The relationship between cardiovascular disease risk prediction scores and vascular function and morphology in rheumatoid arthritis

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Abstract

Objective

Patients with rheumatoid arthritis (RA) are at an increased risk for cardiovascular disease (CVD) resulting from impairments in vascular function and morphology. CVD risk prediction scores can identify patients at high risk of CVD, but little is known about whether they relate with assessments of vascular function and morphology which provide early indication of subclinical atherosclerosis. The objective of the present study was to examine the relationship of several CVD risk prediction scores with assessments of vascular function and morphology in patients with RA.

Methods

Framingham risk score, Systematic Coronary Risk Evaluation for total cholesterol and ratio of total cholesterol to high-density lipoprotein, as well as Reynolds Risk Score, and QRISK2 were calculated in 201 RA patients (155 females, median (25^{th} to 75^{th} percentile) age: 61 (53–67)) who were examined at baseline (2006). The European League Against Rheumatism (EULAR) multiplication factor was also applied to the algorithms. At a 6-year follow-up (2012) visit the patients underwent assessments of microvascular and macrovascular endothelium-dependent and endothelium-independent function, along with assessment of carotid atherosclerosis.

Results

All five CVD risk prediction scores measured at baseline were significantly correlated with vascular function and morphology at follow-up. Application of the EULAR multiplication factor did not change any of the associations.

Conclusion

Five commonly used CVD risk prediction scores associate with assessments of vascular function and morphology over a 6-year follow-up period suggesting that these CVD risk prediction scores may also reflect subclinical atherosclerotic changes.

Key words

endothelium, Framingham, rheumatoid arthritis, cardiovascular disease, QRISK2

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory musculoskeletal disease which is characterised by an increased risk for developing cardiovascular disease (CVD) when compared to the general population (1). It has been suggested that the increased CVD risk might be due to the adverse effects of classical CVD risk factors on the vasculature which result in accelerated atherosclerosis (2).

The prevalence of classical CVD risk factors is increased in patients with RA and are not appropriately managed (3). The risk for CVD can be calculated by incorporating individual CVD risk factors into algorithms to yield CVD risk prediction scores (4-7). These CVD risk prediction scores can then be used to tailor prevention strategies according to the patient's level of risk. The most commonly used CVD risk prediction scores include the Framingham Risk Score (FRS) (4) and the Systematic Coronary Risk Evaluation (SCORE) (5) which incorporate age, gender, smoking, systolic blood pressure and lipids levels. The SCORE can be calculated using total cholesterol levels (TC SCORE) and the ratio of TC to high density lipoprotein (HDL) cholesterol (TC:HDL SCORE). The FRS and SCORE do vary from each other: the FRS estimates the likelihood of a fatal or non-fatal coronary heart disease (CHD) event (*e.g.* myocardial infarction) over the next 10-years (4); SCORE is a CVD risk prediction chart specifically for European populations and unlike FRS, is not limited to just coronary events as it provides the 10 year risk for any first fatal CVD event (*e.g.* stroke) (5).

Importantly, the excess risk for CVD remains even when controlling for classical CVD risk factors, and is likely to be due to high systemic inflammation (8). Elevated C-reactive protein (a marker of systemic inflammation) has been reported to be an independent predictor of CV events in the general population (9) and is chronically raised in RA. The Reynolds risk score includes C-reactive protein (CRP) into its algorithm and categorises patients into low or high risk (6), while the QRISK2 is the most extensive CVD risk algorithm; incorporating the presence of RA, kidney disease, atrial fibrillation, socioeconomic status, and ethnicity along with the other CVD risk factors included in FRS and SCORE (7).

The endothelium is the innermost layer of the vasculature and is responsible for maintaining an atheroprotective environment within the vessel. Damage to the endothelium from injurious stimuli such as oxidative stress and inflammatory mediators results in endothelial dysfunction, primarily through a reduction in the anti-atherogenic molecule, nitric oxide (NO) (10). Several non-invasive assessments of vascular function and morphology examine different stages of sub-clinical atherosclerosis and provide useful information on an individual's CVD risk status.

