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SCORE and REGICOR function charts underestimate the cardiovascular risk in Spanish patients with rheumatoid arthritis

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Abstract

Introduction: Our objective was to determine which one of the two function charts available in Spain to calculate cardiovascular (CV) risk, Systematic COronary Risk Evaluation (SCORE) or Framingham-REGistre Glroní del COR (REGICOR), should be used in patients with rheumatoid arthritis (RA).

Methods: A series of RA patients seen over a one-year period without history of CV events were assessed. SCORE, REGICOR, modified (m)SCORE and mREGICOR according to the European League Against Rheumatism (EULAR) recommendations were applied. Carotid ultrasonography (US) was performed. Carotid intima-media thickness (cIMT) > 0.90 mm and/or carotid plaques were used as the gold standard test for severe subclinical atherosclerosis and high CV risk (US+). The area under the receiver operating curves (AUC) for the predicted risk for mSCORE and mREGICOR were calculated according to the presence of severe carotid US findings (US+).

Results: We included 370 patients (80% women; mean age 58.9 ± 13.7 years); 36% had disease duration of 10 years or more; rheumatoid factor (RF) and/or anticyclic citrullinated peptide (anti-CCP) were positive in 68%; and 17% had extra-articular manifestations. The EULAR multiplier factor was used in 122 (33%) of the patients. The mSCORE was 2.16 ± 2.49% and the mREGICOR 4.36 ± 3.46%. Regarding US results, 196 (53%) patients were US+. The AUC mSCORE was 0.798 (CI 95%: 0.752 to 0.844) and AUC mREGICOR 0.741 (95% CI; 0.691 to 0.792). However, mSCORE and mREGICOR failed to identify 88% and 91% of US+ patients. More than 50% of patients with mSCORE ≥1% or mREGICOR >1% were US+.

Conclusions: Neither of these two function charts was useful in estimating CV risk in Spanish RA patients.

Introduction

Rheumatoid arthritis (RA) is a condition associated with high risk for cardiovascular (CV) morbidity and mortality [1] due to a process of accelerated atherosclerosis [2]. It is the result of a compound effect mediated by the influence of genetic and classic CV risk factors along with inflammation [3,4]. In this regard, a chronic proinflammatory state is of pivotal importance to accentuate the role of classic CV risk factors [5]. Strong evidence reveals that chronic

inflammatory markers are independently associated with CV mortality and morbidity in RA [6-9].

CV disease, especially ischemic heart disease, is one of the most frequent causes of death in Spain [10]. Nevertheless, the incidence of CV disease in general and of ischemic coronary heart disease in particular is lower than in other countries [11].

Based on a pool of datasets from 12 European cohort studies, mainly carried out in general population settings, European experts performed the Systematic COronary Risk Evaluation (SCORE) project to develop a risk scoring system for use in the clinical management of CV risk in European clinical practice [12]. The SCORE system

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estimates the 10-year risk of a first fatal atherosclerotic event, including heart attack, stroke or other occlusive arterial disease and sudden cardiac death. Risk estimates have been produced as charts for high and low risk regions in Europe [12]. Spain was included in the low risk group. In the Spanish population, like in other European countries, a high CV risk has been defined by a SCORE of $\geq 5\%$.

Framingham algorithms have also proved to be extremely useful tools for screening patients and in primary prevention in countries with a high incidence of coronary and CV disease [13]. However, they were found to overestimate the risk of coronary heart disease in some countries [14]. Therefore, a validated methodology to adapt the Framingham algorithm to each specific country was developed [15]. Currently, in Spain, apart from the SCORE function, there is another function to estimate the presence of high CV risk: the Framingham-REGistre Gironí del COR (REGICOR) calibrated function [16]. The VERIFICA study (Validation of the Adapted Framingham Individual Coronary Incident Risk Algorithm) demonstrated the reliability and precision of the REGICOR adaptation in Spain [17]. A high CV risk has been defined by a REGICOR of $\geq 10\%$.

Adequate stratification of the CV risk is an issue of major importance in patients with RA. A task force of the European League Against Rheumatism (EULAR) has recommended a CV risk assessment using National Guidelines for all RA patients on an annual basis [18]. In the absence of National Guidelines, the SCORE function model is recommended. Additionally, to address the excess risk of patients presenting with RA, the experts of the task force proposed to adapt the CV risk by the application of a multiplier factor of 1.5 in those patients with two of the following three criteria: disease duration of >10 years, rheumatoid factor (RF) or anticyclic citrullinated peptide (anti-CCP) antibody positivity, and the presence of certain extra-articular manifestations.

Several validated non-invasive imaging techniques are currently available to determine subclinical atherosclerosis. They can offer a unique opportunity to study the relation of surrogate markers to the development of atherosclerosis. Among them, by the assessment of carotid intima-media thickness (cIMT) and the presence of plaques, carotid ultrasonography (US) has become an affordable efficient technique to measure the presence of subclinical atherosclerosis in RA [19,20].

