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EXTENDED REPORT

Cardiovascular risk stratification in rheumatic diseases: carotid ultrasound is more sensitive than Coronary Artery Calcification Score to detect subclinical atherosclerosis in patients with rheumatoid arthritis

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ABSTRACT

Objective To determine the ability of Coronary Artery Calcification Score (CACS) and carotid ultrasonography in detecting subclinical atherosclerosis in rheumatoid arthritis (RA).

Methods A set of 104 consecutive RA patients without history of cardiovascular (CV) events were studied to determine CACS, carotid intima-media thickness (cIMT) and plaques. Systematic Coronary Risk Evaluation (SCORE) modified according to the EULAR recommendations (mSCORE) was also assessed.

Results The mean disease duration was 10.8 years, 72.1% had rheumatoid factor and/or anti-CCP positivity and 16.4% extra-articular manifestations. Nine were excluded because they had type 2 diabetes mellitus or chronic kidney disease. CV risk was categorised in the remaining 95 RA patients according to the mSCORE as follows: low (n=21), moderate (n=60) and high/very high risk (n=14). Most patients with low mSCORE (16/21; 76.2%) had normal CACS (zero), and none of them CACS>100. However, a high number of patients with carotid plaques was disclosed in the groups with CACS 0 (23/40; 57.5%) or CACS 1–100 (29/38; 76.3%). 72 (75.8%) of the 95 patients fulfilled definitions for high/very high CV as they had an mSCORE ≥5% or mSCORE <5% plus one of the following findings: severe carotid ultrasonography findings (cIMT>0.9 mm and/or plaques) or CACS>100. A CACS>100 showed sensitivity similar to mSCORE (23.6% vs 19.4%). In contrast, the presence of severe carotid ultrasonography findings allowed identifying most patients who met definitions for high/very high CV risk (70/72; sensitivity 97.2% (95% CI 90.3 to 99.7)).

Conclusions Carotid ultrasonography is more sensitive than CACS for the detection of subclinical atherosclerosis in RA.

INTRODUCTION

Rheumatoid arthritis (RA) is the prototype of disease associated with accelerated atherosclerosis and increased rate of cardiovascular (CV) disease.^{1–2} The mechanisms leading to an elevated CV mortality rate in RA are complex, including traditional CV and the presence of other factors such as a chronic inflammatory state and a genetic compound.^{3–6} Therefore, a comprehensive assessment and treatment of traditional and non-traditional CV risk factors should form part of the

routine care of the patient with RA.⁷ However, adequate stratification of the CV risk in patients with RA is still far from being completely established. Classic risk assessment tools used to estimate the CV risk in the general population may not fully predict the development of future CV events in patients with RA. Reports showing patients who did not reach values to be considered as having high CV risk according to these CV risk estimates, such as the Systematic Coronary Risk Evaluation (SCORE) modified according to the European League Against Rheumatism (EULAR) recommendations,⁸ who suffered CV complications, mainly ischaemic heart disease, have been reported.⁹ Therefore, the search for additional tools that may help to identify high-risk patients, who may benefit from active therapy to prevent CV events, is needed. It may be of major importance in RA patients who are not included in the categories of high or very high CV risk according to the classic risk assessment tools.

Several validated non-invasive imaging techniques offer a unique opportunity to study the relation of surrogate markers to the development of atherosclerosis.¹⁰ They may be useful to determine subclinical atherosclerosis in RA patients. Among them, the assessment of carotid intima-media thickness (cIMT) and the presence of plaques by carotid ultrasonography has become an affordable, efficient technique to measure the presence of subclinical atherosclerosis in RA.^{10–11} Both cIMT and carotid plaques were found to be good predictors of CV events in low and intermediate risk groups of non-rheumatic individuals and also in patients with RA.^{12–14} We previously proposed that carotid ultrasonography assessment should be considered in the CV risk assessment of patients with RA who do not fulfil definitions for high CV risk according to the SCORE.¹⁵ In keeping with this proposal, a recent study has confirmed that carotid ultrasonography assessment may be useful to establish the actual CV risk in RA, in particular in patients with moderate SCORE.¹⁶

A question that needs to be answered is whether other non-invasive techniques may also be comparable with carotid ultrasonography to stratify the CV risk of patients with RA. Among them, coronary artery calcification (CAC) has proved to be a predictor of CV events in the general population.¹⁷

In this regard, Coronary Artery Calcification Score (CACS) assessed by the multi-detector CT (MDCT) scan was reported to be useful in the assessment of the extension and severity of atherosclerosis in vascular beds. Using this technique, an increased prevalence of CAC has been observed in patients with RA.¹⁸ A recent study has shown that CAC detected by the MDCT is a good predictor of CV events in patients with RA.¹⁹

Taking together all these considerations, in the present study we aimed to determine the ability of CACS and carotid ultrasonography to detect subclinical atherosclerosis in RA. We also sought to establish the relationship between carotid ultrasonography findings and CACS and whether the use of CACS may improve the stratification of the CV risk of RA patients without clinically evident CV disease.