Laser Doppler Imaging with iontophoresis of NO agonists is commonly used to assess endothelial function in the microvasculature, while flow-mediated dilatation (FMD) (endothelium-dependent function) and glyceryl-trinitrate-mediated dilatation (GTN) (endothelium-independent function) are used to assess macrovascular endothelial function. Assessment of vascular morphology is typically performed using high-resolution B mode ultrasanography in the carotid arteries and provides information on the carotid artery intima-media thickness (cIMT) (10). These assessments are good predictors of future cardiac events in the general population and in patients with CVD (11, 12).

Classical CVD risk factors appear to be strong predictors of vascular function (13) and morphology (14) in RA. In the general population, assessments of microvascular (15) and macrovascular (16, 17) endothelium-dependent function are associated with classical CVD risk, however, to our knowledge, with the exception of one cross-sectional study which reported that CVD risk prediction scores were associated with worse microvascular endothelium-dependent function and macrovascular endothelium-independent function (both early markers of subclinical atherosclerosis) in patients with RA (13), there are no studies which have examined the long-term relationship between

different CVD risk prediction scores and vascular function and morphology in the same group of RA patients. This is not surprising as CVD risk prediction scores are not designed (or validated) to predict abnormalities in the vasculature. Nevertheless, both types of assessment provide early indication of CVD risk and it may be useful for clinicians to understand whether assessments of vascular function and morphology reflect conventional CVD risk prediction tools. The objective of the present RA cohort study was to examine the association of the most commonly used CVD risk prediction scores at baseline, with vascular function and morphology assessed after a six year follow-up period in patients with RA

Methods

Participants

Four hundred consecutive RA patients were recruited from the rheumatology outpatient clinics of the Dudley Group NHS Foundation Trust, United Kingdom in 2006. The patients were part of the Dudley Rheumatoid Arthritis Comorbidity Cohort (DRACCO), a prospective study examining CVD burden in RA. Detailed characteristics of these patients have been reported previously (18). 201 patients agreed to take part in the follow-up vascular study: baseline (2006) and follow up data (2012) from these patients is reported in this manuscript. All patients met the 1987 revised RA criteria of the American College of Rheumatology (19). The study received ethics approval from The Black Country Research Ethics Committee. All participants gave their written informed consent according to the Declaration of Helsinki.

Protocol for baseline visit

All patients reported to the clinical research facility after a 12 hour overnight fast and underwent a detailed review of their medical history and hospital records, physical examination, and contemporary assessments of height, weight, body mass index (BMI), body composition (using a TANITA Body Composition Analyser BC-418), and current disease activity score (DAS28) (20). Separate CVD risk algorithms were utilised to calculate CVD risk: FRS (21), TC SCORE, TC:HDL SCORE (5), Reynolds risk score (6), and the QRISK2 (7). All medications and their indication were also recorded. Venous blood was collected on the same day and a wide range of tests were performed in the Biochemistry Laboratory at Russells Hall Hospital, The Dudley Group NHS Foundation Trust, UK.

Protocol for follow-up visit

Patients reported to a temperature controlled vascular laboratory (22ºC) after a 12 hour overnight fast six years after the baseline assessment. All patients underwent the same examinations and assessments as in the baseline visit. In addition, patients also underwent several functional and morphological vascular assessments including Laser Doppler Imaging with Iontophoresis of acetylcholine (ACh) and sodium nitroprusside (SNP) (microvascular endothelial function), assessments of FMD, GTN (macrovascular endothelial function), and cIMT (carotid atherosclerosis).

Cardiovascular disease risk prediction scores

Two versions of CVD risk scores were produced. The first consisted of the standard values for the risk score (Table I). The other version was the same, other than where European League against Rheumatism (EULAR) criteria was met. The EULAR criterion includes disease duration of more than 10 years, rheumatoid factor or anti-citrullinated peptide antibody positivity and presence of certain extra-articular manifestations. RA patients meeting any two of the EULAR criteria had all of their risk scores, with exception of QRISK2, multiplied by 1.5 (22). The CVD risk scores were only calculated in patients who were within the age ranges for each of the risk scores.

