Cardiovascular risk assessment in rheumatoid arthritis: impact of the EULAR recommendations on a national calibrated score risk index

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Abstract

Objective

To evaluate the impact of the application of the EULAR task force recommendations in the cardiovascular (CV) risk assessment of rheumatoid arthritis (RA) patients according to a national calibrated SCORE.

Methods

Two hundred and one consecutive RA patients seen at the rheumatology outpatient clinics of the University Hospital "San Cecilio", Granada, Southern Spain, were studied. Information on demographic, classic CV risk factors, history of CV events and disease clinical features were obtained. Both the systematic coronary risk evaluation (SCORE) risk index and the modified SCORE (mSCORE) following the EULAR recommendations were performed.

Results

Based on the classic CV risk factors the mean ± standard deviation SCORE was 2.2±2.6 (median 2). Twenty-two (11%) patients were above the threshold of high risk for the Spanish population. Following the EULAR recommendations 52 of the 124 patients (41.93%) initially classified as having intermediate risk were reclassified as having high CV risk. Therefore, the mean mSCORE was 3.3±4 (median 3) and, due to this, 74 (36.8%) patients were above the threshold of high CV risk for the Spanish population. As expected, patients who had experienced CV events were older, had more CV risk factors and higher mSCORE than those without CV events.

Conclusion

These observations support the claim that the mSCORE should be specifically adapted to the population to be assessed. However, the use of additional tools should be considered in an attempt to fully identify high-risk RA patients.

Key words

rheumatoid arthritis, cardiovascular diseases, coronary risk factors, arteriosclerosis

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Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease associated with an increased CV morbidity and mortality as compared with the general population (1-3). It is well known that RA patients frequently develop premature atherosclerosis (AT), which cannot be explained completely by the presence of traditional CV risk factors (4-5). The exact mechanism underlying the association between RA and CV disease is still unknown, but evidence suggests that chronic inflammation plays a pivotal role in the development of this complication. Furthermore, the duration of the disease has also been associated with increased incidence of CV events and CV mortality (6-7). The reported relative risk of CV disease in RA patients varies from 1.5 to 4.0 (8-9) and the standardised CV mortality ratio ranges between 1.6 and 1.7 (9).

The systematic coronary risk evaluation (SCORE) project was initiated to develop a risk scoring system for use in the clinical management of CV risk in European clinical practice (10). The SCORE risk estimation system offers direct estimation of total fatal CV risk in a format suited to the constraints of clinical practice (10). The fourth joint task force on CV disease prevention in clinical practice recommends the use of the SCORE charts to assess CV risk in general population (11); in the same way, the recent task force of the European League against Rheumatism (EULAR) propose to adapt the CV risk assessment in RA patients according to the SCORE function by the application of a multiplier factor of 1.5 in those who meet some clinical and serological criteria (12). EULAR recommends the use of local guidelines for CV risk assessment and treatment; to that respect in our country there is a calibrated SCORE chart published by our cardiology society (13).

To evaluate the impact of the application of the EULAR task force recommendations in the CV risk assessment of RA patients according to a national calibrated SCORE, we have assessed a series of southern Spanish RA patients.

Methods

Patients

The study was performed at the Rheumatology Department of the University Hospital "San Cecilio", a teaching hospital (637 beds), located in Granada, southern Spain. The department has a unit for admissions and two outpatient clinics, one at the hospital and one situated in an affiliated primary care health centre. General practitioners send patients with inflammatory rheumatic diseases from this area to our Rheumatology Department.

Study protocol

We included 201 consecutive patients diagnosed with RA, according to the 1987 classification criteria of American College of Rheumatology (ACR), who were regularly monitored at the outpatient clinics following a pre-established protocol.

In our hospital and affiliated centres, medical records are collected in a computerised programme. For the purpose of the present study, a single clinical evaluation was performed and medical records were reviewed in order to collect the following data:

a) age, sex, systolic arterial blood pressure (SBP), diastolic blood pressure, weight, height and body mass index (BMI);

b) duration of RA, presence of extraarticular manifestations, presence of rheumatoid factor (RF) and anti citrullinated protein antibody (ACPA);

c) disease activity parameters: tender and swollen joint count, patient global assessment by visual analogue scale, DAS28, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP);

d) lipid profile: total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C);

e) classic CV risk factors: smoking history, hypertension, dyslipidaemia, diabetes mellitus and obesity; and finally

f) vascular ischaemic events registered to date.

