The 2013 ACC/AHA 10-year atherosclerotic cardiovascular disease risk index is better than SCORE and QRisk II in rheumatoid arthritis: is it enough?

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Abstract

Objective. To determine the ability of the new American College of Cardiology and American Heart Association (ACC/AHA) 10-year atherosclerotic cardiovascular disease (ASCVD) risk algorithm in detecting high cardiovascular (CV) risk, RA patients identified by carotid ultrasonography (US) were compared with Systematic Coronary Risk Evaluation (SCORE) and QRisk II algorithms.

Methods. SCORE, QRisk II, 2013 ACC/AHA 10-year ASCVD risk and EULAR recommended modified versions were calculated in 216 RA patients. In sonographic evaluation, carotid intima–media thickness >0.90 mm and/or carotid plaques were used as the gold standard test for subclinical atherosclerosis and high CV risk (US+).

Results. Eleven (5.1%), 15 (6.9%) and 44 (20.4%) patients were defined as having high CV risk according to SCORE, QRisk II and ACC/AHA 10-year ASCVD risk, respectively. Fifty-two (24.1%) patients were US + and of those, 8 (15.4%), 7 (13.5%) and 23 (44.2%) patients were classified as high CV risk according to SCORE, QRisk II and ACC/AHA 10-year ASCVD risk, respectively. The ACC/AHA 10-year ASCVD risk index better identified US + patients than SCORE and QRisk II ($P < 0.0001$). With EULAR modification, reclassification from moderate to high risk occurred only in two, five and seven patients according to SCORE, QRisk II and ACC/AHA 10-year ASCVD risk, respectively.

Conclusion. The 2013 ACC/AHA 10-year ASCVD risk estimator was better than the SCORE and QRisk II indices in RA, but still failed to identify 55% of high risk patients. Furthermore adjustment of threshold and EULAR modification did not work well.

Key words: cardiovascular risk estimation, SCORE, QRisk II, ACC/AHA 10-year ASCVD, carotid intima-media thickness.

Rheumatology key messages

- The 2013 ACC/AHA risk estimator is better than systematic coronary risk evaluation and QRisk II in RA.
- The 2013 ACC/AHA risk estimator still failed to identify 55% of high risk RA patients.
- For cardiovascular risk estimation in RA, threshold decrement is better than EULAR modification.

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Introduction

It is now well-established that RA is associated with increased cardiovascular (CV) morbidity and mortality, which are up to 50% and 60% higher compared with the general population, respectively [1–4]. Reports have suggested that this higher risk cannot be fully explained

by traditional risk factors, and indeed is multifactorial with contributions from RA-related inflammatory activity, RA-related medications and genetic background [5, 6]. Therefore, besides monitoring RA disease activity, screening of traditional and non-traditional CV risk factors and identification of high-risk patients are of paramount importance in RA management. In the general population certain CV risk models that assess CV risk are used for guiding preventive or therapeutic strategies [7–12]. Currently EULAR recommends annual CV risk assessment in RA patients using national guidelines or a Systematic Coronary Risk Evaluation (SCORE) model if national guidelines are absent [13]. A further adaptation of the SCORE model is recommended in RA patients by multiplying the SCORE with a correction factor of 1.5 if the patient meets two of the following three criteria: disease duration >10 years, RF and/or anti-CCP positivity, and presence of extra-articular manifestations [13]. However, recent data have shown that CV risk models for the general population including the Framingham Risk Score (FRS), the SCORE and the Reynolds Risk Score (RRS) (involving high sensitive CRP) and QRisk II (including RA as an independent risk factor) do not accurately reflect the true CV risk of RA patients [14–16]. Furthermore, the EULAR recommended multiplication factor of 1.5 does not seem to improve CV risk estimation in RA [16]. Accordingly, some authors recommend carotid ultrasonography (US) for CV risk assessment [17]. Increased carotid intima–media thickness (cIMT) and the presence of plaques detected by carotid US are good surrogate markers for the development of atherosclerosis and good predictors of CV events in non-rheumatic individuals and in patients with RA [18–23].

In 2013 the American College of Cardiology (ACC) and the American Heart Association (AHA) offered a new 10-year atherosclerotic CV disease (ASCVD) risk estimation algorithm to guide cardiovascular disease (CVD) preventive strategies [12]. However, performance of this new algorithm in CV risk estimation of RA patients is not fully assessed yet. In this study we primarily aimed to determine the ability of the new ACC/AHA 10-year ASCVD risk algorithm to detect high CV risk RA patients identified by carotid US, compared with SCORE and QRisk II algorithms. A second objective was to determine the factors that may improve CV risk estimation in RA.