Microvascular endothelial function

Endothelial function of the microvasculature was assessed non-invasively using LDI (Moor LDI 2 SIM, Moor Instruments Ltd, Devon, UK) with iontophoresis of 1% ACh (Miochol-E, Novartis, UK) and 1% SNP (Nitroprussiat Fides, Rottapharm, Spain) in 2.5ml solution containing 0.5% saline by a single observer (AS) according to previously established guidelines (23). The iontophoresis chambers containing the ACh and SNP were attached to the volar aspect of the forearm. Following a baseline LDI scan, a 30µa current was administered through the chambers which forced the vasoactive agents into the underlying blood vessels, while 10 subsequent scans recorded the increase in blood flow in response to these agents. This was followed by 2 recovery scans when no current was being administered. The percentage change in perfusion in response to ACh and SNP was calculated by subtracting baseline perfusion from peak perfusion, then dividing by baseline perfusion followed by multiplication by 100. This technique has an intra-observer co-efficient of variation (CV) for ACh and SNP of 6.5% and 5.9% respectively in our laboratory.

Macrovascular endothelial function

Assessment of macrovascular endothelium-dependent function was performed using FMD with high-resolution ultrasonography of the brachial artery (Acuson Antares ultrasound system, Siemens PLC, Camberley, UK) according to previously established guidelines (24). The participant was seated in a semi-recumbent armchair with their arm comfortably placed at the side. A stereotactic clamp was used to hold the ultrasound probe in place and the brachial artery was continuously imaged throughout the test. The ultrasound machine was connected to Vascular Image Analysis software (25) which automatically detects vascular diameter at 25 frames per second and accounts for variations in diameter that occur during the cardiac cycle. The protocol for FMD included a 2 minute baseline scan, after which a blood pressure cuff placed around the wrist was inflated to suprasystolic pressures for 5 minutes. Following the release of the cuff, the resulting change in diameter in response to the reactive hyperaemia was continually measured for a further 2 minutes to measure peak dilatation. The assessment of endothelium-inde-

Table I. Factors included in the cardiovascular disease risk prediction scores.

CVD Risk Prediction Score	Factors Included in the Risk Prediction Score
Framingham Risk Score (4)	Age, gender, TC, HDL, SBP, DBP, presence of diabetes, smoking status
Systematic Coronary Risk Evaluation for TC (High risk) (5)	Age, gender, TC, SBP, smoking status
Systematic Coronary Risk Evaluation for TC: HDL ratio (High risk) (5)	Age, gender, TC:HDL ratio, SBP, smoking status
Reynolds Risk Score (6)	Age, sex, TC, HDL, CRP, presence of hypertension, smoking status, family history of CVD
QRISK2 (7)	Age, sex, TC:HDL ratio, SBP, BMI, ethnicity, smoking status, diabetes status, family history of CVD, chronic kidney disease, atrial fibrillation, rheumatoid arthritis, receiving anti-hypertensive treatment, Townsend deprivation score

BMI: body mass index; CRP: C-reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; HDL: high density lipoprotein; SBP: systolic blood pressure; TC: total cholesterol.

pendent responses was examined by asking the participant to take a 500μg sublingual GTN tablet for 5 minutes (Alpharma, Barnstaple, UK). The percentage change in diameter for FMD and GTN assessments was calculated by subtracting the baseline diameter from the peak diameter, dividing by the baseline diameter, followed by multiplication by 100. The intra-observer CV for the study ultrasonographer (AS) was 10.7% for FMD and 11.8% for GTN assessments respectively. For all vascular tests analysis was carried out offline by AS who was blinded to the identity of the patient.

Carotid atherosclerosis

High-resolution ultrasonography of the carotid artery was performed by an experienced ultrasonographer (AS) according to previously established guidelines (26) using a 10 MHz linear array probe attached to the same high-resolution ultrasound scanner as for the FMD assessment. The cIMT was defined by determining the thickness between the lines of Pignoli; with the first echogenic line representing the lumen-intima interface, and the second line representing the media-adventitia interface (27). Assessments of cIMT were performed in the far wall, 1cm proximal to the carotid bulb at sites free of plaque in both the right and left common carotid arteries using the longitudinal scanning plane. Three measurements were taken on each side, and these were averaged to give the mean IMT for the right and left carotid arteries separately. The IMT from both sides were further averaged to give the overall IMT. All images were ECG-gated and were taken at the peak of the R wave (diastole). IMT readings were taken using artery measurement software (AMS, Stockholm, Sweden) which automatically detects intima and media interfaces and has been described in detail previously (28). The technique has been described in detail previously (29). The intra-observer CV for AS was 8.6%.

