DISCUSSION

There are several challenges associated with deriving and validating disease-specific algorithms or modifying existing general risk scores to improve risk prediction and stratification. This study identified potential predictors of future CV events that warrant further investigation.

Most studies evaluated performance using clinical variables rather than novel laboratory biomarkers, which may be more difficult to implement in a clinical setting. Findings by Finckh

et al (37) that anti-Apo A-1 significantly improved the predictive accuracy of the FRS demonstrates its potential as a clinically useful CV biomarker, as it is easily measurable and may assist in identification of high risk RA patients (42). Anti-Apo A-I antibodies and NT-proBNP have been found to be associated with increased atherosclerotic plaque vulnerability and cardiac ischemia, respectively (43-45). Other risk markers have shown promise in improving risk discrimination in rheumatic patients. Several non-invasive imaging techniques, including carotid ultrasound (29, 46, 47) and coronary artery calcium (CAC) quantification by computed tomography, have identified markers for determining subclinical atherosclerosis. In RA, carotid atherosclerosis as assessed by ultrasound was found to predict CV events in patients with greater carotid intima-media thickness and in those with bilateral plaques (48). In RA patients stratified according to a modified SCORE, carotid ultrasound was sensitive to detect patients at moderate risk (1-5%) (49). When compared to CAC, carotid ultrasound was found to be more sensitive in the stratification of CV risk (50), and similar results were reported in an axial spondyloarthritis group (51). These results highlight the potential use of carotid ultrasound for improving CV risk stratification in rheumatic patients and encourage further research of this tool in combination with traditional risk scores.

Multipliers have been widely applied to general risk calculators so that they more accurately reflect the effect of each variable in the algorithm while retaining their relative value. Despite EULAR's recommendation (30), recent studies show that applying the multiplication factor does not significantly improve risk prediction (31, 36). In addition, application of the multiplier reduced calibration without improving discrimination or reclassification to the correct CV risk category in RA patients (34). Similar results were found in patients with PsA, where the EULAR multiplier failed to demonstrate improvement in both discrimination and calibration for any of

the five evaluated general risk scores(31). On the other hand, Urowitz et al (41) applied a factor of 2 to the FRS which improved the accuracy of classified SLE patients at moderate/high risk. It should be noted that even after this adaptation, the sensitivity to identify high-risk individuals was only approximately 30% and the study did not assess measures of discrimination and calibration of the suggested adaptation. Whether these results have a similar effect in other SLE populations is questionable, given that the FRS variables were not recalibrated to SLE and retained the same weights derived from the general population. Although multipliers can be used as a means to improve risk prediction, they would improve calibration, but not discrimination, resulting in a missed opportunity to intervene early (33).

Four RA studies included either inflammatory biomarkers, disease-specific variables or a combination of both to modify or develop an algorithm (36, 38-40). The only algorithm to significantly improve predictive performance was the ERS-RA, which could be readily applied to a clinical setting. The ERS-RA does not incorporate novel serum biomarkers, but its use of the CDAI, a composite measure of disease activity, may be representative of systemic inflammation underlying the excess CV risk seen in RA. However, the ERS-RA may lead to inaccuracies in estimation of risk. The score was developed using registry data that did not contain lipid levels or blood pressure measurements, and included a population with a mean follow up rate of less than 3 years. When the ERS-RA was evaluated in an international multi-centre cohort study, it overestimated risk and produced lower risk estimates than current risk algorithms (34). However, it performed well in a Swedish cohort and showed excellent calibration for patients with 5-10% 10-year CV risk, but analyses included partial data on smoking status (32). The CV risk profile of the American cohort in which the ERS-RA was derived and internally validated may be generalizable to other non-American cohorts.