Methods

Study design and patients

For this cross sectional study a set of RA patients who were regularly (3–6 month intervals) followed up with a protocol were recruited over a 1-year period. All patients were older than 18 years of age and fulfilled the 1987 ACR and 2010 ACR/EULAR classification criteria for RA [24, 25]. Patients with a history of CVD (ischaemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure) or type 1 or 2 diabetes mellitus (DM) or chronic kidney disease were excluded from the study. Among 334 RA patients evaluated, 216 were found to be

eligible for the study. Demographic data and disease characteristics including RF and/or anti-CCP positivity, extra-articular manifestations, other comorbidities, all previous and current medications, 28 joint DAS (DAS28)-ESR, ESR (mm/h) and CRP (mg/l) values at the recruitment period were recorded. All previous patient visits [median visit count (min – max) was 8 (2–24)] were also examined retrospectively, and 3–6 monthly visits' DAS28 scores, ESR and CRP values were noted. The average of all visits' DAS28 scores, ESR and CRP values were calculated and recorded as average DAS28 score, average ESR and average CRP, respectively. The ratios of high disease activity (HDA; defined as DAS28 >5.1) and moderate disease activity (MDA; defined as DAS28 > 3.2 and ⩽5.1) to total visits were also calculated and recorded as HDA and MDA visits ratios [26]. CV risk factors including hypertension (HT), smoking status and family history of CVD were determined. HT was defined by use of antihypertensive medication or systolic blood pressure of 140 mmHg or more or diastolic blood pressure of 90 mmHg or more on at least two occasions. At the time of recruitment, blood pressure, waist circumference (cm), weight (kg) and height (m) were measured, and BMI was calculated. All patients' lipid concentrations and fasting glucose levels were recorded within the previous 6 months, measured enzymatically with a commercially available assay kit (AU5800, Beckman Coulter, Brea, CA, USA; and E170 Modular, Roche, Basel, Switzerland, respectively) in our hospital laboratory. Atherogenic index [total cholesterol/high density lipoprotein (HDL)-cholesterol] was calculated. Patients with impaired fasting glucose (defined as fasting plasma glucose 100–125 mg/dl) were regarded as prediabetes [27]. However, to exclude DM diagnosis those patients underwent a 75 g oral glucose tolerance test (OGTT). In the 75 g OGTT, patients with 2-h glucose levels of 140–199 mg/dl were again regarded as prediabetes but patients with 2-h glucose ⩾200 mg/dl (also in a repeat test) were diagnosed as DM and excluded from the study [27]. None of the OGTT-tested patients were diagnosed as DM. All patients were also evaluated for the presence of metabolic syndrome, which was defined according to the National Cholesterol Education Programme's Adult Treatment Panel III definition [28]. The study was approved by the Marmara University Institutional Research Ethics Board (Istanbul, Turkey) and informed consent was obtained from all patients according to the Declaration of Helsinki.

Cardiovascular risk assessment

Three CV risk assessment algorithms, namely SCORE, QRisk II and 2013 ACC/AHA 10-year ASCVD, were used to calculate the 10-year risk of a CV event [7, 8, 12]. All risk algorithms included gender, smoking, total cholesterol/HDL-cholesterol ratio and systolic blood pressure. The 2013 ACC/AHA 10-year ASCVD and QRisk II additionally included treatment for high blood pressure (Y/N) and presence of DM (Y/N) [8, 12]. Also QRisk II included RA as an independent risk factor as well as the presence of family history of early CVD, chronic kidney disease, atrial

fibrillation, BMI and the Townsend deprivation score [8]. The latter was not available in our cohort, and therefore CV risk was calculated using an adjusted QRisk II algorithm excluding this variable. Modified versions of these risk indices were also calculated according to EULAR recommendations as described above and recorded as modified (m)SCORE, mQRisk II and mASCVD, respectively. Patients with SCORE ⩾5% or QRisk II ⩾20% or ASCVD ⩾7.5% were categorized as high CV risk patients.