Statistical analysis

All statistical analysis was performed using IBM SPSS 20 (IBM SPSS Inc, Chicago, IL, USA). Data is presented as median (25^{th} – 75^{th} percentile), number (percentage) or mean ± standard deviation as appropriate.

Standard CVD risk prediction scores and vascular function and morphology

Spearman's correlation coefficients were calculated to quantify the relationships between the standard CVD risk scores measured at baseline (2006) and the vascular outcomes at the end of follow-up (2012). The CVD risk score most strongly correlated with each of the outcomes was then identified. Meng's Z-test for correlated correlations was then used to compare this risk score with each of the remaining four scores, in order to ascertain whether it had significantly greater accuracy than the alternatives. Due to the number of comparisons being made, the resulting *p*-values were assessed at both the standard critical value of 0.05, and after Bonferroni-correction for the total potential number of multiple comparisons.

EULAR adjusted CVD risk prediction scores and vascular function and morphology

The Spearman correlation coefficients between standard and EULAR adjusted scores, and vascular outcomes were calculated. For each outcome, the standard and EULAR adjusted scores were compared using Meng's test. A *p*-value <0.05 was deemed to be indicative of statistical significance.

Results

Patient characteristics

All 201 patients successfully underwent assessments at both time points. A summary of the patient characteristics is displayed in Table II. The majority of patients were females with moderate-high disease activity at baseline, but with relatively lower disease activity during follow-up.

CVD risk prediction scores and the vasculature

The FRS increased at follow-up when compared to baseline (9±6 and 6±6 respectively). Both of the SCORE algorithms performed the same and were similar at baseline (3±3) and at follow-up (2±2). The Reynolds risk score was also similar between both time points (baseline: 9±8 *versus*. follow-up 10±8). QRISK2 at baseline (19±14) was lower than at follow-up (27±15). All of the CVD risk scores were found to be significantly associated with all five vascular parameters being considered, with $p<0.001$ in each case. The CVD risk prediction scores were also ranked by the magnitude of their correlation with each of the vascular assessments. The QRISK2 score consistently shows the strongest associations with assessments of vascular function, being ranked first for three of the outcomes, and second for another. Where the QRISK2 is not the highest ranked score, this falls to the Reynolds risk

Table II. Patient characteristics.

	Baseline (2006)	Follow-up (2012)
General characteristics		
Age (years)	61 (53 – 67)	67 (59 – 73)
Sex female n (%)	155 (77)	155 (77)
Body mass index (kg/M^2)	27 (24 – 30)	28 (24 – 32)
Disease characteristics		
Age at onset of RA	46 ± 13	--
Disease duration (years)	10 (4 – 18)	16 (11 – 25)
Rheumatoid factor positive n (%)	148 (74)	148 (74)
Anti-CCP positive n (%)	123 (61)	123 (61)
DAS28	4.0 (3.1 – 4.8)	3.1 (2.5 – 4.0)
C-reactive protein (mg/l)	7.5 (4.3 – 16)	3 (2.9 – 8.5)
Erythrocyte sedimentation rate (mmhr)	17 (8 – 30)	12 (5 – 23)
HAQ	1.3 ± 0.9	1.6 ± 0.9
Extra-articular manifestations n (%)*	147 (73)	--
Cardiovascular Disease Risk Factors		
Hypertension n (%)	132 (66)	130 (65)
Dyslipidaemia n (%)	115 (57)	158 (79)
Insulin resistance n (%)	65 (32)	53 (26)
Diabetes n (%)	7 (4)	21 (10)
Current Smokers	33 (16)	23 (11)
Global Cardiovascular Disease Risk		
Framingham Risk Score (%)	4.6 ± 5.3	9.2 ± 6.3
TC SCORE (%)	3 ± 3	3 ± 3
TC:HDL SCORE (%)	3 ± 3	3 ± 3
Reynolds Risk Score (%)	6.3 ± 6.4	9.6 ± 8.3
QRISK2	19 ± 14	27 ± 15
RA Medications		
Methotrexate n (%)	128 (64)	122 (61)
Hydroxychloroquine n (%)	36 (18)	50 (25)
Prednisolone n (%)	58 (29)	51 (25)
Prednisolone dose (mg)	6 ± 3	7 ± 8
NSAIDs n (%)	47 (23)	26 (13)
Cyclooxygenase II inhibitors N (%)	14 (7)	5 (2.5)
Anti-TNF-α therapy n (%)	20 (10)	57 (28)
Tociluzimab n (%)	--	3 (1.5)
Cardiovascular Medications		
Antihypertensive n (%)	81 (40)	79 (39)
Antihypercholesterolemic n (%)	33 (16)	74 (37)
Beta-blocker n (%)	32 (16)	22 (11)
Calcium channel blocker n (%)	26 (13)	27 (13)