PATIENTS AND METHODS

Patients

A set of 104 consecutive patients with a diagnosis of RA recruited from Hospital Universitario Marqués de Valdecilla (Santander, Northern Spain) who were seen over a 3-month period were included in the present study. All the patients who were assessed for MDCT and carotid ultrasonography fulfilled the 1987 American College of Rheumatology classification criteria and the 2010 classification criteria for RA.^{20–22} Patients with a history of CV events (ischaemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure that were defined as previously reported) were not recruited in this study.^{5 13} Then, clinical records of all patients were again reviewed in an attempt to fully establish comorbidities. Patients with type 1 diabetes with target organ damage, type 2 diabetes mellitus or those who had severe chronic kidney disease are considered as having very high CV risk according to current guidelines and they were excluded from the final analysis.^{5 23} Patients were considered as having extra-articular manifestations as previously reported.⁵

SCORE risk estimation

Based on a pool of datasets from 12 European cohort studies, mainly carried out in general population settings, European experts performed the SCORE project to develop a risk scoring system for use in the clinical management of CV risk in the European clinical practice.²³ The SCORE risk estimation system offers direct estimation of fatal CV risk in a format suited to the constraints of clinical practice.²⁴ It estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high- and low-risk regions in Europe.²³ Spain was included in the low-risk region in Europe.

Both SCORE and EULAR modified SCORE (mSCORE) according to the EULAR recommendations were calculated to determine the 10-year risk of fatal CV disease in a population at a low CV disease risk.^{8 23} SCORE chart assessment was based on the following risk factors: age, gender, smoking, systolic blood pressure and atherogenic index (total cholesterol/high-density lipoprotein-cholesterol).^{8 23} The subject's written consent was obtained in all the cases. The study was approved by the local Ethical Committee.

MDCT imaging assessment and analysis of data

To determine CACS, all subjects underwent CT imaging of coronary arteries using a 32-slice multi-detector computed tomography (MDCT) scanner (Lightspeed, Pro 32, GE Healthcare, USA). It was performed following current guidelines on the

screening for CAC for cardiac risk assessment.²⁵ Patient's score was calculated as the sum of calcium score in the left main coronary artery, left anterior descending artery, left circumflex coronary artery, right coronary artery and posterior descending artery. Patients were further stratified into four groups according to their range of CACS: CACS=0, CACS=1–100, CACS=101–400 and CACS>400.

In general, the higher the score the more likely the patient is going to have coronary heart disease. CACS>100 indicates a high probability of coronary artery disease. Based on CACS results, a CACS 0 is normal; CACS 1–10 indicates low CV risk; CACS 11–100 moderate CV risk; CACS 101–400 moderate to high CV risk; and CACS>400 high CV risk.²⁶ For the purpose of estimation of high/very high CV risk we used as cut-off a CACS>100.

Carotid ultrasonography examination

Carotid ultrasonography examination included the measurement of cIMT in the common carotid artery and the detection of focal plaques in the extracranial carotid tree.^{16 27} Additional information on Methods is provided in the online supplementary material.

Like in the general population, cIMT>0.90 or the presence of plaques are predictors of CV events in RA.^{13 14} Therefore, patients having cIMT>0.90 or plaques were included in the category of high/very high CV risk.

Statistical analysis

Results were expressed as number (percentage) or mean±SD. Equality of percentages was tested using the Fisher exact test (two-tailed). To estimate the sensitivity to establish the presence of high/very high CV risk we considered the presence of mSCORE≥5% or mSCORE≥1% and <5% plus one of the following imaging findings: severe carotid ultrasonography findings (cIMT>0.9 mm and/or carotid plaques) or CACS>100; 95% CI for sensitivity were estimated assuming a binomial distribution. Goodman–Kruskal γ test was used to measure the strength of association and correlation of the cross-tabulated data on CACS and the variables measured at the ordinal levels. This test was used to determine correlation between CACS and cIMT and between CACS and carotid plaques. A p value <0.05 was considered statistically significant. All the statistical tests were performed with the package Stata V.12/SE (Stata Corp, College Station, Texas, USA).

RESULTS

Most patients from this series of 104 RA patients without CV events were women (73; 70.2%). The age at the time of the study and disease duration (mean±SD) was 59.3±10.3 and 10.8±8.3 years, respectively. Rheumatoid factor and/or anticyclic citrullinated peptide (anti-CCP) positivity was found in 75 (72.1%) cases and 17 (16.4%) had extra-articular manifestations. The SCORE (mean±SD) was 2.30±2.53 and the EULAR mSCORE 2.78±3.28. A cIMT>0.90 mm was observed in 17 (16.4%) patients and carotid plaques in 77 (74.0%); 16 of the 17 patients with cIMT>0.90 also had carotid plaques. Other characteristics of this series are shown in table 1.