Total fatal CV risk was calculated using the SCORE chart calibrated for Spain (SCORE) according to data on the age at the time of the study, sex, smoking history, SBP and TC serum level. In the

Spanish population, high CV risk has been defined by a SCORE ≥5% (13).
Following the EULAR task force recommendations, the SCORE was multiplied by a 1.5 factor in those patients who fulfilled at least two of the following criteria: a) disease duration of more than 10 years; b) RF or ACPA positivity, and c) presence of extraarticular manifestations (rheumatoid nodules, secondary Sjögren syndrome, interstitial lung disease, pleural effusion and rheumatoid vasculitis) (12).
The ethics committee of the University Hospital "San Cecilio" approved the study protocol, and informed consent was obtained from all patients.

Definitions

1) Classic CV risk factors were defined as previously described (11). They included smoking history (encompassing both current and past smokers), hypertension (blood pressure greater than 140/90mmHg in two different determinations performed on different days), dyslipidaemia (total cholesterol equal to or greater than 5mmol/L (190 mg/dl), diabetes mellitus (two fasting pre-prandial plasma glucose levels greater than 6 mmol/L (110 mg/dl), and obesity (BMI greater than 30 kg/m^2).
2) CV events: ischaemic heart disease was electrocardiographically confirmed; cerebrovascular accidents by magnetic resonance imaging and/or computerised tomography brain scan; and peripheral arterial disease by Doppler and arteriography.

Statistical analysis

Data were collected in an Excell 2007 database and analysed with the statistical software SPSS V15. Descriptive data were shown as percentages or mean ± standard deviation (SD). Median and interquartile range (IQR- p25-p75) was used if variables were not normally distributed. Differences between qualitative variables were assessed using Chi-squared test. Mann-Whitney U-test was performed to determine differences between both groups of patients. Pearson correlation coefficient was used for the analysis of continuous variables. Spearman corre-lation coefficient was used if variables were not normally distributed. To assess concordance between values obtained after application of both scores we used the lineal kappa index and the weighted kappa. The limit of statistical significance was located in the α error of 0.05.

Table I. Demographic, anthropometric, analytical parameters of disease activity and lipid profile of RA patients included in the study.

Age* (mean ± SD; median, p25-p75)	60.0 ± 13.5; 61 (50-72)
Gender (women)	160 (79.6%)
BMI (mean ± SD)	28.2 ± 5.2
SBP (mean ± SD)	131.8 ± 17.1
ESR (mean ± SD; median, p25-p75)	25.4 ± 18; 20 (10-34)
CRP (mean ± SD; median, p25-p75)	0.93 ± 1.37; 0,47 (0.10-1.14)
Total cholesterol (mean ± SD; median, p25-p75)	205.6 ± 34.2; 207 (184-227)
Triglycerides (mean ± SD; median, p25-p75)	122.8 ± 59.9; 108 (79-151)
HDL-C (mean ± SD; median, p25-p75)	56.6 ± 17; 53 (45-67)
LDL-C (mean ± SD; median, p25-p75)	124.6 ± 31.9; 122 (104-145)

*Age expressed in years at the time of recruitment for the study,
RA: Rheumatoid arthritis; BMI: Body mass index; SBP: Systolic blood pressure (mmHg); ESR: Erythrocyte sedimentation rate (mm/1st hour); CRP: C reactive protein (mg/dl); HDL-C: High density lipoprotein cholesterol (mg/dl); LDL-C: Low density lipoprotein cholesterol (mg/dl).

Table II. Concordance between SCORE and mSCORE (three categories).

			mSCORE			Total
			Low (n=55)	Intermediate (n=72)	High/Very high (n=74)	
SCORE	Low (n=55)	Count	55	0	0	55
		% total	27.4%	0%	0%	27.4%
	Intermediate (n=124)	Count	0	72	52	124
		% total	0%	35.8%	25.9%	61.7%
	High/very high (n=22)	Count	0	0	22	22
		% total	0%	0%	10.9%	10.9%
Total		Count	55	72	74	201
		% total	27.4%	35.8%	36.8%	100%

SCORE: Systematic Coronary Risk Evaluation calibrated for Spanish population
mSCORE: Modified Systematic Coronary Risk Evaluation (following the EULAR recommendations)