Results are expressed as median (25th to 75th percentile values), number (percentage) or mean ± standard deviation. Anti-CCP: anti-cyclic citrullinated peptide autoantibodies; Anti-TNF-α: anti tumour necrosis factor alpha; DAS28: disease activity score in 28 joints; HAQ: Health Assessment Questionnaire; HDL: high density lipoprotein; NSAIDs: non steroidal anti-inflammatory drugs; SCORE: systematic coronary risk evaluation; TC: total cholesterol. Extra-articular manifestation includes the presence of nodules, eye abnormalities, systemic vasculitis, erosions, nailfold vasculitis, sicca, pulmonary fibrosis, serositis. *Data available for patients at baseline only.

score, being the highest ranked for both macrovascular endothelium-dependent function and carotid atherosclerosis. The TC SCORE reveals weak correlations with the vascular assessments and is consistently ranked in the bottom two places.

In order to test whether any of these differences were significant, Meng's Z-test was used to compare the best scoring system in each case to all of the other scoring systems (see Table III). This analysis revealed that there is generally no evidence that the best scoring system for each vascular paremeter is significantly better than any of the alternatives. After taking into account the effect of multiple comparisons, the only comparison found to be significant was the comparison of the QRISK2 and FRS correlations with macrovascular endothelium-independent function (coefficients = -0.51, -0.33, p<0.001).

EULAR adjusted CVD risk scores

Table IV displays the correlation coefficients for risk scores with and without EULAR adjustment. None of the comparisons between the standard and EULAR scores were found to be significant.

Discussion

The present study was conducted in a large prospective cohort of RA patients who were followed-up for six years. The findings revealed that five separate CVD risk prediction scores measured at baseline were significantly correlated with functional and morphological vascular assessments during follow-up, which suggests that CVD risk prediction scores could reflect early atherosclerotic changes in the vasculature.

The present study showed that when the CVD risk prediction scores were ranked according to the magnitude of their correlations with the vascular assessments, the QRISK2 consistently had the strongest associations with most of the vascular parameters. The QRISK2 is updated annually from over 13 million patients from general practice surgeries all over the United Kingdom, so relative to the other risk scores, the weighting of the algorithm is modified to reflect changes in population characteristics. Interestingly, despite QRISK2 having the strongest associations with vascular outcomes, it was not significantly better than any of the other algorithms. The QRISK2 incorporates all of the CVD risk factors included in the FRS and SCORE, but also includes other co-morbidities (chronic kidney disease, atrial fibrillation), ethnicity, and the Townsend deprivation scale. Consequently, the combination of these risk factors may have a greater impact on the vasculature. Indeed, in a previous study in individuals with CVD risk factors, but absence of any overt CVD, vascular function decreased as the number of CVD risk factors increased (30). We have previously shown that a number of different classical CVD risk factors are associated with microvascular and macrovascular function in RA (13, 31, 32). Thus, it is possible that the utilisation of CVD risk prediction scores which incorporate a variety of risk factors (such as QRISK2) could show stronger relationships with vascular function and morphology than risk prediction

Table III. Comparisons of the correlations between CVD risk scores and vascular assessments.