This study identified one disease-specific algorithm (ERS-RA), and its performance varied after being externally validated in Swedish and international cohorts. Further validation and tailoring of the ERS-RA to specific populations is needed before recommendations can be made. Our review also affirmed that general risk algorithms do not perform well in rheumatic patients. These models were largely derived in cohorts established in the late twentieth century when participants were less socioeconomically and ethnically diverse, and CV event rates were more than double the current rates (52). Only the QRISK equations are regularly updated in modern cohorts and include several predictors, including deprivation measures, but their applicability outside the UK is limited (52). Though it is possible to update existing algorithms, this approach has limitations. Yadlowsky et al. evaluated two approaches for improving the PCEs: using the PCE with updated cohort data and using both updated data and new derivation methods (53). The first approach modestly improved discrimination, whereas the second approach improved both calibration and discrimination. Most general risk algorithms are also likely to be out-of-date due to major changes in preventive treatments over recent decades (52, 54). Among the risk-factor-modifying drugs, statins have been recently studied in rheumatic patients due to their lipid-lowering effects and anti-inflammatory properties. A randomized trial of patients with RA found that the addition of statins to disease-modifying antirheumatic drug treatment improved disease parameters, such as swollen joint count, and inflammatory markers (55). However, a separate trial in RA showed that statins had no effect on disease activity (56). A recent randomized trial was initiated to examine the impact of atorvastatin in preventing CV events in RA patients, but the trial was terminated early due to a low event rate (57). Other recently published studies also highlight the role of statins in carotid plaque regression (58) and mortality reduction (59, 60) in

RA, AS and PsA. The lack of account for treatment effect can cause difficulties in the use of CV risk algorithms and underestimation of CV risk. Ideally, risk algorithms should be derived from populations free of treatment. With respect to outcome definitions, most algorithms predicted the risk of fatal or non-fatal coronary heart disease or the combined outcome of CV disease. Since different definitions of CV outcomes lead to different estimated predictor effects, international consensus on a more uniform definition is necessary to aid comparison of developed risk algorithms. Given the challenges associated with using outdated cohort data, increased use of preventive therapy for CV events, and variation in outcome definitions, it is not possible to recommend a general risk algorithm for rheumatic patients.

It appears that subclinical vascular disease is not accurately reflected in risk algorithms, leading to underestimated CV risk and preventable CV events (61-63). We suggest that measures of subclinical vascular disease be used to improve risk estimates beyond models that use traditional CV risk factors alone. Carotid ultrasonography or CAC may optimize CV risk estimation and aid in more accurate CV risk stratification. Additional predictors, including measures of ethnicity and socioeconomic status, are also needed to avoid undertreatment of high-risk groups. Although recalibration is likely to reduce overtreatment, general risk algorithms will continue to underperform in rheumatic patients. Unless risk of CV disease is estimated using algorithms derived or recalibrated in present-day populations that represent the patients they are applied to, under- or overestimation of risk is likely to persist.

Our study confirmed that general risk algorithms mostly underestimate and at times overestimate CV risk in rheumatic patients and the excess CV risk in these patients cannot be explained by

traditional risk factors alone. Efforts to include non-traditional risk factors, disease-related variables, multipliers, and biomarkers largely failed at substantially improving risk estimates. Rather than recalibrating general risk algorithms, future research should place more emphasis on developing new models and identifying new disease-specific predictors. With respect to the ERS-RA, further validation and recalibration to target populations is needed before recommendations can be made for use in patients with RA.

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8. Figure Legend

Figure 1 - PRISMA diagram for systematic literature review and Meta Analysis. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PloS Med 2009;6(7):e1000097. Distributed under the terms of the Creative Commons Attribution License.

