

The Expanded Risk Score in Rheumatoid Arthritis (ERS-RA): performance of a disease-specific calculator in comparison with the traditional prediction scores in the assessment of the 10-year risk of cardiovascular disease in patients with rheumatoid arthritis

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Summary

AIMS OF THE STUDY: To assess the performance of the Expanded Risk Score in Rheumatoid Arthritis (ERS-RA), a disease-specific cardiovascular disease (CVD) prediction score, in evaluating the 10-year risk, in comparison with other traditional algorithms in patients with rheumatoid arthritis (RA).

METHODS: Consecutive RA patients, aged 40–75 years, without established CVD, were included. We calculated the disease-specific ERS-RA and four traditional CVD prediction scores: the modified Systematic Coronary Risk Evaluation (mSCORE), the Framingham Risk Score using body mass index (FRS BMI), the calculator developed by the American College of Cardiology / American Heart Association in 2013 (ACC/AHA 2013) and the QRISK3. Subjects also underwent ultrasound assessment of the carotid arteries. The presence of a carotid intima-media thickness (CIMT) >0.90 mm or of carotid plaques identified the high-risk patients.

RESULTS: Of the 84 patients evaluated, 33 (39.3%), 16 (19.0%), 24 (28.6%), 25 (29.8%) and 33 (39.3%) subjects were defined as having high CVD risk according to ACC/AHA 2013, mSCORE, FRS BMI, QRISK3 and ERS-RA, respectively. Compared with the ultrasound results, all the areas under the receiver operating characteristic curves (AUC-ROC) showed good discrimination properties (0.848 – FRS BMI, 0.816 – mSCORE, 0.828 – ACC/AHA 2013, 0.844 – QRISK3, 0.869 – ESR-RA). Comparison of the AUC-ROCs did not show that discriminative ability for detecting subclinical atherosclerotic damage was improved with ESR-RA.

CONCLUSIONS: Using a surrogate marker of subclinical atherosclerotic organ damage as indicator of CVD burden, the newly ERS-RA risk score that incorporates specific aspects of RA performs as well as ACC/AHA 2013, mSCORE, FRS BMI and QRISK3 estimators.

Keywords: *rheumatoid arthritis, cardiovascular disease risk, prediction scores*

Introduction

Rheumatoid arthritis (RA) is a chronic and disabling inflammatory disease with an unpredictable course and wide variations in severity that affects about 0.5% of the Italian population [1].

During recent years, the recognition of an increased risk of cardiovascular disease (CVD) has emerged as a major issue in RA patients [2]. It has been estimated that the CVD burden in RA is comparable to that of diabetes mellitus [3]. This knowledge translates into an increased standardised CVD mortality ratio, which ranges between 1.5 and 1.7 [4, 5]. Compared with the general population, RA patients have a 50% augmented risk of CVD-related death (standardised mortality ratio 1.5) [5]. CVD is the primary cause of death in RA patients, whose median life expectancy is shortened by 6 to 7 years [6].

The major traditional CVD risk scores, derived from the general population, including the Framingham Risk Score (FRS) [7], the Systematic COronary Risk Evaluation (SCORE) [8], the Reynolds Risk Score (RRS) [9], and the algorithm developed by the American College of Cardiology/American Heart Association in 2013 (ACC/AHA 2013) [10], have been tested in patients with RA and all of them seem to perform suboptimally in this population, resulting

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FS, AG, AB, and EGF contributed to the study design, protocol, analysis, and data interpretation. MDC, MT, VL, AD, and MC contributed to the data collection and to the manuscript revision. FS and MDC wrote the manuscript. All authors approved the final version of the manuscript.

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in an underestimation of the CVD risk [11, 12]. Different approaches to solve this issue have been proposed, such as applying a multiplier of 1.5 [13], or adding 10 years to the age of patients with RA [14]. However the validity of these proposals has not been rigorously tested [13].

QRISK3 incorporates more factors than QRISK2 to help physicians to identify those at most risk of heart disease and stroke, such as chronic kidney disease, migraine, corticosteroids use, systemic lupus erythematosus (SLE), atypical antipsychotics, severe mental illness, erectile dysfunction, and a measure of systolic blood pressure variability [14, 15].

The need of effective CVD risk stratification tools specific to RA patients is recognised by the European League Against Rheumatism (EULAR) recommendations, as well as by other experts [13, 16, 17].