SCORE risk, EULAR mSCORE risk, CACS and carotid ultrasonography results

RA patients were stratified according to the SCORE analysis (table 2). When the risk model was adapted using the multiplication factor to establish the EULAR mSCORE, only 4 (5.7%) of the 70 patients initially categorised as having moderate CV

Table 1 Main features of a series of 104 patients with rheumatoid arthritis without cardiovascular events

| Variable | Category | Number (%) |
|---------------------------------------------|-------------------------------|------------|
| Sex | Women | 73 (70.2) |
| Rheumatoid factor | Positive | 61 (58.7) |
| Anti-CCP | Positive | 60 (57.7) |
| Rheumatoid factor and/or anti-CCP | At least one of them positive | 75 (72.1) |
| Presence of extra-articular manifestations* | Yes | 17 (16.4) |
| Smoking | Yes | 42 (40.4) |
| Carotid intima-media thickness >0.90 mm | Yes | 17 (16.4) |
| Carotid plaques | Yes | 77 (74.0) |
| CACS>100 | Yes | 21 (20.2) |

| Variable | Mean (SD) |
|-----------------------------------------------------------------------|--------------|
| Age at the time of the carotid ultrasonography assessment (SD), years | 59.3 (10.3) |
| Disease duration (SD), years | 10.8 (8.3) |
| Systolic blood pressure (SD), mm Hg | 135.6 (19.9) |
| Diastolic blood pressure (SD), mm Hg | 78.9 (8.1) |
| Total cholesterol (SD), mg/dL | 215.2 (43.6) |
| HDL-cholesterol (SD), mg/dL | 63.4 (19.2) |
| Atherogenic index (SD) | 3.62 (1.11) |
| SCORE† (SD) | 2.30 (2.53) |
| Modified SCORE‡ (SD) | 2.78 (3.28) |
| Carotid intima-media thickness (SD), mm | 0.75 (0.16) |

*Extra-articular manifestations: Secondary Sjögren's syndrome in eight cases, nodular disease in six patients (one of them with pulmonary nodules), pulmonary fibrosis in three patients, pleuritis/pericarditis in three cases, peripheral neuropathy in one case and Raynaud's phenomenon in one case.⁵

†According to SCORE for the general population.^{23 24}

‡Modified SCORE for rheumatoid arthritis: according to the EULAR recommendations.⁸

CACS, Coronary Artery Calcification Score; EULAR, European League Against Rheumatism; HDL, high-density lipoprotein; SCORE, Systematic Coronary Risk Evaluation.

risk ($\geq 1\%$ and $< 5\%$) fulfilled definitions for high and/or very high CV risk (EULAR mSCORE $\geq 5\%$). The frequency of normal MDCT results, manifested by a CACS 0, was higher in patients with low mSCORE ($< 1\%$) (16 of 21; 76.2%) than in patients with moderate/high/very high mSCORE (25 of 83; 30.1%); OR=7.4 (95% CI 2.2 to 28.2; $p=0.0001$).

None of the patients from this series had type 1 diabetes with target organ damage. However, nine fulfilled definitions for type 2 diabetes mellitus or had severe chronic kidney disease and were excluded from further analyses. Because of this, SCORE, mSCORE, carotid ultrasonography and CACS data were reassessed in the remaining 95 cases (tables 3 and 4). Following this procedure, only 3 (4.8%) of the 63 patients

categorised as having moderate CV risk according to the SCORE were reclassified as having high or very high CV risk when the EULAR mSCORE was applied.

A good correlation between the mSCORE and the CACS score was found (Goodman-Kruskal γ test=0.6104; $p<0.001$). In this regard, most patients with a low mSCORE (16/21 (76.2%)) had normal score (CACS 0), and none of these patients with a low mSCORE had a CACS>100. Also, most patients with a high or very high mSCORE (12/14 (85.7%)) had an abnormal score (CACS ≥ 1). However, 38 of 60 patients (63.3%) with a moderate mSCORE had a CACS ≥ 1 and 12 (20%) had a CACS>100. Therefore, although a low mSCORE was associated with a normal CACS, it was not the case for

Table 2 Cardiovascular risk stratification according to SCORE risk* and EULAR modified SCORE risk† in 104 rheumatoid arthritis patients without cardiovascular events

| | SCORE* | EULAR modified SCORE† | | | | |
|-------------------------------------|--------|-----------------------|------------------|---------------------------|-------------------------------|------------------|
| | | CACS | Normal‡ (CACS 0) | Low-moderate (CACS 1–100) | Moderate-high (CACS >100–400) | High (CACS >400) |
| | n | n | n=41 (%) | n=42 (%) | n=12 (%) | n=9 (%) |
| Low (<1%) | 21 | 21 | 16/21 (76.2.0) | 5/21 (23.8) | 0/21 (0.0) | 0/21 (0.0) |
| Moderate ($\geq 1\%$ and $< 5\%$) | 70 | 66 | 22/66 (33.3) | 28/66 (42.4) | 9/66 (13.6) | 7/66 (10.6) |
| High ($\geq 5\%$ and $< 10\%$) | 11 | 13 | 2/13 (15.4) | 7/13 (53.8) | 3/13 (23.1) | 1/13 (7.7) |
| Very high ($\geq 10\%$) | 2 | 4 | 1/4 (25.0) | 2/4 (50.0) | 0/4 (0.0) | 1/4 (25.0) |
| High plus very high‡ | 13 | 17 | 3/17 (17.7) | 9/17 (52.9) | 3/17 (17.7) | 2/17 (11.7) |

EULAR modified SCORE risk stratification according to the Coronary Artery Calcification Score (CACS).