In the general population, cIMT was independently associated with future risk of ischemic coronary events and stroke in middle-aged and older individuals. Furthermore, the finding of an atherosclerotic plaque increased the predicted coronary artery disease risk at any level of cIMT [21-24].

Increased cIMT and increased frequency of plaques have been found in patients with RA, even in selected patients without classic CV risk factors [25,26]. In keeping with the results observed in the general population, cIMT was found to predict the development of CV events in RA. In this regard, RA patients without classic CV risk factors at the time of the US assessment who had cIMT values greater than 0.90 mm had increased risk of suffering CV events over a five-year follow-up period [27]. Evans *et al.* also confirmed the implication of carotid plaques as predictors of future CV events in RA. They found a 2.5 increased risk of CV complications among RA patients with unilateral plaques, and 4.3 among those with bilateral plaques [28]. These results highlight the potential role of carotid US as a predictor of high CV risk in RA.

Taking these considerations together, we designed a study to establish which one of the two function charts available in Spain to calculate the CV risk, SCORE or REGICOR, should be used in patients with RA, taking as the gold standard test the result of carotid US.

Materials and methods

Patients and study protocol

A set of 370 consecutive Spanish patients with a diagnosis of RA recruited from Hospital Universitario Marqués de Valdecilla (Santander, Spain), who were assessed for carotid US over a one-year period, were included in the present study [29]. All the patients fulfilled the 1987 American College of Rheumatology classification criteria for RA and also fulfilled the 2010 classification criteria for RA [30,31]. Patients with a history of CV events (ischemic heart disease, cerebrovascular accident, peripheral arterial disease or heart failure) were excluded from the study. Then, clinical records of all patients were again reviewed in an attempt to fully establish comorbidities.

A subject's written consent was obtained in all the cases. The study was approved by the Ethical Committee of the Hospital Universitario Marqués de Valdecilla (Ethical Committee of Cantabria, Spain).

CV risk assessment

The SCORE CV risk index was calculated according to data on the age at the time of the study, sex, smoking history, the systolic arterial blood pressure and atherogenic index (total serum cholesterol level/high density lipoprotein serum (HDL) cholesterol). In parallel, the REGICOR CV risk index was calculated with age, sex, total cholesterol and HDL-cholesterol, systolic and diastolic arterial blood pressure, and history of diabetes mellitus and smoking.

Both modified (m)SCORE and mREGICOR were calculated according to the EULAR recommendations, as described above [18].

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. A commercially available scanner, Mylab 70, Esaote (Genoa, Italy) equipped with a 7 to 12 MHz linear transducer and the automated software guided technique radiofrequency - Quality Intima Media Thickness in real-time (QIMT, Esaote, Maastricht, The Netherlands) - was used [29]. The plaque criteria in the accessible extracranial carotid tree (common carotid artery, bulb and internal carotid artery) were 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 the Mannheim consensus criteria [32]. Carotid plaques were counted in each territory and defined as no plaque, unilateral plaque or bilateral plaques. We considered cIMT > 0.90 mm and/or carotid plaques as the gold standard for severe subclinical atherosclerosis [29]. For the purpose of the present study, patients with any of these severe US findings were defined as US+.

Statistical analysis

Results were expressed as number (percentage) or mean \pm standard deviation (SD).

The area under the receiver operating curve (AUC) for the predicted risk both by mSCORE and mREGICOR was calculated according to the presence of severe carotid US findings (US+).

Using the same gold standard, we also calculated the sensitivity, specificity, positive predictive value and negative predictive value for each integer between 1% and 5% for mSCORE and between 1% and 10% for mREGICOR.

All statistical tests were performed with the package Stata V.12/SE (Stata Corp, College Station, TX, USA).

Results

Most patients from this series of 370 patients without CV events were women (298; 80%). The age at the time of the study and disease duration was 58.9 ± 13.7 and 9.8 ± 8.3 years, respectively. One hundred thirty-four patients (36%) had a disease duration of ≥ 10 years; RF and/or anti-CCP positivity were found in 250 (68%) cases; a total of 61 subjects (17%) had extra-articular manifestations (nodular disease in 24 patients, secondary Sjögren's syndrome in 21, pleuritis/pericarditis in 8, pulmonary fibrosis in 7, Raynaud's phenomenon in 3, rheumatoid vasculitis in 2, scleritis/episcleritis in 2, sclerosing cholangitis in 1 case and Felty's syndrome in 1 case).

The EULAR multiplier factor was required to be used in 122 (33%) of the patients. Due to this, the mSCORE was $2.16 \pm 2.49\%$ and the mREGICOR, $4.36 \pm 3.46\%$. Regarding US results, cIMT > 0.90 mm was observed in 46 (12%) patients and carotid plaques in 195 (53%). Interestingly, 45

of the 46 patients with cIMT > 0.90 also had carotid plaques. According to our previous definition, 196 (53%) patients were US+.