Several studies demonstrated an association between CVD risk factors, markers of RA severity and atherosclerosis [18–20].

Recently, the Expanded Risk Score in RA (ERS-RA) calculator was developed and internally validated using data from the Consortium of Rheumatology Researchers of North America (CORRONA) registry in the USA [21]. This risk score incorporates several RA-specific factors such as corticosteroid use, disease duration, disease activity – measured with the Clinical Disease Activity Index (CDAI) – and function – evaluated with the modified Health Assessment Questionnaire (mHAQ).

During recent years the use of measures to assess the subclinical atherosclerosis burden *in vivo*, as well as of risk prediction scores, has become widespread. The ultrasound examination of both carotid arteries in subjects with inflammatory joint diseases, next to the conventional cardiovascular risk factors, helps to stratify the patients. Through ultrasound, a high frequency of carotid plaques in RA patients is detectable, leading to early initiation of statin use [22]. Moreover, ultrasound allows evaluation of the carotid intima-media thickness (CIMT), which is a safe, noninvasive and cost effective method to detect atherosclerotic disease early [23–25]. CIMT has been reported as representative of subclinical and asymptomatic atherosclerosis, a manifestation of a raised CVD risk [26].

The objective of this study was to assess the performance of the ERS-RA in evaluating the 10-years CVD risk in comparison with the traditional algorithms, the modified SCORE (mSCORE), the FRS using body mass index (FRS BMI), the ACC/AHA 2013, and the QRISK3; the presence of a CIMT over 0.9 mm and/or the presence carotid plaque was considered an indicator of high-risk patients with subclinical atherosclerotic organ damage.

Materials and methods

Study population

Consecutive RA patients, aged from 40 to 65 years and fulfilling the 2010 American College of Rheumatology (ACR) / EULAR classification criteria for RA [27], were recruited from the outpatient clinics of two Italian tertiary rheumatology centres (Rheumatological Clinic, Università Politecnica delle Marche, Jesi, Ancona, Italy and Rheumatology Department, ASST Gaetano Pini - CTO, Milano,

Italy) from September 2017 to November 2017. Subjects fulfilled the following inclusion criteria: disease duration ≥ 5 years; current treatment with ≥ 1 synthetic or biological disease-modifying anti-rheumatic drug (s/bDMARD) for a period ≥ 3 months. Patients were excluded if suffering from pre-existing CVD (including ischaemic heart disease, cerebrovascular accident, peripheral arterial disease, heart failure), or if they were already taking prescribed statins. We also excluded patients with diabetes and moderate (estimated glomerular filtration rate [eGFR] 30–59 ml/min/1.73 m²) or severe (eGFR <30 ml/min/1.73 m²) chronic kidney disease, since these conditions represent high or very high CVD risk. Hypertension was defined as a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg, and/or a diagnosis of hypertension by a physician and current treatment according to guidelines for the management of hypertension [28].

All the procedures applied in this research were in accordance to the Helsinki Declaration as revised in 2013. All the patients gave their written informed consent for the anonymous collection of data, and the study was approved by the Ethics Board of the University-Hospital (Comitato Unico Regionale – ASUR Marche).

Laboratory measurements

A standardised set of fasting blood measurements was performed for each patient, in particular total cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glucose, rheumatoid factor, and anti-citrullinated protein antibodies (ACPA).

Clinical assessments

Clinical assessment included the mHAQ [29], as a function index, and the CDAI for assessing disease activity [30]. In the mHAQ, the number of activities of daily living was reduced from 20 (HAQ) to 8 (mHAQ). The mHAQ total score is between 0.0 and 3.0, in 0.125 increments. Higher scores indicate worse function and greater disability [31].

The CDAI range is from 0 to 76, and it is based on the simple summation of the swollen and tender joint count of 28 joints, with patient and physician global assessments on visual analogue scales (VASs) (0–10 cm). It can essentially be used everywhere and anytime to assess disease activity. Moreover, CDAI cut-off values for remission are more stringent than those of Disease Activity Score-28 joints (DAS-28) [32].

Cardiovascular disease risk prediction scores

CVD risk was calculated with FRS BMI, mSCORE, ACC/AHA 2013, QRISK3, and ERS-RA, via the official web sites. The results of the algorithms that do not include RA among the variables were multiplied by 1.5, in accordance to the EULAR 2015/2016 recommendations [16].

Table 1 summarises the principal features of each index.