Carotid US examination

All patients were evaluated with carotid US by an experienced sonographer cardiologist (M.S.) via a commercially available Vivid 7 (GE Healthcare, Horten, Norway) ultrasound system with a 10-MHz linear transducer. Carotid US examination included measurement of cIMT in the common carotid artery and detection of focal plaques in the extracranial carotid tree. cIMT >0.90 mm and/or carotid plaques were used as the gold standard test for subclinical atherosclerosis and high CV risk [15]. Patients with any of the mentioned US findings were regarded as true high CV risk patients (US+).

Statistical analysis

Statistical analysis was performed using SPSS software version 16.0 (SPSS, Chicago, IL, USA). Continuous variables were presented as the mean ± S.D. Correlations between carotid US findings, and clinical and laboratory parameters were analysed by Pearson's correlation coefficient. The univariate analysis to identify variables associated with high CV risk (US+) was investigated using either χ^2 and Student's t-tests or a non-parametric test (Wilcoxon's signed rank test, Mann–Whitney U-test), as applicable. To evaluate the capacity of the CV risk indices to discriminate between patients with and without subclinical atherosclerosis, receiver operating characteristic curves with corresponding area under the curve (AUC) were calculated. The candidate variables identified in univariate analysis with P values of <0.05 were analysed using a stepwise multivariable logistic regression model to determine independent risk factors for high CV risk in RA patients. The following variables were included in the analysis: age >45 years, gender, age at diagnosis >55 years, ever-smoked, prediabetes, atherogenic index, increased waist circumference (⩾102 cm in males, ⩾88 cm in females), elevated ESR at the study entry, average CRP, being at HDA or MDA >30% of the total follow-up period and ever-tumour necrosis factor-α inhibitor (TNFi) usage. Hosmer–Lemeshow goodness of fit statistics were used to assess model fit. Level of significance was chosen to be P < 0.05.

Results

Patient characteristics

The study cohort consisted of 216 RA patients (F/M = 173/43, mean age 52.4 ± 11.4 years) with a mean disease duration of 11.2 ± 7.1 years. RF and anti-CCP positivity were 68.7% and 59.8%, respectively. Ninety-five patients

TABLE 1 Patient characteristics (n = 216)

Age, mean (S.D.), years	52.4 (11.4)
Female, n (%)	171 (79.5)
Disease duration, mean (S.D.), years	11.2 (7.1)
RF and/or Anti-CCP positivity, n (%)	167 (78)
Extra-articular involvement[a], n (%)	56 (26.2)
Current smoker, n (%)	31 (14.5)
Ever-smoked, n (%)	66 (30.8)
ESR at the study entry, mean (S.D.), mm/h	21.5 (15.5)
CRP at the study entry, mean (S.D.), mg/l	10.7 (1.8)
Average ESR, mean (S.D.), mm/h	26.3 (13.0)
Average CRP, mean (S.D.), mg/l	10.1 (9.5)
DAS28 score at the study entry, mean (S.D.)	3.35 (1.32)
Average DAS28 score, mean (S.D.)	3.69 (1.01)
HDA visits/total visits, mean (S.D.), %	17.7 (2.2)
MDA + HDA visits/total visits, mean (S.D.), %	57.0 (31.1)
HAQ score, mean (S.D.)	0.56 (0.62)
HT, n (%)	73 (34.1)
Systolic blood pressure, mean (S.D.), mmHg	124.7 (18.5)
Diastolic blood pressure, mean (S.D.), mmHg	78.2 (10.1)
Total cholesterol, mean (S.D.), mg/dl	197.5 (40.4)
HDL-cholesterol, mean (S.D.), mg/dl	58.4 (17.3)
LDL-cholesterol, mean (S.D.), mg/dl	115.3 (38.9)
Atherogenic index, mean (S.D.)	3.62 (1.25)
BMI, mean (S.D.), kg/m^2	28.0 (5.85)
Obesity, n (%)	70 (32.7)
Metabolic syndrome[b], n (%)	52 (24.3)
Current bDMARD treatment, n (%)	98 (45.8)
Ever bDMARDs treatment, n (%)	117 (54.7)
Prednisolone, n (%)	115 (53.7)
Current prednisolone dose, mean (S.D.), mg/day	5.1 (3.9)

[a]Includes secondary Sjögren's syndrome, rheumatoid nodule, interstitial lung disease, rheumatoid vasculitis, pleuritis/pericarditis and scleritis. [b]Metabolic syndrome is defined according to the National Cholesterol Education Programme's Adult Treatment Panel III definition. bDMARD: biologic DMARD; HAQ: health assessment questionnaire; HDA: high disease activity; HDL: high-density lipoprotein; HT: hypertension; LDL: low-density lipoprotein; MDA: moderate disease activity.