*According to SCORE for the general population.^{23 24}

†Modified SCORE for rheumatoid arthritis: according to the EULAR recommendations.⁸

‡Modified SCORE was calculated by the application of a multiplier factor of 1.5 in those patients with two of three criteria: disease duration >10 years, rheumatoid factor and/or anticyclic citrullinated peptide antibody positivity, and presence of extra-articular manifestations.⁸

EULAR, European League Against Rheumatism; SCORE, Systematic Coronary Risk Evaluation.

Table 3 Cardiovascular risk stratification according to SCORE risk* and EULAR modified SCORE risk† in 95 rheumatoid arthritis patients without cardiovascular events, diabetes mellitus or severe chronic kidney disease‡

| Cardiovascular risk | SCORE* n | EULAR modified SCORE§ | | | | |
|------------------------|-------------|-----------------------|------------------------------|------------------------------------------|---------------------------------------------|--------------------------------|
| | | n | CACs | | | |
| | | | Normal‡ (CACs 0) n=40 (%) | Low-moderate (CACs 1–100) n=38 (%) | Moderate-high (CACs >100–400) n=9 (%) | High (CACs >400) n=8 (%) |
| Low (<1%) | 21 | 21 | 16/21 (76.2) | 5/21 (23.8) | 0/21 (0.0) | 0/21 (0.0) |
| Moderate (≥1% and <5%) | 63 | 60 | 22/60 (36.7) | 26/60 (43.3) | 6/60 (10.0) | 6/60 (10.0) |
| High (≥5% and <10%) | 9 | 10 | 1/10 (10.0) | 5/10 (50.0) | 3/10 (30.0) | 1/10 (10.0) |
| Very high (≥10%) | 2 | 4 | 1/4 (25.0) | 2/4 (50.0) | 0/4 (0.0) | 1/4 (25.0) |
| High plus very high | 11 | 14 | 2/14 (14.3) | 7/14 (50.0) | 3/14 (21.4) | 2/14 (14.3) |

EULAR modified SCORE risk stratification according to the Coronary Artery Calcification Score (CACs).

*According to SCORE for the general population.^{23,24}

†Modified SCORE for rheumatoid arthritis: according to the EULAR recommendations.⁸

‡Six patients with moderate modified SCORE and three with high and/or very high modified SCORE had type 2 diabetes or severe chronic kidney disease and, due to this, met definitions for very high cardiovascular risk and were excluded from the analysis.

§Modified SCORE was calculated by the application of a multiplier factor of 1.5 in those patients with two of three criteria: disease duration >10 years, rheumatoid factor and/or anticyclic citrullinated peptide antibody positivity, and presence of extra-articular manifestations.⁸

EULAR, European League Against Rheumatism; SCORE, Systematic Coronary Risk Evaluation.

moderate mSCORE. Of note, table 4 showed a high frequency (85.0%) of severe carotid ultrasonography abnormalities in patients with a moderate mSCORE.

Correlation between CACS and the cIMT

A cIMT >0.90 mm was the cut-off associated with increased risk of CV events in the general population and in patients with RA.¹³ Most patients with cIMT ≤0.9 mm had a normal CACS (Agatston 0) (table 5). The frequency of cIMT >0.9 mm was increased in patients with abnormal CACS (≥1). Therefore, a significant correlation between cIMT and CACS was found (p=0.02).

Correlation between CACS and the presence of carotid plaques

Table 6 shows the presence of carotid plaques in RA stratified according to CACS. Significant correlation between CACS and presence of carotid plaques was observed (Goodman-Kruskal γ test=0.6375; p<0.001). The correlation remained statistically significant when patients were stratified according to the presence of unilateral or bilateral carotid plaques (table 7). Most patients with CACS ≥1 had carotid plaques (46/55 (83.6%)). It

was especially true for those with a CACS >100 as all of them (17/17) exhibited carotid plaques. In addition, the majority of patient with a CACS >100 had bilateral plaques that indicated the presence of severe atherosclerotic disease.

However, a high number of RA patients with carotid plaques was disclosed in the group of patients with a CACS=0 (23/40 (57.5%)). Therefore, the use of carotid ultrasonography allowed classifying more than 50% of patients as having very high CV risk who would have not been included in this category if the only tool for classification had been CACS results. It was also the case for a CACS 1–100 as 29/38 (76.3%) patients with a CACS 1–100 had carotid plaques.