	Microvasculature		Macrovasculature		
Risk Prediction Score	Endothelium-dependent (ACh%)	Endothelium-independent (SNP%)	Endothelium-dependent (FMD%)	Endothelium-independent (GTN%)	Carotid Atherosclerosis (cIMT)
QRISK2	**-0.42**	**-0.32**	-0.30 (p=0.625)	**-0.51**	0.41 (p=0.940)
Framingham	-0.39 (p=0.390)	-0.28 (p=0.385)	-0.30 (p=0.832)	-0.33 (p<0.001**)	0.40 (p=0.963)
TC SCORE	-0.38 (p=0.290)	-0.20 (p=0.235)	-0.29 (p=0.772)	-0.36 (p=0.156)	0.36 (p=0.587)
TC: HDL SCORE	-0.42 (p=0.509)	-0.24 (p=0.419)	-0.31 (p=0.557)	-0.40 (p=0.395)	0.40 (p=0.789)
Reynolds	-0.34 (p=0.040*)	-0.27 (p=0.267)	**-0.33**	-0.44 (p=0.093)	**0.41**

Data represented as the Spearman's correlation coefficient between the risk score and vascular assessment, and the p-value comparing this to the risk score which is the best predictor of the outcome (highlighted in bold) *Significant at p<0.05 **Significant at p<0.001 (Bonferroni correction for 10 pairs of risk scores across 5 vascular outcomes). ACh: acetylcholine; FMD: flow-mediated dilatation; GTN: glyceryl trinitrate mediated dilatation; HDL: high density lipoprotein; cIMT: carotid intima-media thickness; SCORE: systematic coronary risk evaluation; SNP: sodium nitroprusside; TC: total cholesterol.

Table IV. Comparison of spearman correlation coefficients between risk scores with and without EULAR adjustment (cIMT).

	Microvasculature		Macrovasculature		
Risk Prediction Score	Endothelium-dependent (ACh%)	Endothelium-independent (SNP%)	Endothelium-dependent (FMD%)	Endothelium-independent (GTN%)	Carotid Atherosclerosis (cIMT)
Framingham	-0.389	-0.279	-0.302	-0.333	0.403
Framingham EULAR	-0.396	-0.275	-0.295	-0.354	0.417
p-value	*0.599*	*0.802*	*0.582*	*0.145*	*0.311*
TC SCORE	-0.382	-0.204	-0.293	-0.363	0.363
TC SCORE EULAR	-0.372	-0.185	-0.276	-0.371	0.385
p-value	*0.452*	*0.154*	*0.210*	*0.519*	*0.101*
TC:HDL SCORE	-0.416	-0.237	-0.315	-0.399	0.398
TC:HDL SCORE EULAR	-0.406	-0.217	-0.290	-0.412	0.417
p-value	*0.491*	*0.195*	*0.101*	*0.389*	*0.196*
Reynolds Risk Score	-0.343	-0.267	-0.329	-0.438	0.408
Reynolds Risk Score EULAR	-0.347	-0.255	-0.317	-0.455	0.436
p-value	*0.738*	*0.429*	*0.407*	*0.239*	*0.055*

Data represented as the Spearman's correlation coefficient between the standard and EULAR adjusted risk score and vascular outcome. p-values from Meng's test for correlated correlations. ACh: acetylcholine; EULAR: European League against Rheumatism; FMD: flow-mediated dilatation; GTN: glyceryl trinitrate mediated dilatation; HDL: high density lipoprotein; cIMT: carotid intima-media thickness; SCORE: systematic coronary risk evaluation; SNP: sodium nitroprusside; TC: total cholesterol.

scores which only include a few CVD risk factors.

The Reynolds Risk Score includes several classical CVD risk factors but also includes novel CVD risk factors such as CRP, which in itself is an independent predictor of CVD (33), possibly due to direct adverse effects on the vasculature (34). Although some studies have reported associations between CRP and vascular function and morphology (35), we have previously reported that CRP measured at a single time point and cumulatively over six years does not associate with assessments of the vasculature (13, 29). In a study comparing RA to diabetes, macrovascular endothelium-dependent function was similar between groups despite RA patients having considerably higher levels of CRP than diabetics patients (36). Furthermore, a systematic review of the literature reported that RA disease activity (including CRP) does not consistently associate with vascular function and morphology (37). Collectively, these findings could explain why the Reynolds Risk Score did not show stronger associations with vascular assessments when compared to the other CVD risk prediction scores.