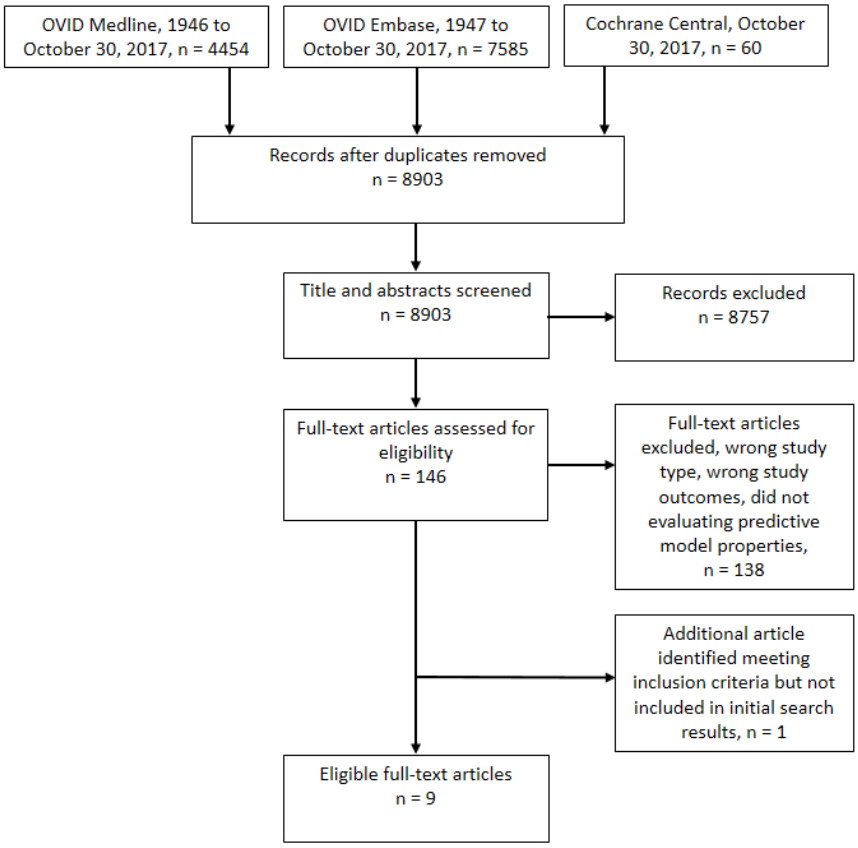

Figure 1. PRISMA diagram for systematic literature review and Meta Analysis. PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses. From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA statement. PloS Med 2009;6(7):e1000097. Distributed under the terms of the Creative Commons Attribution License.

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Table 1. Characteristics of the studies included in the systematic review

Author and Year	Disease	Country	Mean Follow-up, years (inclusion years)	Mean age (years)	Males (%)	Data source	Sample size (number of events)	Incidence rate of CV events (per 100 patient years)	Evaluated predictors	Outcomes	Outcome ascertainment	Model properties statistics
Alemao 2017	RA	UK	6.0 (1997-2010)	58.5	29 (RA), 31.6 (non-RA)	Patient registry	12,747	RA: 4.29 (FRS), 1.78 (QRISK2) Non-RA: 3.1 (FRS), 1.3 (QRISK2)	FRS: All traditional risk factors, except dyslipidemia QRISK2: All traditional risk factors, except dyslipidemia, obesity, atrial fibrillation, renal disease	FRS: MI, stroke, HF, aortic aneurysm, TIA, unstable angina, IC. QRISK: MI, CHD, stroke, TIA	ICD code	C-statistic, NRI
Arts 2015	RA	Netherlands	1985/1990 to 2011	54 (without CVD event =	34	Patient registry	1,157 (149)	1.14	FRS, SCORE, RRS (excluding	ACS, angina,	Chart review	C-statistic, sensitivity,

				53; with CVD event = 61)					hsCRP), QRISK2	CVA, TIA, PVD, HF		specificity, PPV, NPV
Arts 2016	RA	Netherlands	N/A (1985-2011)	54 (without CVD event =53; with CVD event =62)	33.7	Patient registry	1,016 (103)	N/A	SCORE vs. mSCORE (smoking status, systolic BP, TC:HDL ratio, BMI, diabetes mellitus, hypertension, DAS28)	ACS, CVA, HF, CV death	Chart review	C-statistic
Crowson 2012	RA	USA	8.4 (1988-2008)	57	31	Population administrative data	525 (84)	N/A	mFRS (1.8 multiplication factor), FRS, RRS	MI, CV death, angina, stroke, IC, HF	ICD code, Chart review	C-statistic
Crowson 2017[40]	RA	UK, Norway, Netherlands, USA,	5.8 (1985-2014)	55	24	Several international	5,638 (389)	1.3% / year	Model A (with DAS28ESR), Model B (with HAQ), FRS,	ACS, chronic ischemic heart	N/A	C-statistic

		Sweden, Greece, South Africa, Spain, Canada, Mexico				patient registries			PCE, QRISK2, SCORE Age, sex, hypertension, current smoker, TC:HDL ratio, DAS28ESR, HAQ	disease, coronary revascularization, coronary death, other CV death, cerebrovascular events, peripheral vascular events		
Crowson 2017[34]	RA	UK, Norway, Netherlands, USA, South Africa, Canada, Mexico	6.9 (1985-2013, varies based on cohort)	54	26	Several international patient registries	1,796 (100)	0.8	QRISK2, EULAR, multiplier, and ERS-RA, versus PCE, FRS-ATP, and RRS	MI, ischemic stroke, CV death	N/A	C-statistic, NRI
Finckh 2012	RA	Switzerland	9	77 (MACE);	42 (MACE); 23	Patient registry	118 (19)	1.70	FRS, mFRS (CRP, RF, anti-CCP, ox-	ACS, stroke	Chart review	C-statistic, IDI