Model to establish the presence of high/very high CV risk in patients with RA and moderate mSCORE

We aimed to establish whether CACS assessed by MTCd and carotid ultrasonography may enhance the identification of high/very high CV risk in patients with RA and moderate EULAR mSCORE. For this purpose, we defined high/very high CV risk regardless of mSCORE results if patients had severe ultrasonography findings (cIMT >0.90 mm and/or plaques) or a CACS >100.

Table 4 Cardiovascular risk stratification according to SCORE risk* and EULAR modified SCORE risk† in 95 rheumatoid arthritis patients without cardiovascular events, diabetes mellitus or severe chronic kidney disease

| Cardiovascular risk | SCORE* n | EULAR modified SCORE‡ | | | | | |
|------------------------|-------------|-----------------------|-----------------------|---------------------------|-----------------------------|--------------------------------------------------|-------------------------------------------------------|
| | | n | CACs | | Carotid ultrasonography | | cIMT ≤0.90 mm and without carotid plaques n=25 (%) |
| | | | CACS >100 n=17 (%) | cIMT >0.90 mm n=14 (%) | Carotid plaques n=69 (%) | cIMT >0.90 mm and/or carotid plaques n=70 (%) | |
| Low (<1%) | 21 | 21 | 0/21 (0.0) | 0/21 (0.0) | 7/21 (33.3) | 7/21 (33.3) | 14/21 (66.7) |
| Moderate (≥1% and <5%) | 63 | 60 | 12/60 (20.0) | 8/60 (13.3) | 51/60 (85.0) | 51/60 (85.0) | 9/60 (15.0) |
| High (≥5% and <10%) | 9 | 10 | 4/10 (40.0) | 5/10 (50.0) | 8/10 (80.0) | 9/10 (90.0) | 1/10 (10.0) |
| Very high (≥10%) | 2 | 4 | 1/4 (25.0) | 1/4 (25.0) | 3/4 (75.0) | 3/4 (75.0) | 1/4 (25.0) |
| High plus very high | 11 | 14 | 5/14 (35.7) | 6/14 (42.8) | 11/14 (78.6) | 12/14 (85.7) | 2/14 (14.3) |

EULAR modified SCORE risk stratification according to the Coronary Artery Calcification Score (CACs) >100, carotid intima-media thickness (cIMT) >0.90 mm and carotid plaques.

*According to SCORE for the general population.^{23,24}

†Modified SCORE for rheumatoid arthritis: according to the EULAR recommendations.⁸

‡Modified SCORE was calculated by the application of a multiplier factor of 1.5 in those patients with two of three criteria: disease duration >10 years, rheumatoid factor and/or anticyclic citrullinated peptide antibody positivity, and presence of extra-articular manifestations.⁸

EULAR, European League Against Rheumatism; SCORE, Systematic Coronary Risk Evaluation.

Table 5 Correlation between the Coronary Artery Calcification Score (CACs) and the carotid intima-media thickness (cIMT) in 95 patients with rheumatoid arthritis

| CACs | cIMT | |
|---------|-------------------|-------------------|
| | ≤0.90 mm n (%) | >0.90 mm n (%) |
| 0 | 37/40 (92.5) | 3/40 (7.5) |
| 1–100 | 32/38 (84.2) | 6/38 (15.8) |
| 101–400 | 5/9 (55.6) | 4/9 (44.4) |
| >400 | 7/8 (88.8) | 1/8 (12.5) |
| ≥1 | 44/55 (80.0) | 11/55 (20.0) |

Goodman–Kruskal γ test=0.4229; p=0.02.

In all, 60 RA patients fulfilled definitions for moderate CV mSCORE (≥1% and <5%) (tables 3 and 4). Overall, 51 of these 60 patients were reclassified as having a high or very high mSCORE risk because of the presence of severe ultrasonography findings (cIMT>0.9 mm and/or carotid plaques) or CACS>100. Interestingly, carotid ultrasonography allowed reclassifying as having high/very high CV risk all these 51 patients while using only a CAC>100 as the criterion for high/very high CV risk we only reclassified 12 of these 51 patients.

Taking together these results, in patients with a moderate mSCORE (≥1% and <5%), the sensitivity for high/very high CV risk using carotid ultrasonography definitions of severity (cIMT>0.90 mm and/or plaques) was 100%. In contrast, the sensitivity shown by CACS assessed by MDCT using CACS>100, a criterion of high/very high CV risk, was 23.5%. Therefore, CACS seems to be inferior to carotid ultrasonography to detect high/very high CV risk in patients with moderate mSCORE.