FRS BMI

The 10-year risk for CVD was calculated using the Framingham equation [33], available as a web-based tool (<http://hivpv.org/Home/Tools>). The assessed factors include gender, age, systolic blood pressure, antihyperten-

sive treatment, smoking status, type 2 diabetes, total cholesterol and HDL cholesterol or BMI in a simplified model [34]. The score was categorised as follows: <10% low risk; 10–20% moderate risk; ≥20% high risk.

mSCORE

This model evaluates the 10-year risk of the first fatal atherosclerotic event. The SCORE was developed from large European cohort studies. It estimates the risk of dying from CVD (not just coronary artery disease), based on age, gender, smoking habits, total cholesterol and systolic blood pressure [8]. The SCORE model allows calibration of the charts for individual European countries. At the international level, two sets of charts are provided: one for high-risk and one for low-risk countries. We used the SCORE equation for low-risk countries, since the guidelines consider Italy to be a low-risk country. Subjects were considered at low risk if the score was <1%, at moderate risk if score was 1–5%, and at high risk if the score was ≥5%. In this study we used the mSCORE, with the 1.5 multiplication factor for RA patients.

ACC/AHA 2013

This risk score employs the AHA/ACC pooled cohort equation [12, 35, 36], which estimates 10-year cardiovascular risk as low (<5%), intermediate (≥5 to <7.5%), and high (≥7.5%).

QRISK3

The calculator considers RA as a separate CVD risk factor. It calculates the percentage of the risk in the population aged between 24 and 84 years. As well as the variables already included in QRISK2 (age, ethnicity, deprivation, systolic blood pressure, BMI, total/HDL cholesterol ratio, smoking, family history of coronary heart disease in a first

degree relative aged less than 60 years, type 1 diabetes, type 2 diabetes, treated hypertension, RA, atrial fibrillation, chronic kidney disease [stage 4 or 5]), QRISK3 takes into account additional factors such as chronic kidney disease (stage 3, 4, or 5), a measure of systolic blood pressure variability (standard deviation of repeated measures), migraine, corticosteroids, SLE, atypical antipsychotics, severe mental illness, human immunodeficiency virus infection / acquired immunodeficiency syndrome) and erectile dysfunction in men.

Pharmacological intervention (statins) is recommended in patients with the threshold of 20% probability of the end event over the following 10 years [14]. It was calculated using QRISK3 -2017 risk calculator <https://qrisk.org/three/>.

ERS-RA

The ERS-RA was calculated using a publically available Excel macro. For ESR-RA, high risk was defined as a 10-year CVD risk ≥7.5%. As mentioned above, the novel feature of this calculator is the inclusion of RA-specific features in the CVD risk assessment, which contribute to a significantly improved model for the prediction of cardiovascular events [21].

Ultrasound evaluation of the carotid arteries

The ultrasound assessment followed the American Society of Echocardiography (ASE) guidelines [37]. The same, trained sonographer (MC), blinded to the clinical and laboratory data, evaluated the carotid arteries in B-mode, using a 5–12 MHz linear probe (iU22 Philips). Intraobserver reproducibility of readings of mean CIMT was evaluated in 20 patients within one week of the first ultrasound examination. The intraclass correlation coefficient for CIMT was 0.91. Patients were placed in the supine position for ul-

Table 1: Characteristics of the cardiovascular risk prediction scores.