(44.4%) had disease duration longer than 10 years. All patients were receiving synthetic DMARDs (sDMARDs) or biologic DMARDs (bDMARDs) either as monotherapy or combination therapy. Patient characteristics are presented in Table 1.

Cardiovascular risk algorithms and carotid US results

The mean SCORE was 1.3 ± 1.9%, QRisk II was 8.0 ± 7.7% and ACC/AHA 10-year ASCVD risk was 4.8 ± 6.0%. Eleven (5.1%), 15 (6.9%) and 44 (20.4%) patients were defined as having high CV risk according to SCORE (⩾5%), QRisk II (⩾20%) and ACC/AHA 10-year ASCVD risk (⩾7.5%), respectively. Concerning US results, mean cIMT was 0.68 ± 0.14 mm and 52 (24.1%) patients had either cIMT >0.90 mm or carotid plaques (US+). Among US + patients 39 had carotid plaques, 33 had cIMT

>0.90 mm and 20 had both increased cIMT and carotid plaques.

Discrimating capacities of the three risk indices were good with AUC 0.741 (CI 95%: 0.661–0.822) of SCORE, AUC 0.722 (CI 95%; 0.646–0.797) of QRisk II and AUC 0.738 (CI 95%: 0.663–0.814) of ACC/AHA 10-year ASCVD risk (Fig. 1). Nevertheless, the ability to identify the patients with subclinical atherosclerosis, i.e. high CV risk patients, was not satisfactory. Of those 52 US+ patients, 8 (15.4%) were classified as high CV risk according to SCORE, 7 (13.5%) were classified as high CV risk according to QRisk II and 23 (44.2%) were classified as high CV risk according to ACC/AHA 10-year ASCVD risk (Fig. 2A). The ACC/AHA 10-year ASCVD risk index better identified US+ patients than SCORE and QRisk II (P < 0.0001). However, it still failed to identify 55.8% of US+ patients. The EULAR multiplier factor was used in 98 (45.4%) patients. With this modification, mASCVD reclassified only seven US+ patients who were in moderate ACC/AHA 10-year ASCVD risk category into high CV risk. Similarly mSCORE and mQRisk II reclassified only two and five of US+ patients with moderate risk scores into high CV risk. None of the US+ patients with low risk scores (42 patients, 40 patients and 16 patient according to SCORE, QRisk II and ACC/AHA 10-year ASCVD risk, respectively) were reclassified as high CV risk by using the EULAR multiplier factor. However, when cut-off values for risk indices were lowered and moderate CV risk patients (SCORE >1% and <5%, QRisk II >10% and <20%, ASCVD >5% and <7.5%) were included in the high risk category, detection of US+ patients, i.e. sensitivity, increased dramatically, with slight decrease in specificity (Fig. 2B).

Predictors of subclinical atherosclerosis

Comparison of demographics, disease characteristics and traditional risk factors of US+ and US− patients is shown in Table 2. US+ patients were older and had higher average DAS28 scores, HDA visit ratios, average ESR and CRP levels. Current ESR levels and number of patients with elevated ESR (>20 mm/h) (60.8% vs 39.9%; P = 0.009) were also higher in US+ patients than US− patients. Disease duration, RF and/or anti-CCP positivity, extra-articular involvement and joint replacement surgery rates did not significantly differ between US+ and US− patients. Concerning traditional risk factors, we found that prediabetes, being ever-smoked and atherogenic index were significantly higher in US+ patients (Table 2). All patients were receiving sDMARD treatment and almost all were exposed to corticosteroids previously; previous and current sDMARD, current corticosteroid treatment and daily doses and NSAID usage (defined as ⩾3 NSAID pills/week during the last year) were all comparable. On the other hand US+ patients had significantly lower TNFi treatment (ever-TNFi used is defined as active or previous TNFi treatment of at least 1 year duration) (35.3% vs 52.8%; P = 0.029).