Sensitivity to establish the presence of high/very high CV risk in patients with RA using mSCORE, carotid ultrasonography or MDCT

A total of 72 of the 95 patients without diabetes mellitus or severe chronic kidney disease fulfilled definitions for high/very high CV risk: a) mSCORE≥5% or b) mSCORE<5% plus one of the following: severe carotid ultrasonography findings (cIMT>0.9 mm and/or plaques) or CACS>100 (table 8). A CACS>100 was found to have sensitivity similar to that observed using only mSCORE charts (23.6% and 19.4%, respectively). A slight increase in the sensitivity was observed when an mSCORE>5% plus the presence of a CACS>100 in patients with an mSCORE<5% was used (36.1% (95% CI 25.2 to 48.3)). Interestingly, the presence of severe ultrasonography

Table 6 Correlation between the Coronary Artery Calcification Score (CACs) and the presence of carotid plaques in 95 patients with rheumatoid arthritis

| CACs | Carotid plaques | |
|---------|-----------------|--------------|
| | No n (%) | Yes n (%) |
| 0 | 17/40 (42.5) | 23/40 (57.5) |
| 1–100 | 9/38 (23.7) | 29/38 (76.3) |
| 101–400 | 0/9 (0.0) | 9/9 (100.0) |
| >400 | 0/8 (0.0) | 8/8 (100.0) |
| ≥1 | 9/55 (16.4) | 46/55 (83.6) |

Goodman–Kruskal γ test=0.6375; p<0.001.

Table 7 Correlation between the Coronary Artery Calcification Score (CACs) and the presence of unilateral or bilateral carotid plaques in 95 patients with rheumatoid arthritis

| CACs | Carotid plaques | | |
|---------|-----------------|------------|-----------|
| | No | Unilateral | Bilateral |
| 0 | 17 | 12 | 11 |
| 1–100 | 9 | 14 | 15 |
| 101–400 | 0 | 1 | 8 |
| >400 | 0 | 1 | 7 |

Goodman–Kruskal γ test=0.5644; p<0.001.

findings allowed identifying most patients categorised as having high/very high CV risk (70 of 72; sensitivity 97.2% (95% CI 90.3 to 99.7)). In addition, the use of mSCORE>5% plus an mSCORE<5% and the presence of severe carotid ultrasonography results (cIMT>0.9 mm and/or carotid plaques) allowed identifying all the 72 patients (sensitivity 100% (95% CI 95.0 to 100)).

DISCUSSION

Adequate stratification of the CV risk is an issue of major importance in the management of patients with RA. CACS determined by MDCT scanner and carotid ultrasonography are non-invasive tools to measure atherosclerosis that have been recommended as possible additions to risk factor assessment charts for predicting the probability of occurrence of CV events in non-rheumatic patients. In the present study we assessed for first time a comparative relation of CACS and carotid ultrasonography results after integration into the EULAR mSCORE in patients with RA.

Unlike carotid ultrasonography, the mSCORE does not significantly improve the identification of RA patients with high CV risk.¹⁶ In the present study, we observed good correlation

Table 8 Sensitivity to establish the presence of high/very high cardiovascular risk in rheumatoid arthritis patients without cardiovascular events, diabetes mellitus or severe chronic kidney disease using the modified EULAR SCORE, severe carotid ultrasound findings (cIMT>0.90 mm or carotid plaques) or a Coronary Artery Calcification Score (CACs)>100

| Model | Sensitivity |
|-----------------------------------------------------------------------------------------------------|----------------------------------------------|
| Gold standard* | n=72/95 |
| Modified SCORE >5% | n=14 of 72 19.4% (95% CI 11.1 to 30.5) |
| CACS>100 | n=17 of 72 23.6% (95% CI 14.4 to 35.1) |
| cIMT>0.90 mm and/or carotid plaques | n=70 of 72 97.2% (95% CI 90.3 to 99.7) |
| Modified SCORE >5% or modified SCORE <5% plus CACS>100 | n=26 of 72 36.1% (95% CI 25.2 to 48.3) |
| Modified SCORE >5% or modified SCORE <5% plus one of the following: cIMT>0.90 mm or carotid plaques | n=72 of 72 100% (95% CI 95.0 to 100) |

*Gold standard for high/very high cardiovascular risk: Modified SCORE ≥5% OR Modified SCORE <5% plus one of the following: severe carotid ultrasound findings (cIMT>0.90 mm or carotid plaques) or a CACS>100. EULAR, European League Against Rheumatism; SCORE, Systematic Coronary Risk Evaluation.

between the mSCORE and the CACS. We also observed good correlation between CACS and cIMT as only a few patients from our series with CACS 0 had cIMT > 0.90 mm while the frequency of cIMT > 0.90 was higher among patients with CACS ≥ 1. However, several reports indicate that in the general population measurements of carotid ultrasonography and CACS are often discordant.^{28, 29} In keeping with these observations, we disclosed that a substantial number of RA patients without CV disease, who apparently did not have atherosclerosis according to CACS results, had severe carotid ultrasonography abnormalities, mainly carotid plaques. Carotid ultrasonography disclosed the presence of plaques in a high number of RA patients with CACS 0 or CACS 1–100. This finding is of particular relevance as the presence of severe carotid ultrasonography findings predicts CV events in RA.^{13, 14}

The high number of cases with severe ultrasonography findings among patients with moderate mSCORE might raise doubts on the possibility that some of them would be wrongly overtreated. Nevertheless, previous studies have confirmed that a cIMT > 0.90 mm is indicative of atherosclerosis and increased risk of CV disease (0.90 mm was found to be a useful cut-off value to predict the presence of coronary artery disease).³⁰ Carotid plaques are also predictors of coronary disease progression and closely associated with coronary artery disease.³¹