The present study showed that while FRS was associated with all of the vascular parameters; it was a significantly poorer predictor of macrovascular endothelium-independent function when compared to QRISK2. The FRS has been reported to under-represent risk of cardiac events in other clinical conditions such as diabetes and systemic lupus erythematosus (38, 39). In addition, two studies that compared RA patients with healthy controls matched for FRS reported lower macrovascular endothelium-dependent function and greater arterial stiffness and cIMT in the RA patients (40, 41). This suggests that the combination of CVD risk factors included in the FRS does not sufficiently account for vascular impairments in RA. It has been suggested that incorporating coronary artery calcification into the FRS would increase the accuracy of estimating CVD risk, as a high FRS independently associates with coronary artery calcification in RA (42).

Application of the EULAR multiplication factor to the CVD risk prediction scores did not increase the strength of associations with vascular parameters. The EULAR guidelines are applied in patients who meet two of the following criteria; disease duration greater than 10 years, rheumatoid factor or anti-cyclic citrullinated peptide antibody positivity or presence of extra articular manifestations (22). However, cardiac events still occur in patients who do not meet these criteria (43). The criteria used to apply the EULAR multiplication does not adequately reflect the risk of CVD during the course of RA, as there is evidence suggesting that the relative risk for CVD events is quite elevated early in the disease course (44, 45), and hospital admissions for CVD are increased in the first 7 years of diagnosis (46). Interestingly, application of EULAR task force recommendations to the SCORE tool can improve identification of RA patients with high CVD risk (47), but such tools can fail to adequately identify patients with vascular abnormalities (48). Therefore, further research is needed to develop a CVD risk prediction tool which is RA-specific and accounts for CVD risk from the point of RA diagnosis.

At present, with the exception of one small pilot study (49), to our knowledge, there is very little research examining whether assessments of vascular function and morphology are indicative of adverse CV outcomes in patients with RA. The findings of our study support a link between high CVD risk at baseline and worse vascular outcomes after a long follow-up period. This bi-directional relationship suggests that non-invasive vascular assessments can reflect risk for cardiac events in RA, as measured by conventional CVD risk prediction tools, and may therefore be useful tools to monitor *in vivo* progression of subclinical CVD. Further prospective studies examining relationships between baseline vascular function and morphology and subsequent development of cardiac events over a protracted timescale are warranted.

The strengths of the present study are the inclusion of a large sample of RA survivors from the DRACCO study who were prospectively followed up over a lengthy period of time, calculation of five well-established CVD risk prediction scores, and examination of several assessments of vascular function and morphology in the microvasculature and the macrovasculature. Such a study design made it possible to examine the association between CVD risk prediction scores and vascular outcomes over a protracted timescale. In addition, there was minimal loss in data during follow-up, and all CVD risk prediction scores had comparative performance. It is important to note that the CVD risk prediction scores utilised in the present study are not designed or validated to predict impairments in vascular function and morphology. CVD risk prediction scores specifically predict risk of developing CVD, while assessments of vascular function and morphology reflect subclinical atherosclerotic changes in the vasculature (12). Nevertheless, the current study helps highlight the link between actual CVD risk and early alterations in vascular function and morphology in RA. Unfortunately, medication use was different between baseline and follow-up assessments and might have impacted on our findings. The most notable changes were an increase in anti-TNF and anti-hypercholesterolemic use. It is noteworthy that such changes might actually improve vascular function (37, 50) making an association with CVD risk prediction scores less likely. It is clear that further prospective studies which evaluate changes in CVD risk prediction scores and vascular status over time are needed.

Conclusion

In summary, the present study revealed that five commonly used CVD risk prediction scores associate with assessments of subclinical atherosclerosis in RA suggesting that these CVD risk prediction scores may also reflect subclinical atherosclerotic changes. Further detailed prospective studies are required confirming these findings.

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