				64 (No MACE)	(No MACE)				LDL, NT-proBNP, anti-Apo A1)			
Ljung 2018	RA	Sweden	2.4-7.6 (2006-2015); varies based on cohort	54.9-61.2	25.8-28.3	Patient registry	Cohort 1: 20,822 (2017); Cohort 2: 2047 (136); Cohort 3: 15,575 (427)	N/A	ERS-RA	MI, stroke, CV death	ICD code	C-statistic
Navarini 2018	PsA	Italy	N/A	48	39	Patient registry	155 (21)	1.35	FRS, QRISK2, RRS, SCORE, CUORE, EULAR multiplier	CV death, CAD (stable and unstable angina, MI), CVA, TIA, PAD, HF	Chart review	C-statistic, sensitivity, specificity, PPV, NPV
Solomon 2015	RA	USA	2.9 (2001-2011)	57	22	Patient registry	23,605 (161)	2.5 (MI), 3.0 (stroke), 1.0 (CV death)	FRS, PCE, ERS-RA (CDAI, m-HAQ DI, prednisone	MI, stroke, CV death	Chart review	C-statistic, NRI

									use, disease duration)			
Urowitz 2016	Lupus	Canada	9.0 (1970-present)	43.7 (part 1) 42.4 (part 2)	10.1 (part 1), 10.9 (part 2)	Patient registry	1,013 (95)	N/A	FRS (age, sex, disease duration, hsCRP, smoking, blood pressure, cholesterol, HDL), SLEDAI-2K	CAD = MI, angina, sudden death	N/A	Sensitivity, specificity

ACS: acute coronary syndrome; anti-CCP: anti-cyclic citrullinated peptide; anti-Apo A1: anti-apolipoprotein A1; BMI: body mass index; CAD: coronary artery disease; CHD: coronary heart disease; CDAI: clinical disease activity index; CRP: C-reactive protein; CV: cardiovascular; CVD: cardiovascular disease; CVA: cerebrovascular accident; DAS28: disease activity score-28 for rheumatoid arthritis; DAS28ESR: disease activity score-28 for rheumatoid arthritis with erythrocyte sedimentation rate; ERS-RA: expanded cardiovascular risk score for rheumatoid arthritis; EULAR: European League Against Rheumatism; FRS: Framingham Risk Score; FRS-ATP: Framingham Risk Score in Adult Treatment Panel; HAQ: health assessment questionnaire; HDL: high-density lipoprotein; HF: heart failure; IC: intermittent claudication; ICD: International Classification of Diseases; IDI: integrated discrimination improvement; MACE: major adverse cardiovascular event; mFRS: modified Framingham Risk Score; m-HAQ DI: modified health assessment questionnaire disability index; MI: myocardial infarction; mSCORE: modified systematic coronary risk evaluation; NPV: negative predictive value; NRI: net reclassification improvement; NT-proBNP: N-terminal pro-brain natriuretic peptide; ox-LDL: oxidized low-density lipoprotein; PAD: peripheral artery

disease; PCE: American College of Cardiology/American Heart Association Pooled Cohort Equation; PsA: psoriatic arthritis; PPV: positive predictive value; RA: rheumatoid arthritis; RF: rheumatoid factor; RRS: Reynolds Risk Score; SCORE: Systematic Coronary Risk Evaluation; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000; TC: total cholesterol; TIA: transient ischemic attack.

Table 2 – Summary of Results of studies included in the systematic review

Author (year)	Objective(s)	Evaluated Algorithms	C-statistics	Other statistics	Major findings
Alemao 2017	To compare the performance of FRS and QRISK2 in RA and matched non-RA patients and to evaluate whether their performance could be enhanced by the addition of CRP	FRS	0.764	**FRS + CRP:** NRI = 3.2% (95% CI: -2.8, 5.7%)	• The FRS and QRISK2 underestimated CV risk • Discrimination of both the FRS and QRISK2 was lower in the RA population compared to the general population. • The addition of CRP to both risk scores was not associated with a significant improvement in reclassification of CV risk.
		FRS + CRP	0.767		
		QRISK2	0.764	**QRISK2 + CRP:** NRI = -2.0% (95% CI: -5.8, 4.5%)	
		QRISK2 + CRP	0.765		
Arts 2015	To assess the predictive ability of 4 established cardiovascular (CV) risk	FRS	0.80		• The FRS, RRS and SCORE underestimated risk of future CV events, while QRISK2 overestimated risk.
		QRISK2	0.79		