In assessing the correlation between CACS and carotid plaques, we found that the frequency of carotid plaques was higher in RA patients with CACS > 100 than in those with CACS 0 or 1–100. However, only 20% of patients with moderate mSCORE had CACS > 100 while 85% of them exhibited carotid plaques in the ultrasonography evaluation. These findings indicate that in patients with RA carotid ultrasonography may be a more sensitive test than CACS for the detection of subclinical atherosclerosis. These results support the use of carotid ultrasonography as the imaging technique of choice for detection of high/very high CV risk in RA patients with moderate mSCORE. The value of CACS is probably limited for this group of patients. In this regard, although arterial calcification indicates a later stage of vascular disease, its absence does not exclude the presence of non-calcified ‘vulnerable’ plaques. In keeping with our observations, in a series of 118 young to middle-aged, low-risk population who reported 1 or more CV risk factors and were seeking primary prevention but who did not have symptoms of CV disease, a high frequency of severe carotid ultrasonography findings in individuals with CACS 0 was observed.³² Similarly, in another series of 136 asymptomatic individuals without CV disease, severe carotid ultrasonography findings defined by cIMT ≥ 75 percentile and/or plaques were more likely to revise Framingham risk score than CACS.³³ In this series, 52% of the subjects with CACS 0 had plaques.³³ This percentage was remarkably similar to that observed in our series as we found carotid plaques in 57.5% of RA patients with CACS 0.

In conclusion, the use of an mSCORE does not allow identifying properly high/very high CV risk RA patients. Carotid ultrasonography assessment can detect subclinical vascular disease in RA with CACS ≤ 100. Therefore, carotid ultrasonography seems to be more sensitive than CACS in the stratification of the CV risk of patients with RA.

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Contributors AC performed the carotid ultrasound study, contributed to the elaboration of the protocol of study, helped in the interpretation of data and in the elaboration of the manuscript. JAP performed the multi-detector CT study, contributed to the elaboration of the protocol of study, helped in the interpretation of data and in the elaboration of the manuscript. CG-J contributed to the elaboration of the protocol of study, helped in the interpretation of data and the elaboration of the manuscript. JR-G contributed to the elaboration of the manuscript. RB recruited patients for the study and contributed to the elaboration of the manuscript. JL contributed to the elaboration of the protocol of study, helped in the interpretation of data and the elaboration of the manuscript and performed the statistical analysis. MAG-G recruited patients for the study, contributed to the elaboration of the protocol of study, helped in the interpretation of data and was responsible of the final drafting and elaboration of the manuscript.

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Supplementary material Text- Methods*SCORE risk estimation*

Based on a pool of datasets from 12 European cohort studies, mainly carried out in general population settings, European experts performed the SCORE project to develop a risk scoring system for use in the clinical management of CV risk in European clinical practice.[23] The SCORE risk estimation system offers direct estimation of fatal CV risk in a format suited to the constraints of clinical practice.[24] It estimates the 10-year risk of a first fatal atherosclerotic event, whether heart attack, stroke, or other occlusive arterial disease, including sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe.[23] Spain was included in the low risk region in Europe.

A task force of the European League Against Rheumatism (EULAR) has proposed to adapt the CV risk management calculated in RA patients according to the SCORE function by the application of a multiplier factor of 1.5 in those patients with 2 of 3 criteria: disease duration >10 years, rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide (anti-CCP) antibody positivity, and presence of severe extra-articular manifestations.[8] (information shown as a footnote in **Tables 2A,2B and 2C**).

Both SCORE and EULAR modified SCORE (mSCORE) according to the EULAR recommendations were calculated to determine the 10-year risk of fatal CV disease in a population at low CV disease risk (as it was considered for the Spanish population).[8,23] SCORE chart assessment was based on the following risk factors: age, gender, smoking, systolic blood pressure, atherogenic index (total cholesterol/HDL-cholesterol).[8,23] A subject's written consent was obtained in all the cases. The study was approved by the local Ethical Committee.

Multi-detector computed tomography imaging assessment and analysis of data

To determine the CACS all subjects underwent computed tomography imaging of coronary arteries using a 32-slice MDCT scanner (Lightspeed, Pro 32, GE Healthcare, USA). It was performed following current guidelines on the screening for CAC for cardiac risk assessment.[25] As previously described,[19] all scans were performed with the subjects in the supine position which included regions from the carina to the fundus of the heart. Prospective electrocardiogram-gated cardiac scan was obtained with following scan parameters: rotation time=0.35s; slice thickness=2.5mm; 120kV; trigger delay=70% R-R interval. Patients were instructed to hold their breath during scanning. The acquired MDCT images were reviewed at the post-processing image workstation (Advantage Windows 4.02, GE Healthcare, USA). Measurement of CACS was performed by a commercially available software “smart_score” (General Electric Healthcare, USA) using the threshold option set for pixels greater than 130 Hounsfield units and expressed in Agatston unit. Agatston CACS is based on the amount of calcium found in the coronary arteries.