ACC/AHA 2013	This algorithm predicts the 10-year risk of heart disease or stroke (cardiovascular morbidity), in patients aged 20 to 79 years. Gender, age, race, diagnosis of diabetes, smoking, treated hypertension, SBP and lipid profile values (TC and HDL-C) are included as variables.
ERS-RA	This tool, developed to assess cardiovascular morbidity, includes four RA-specific factors as variables: disease duration, disease activity, disability and use of corticosteroids. It was developed and internally validated from data in the CORRONA registry, but it has not been externally validated. Laboratory data are not needed.
FRS BMI	This algorithm predicts the 10-year risk of coronary death, myocardial infarction, coronary insufficiency, angina, ischaemic and haemorrhagic stroke, transient ischaemic attack, peripheral artery disease and heart failure (cardiovascular morbidity and mortality). Variables include age, gender, and traditional CV risk factors (presence of diabetes, smoking, and treated hypertension), as well as values of systolic blood pressure and BMI. CV risk can be calculated for individuals aged 30 to 74 years.
QRISK3	The updated QRISK3 prediction model was developed and validated to quantify absolute risks of cardiovascular disease (cardiovascular morbidity – coronary heart disease, ischaemic stroke, or transient ischaemic attack) in people aged 25 to 84 years. This algorithm includes established risk factors and new risk factors such as an expanded definition of chronic kidney disease, migraine, corticosteroid use, SLE, atypical antipsychotic use, severe mental illness, erectile dysfunction and a measure of blood pressure variability. There is no need to apply a 1.5 multiplication factor according to the EULAR recommendations because RA is included as a variable.
SCORE	This calculator evaluates the 10-year risk of cardiovascular mortality (first fatal atherosclerotic event, (for example, myocardial infarction, stroke, and aortic aneurysm). It is based on age, gender, smoking habits, total cholesterol and SBP. The SCORE model allows calibration of charts for individual countries, which has been done for numerous European countries. At the international level, two sets of charts are provided: one for high-risk and one for low-risk countries. We used the SCORE equation for low-risk countries, since the guidelines consider Italy as a low-risk country. The modified SCORE (mSCORE) refers to the SCORE calculation multiplied by 1.5.

ACC/AHA 2013 = American College of Cardiology/American Heart Association 2013 calculator; SBP = systolic blood pressure; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; ESR-RA = Expanded Risk Score in Rheumatoid Arthritis; RA = rheumatoid arthritis; CORRONA = Consortium of Rheumatology Researchers of North America registry; SCORE = Systematic Coronary Risk Evaluation; FRS BMI = Framingham Risk Score using body mass index; CV = cardiovascular; BMI = body mass index; EULAR = European League Against Rheumatism; SCORE = Systematic Coronary Risk Evaluation.

trasound examination of the common carotid arteries, resting in the supine position for 15 minutes before the assessment.

The CIMT, in accordance with the Mannheim consensus recommendations, was measured on the far wall of the common carotid artery at least 5 mm below its end, which avoids interindividual variability induced by physiological remodeling and reduces gain dependence [38]. Three measurements along a minimum length of 10 mm of a straight arterial segment on both the right and left sides were made. The average of three measurements of the far wall of the artery was recorded for each patient. An upper limit of 0.90 mm was chosen for the present study, based on epidemiological data currently available.

Plaque is defined as a focal structure that encroaches into the arterial lumen by at least 0.5 mm or 50% of the surrounding IMT value or has a thickness of >1.5 mm as measured from the media-adventitia interface to the intima-lumen interface [38]. Plaque presence was evaluated in the bilateral common carotid arteries, internal carotid arteries and carotid artery bulbs. Carotid plaques were counted in each territory and defined as no plaque, unilateral or bilateral plaques. The presence of a CIMT >0.9 mm or of unilateral/bilateral plaques defined the high-risk subjects (US+) with subclinical vascular damage [39].

Statistical analysis

Values were expressed as the mean $\pm$ standard deviation (SD) unless indicated otherwise. The univariate analysis to identify variables associated with high-risk patients was investigated using the student's t-test (parametric data) or the one-way analysis of variance (ANOVA) to compare means of more samples. Qualitative variables were tested using chi-square tests. The ability of the ERS-RA to discriminate between patients with and without subclinical atherosclerosis compared with the other CVD risk indices was determined through area under the receiver operating characteristic curves (AUC-ROCs) analysis.

All statistical analyses were performed using MedCalc 11.3.1.0 version (MedCalc Software, Ostend, Belgium).

Results

Patients

The cross-sectional cohort was composed of 98 eligible patients; 84 were included in the final analysis. Fourteen patients were excluded: 11 because they did not complete the ultrasound assessment and 3 because they were already taking statins. The population's demographic and clinical characteristics are shown in table 2. Women accounted for the majority of our population (71.4%). Thirty patients (35.7%) were active smokers, and 32 (38.1%) had hypertension. Lipid profile values showed mean total cholesterol of 206.1 ± 44.8 mg/dl, HDL cholesterol 56.7 ± 15.2 mg/dl and total/HDL cholesterol ratio 3.8 ± 1.2 .