In univariate analyses, we identified 11 baseline variables that were associated with subclinical atherosclerosis at a

P value of <0.05: age >45 years, gender, age at diagnosis >55 years, ever-smoked, prediabetes, atherogenic index, increased waist circumference, elevated ESR at the study entry, average CRP, being at HDA or MDA >30% of the total follow-up period and ever-TNFi usage (Table 2). In multivariable logistic regression analysis, age >45 years, being ever-smoked, elevated ESR, average CRP and being never used TNFi were independently associated with subclinical atherosclerosis, i.e. high CV risk in RA patients (Table 3).

Discussion

In the era of biologic agents for the treatment of inflammatory arthritis, CVD is still the major cause of death in RA. One of the most challenging questions when treating RA patients in clinical practice is how to estimate CV risk in an RA patient. While it has been demonstrated that CV risk algorithms for the general population like FRS, RRS, SCORE and QRisk II do not work well in RA [14–16], the performance of the new 2013 ACC/AHA ASCVD risk algorithm in RA has not been fully elucidated yet.

In the present study, we found that the ACC/AHA ASCVD risk algorithm failed to identify the majority (~55%) of the patients with increased cIMT and/or carotid plaques. However the ASCVD risk index was better than SCORE and QRisk II in detecting patients with subclinical atherosclerosis when the high risk thresholds (>7.5%, >5%, >20%, respectively) for all three risk indices were used. As the majority of the patients with subclinical atherosclerosis reside in the low/moderate risk category according to risk indices, we lowered the threshold for risk stratification (SCORE >1%, QRisk II >10% and ASCVD >5% as high CV risk). This modification resulted in increased sensitivity of all three risk indices with similar detection rates of subclinical atherosclerosis reaching about 60% for all. However, still 40% of patients with high CV risk were misclassified in the low risk category according to these risk indices. This reduction in threshold also caused classification of some patients without subclinical atherosclerosis as having high risk, i.e. a decrease in specificity to ~75%. The performance of the ACC/AHA ASCVD risk index in RA patients has only been evaluated in one study so far [29]. Although the definition of high risk patients was different (high coronary artery calcification score) in that study, the results were consistent with ours that the ACC/AHA ASCVD risk index was unable to detect almost 60% of RA patients with high coronary artery calcification scores [29]. Moreover this new risk estimator was not found to be superior to the FRS and RRS indices. On the other hand reduction of threshold in that study did not dramatically increase the sensitivity of FRS and RRS risk indices. Our study also showed that the EULAR multiplier factor failed to improve the performance of the ASCVD and QRisk II risk indices as previously described for SCORE [15,16].

Current evidence along with the findings of our study indicates that none of the risk models, including the new ACC/AHA ASCVD risk index, used for the general population have the ability to estimate the true CV risk of RA

FIG. 1 Receiver operating characteristic-curves of the different risk algorithms
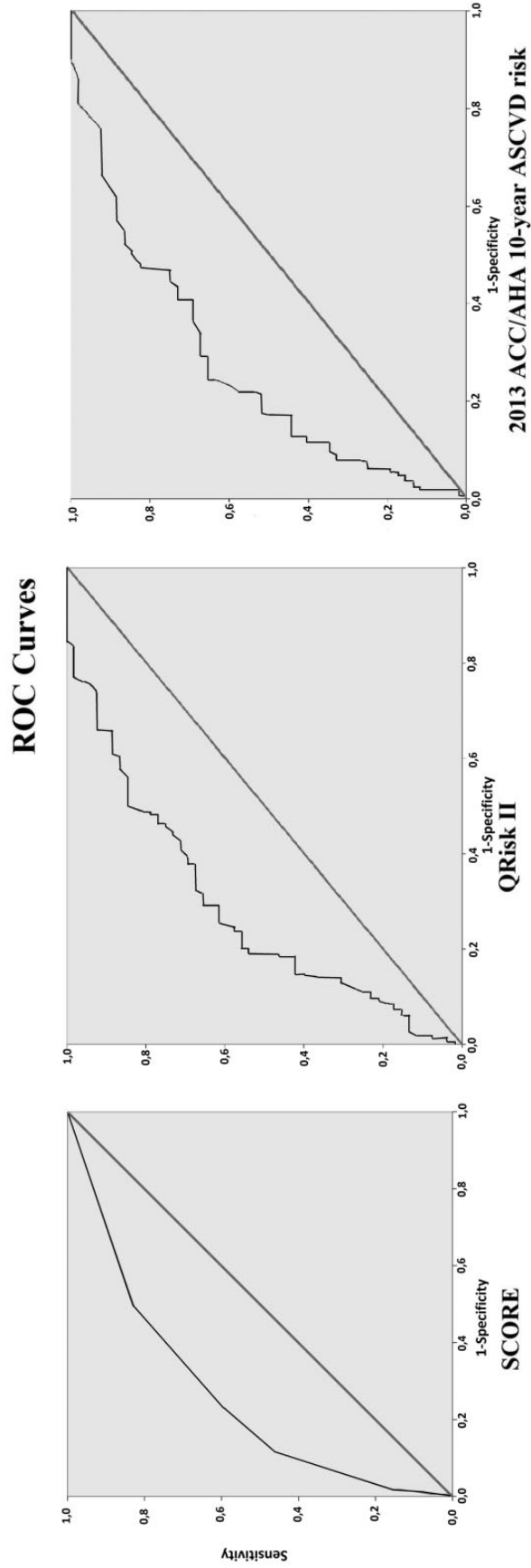
ROC: receiver operating characteristic.