Analysis of all the scans and interpretation of calcium scores was performed by a radiologist (JAP), who was blind to the clinical information. The intraobserver variability correlation coefficient of CAC score measurements was 0.93.

Carotid US examination

Carotid US examination included the measurement of cIMT in the common carotid artery and the detection of focal plaques in the extracranial carotid tree that was performed as recently described.[16] A commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with 7-12 MHz linear transducer and the automated software guided technique radiofrequency -Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, Holland)- was used. Automated radiofrequency -based US measurement of the common cIMT was measured at the far wall of the right and left common carotid arteries, 10 mm from

the carotid bifurcation, over the proximal 15 mm-long segment, using US technology based on radiofrequency. The reproducibility of the cIMT measurements was evaluated in 20 patients within 1 week of the first US examination. The correlation coefficient for cIMT was 0.97. The plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb and internal carotid artery) were defined as previously reported.[16,27] Plaque was defined as a focal protrusion in the lumen at least cIMT>1.5 mm, protrusion at least 50% greater than the surrounding cIMT, or arterial lumen encroaching>0.5 mm, according to Mannheim consensus criteria.[27] Carotid plaques were counted in each territory and defined as no plaque, unilateral plaque or bilateral plaques.[16].

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charts including HDL-C are available as Addendum I to these guidelines on the ESC website (www.escardio.org/guidelines).

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Watching the Risk Symposium, 13th and 15th European Stroke Conferences, Mannheim, Germany, 2004, and Brussels, Belgium, 2006. *Cerebrovasc Dis* 2007; 23:75-80.

Lay summaries for the non-clinician

How do you measure heart-disease risk in people with rheumatoid arthritis?

INTRODUCTION

A test called carotid ultrasound may be the best way to tell whether individuals with rheumatoid arthritis are at high risk of heart disease, according to a new study.

WHAT DO WE KNOW ALREADY?

As a general rule, we know that people with rheumatoid arthritis have a higher risk of heart disease compared with the general population. Doctors aren't sure why this is, but they think that the inflammation (swelling) that affects the joints might affect other parts of the body, such as the arteries. It is thought that this inflammation might increase the chance of hardening of the arteries, which may lead to heart and circulation problems.

So it's important that people with rheumatoid arthritis know whether they are at high risk of heart disease. If people know they are more likely than usual to have heart problems, there are things they can do about it, such as stopping smoking, changing their diet, taking more exercise, and losing weight if they are overweight.

But the usual ways of checking heart-disease risk aren't very useful for many people with rheumatoid arthritis. For example, a method called SCORE (Systematic COronary Risk Evaluation) can work out people's risk of heart problems based on so-called 'risk factors'. These include things like whether they smoke, their age, their sex (men are more likely to have heart problems), their blood pressure, and their cholesterol level. But tools like this don't take into account the extra heart-disease risk in people with rheumatoid arthritis. So they are likely to miss people with rheumatoid arthritis who are at risk.

The new study looked at two ways of checking heart-disease risk in people with rheumatoid arthritis, carotid ultrasound, and the Coronary Artery Calcification Score – CACS for short. Previous studies have shown that both of these tests are better than tools like SCORE at showing heart-disease risk in people with rheumatoid arthritis.

Now the researchers wanted to find out which test was the most reliable. They examined 95 people with rheumatoid arthritis who had never had any heart problems, and whose average age was 59. The people were given both tests, and the results were compared to see which test was the best at detecting who was at high risk of heart disease.

The tests work in slightly different ways. With CACS, your doctor adds up a score based on how much calcium you have in six major arteries. With carotid ultrasound, your doctor looks for two things: thickening of the artery walls and the build up of substances called plaques in the arteries, which can cause the blood vessels to become too narrow. Both these tests involve a doctor using a scanner. They don't hurt, there are no needles, and the doctor doesn't need to take your blood.

WHAT DOES THE NEW STUDY SAY?

The study found that carotid ultrasound was better at detecting which people with rheumatoid arthritis were more likely to get heart disease. When compared with the SCORE system, testing with CACS found an extra 12 people who were at high risk, who had been missed by the SCORE test. But testing with carotid ultrasound found an extra 51 people at high risk who had been missed when tested with SCORE.

HOW RELIABLE ARE THE FINDINGS?

The main reason to be cautious about this study is that it's quite small. It's also important to remember that tests like the ones in this study can't say who will definitely develop heart problems. They can only tell us who is more likely to have problems, based on doctors' past experience.

WHAT DOES THIS MEAN FOR ME?

If you have rheumatoid arthritis it's important to know that you may have a greater chance than most people of getting heart disease. Having a test like carotid ultrasound can help show you how big that risk might be. If you are at higher risk you can make changes to your lifestyle, and get treatment to lower your blood pressure and the amount of fats in your blood.

But even without a test, it may be more important for you than for most people to look after your heart. If you want to know more about tests like carotid ultrasound, or about avoiding heart problems, you can talk to your doctor or rheumatologist.

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