Patients presented a mean CDAI of 10.9 ± 6.8 and a mean mHAQ of 0.67 ± 0.43 . Severe extra-articular manifestations were found in only three patients (3.6%). Rheumatoid factor seropositivity was found in 51 (60.7%), ACPA seropositivity in 48 (57.1%), and both (ACPA and any rheumatoid factor isotype) in 41 (48.8%). A total of 38 (45.2%) subjects were taking methotrexate, with a median

dose of 12.5 mg per week. Use of a bDMARD was reported in 31 (36.9%) patients. Daily use of prednisone was documented in 29 subjects (34.5%), with a median dose of 5 mg.

The 10-year cardiovascular disease prediction scores

The mean $\pm$ SD values of the 10-year CVD prediction scores were: 14.5 ± 14.2 , 95% confidence interval (CI) for the mean 11.3–17.6 for FRS BMI; 3.4 ± 4.2 , 95% CI for the mean 2.5–4.3 for mSCORE; 16.6 ± 17.7 , 95% CI for the mean 12.7–20.5 for ACC/AHA 2013; 17.5 ± 16.9 , 95% CI for the mean 13.7–21.2 for QRISK3; and 13.9 ± 16.4 , 95% CI for the mean 10.3–17.6 for ERS-RA. Thirty-three (39.3%), 16 (19.0%), 24 (28.6%), 26 (30.5%) and 33 (39.3%) patients were defined as having high CVD risk according to ACC/AHA 2013, mSCORE, FRS BMI, QRISK3 and ERS-RA, respectively. All the calculators showed a significantly greater risk in male patients.

Carotid artery ultrasound results

The mean CIMT was 0.806 ± 0.209 mm. CIMT values were significantly higher in men than in women (0.944 ± 0.201 vs 0.756 ± 0.181 ; $p = 0.001$). Among all patients, 39 (46.4%) had carotid plaques and 33 (39.3%) a CIMT >0.90 mm; 41 (48.8%) patients had either CIMT >0.90 mm or carotid plaques (US+) (table 2).

Discriminating ability of the cardiovascular risk prediction scores

Discriminating ability (to identify the presence of a CIMT >0.9 mm or unilateral/bilateral plaques) of the five risk indices was good, with an AUC-ROC of 0.848 (95% CI 0.729–0.902) for FRS BMI, 0.816 (95% CI 0.715–0.893) for mSCORE, 0.828 (95% CI 0.724–0.902) for ACC/AHA 2013, 0.845 (95% CI 0.749–0.919) for QRISK3 and 0.869 (95% CI 0.776–0.933) for ERS-RA (table 3). The AUC-ROCs of the different CVD risk prediction models are depicted in figure 1. All AUCs showed good discrimination properties, with that of ERS-RA being the best. However, no statistically significant difference between the ERS-RA AUC and those of the other four indices was observed (table 4).

Discussion

In the present study, we compared the ability of the ERS-RA, a disease-specific CVD prediction score, with that of four risk algorithms developed for the general population, to predict CVD mortality risk in an Italian RA population. The main finding was a good concurrent and discriminant validity of all the five 10-year CVD risk calculators. Although ERS-RA gave a better AUC-ROC compared with the other four tools, this difference was not statistically significant.

The fact that disease-specific calculators, such as ERS-RA, do not bring significant improvements in CVD risk prediction compared with the traditional instruments has been already highlighted in results derived from a large cohort of patients (1796 subjects) of the Trans-Atlantic Cardiovascular Consortium for RA [42].

CVD risk is an important, but frequently underassessed, topic in RA [43]. The reasons for increased CVD risk in

RA patients are complex and are postulated to be related to chronic autoimmune and inflammatory mechanisms, endothelial dysfunction and inadequate management of mod-

ifiable risk factors, and potentially to medication including corticosteroids and non-steroidal anti-inflammatory drugs [35, 44, 45].

Table 2: Demographic characteristics of the whole cohort (84 subjects) and of the subgroups of patients according to carotid intima-media thickness (CIMT) stratification and plaque presence (CIMT ≤ 0.90 mm, n = 43 subjects; >0.90 mm, n = 33 subjects and n = 41 subjects >0.90 mm + carotid plaques).