Fig. 2 CV risk stratification of US+ and US – patients according to three different CV risk indices with different thresholds
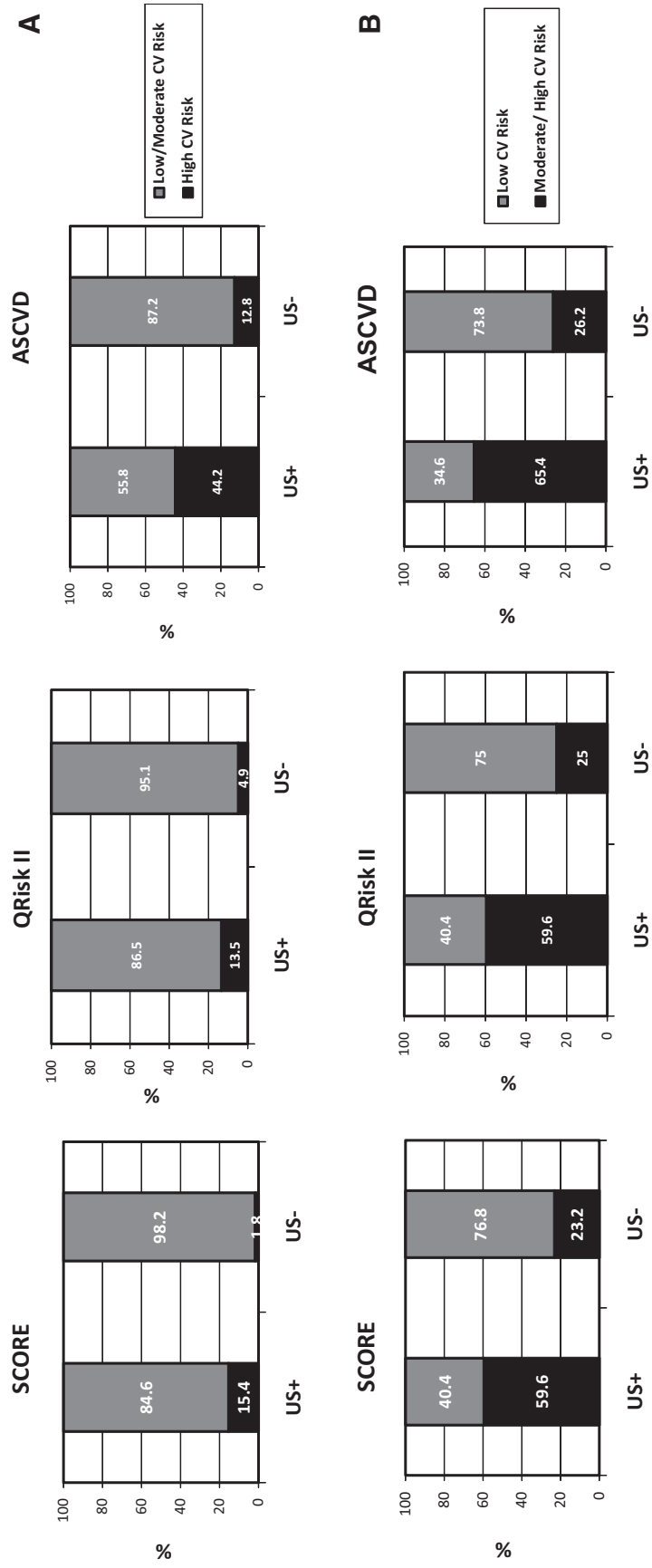
ASCVD: atherosclerotic cardiovascular disease; SCORE: systematic coronary risk evaluation; CV: cardiovascular.