	models for the 10-year risk of fatal and non-fatal CV diseases in European patients with RA	RRS	0.78		
		SCORE	0.78		
Arts 2016	To adapt SCORE with determinants of CV risk in RA patients and to compare the performance of the modified SCORE to the original SCORE with regard to CV risk prediction in RA patients	SCORE	0.78		• The original and adapted SCORE underestimated risk in low- and moderate-risk groups, and overestimated risk in high-risk groups • The recalibrated SCORE underestimated risk in all risk groups • Recalibrated and adapted SCORE models do not provide sufficient improvement in risk estimates compared to the original SCORE.
		Recalibrated SCORE	0.78		
		Adapted SCORE	0.80		
Crowson	To assess the accuracy	FRS (overall)	0.786		

2012	of the FRS and RRS for predicting CV events in RA patients	FRS (low risk)	0.562		• The FRS significantly underestimated CV risk (especially in older ages, patients with positive RF, and those with persistently elevated ESRs). • In an attempt to improve calibration, FRS was multiplied by 1.8 and had no effect on discrimination. • The RRS underestimated risk in women, despite inclusion of CRP.
		FRS (intermediate risk)	0.505		
Crowson 2017[40]	To develop a CV risk calculator for patients with RA	Model A [DAS28ESR]	0.70		• The developed models, SCORE and QRISK2 overestimated CV risk, while the FRS and PCE underestimated risk in the highest risk groups. • Neither developed model (with the addition of HAQ and DAS28ESR) demonstrated improved performance compared to general calculators (FRS, ACC/AHA PCE, SCORE, QRISK2).
		Model B [HAQ]	0.71		
		FRS	0.71		
		PCE	0.72		
		SCORE	0.70		
		QRISK2	0.72		

Crowson 2017[34]	To externally validate risk algorithms recommended for use in patients with RA including the EULAR 1.5 multiplier, the ERS-RA and QRISK2	ERS-RA	0.69	**ERS-RA vs. PCE:** NRI = -0.8% (95% CI: -8.2, 7.1)	• RRS underestimated CV risk • QRISK2, FRS, and ACC/AHA PCE significantly overestimated CV risk • ERS-RA overestimated CV risk, but it was less pronounced than the other risk algorithms • RA-specific risk calculators (EULAR multiplier, ERS-RA, QRISK2) did not predict cardiovascular disease more accurately than general population risk calculators (FRS-ATP, ACC/AHA PCE, RRS).
		QRISK2	0.72		
		RRS	0.72		
		FRS-ATP	0.75	**ERS-RA vs. FRS:** NRI = 2.3% (95% CI: -8.3, 26.6)	
		FRS-ATP + EULAR multiplier	0.75		
		PCE	0.72	**QRISK2 vs PCE:** NRI = -2.4% (95% CI: -10.9, 6.5)	
		PCE + EULAR multiplier	0.72		

				QRISK2 vs. FRS: NRI = 25% (95% CI: -9.4, 34.7)	
Finckh 2012	To determine whether including CV biomarkers offers added predictive ability over the established FRS for CV risk prediction in patients with RA	FRS + CRP	0.73	**FRS + anti-Apo A1:** IDI = +175.4% (p=0.01)	NT-proBNP was moderately predictive of subsequent MACE, but did not substantially improve predictive ability of traditional risk factors. Only anti-Apo A1 substantially enhanced the discrimination of the FRS (improvement in AUC +0.09).
		FRS + RF	0.73		
		FRS + anti-CCP	0.76		
		FRS + ox-LDL	0.73		
		FRS + NT-proBNP	0.76		
		FRS + anti-Apo A1	0.81		
Ljung 2018	To perform an external validation of the ERS-RA in a Swedish cohort of	ERS-RA (Cohort 1)	0.78		• The ERS-RA had good discriminatory capability, but underestimated the 10-year CV risk in high-risk groups and in the
		ERS-RA (Cohort 2 – including smoking	0.77		