Variable	Overall (n = 84)	CIMT ≤ 0.90 mm (n = 43)	CIMT >0.90 mm without plaques n = 33	CIMT >0.90 mm or plaques n = 41	p-value*
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age (years)	59.3 $\pm$ 10.3	58.6 $\pm$ 10.6	60.5 $\pm$ 10.8	59.9 $\pm$ 11.1	n.s.
Disease duration of RA (years)	11.4 $\pm$ 6.7	10.4 $\pm$ 7.4	12.4 $\pm$ 5.8	11.8 $\pm$ 6.1	n.s.
TC (mg/dl)	206.1 $\pm$ 44.8	199.8 $\pm$ 47.3	215.5 $\pm$ 48.7	219.1 $\pm$ 50.1	0.041
HDL-C (mg/dl)	56.7 $\pm$ 15.2	56.5 $\pm$ 14.4	55.7 $\pm$ 15.5	56.9 $\pm$ 13.9	n.s.
TC/HDL-C ratio	3.8 $\pm$ 1.2	3.7 $\pm$ 1.4	3.9 $\pm$ 1.2	3.9 $\pm$ 1.7	n.s.
Systolic blood pressure (mm Hg)	132.9 $\pm$ 14.5	126.7 $\pm$ 12.6	143.8 $\pm$ 15.5	144.1 $\pm$ 16.1	0.033
Body mass index (kg/m ²)	24.8 $\pm$ 4.3	24.2 $\pm$ 4.3	25.9 $\pm$ 3.2	26.1 $\pm$ 4.1	n.s.
CDAI	10.9 $\pm$ 6.8	9.9 $\pm$ 6.2	12.5 $\pm$ 7.3	11.9 $\pm$ 7.9	n.s.
mHAQ	0.67 $\pm$ 0.43	0.59 $\pm$ 0.41	0.80 $\pm$ 0.43	0.78 $\pm$ 0.41	n.s.
CIMT	0.806 $\pm$ 0.209	0.684 $\pm$ 0.131	0.928 $\pm$ 0.141	0.933 $\pm$ 0.151	<0.001
CVD risk scores					
FRS BMI	14.5 $\pm$ 14.2	8.4 $\pm$ 9.3	21.1 $\pm$ 13.8	21.9 $\pm$ 12.3	<0.001
mSCORE	3.4 $\pm$ 4.2	1.9 $\pm$ 3.2	5.1 $\pm$ 4.9	5.3 $\pm$ 4.3	<0.001
ACC/AHA 2013	16.6 $\pm$ 17.7	9.9 $\pm$ 11.2	23.8 $\pm$ 21.9	22.9 $\pm$ 19.8	<0.001
QRISK3	17.5 $\pm$ 16.1	10.8 $\pm$ 10.1	24.0 $\pm$ 17.7	23.6 $\pm$ 15.5	<0.001
ESR-RA	13.9 $\pm$ 16.4	7.2 $\pm$ 9.0	20.9 $\pm$ 22.8	20.5 $\pm$ 17.9	<0.001
Education	n (%)	n (%)	n (%)	n (%)	
Primary school	18 (21.4)	8 (18.6)	8 (24.2)	11 (26.8)	n.s.
Secondary school	39 (46.2)	20 (46.5)	16 (48.5)	18 (43.9)	n.s.
High school or university	27 (32.4)	15 (34.8)	9 (27.3)	12 (29.3)	n.s.
Current smoker	30 (35.7)	15 (34.8)	15 (45.5)	19 (46.3)	0.027
Hypertension	32 (38.1)	17 (39.5)	11 (33.3)	15 (36.5)	n.s.
Hypertension treatment	29 (34.5)	15 (34.8)	13 (30.3)	14 (34.1)	n.s.
RF positivity	51 (60.7)	28 (65.1)	20 (51.5)	22 (53.6)	n.s.
ACPA positivity	48 (57.1)	27 (62.8)	18 (54.5)	23 (56.1)	n.s.
Double seropositivity (ACPA and RF)	41 (48.8)	22 (51.1)	16 (48.5)		n.s.
Methotrexate treatment	38 (45.2)	20 (46.5)	15 (45.5)	19 (46.3)	n.s.
Biological DMARDs	31 (36.9)	17 (39.5)	11 (33.3)	14 (34.1)	n.s.
Daily use of prednisone	29 (34.5)	15 (34.8)	11 (33.3)	14 (34.1)	n.s.