Although the values of the area under the receiver operating curves of both functions in their modified versions - AUC mSCORE: 0.798 (CI 95%: 0.752 to 0.844) and AUC mREGICOR: 0.741 (CI 95%; 0.691 to 0.792) (Figure 1) were promising with respect to their discriminating capacity, the behavior of both functions in the identification of the patients with subclinical atherosclerosis and, therefore, high CV risk was disappointing. In this regard, the mSCORE and the mREGICOR only classified 11% and 6% as patients with high CV risk, respectively. Inversely, mSCORE and mREGICOR misclassified as having high CV risk 4% and 2% of the patients without subclinical atherosclerosis. Also, the mSCORE and the mREGICOR failed to classify as having high CV risk 82% and 91% of the patients, respectively. Therefore, neither of these two functions to estimate CV risk was proved to be effective in Spanish RA patients.

More than 50% of patients with an mSCORE $\geq 1\%$ or mREGICOR > 1% had US+. In consequence, to disclose the presence of severe subclinical atherosclerotic disease in at least 50% of these patients, carotid US would have to be performed on 73% and 86% of them, respectively.

In Table 1, we describe the sensitivity, specificity, positive predictive value and negative predictive value for each integer between 1% and 5% for mSCORE and between 1% and 10% for mREGICOR.

Since many rheumatologists do not have access to carotid US in their daily clinical practice, we tried to find the CV risk threshold that may be useful in indicating

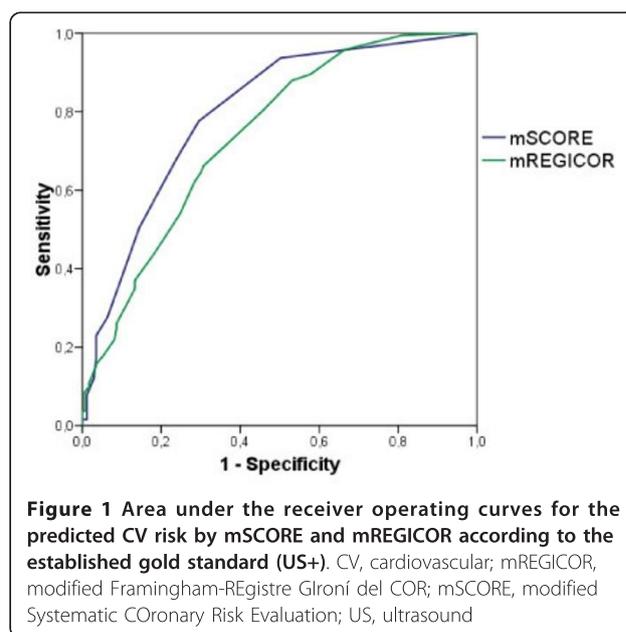


Figure 1 Area under the receiver operating curves for the predicted CV risk by mSCORE and mREGICOR according to the established gold standard (US+). CV, cardiovascular; mREGICOR, modified Framingham-Registre Gronl del COR; mSCORE, modified Systematic COronary Risk Evaluation; US, ultrasound

Table 1 Sensitivity, specificity, positive predictive value and negative predictive value for each integer between 1% and 5% for mSCORE and between 1% and 10% for mREGICOR

Threshold	Sensibility	Specificity	Positive predictive value	Negative predictive value	
mSCORE	≥1% (n: 271)	0.939	0.500	0.679	0.879
	≥2% (n: 174)	0.679	0.764	0.764	0.679
	≥3% (n: 125)	0.510	0.856	0.800	0.608
	≥4% (n: 66)	0.281	0.937	0.833	0.536
	≥5% (n: 45)	0.179	0.966	0.854	0.511
mREGICOR	≥1% (n: 355)	-	0.058	0.541	-
	≥2% (n: 299)	0.958	0.335	0.615	0.879
	≥3% (n: 233)	0.802	0.543	0.661	0.712
	≥4% (n: 168)	0.620	0.717	0.708	0.629
	≥5% (n: 117)	0.443	0.815	0.726	0.569
	≥6% (n: 90)	0.349	0.867	0.744	0.545
	≥7% (n: 63)	0.250	0.913	0.762	0.523
	≥8% (n: 43)	0.177	0.948	0.791	0.509
	≥9% (n: 35)	0.151	0.965	0.829	0.506
	≥10% (n: 21)	0.094	0.983	0.857	0.495

mREGICOR, modified Framingham-REGistre Gironí del COR; mSCORE, modified Systematic COronary Risk Evaluation

high risk and, therefore, the need of a lipid lowering or an antihypertensive treatment.