Results

Demographic, anthropometric, analytical disease activity parameters and lipid profile of the patients included in the study are shown in Table I.
Twenty five (12.4%) patients had a smoking history, 72 (35.8%) hypertension, 23 (11.4%) diabetes mellitus, 41 (20.4%) dyslipidaemia and 53 (26.4%) obesity. Overall, 125 (62.2%) patients from this series had at least one CV risk factor. In this regard, 67 (33.3%) had one CV risk factor, 33 (16.4%) two, 20 (10%) three, 4 (2%) four and 1 (0.5%) had five classic CV risk factors.
Based on the classic CV risk factors the mean ± SD SCORE was 2.2±2.6 (median 2; IQR 0-3). Fifty-five (27.4%) patients were classified as having low CV risk, 124 (61.7%) intermediate CV risk and 22 (10.9%) patients were above the threshold of high CV risk for the Spanish population.
Most of our patients had high disease activity according to the composite index DAS28 (mean ± SD; median, p25-p75) = 3.5±1.3; 3.5 (2.6-4.5). In this regard, 53 (26.4%) patients had low disease activity, 33 (16.4%) and 115 (57.2%) patients had moderate and high disease activity, respectively. According with this, 176 (87.6%) patients were on treatment with disease modifying anti rheumatic drugs, 52 (25.9%) were on anti tumour necrosis factor alpha treatment, 134 (66.7%) were receiving systemic corticosteroids and 151 (75.1%) patients were receiving non-steroidal anti-inflammatory drugs at the time of the study.

Table III. Correlations and differences of score values with cardiovascular risk factors and the RA-associated parameters.

Variable	Category	SCORE (mean±SD)	*p*-values	mSCORE (mean±SD)	*p*-values
Age		ϱ=0.503	0.000	ϱ =0.517	0.000
Sex	Men	4.39 ± 4.35	0.000	6.63 ± 6.64	0.000
	women	1.59 ± 1.52		2,49 ± 2.36	
EULAR criteria	Yes	3.49 ± 3.33	0.000	5,39 ± 5,03	0.0000
	No	1.33 ± 1.58		2.02 ± 2.43	
RA duration		ϱ=0.391	0.0000	ϱ=0.401	0.0000
Number CVRF		ϱ=0.272	0.0001	ϱ=0.288	0.0000
Smoking	Yes	4.16 ± 5.51	0.000	6.24 ± 8.41	0.0001
	No	1.88 ± 1.75		2,92 2,69	
Hypertension	Yes	2.85 ± 3	0.0056	4.46 ± 4.63	0.0027
	No	1.78 ± 2,3		2.71 ± 3.48	
TG		ϱ=0.153	0.029	ϱ=0.166	0.017
HDL-C		ϱ=-0.168	0.016	ϱ=-0.167	0.017
LDL-C		ϱ=0.150	0.033	ϱ=0.153	0.029

SCORE: Systematic Coronary Risk Evaluation; mSCORE: Modified Systematic Coronary Risk Evaluation; EULAR: European League Against Rheumatism; RA: Rheumatoid arthritis; CVRF: Cardiovascular risk factors; TG: tryglicerides; HDL-C: High density lipoprotein cholesterol: LDL-C: Low density lipoprotein cholesterol.

Table IV. Differences between the patients who suffered at least one CV event (with) and the remaining RA patients who did not experience CV events (without).

Category	With CV events (n=19)	Without CV events (n=182)	*p*-values
Age, years	69.68 ± 9.21	59 ± 13.47	0.0009
Number CVRF	1.89 ± 1.15	0.98 ± 1.07	0.0005
Hypertension	73%	31%	0.001
Diabetes	42%	8%	0.000
Dyslipidaemia	47%	17%	0.005
SCORE %	3.58 ± 1.35	2.02 ± 2.69	0.013
mSCORE %	5.68 ± 1.86	3.09 ± 4.09	0.006

CV: Cardiovascular; CVRF: CV risk factors; SCORE: Systematic Coronary Risk Evaluation; mSCORE: Modified Systematic Coronary Risk Evaluation.

Concerning the clinical and serological characteristics of these patients, seventy eight (38.8%) patients met at least 2 of the EULAR criteria for the application of the multiplier factor. At this respect, 75 (37.3%) patients had a disease duration of more than 10 years; 166 (82.6%) and 86 (42.8%) patients were positive for RF and ACPA respectively; and 33 (16.4%) had extraarticular manifestations.

For this reason, following the EULAR recommendations, the mean modified SCORE (mSCORE) was 3.3±4 (median 3, IQR 0-5). Fifty-five (27.4%) patients were classified as having low CV risk, 72 (35.8%) intermediate risk and 74 (36.8%) patients were above the threshold of high risk for the Spanish population.