RA = rheumatoid arthritis; TC = total cholesterol; HDL-C = high density lipoprotein cholesterol; SBP = systolic blood pressure; BMI = body mass index; CDAI = clinical disease activity index; mHAQ = modified Health Assessment Questionnaire; CIMT = carotid intima-media thickness; FRS BMI = Framingham Risk Score using body mass index; mSCORE = modified Systematic Coronary Risk Evaluation; ACC/AHA 2013 = American College of Cardiology/American Heart Association 2013 calculator; ESR-RA = Expanded Risk Score in Rheumatoid Arthritis; RF = rheumatoid factor; ACPA = anti-citrullinated protein antibody; DMARD = disease modifying antirheumatic drugs. * One-way ANOVA

Table 3: Area under the receiver operating characteristic curves (standard error and 95% confidence intervals) to distinguish patients in regard to presence of subclinical atherosclerosis as defined by the presence of carotid intima-media thickness over 0.9 mm and/or carotid plaques (US+).

Variable	AUC	SE [†]	95% CI [†]
FRS BMI	0.848	0.0447	0.752 to 0.918
mSCORE	0.816	0.0474	0.715 to 0.893
ACC/AHA 2013	0.828	0.0474	0.729 to 0.902
QRISK3	0.845	0.0439	0.749 to 0.919
ERS-RA	0.869	0.0409	0.776 to 0.933

AUC = area under the curve; CI = confidence interval; FRS BMI = Framingham Risk Score using body mass index; mSCORE = modified Systematic Coronary Risk Evaluation; ACC/AHA 2013 = American College of Cardiology/American Heart Association 2013 calculator; ESR-RA = Expanded Risk Score in Rheumatoid Arthritis. * Hanley and McNeil, 1982 [40] † Binomial exact

Table 4: Comparison of the Expanded Risk Score in Rheumatoid Arthritis area under the receiver operating characteristic curve to the areas of the other four cardiovascular risk prediction scores.

Variable	Difference between areas	SD [†]	95% CI	Significance level (p-value)
ERS-RA vs ACC/AHA 2013	0.0407	0.0331	-0.0241 to 0.105	0.2187
ERS-RA vs FRS BMI	0.0206	0.0347	-0.0474 to 0.0887	0.5522
ERS-RA vs QRISK3	0.0241	0.0391	-0.0531 to 0.102	0.5381
ERS-RA vs mSCORE	0.0529	0.0352	-0.0161 to 0.122	0.1329

ERS-RA = Expanded Risk Score in Rheumatoid Arthritis; ACC/AHA 2013 = American College of Cardiology/American Heart Association 2013 calculator; FRS BMI = Framingham Risk Score using body mass index; mSCORE = modified Systematic Coronary Risk Evaluation. * Hanley and McNeil 1983 [41]

Several well-known models for CVD mortality risk prediction, which utilise data from multiple risk factors, have been developed and updated in the USA, Japan and Europe in recent decades [7–9, 46–49]. Their values and limitations have been reviewed [50], and it has been demonstrated that algorithms for the general population do not work well in RA patients [11, 12].

Moreover, application of the scores suggested in the international guidelines for cholesterol management in patients with RA can lead to quite discordant results. In a French cohort, eligibility for statin treatment was tested in accordance with the guidelines of the European Society of Cardiology (ESC) (the SCORE), with the 1.5 multiplication factor according to the EULAR, with the Adult Treatment Panel III (ATP-III) (the FRS), and to the ACC/AHA (the Pooled Cohort Equations): statin therapy was recommended in 9.6% of the women and 26.1% of the men according to the SCORE algorithm, whereas according to the ATP-III guidelines statins should be started in 15.5% of the women and 51% of the men [51]. As SCORE and FRS were created for the general population, the EULAR experts recommend multiplying cardiovascular risk in RA patients by a factor of 1.5 [16]. This coefficient has been criticised, since it was derived from the experts' opinion, with no supporting data, and whereas FRS, SCORE, and RRS seem to underestimate, QRISK2 has been judged to overestimate the CVD risk [11].

Crowson et al., in a study of 525 RA patients aged over 30 years, analysed FRS and RRS, concluding that these tools substantially underestimate cardiovascular risk in RA patients (both genders), mainly in advanced age, in rheumatoid factor positive subjects, and in patients with a persistently high ESR, which is an important marker of inflammatory activity of the disease [12].

Galarza-Delgado et al. in a cohort of Mexican Mestizo RA patients, showed a significant difference between of

CVD risk calculators [52]. In the individual comparison, QRISK3 did not show a statistical difference when compared with ERS-RA. In this study, FRS BMI delivered the highest values of predicted CVD risk. Ozen et al. found that the ACC/AHA 2013 algorithm failed to identify the majority (~55%) of the patients with increased CIMT and/or carotid plaques. However, the ACC/AHA 2013 calculator was better than SCORE and QRISK2 in detecting patients with subclinical atherosclerosis when the high risk thresholds (>7.5%, >5% and >20%, respectively) for all three indices were used [53]. Thus, data coming from the literature revealed differences between the scores, with a trend to underestimation for some prediction tools.