TABLE 2 Characteristics of US + and US − RA patients

	US + (n = 52)	US– (n = 164)	P
Male, n (%)	17 (33.3)	26 (16)	0.007
Age, mean (s.d.), years	59.0 (8.4)	50.4 (11.4)	<0.0001
Age at disease onset, mean (s.d.), years	48.7 (9.1)	39.1 (12.1)	<0.0001
Disease duration, mean (s.d.), years	10.3 (7.6)	11.4 (6.9)	0.33
RF positivity, n (%)	38 (73.1)	111 (67.7)	0.46
Anti-CCP positivity, n (%)	30 (57.7)	98 (59.8)	0.79
Extra-articular involvement, n (%)	11 (21.6)	45 (27.6)	0.39
Average DAS28[a], mean (s.d.)	4.04 (1.1)	3.59 (0.96)	0.005
HDA visit count/Total visit count, mean (s.d.)	24.3 (26.7)	15.6 (21.2)	0.017
Average ESR[a], mean (s.d.), mm/h	32.8 (14.3)	24.2 (12.0)	<0.0001
Average CRP[a], mean (s.d.), mg/l	14.3 (12.2)	8.8 (8.0)	<0.0001
ESR at the study entry, mean (s.d.), mm/h	26.6 (18.0)	20.0 (14.4)	0.008
CRP at the study enrty, mean (s.d.), mg/l	12.6 (16.9)	10.0 (18.4)	0.37
HAQ score, mean (s.d.)	0.49 (0.49)	0.59 (0.65)	0.30
BMI, mean (s.d.), kg/m^2	28.5 (6.8)	27.9 (5.5)	0.52
Waist circumference, mean (s.d.), cm	99.1 (15.6)	96.6 (13.8)	0.28
HT, n (%)	19 (37.3)	54 (33.1)	0.58
Prediabetes, n (%)	13 (25.5)	20 (12.3)	0.023
Metabolic syndrome[b], n (%)	16 (31.4)	36 (22.1)	0.17
Ever-smoked, n (%)	23 (45.1)	43 (26.4)	0.012
Total cholesterol/HDL-cholesterol, mean (s.d.)	3.97 (1.63)	3.52 (1.09)	0.022
LDL-cholesterol, mean (s.d.), mg/dl	120.6 (31.4)	113.7 (40.9)	0.26
Low HDL-cholesterol[c], n (%)	14 (27.5)	51 (31.3)	0.60
Triglyceride ⩾150 mg/dl, n (%)	11 (21.6)	33 (20.2)	0.83
NSAID usage[d], n (%)	13 (25.5)	25 (15.3)	0.098
Current corticosteroid treatment, n (%)	30 (58.8)	85 (52.1)	0.40
Current corticosteroid dose, median (IQR), mg/day	5.0 (2.5–5.0)	5.0 (2.5–5.0)	0.41
bDMARDs ever, n (%)	23 (45.1)	94 (57.7)	0.11
Ever-TNFi	18 (35.3)	86 (52.8)	0.029
Other bDMARDs	4 (7.8)	6 (3.7)	0.21

[a]The average DAS28, ESR and CRP of all recorded visits. [b]Metabolic syndrome is defined according to National Cholesterol Education Programme's Adult Treatment Panel III definition. [c]Low HDL-cholesterol is defined as HDL-cholesterol <40 mg/dl in males and <50 mg/dl in females. [d]NSAID usage is defined as ⩾3 NSAID pills/week during the last year. bDMARD: biologic DMARD; HDA: high disease activity; HAQ: Health Assessment Questionnaire; HDL: high-density lipoprotein; IQR, interquartile range; LDL: low-density lipoprotein; TNFi: tumour necrosis factor-α inhibitor.