The concordance of the stratification between SCORE and mSCORE considering three categories: 1) low risk (2) intermediate risk and 3) high and very high risk (SCORE≥5); was expressed by the McNemar Chi-square test $p<0.001$; Kappa=0.61 CI95% (0.51–0.70); weighted kappa=0.793 CI95% (0.69-0.88). Interestingly, we observed that 52 of the 124 patients (41.93%) classified as having intermediate CV risk according to the classic SCORE were reclassified as having high CV risk after applying the mSCORE following the EULAR recommendations (Table II).

As shown in Table III, a significant correlation between age, male gender, accomplishment of the EULAR criteria, disease duration, number of CV risk factors and some of the classic CV risk factors were disclosed with the mean values of the SCORE and the mSCORE. Likewise, a significant difference between the mean SCORE and mSCORE was observed when patients were stratified according to RF status ($p=0.02$ and $p=0.02$) respectively. Also, levels of triglycerides, high density lipoprotein cholesterol and low density lipoprotein cholesterol showed a significant correlation with the mean SCORE and mSCORE (Table III). However, CRP, ESR and DAS28 values obtained at the time of the assessment as well as ACPA status did not show a significant correlation with the mean values obtained with both SCORE charts.

With respect to the CV events, 19 (9.5%) patients had coronary and/or cerebrovascular events. In our series, patients who experienced at least one CV event were older, had more CV risk factors including hypertension, diabetes and dyslipidaemia; had higher values of SCORE and mSCORE than those RA patients who did not experience CV events (Table IV).

Discussion

Since CV complications are the leading cause of premature death in RA patients, an issue of major importance may be the search for tools that may allow us to identify patients at risk. With respect to this, chronic inflammation in the setting of long disease duration, disease severity, as well as some markers of RA such as ACPA have been associated with increased risk of subclinical atherosclerosis and CV events (7, 13-16). Because of that, the EULAR task force established a series of guidelines for the use of a mSCORE that included these variables at the time of assessing CV risk in RA patients. Interestingly, the present study in a southern European population, traditionally considered as having low CV risk, disclosed that the reclassification of patients using the mSCORE index categorised as having

high or very high CV risk to a relatively high number of patients 52 (41.93%) that had initially been included in the category of intermediate risk according to the classic SCORE.

Attempts to determine the impact of the application of EULAR task force recommendations in the CV risk of RA patients have previously been performed. In this regard, using the SCORE tables adapted to the southern european population, Gómez-Vaquero *et al*. found that after the application of the mSCORE in a series of RA patients from north-eastern Spain, the proportion of patients that achieved the definitions for high CV risk only increased from 11 to 14% (17). The reasons for the discrepancy between our results and those from north-eastern Spain are unknown. It is possible that some kind of selection biased might have accounted for the differences. However, disease duration in the study by Gomez-Vaquero *et al*. was not different from that found in our series. A plausible difference may be that in our study we used SCORE tables specifically adapted to the Spanish population while Gomez-Vaquero *et al*. utilised SCORE tables adapted to southern European people in general.

Another question that still remains unanswered is whether the mSCORE may establish accurately the actual number the RA patients with high or very high CV risk. Regarding this point, several investigators have emphasised that the CV risk assessment tools designed for the general population may not accurately estimate the CV risk for individual patients with RA, even if a mSCORE is applied (18). Patients not satisfying the criteria for use of the multiplier factor may also have increased risk and develop CV events (18). In keeping with these considerations, carotid plaques and abnormally high carotid intima-media thickness that are predictors of CV events in RA patients (19-21), have frequently been observed in patients without classic CV risk factors (14).

The American College of Cardiology Foundation and the American Heart Association guidelines support the assessment of the carotid artery intima-media thickness by carotid ultrasonography to determine the CV risk in asymptomatic adults at intermediate risk (22). In accordance with these considerations, recent reports support the use of carotid ultrasonography in RA patients when the mSCORE does not yield results of high CV risk and at least one of the following features is present: extraarticular manifestations, RF or ACPA positivity or 10 years disease duration or longer (23-25).

In conclusion, at present adequate stratification of CV risk still remains as one of the major points of concern in the management of RA patients. The results found in the present study shows that the mSCORE adapted to the Spanish population may be useful to identify Spanish RA patients with high CV risk. These observations support the claim that the mSCORE should be specifically adapted to the population that is going to be assess. However, the use of additional tools should be considered in an attempt to fully identify high-risk RA patients who may benefit from active therapy to prevent the development of CV disease.

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