One reason for the underestimate of CVD risk in RA may be the high frequency of asymptomatic atherosclerosis [54–56], which can be visualised by ultrasound of the carotid arteries.

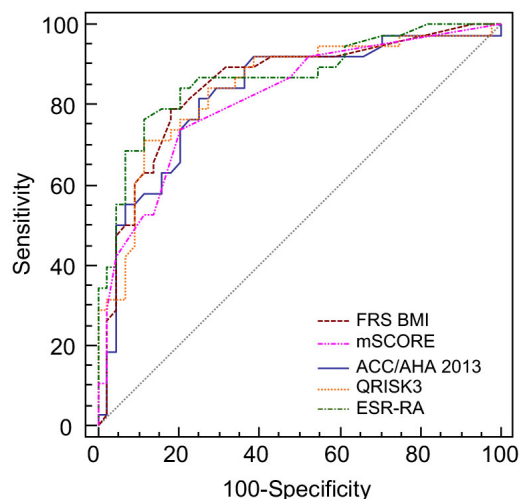
The assessment of CIMT and the presence of carotid plaques with ultrasound has become an efficient technique to measure the presence of subclinical atherosclerosis in RA [57, 58]. Both CIMT and carotid plaques were found to be predictors of cardiovascular events in low and intermediate risk groups of non-rheumatic individuals, and also in RA patients [24, 25, 59]. CIMT is a measure of early atherosclerosis and vascular remodelling. CIMT has been employed as an indicator of atherosclerosis in epidemiological, observational and interventional clinical studies. It has been also applied as a primary endpoint for therapeutic efficacy with various pharmacological therapies and it has been employed as an exposure variable in studies on the prognostic value of predicting coronary artery disease and stroke [60, 61]. Both CIMT >0.90 mm and the presence of carotid plaques are considered expressions of subclinical organ damage, and as factors influencing the CVD prognosis in the general population and in RA patients [24, 25, 28].

In clinical practice the assessment of CIMT is not yet a routine investigation, but the predictive value of this measure has been established in several prospective studies, guidelines and consensus statements [23, 38, 62]. However, the CIMT is not recommended as a screening tool by the ESC, and the correct integration of additional information into the traditional risk models is a sensitive issue [63].

Three potential limitations to our study deserve to be mentioned. First of all, our study was a cross-sectional evaluation, with a small number of patients included, and lacked CVD outcomes. We tried to overcome this limitation with the carotid ultrasound assessment. However, follow-up of these patients is needed. Secondly, the generalisability of our results may be limited because all of our patients were recruited from two Italian centres. An additional limitation is that the “cardiovascular disease-free” criteria might induce a selection bias, especially in patients with longstanding RA.

In conclusion, CVD risk assessment remains inadequate in RA at present. The main finding in our present study was good concurrent and discriminant validity of the five 10-year CVD risk calculators. The ERS-RA does not seem to add significant advantages compared with ACC/AHA 2013, mSCORE, FRS BMI and QRISK3 estimators.

Figure 1: Receiver operating characteristic curves of the different risk prediction algorithms. The curves plot the relationship between sensitivity and complement of specificity of each risk score for different cut-off levels of test positivity. ESR-RA = Expanded Risk Score in Rheumatoid Arthritis; ACC/AHA 2013 = American College of Cardiology/American Heart Association 2013 calculator; FRS BMI = Framingham Risk Score using body mass index; mSCORE = modified Systematic Coronary Risk Evaluation



The use of surrogate markers of subclinical atherosclerotic organ damage increases the proportion of correct risk stratification. Up to now, CIMT measured by B-mode ultrasound is the most studied measure and has been validated by official medical agencies [26, 38, 63, 64], but new techniques (i.e., the coronary calcium score) probably will be widely available in the near future [65].

Larger heterogeneous RA cohorts followed longitudinally for clinical CVD endpoints, such as stroke or myocardial infarction, would provide a better assessment of the utility of CVD risk calculators, helping to identify the contribution of RA specific factors to the total predicted burden.

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