TABLE 3 Predictors of subclinical atherosclerosis in RA patients

Variables	β	OR (95% CI)	P
Age >45 years	2.510	12.3 (2.7–56.5)	0.001
Ever-smoked	0.805	2.2 (1.1–4.6)	0.031
Average CRP	0.052	1.05 (1.01–1.1)	0.008
Elevated ESR (>20 mm/h) at the study entry	0.981	2.7 (1.3–5.5)	0.008
Ever-TNFi treatment	−0.866	0.42 (0.20–0.86)	0.018

OR: odds ratio; TNFi: tumour necrosis factor-α inhibitor.

patients [14–16, 29]. This misestimation mainly results from focusing entirely on traditional CV risk factors, lack of reliable and feasible markers of cumulative inflammatory burden of RA patients in these risk models and the different impact of some traditional risk factors on CV risk in RA patients. The EULAR recommended multiplier factor also does not overcome shortcomings of CV risk models in RA [15, 16]. The number 1.5 comes from relevant standardized mortality ratios of disease duration, seropositivity and extra-articular involvement. However, certain other disease characteristics and traditional risk factors, such as use of corticosteroids, NSAIDs or biologics and BMI may modify the CVD risk in RA as well [30, 31]. It has also been shown that the increased CVD risk begins not only after 10 years of disease duration, but begins even prior to or within 1 year of the clinical onset of

RA [32]. Despite these data about CV risk in RA, currently there are a number of unanswered questions regarding the ways to improve CV risk assessment in RA patients and the relative impact of disease characteristics and CV risk factors on CVD. Therefore in this study we also analysed the data to determine the factors associated with subclinical atherosclerosis that may improve CV risk estimation in RA. In multi-variate logistic regression analysis we found that increased age, being ever-smoked, increased ESR and increased average CRP were all independently associated with subclinical atherosclerosis. All the CV risk models already include age and smoking status as a risk factor. However, currently there is only one risk index, RRS, that includes an inflammatory marker, high sensitive CRP, as a risk factor. Still, RRS seems to underestimate the CV risk of RA patients similarly to SCORE or FRS, which do not include CRP [14]. In our study, CRP level during the evaluation period was not predictive of subclinical atherosclerosis when other factors were adjusted. Instead elevated ESR (>20 mm/h) at the evaluation period and the cumulative CRP, calculated as average CRP of total visits, were independently associated with subclinical atherosclerosis. It has been reported that CRP is associated with atherosclerosis and CVD in the general population and in the RA patients [33, 34]. Each of these parameters denotes the inflammatory activity, and for a better CV risk estimation in RA it is clearly necessary to incorporate a marker that reflects inflammatory burden to the CV risk model. But the best marker, a single time-point measurement of ESR or an average value of CRP or any other biomarker, and the coefficient of inflammatory marker relative to traditional risk factors should be determined. Besides these, there was only one parameter that seems to protect against development of atherosclerosis: being ever-used TNFi. Considering the importance of inflammation in the development of atherosclerosis, a positive impact of TNFis is reasonable as they are effective therapies reducing the disease activity in RA. However, there are controversial data about the effects of TNFi treatment on CVD in RA [35–38]. Some studies showed no associations between TNFi treatment and risk of CVD in RA, but there is growing evidence that TNFi treatment improves vascular function [39, 40] and significantly decreases the CVD in RA especially in responders [41–44]. In the future TNFi exposure may be involved in the CV risk models for RA.

Several strengths and weaknesses of this study should be considered. Despite not being an inception cohort, this is a well-monitored cohort in that patients' disease activity (DAS28) and acute phase reactants (ESR and CRP) were all recorded throughout the entire follow-up period. However we could not retrieve the data about cumulative corticosteroid dose and total NSAID exposure. We also could not determine the ability of risk scores to predict CV events because of the cross-sectional design of the study. Instead we used increased cIMT and/or carotid plaques as a surrogate marker for future atherosclerotic CV events. Finally, as with all observational studies, some residual confounding may exist in the current study.

In conclusion, the 2013 ACC/AHA 10-year ASCVD risk estimator is better than the SCORE and QRisk II indices when the high risk threshold for risk indices is used. Despite this, ACC/AHA 10-year ASCVD failed to identify about 55% of high CV risk patients detected by carotid US. However, when the threshold of the risk stratification was lowered, all three risk indices similarly identified US + patients (∼60%). New RA-specific risk algorithms are required to identify high-risk patients who may benefit from active therapy to prevent CV events. Until there is development of a good RA-specific CV risk estimator, adjustment of the threshold may be a better modification than the EULAR multiplier factor. Evidence from this study and other studies about CV risk estimation indicates that the ACC/AHA 10-year ASCVD risk index works better than the others in RA. Therefore for the development of an RA-specific CV risk estimator, the ACC/AHA 10-year ASCVD risk model may provide the infrastructure. Elevated ESR and TNFi usage may also be a part of this risk estimator.

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