	patients with RA	data)			absence of data on smoking.
		ERS-RA (Cohort 2 – excluding smoking data)	0.75		
		ERS-RA (Cohort 3)	0.76		
Navarini 2018	To evaluate the performance of FRS, SCORE, QRISK2, RRS, and CUORE, and adapt them to EULAR guidelines in patients with PsA	SCORE	0.7679		• All evaluated algorithms underestimated CV risk. • The EULAR multiplier did not increase the discriminative ability or calibration of any of the evaluated algorithms.
		SCORE + EULAR multiplier	0.7679		
		CUORE	0.864		
		CUORE + EULAR multiplier	0.8648		
		FRS	0.7575		
		FRS + EULAR multiplier	0.7584		
		QRISK2	0.8660		
		QRISK2 + EULAR	0.8664		

		multiplier			
		RRS	0.7183		
		RRS + EULAR multiplier	0.7183		
Solomon 2015	To develop and internally validate an expanded CV risk prediction score for RA	Base algorithm	0.7261	**Base model vs. ERS-RA (FRS)**: NRI = 40% (95% CI: 37, 44%)	• Model discrimination improved significantly from the base model to the expanded model (ERS-RA). • RA disease activity, disability, daily prednisone use and disease duration contributed to a significantly improved model.
		Developed algorithm (ERS-RA)	0.7609	**Base model vs. ERS-RA (PCE)**: NRI = 7% (95% CI: 6, 8%)	

Urowitz 2016	To determine whether an adjustment to the FRS would more accurately reflect the higher prevalence of coronary artery disease among patients with lupus.	FRS	N/A	Sensitivity: 13.0 Specificity: 98.2	• Applying a multiplication factor of 2 to the FRS more accurately identified patients at moderate/high risk of coronary artery disease and more accurately predicts subsequent coronary artery disease.
		1.5 FRS		Sensitivity: 19.7 Specificity: 89.4	
		2 FRS		Sensitivity: 31.5 Specificity: 80.9	
		3 FRS		Sensitivity: 45.5 Specificity: 72.0	
		4 FRS		Sensitivity: 46.1 Specificity: 68.8	

anti-CCP: anti-cyclic citrullinated peptide; anti-Apo A1: anti-apolipoprotein A1; CRP: C-reactive protein; CV: cardiovascular; DAS28ESR: disease activity score-28 for rheumatoid arthritis with erythrocyte sedimentation rate; ERS-RA: expanded cardiovascular risk score for rheumatoid arthritis; EULAR: European League Against Rheumatism; FRS: Framingham Risk Score; FRS-ATP: Framingham Risk Score in Adult Treatment Panel; HAQ: health assessment questionnaire; IDI: integrated discrimination improvement; MACE: major adverse cardiovascular event; NRI: net reclassification improvement; NT-proBNP: N-terminal pro-brain natriuretic peptide; ox-LDL: oxidized low-density lipoprotein; PCE: American College of Cardiology/American Heart Association Pooled Cohort Equation; PsA: psoriatic arthritis; RA: rheumatoid arthritis; RF: rheumatoid factor; RRS: Reynolds Risk Score; SCORE: Systematic Coronary Risk Evaluation.

Table 3. Newcastle-Ottawa Quality Assessment Scale for Cohort Studies

Source	Selection (4 stars)	Comparability (2 stars)	Outcome (3 stars)	Score (9 stars)	Risk of bias
Alemao 2017	★★★	★★	★★★	8	Moderate
Arts 2015	★★★	★★	★★	7	Moderate
Arts 2016	★★★	★★	★★	7	Moderate
Crowson 2012	★★★★	★★	★★★	9	Low
Crowson 2017[38]	★★★	★★	★	6	High
Crowson 2017[33]	★★★	★★	★	6	High
Finckh 2012	★★★	★★	★★	7	Moderate
Ljung 2018	★★★★	★★	★★★	9	Low
Navarini 2018	★★★	★★	★★	7	Moderate
Solomon 2015	★★★	★★	★★★	8	Moderate
Urowitz 2016	★★★★	★★	★★	8	Moderate

Risk of bias was assessed using the Newcastle-Ottawa scale. Studies were judged on three broad perspectives: the selection of study groups; the comparability of the groups; and the ascertainment of the outcome of interest for cohort studies. A study is awarded stars for items within each category for a maximum of nine stars. We decided to rate studies as low risk of bias if they received nine

stars, moderate risk of bias if they received seven or eight stars, and high risk of bias if they received less.