Patients with type 1 diabetes with target organ damage, type 2 diabetes mellitus or those who have severe chronic kidney disease are considered as having very high CV risk according to current guidelines, regardless of chart function results [24]. Forty three patients from this series had type 2 diabetes or chronic renal disease and were excluded from further analyses. Interestingly, 34 (79%) of them also had severe US findings, that is, US+.

When we used lower thresholds of mSCORE and mREGICOR than those usually recommended in the 327 RA patients without diabetes or severe chronic kidney disease, we increased the number of patients classified as having high CV. Using a threshold of 3% for mSCORE or 4% for mREGICOR, we identified more than 50% of US+ patients, even at the risk of misclassification as high CV risk in 20 to 30% of the patients without severe subclinical atherosclerosis. Specifically, an mSCORE ≥ 3% classified correctly as having high CV risk in 55% of patients and incorrectly in 18% of patients. Likewise, an mREGICOR ≥ 4% classified as having high CV correctly in 63% of patients and incorrectly in 30% of patients.

Discussion

Comparisons between SCORE and REGICOR did not disclose that one of them might be better than the other in establishing the CV risk in Spanish individuals without rheumatic diseases [33-37]. In the present study, neither mSCORE nor mREGICOR were shown to be effective in the stratification of the CV risk of Spanish RA patients. In this regard, when CV risk was defined by the presence of

carotid subclinical atherosclerosis, we observed that both CV risk function charts identified a very low proportion of RA patients with high CV risk and misclassified as having high CV risk a substantial proportion of the patients without subclinical atherosclerosis. Nevertheless, SCORE and REGICOR predict CV mortality and CV events, respectively, and none of them has been tested for the prediction of subclinical atherosclerosis. In addition, these two CV risk function charts have been designed to detect more than just atherosclerotic disease. Therefore, some of the apparently misclassified patients might not truly be misclassified if other CV outcomes were considered in this study.

This study has some limitations. First, actual CV events and mortality were not available and carotid US was used as a surrogate marker of CV risk. Second, our results cannot be generalized to other populations within and outside Spain.

Several years ago, del Rincon *et al.* stated that physicians who provide care to individuals with RA should be aware of the increased risk of CV events in these patients and implement appropriate diagnostic and therapeutic measures [38]. More recently, Crowson and Gabriel emphasized 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 the multiplication factor indicated by the EULAR task force is applied [39]. These authors concluded that although in some circumstances patients with RA satisfying the criteria for use of the multiplier factors may have increased risk of CV disease, some others that do not meet these criteria may also have increased CV risk [39].

A good method of predicting CV events would allow us to establish a high risk threshold to identify, with high sensitivity and specificity, those patients who have a high probability of presenting a CV event; and also a low risk threshold below which we could establish a very low probability of having a CV event. With the help of these two thresholds, we would have to set up a strategy consisting of an indication of therapy to patients who are above the threshold of high CV risk, no specific therapy to those patients who are below the low risk threshold, and the need for performing a diagnostic test in those patients included in the category of moderate/intermediate risk.

Recent studies indicate that carotid US may be a useful diagnostic tool to disclose subclinical atherosclerosis [29], but universal screening is not always feasible in many rheumatology clinics. Therefore, it would be interesting to define a CV risk threshold above which the indication of intensive lipid lowering or antihypertensive treatment was required in patients with RA.

Patients with type 1 diabetes with target organ damage, type 2 diabetes mellitus or those with severe chronic kidney disease (if glomerular filtration rate <60 ml/min/1.73 m²) are considered as having very high CV risk according to current guidelines [24]. In keeping with that, 79% of the RA patients with diabetes or severe kidney disease of our study were US+. Therefore, these patients are considered as having high CV risk and, because of that, non-invasive techniques used to detect the presence of subclinical atherosclerosis would not be required in these patients. According to our present results, in the remaining patients, SCORE and REGICOR do not seem to be useful in identifying RA Spanish patients with subclinical atherosclerosis and increased CV risk.

Conclusions

Neither of the two function charts used in Spain to estimate the CV risk in the general population proved to be effective in stratifying the CV risk in patients with RA. Nevertheless, further assessment of the accuracy of the SCORE to identify high CV risk RA patients is needed in other populations.

Abbreviations

anti-CCP: anticyclic citrullinated peptide; AUC: area under the receiver operating curve; cIMT: carotid intima-media thickness; CV: cardiovascular; EULAR: European League Against Rheumatism; HDL: high density lipoprotein serum; m: modified; RA: rheumatoid arthritis; REGICOR: Framingham-REGistre Groní del COR; RF: rheumatoid factor; SCORE: Systematic COronary Risk Evaluation; SD: standard deviation; US: ultrasonography; VERIFICA: Validation of the adapted Framingham individual coronary incident risk algorithm.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

CGV made substantial contributions to the conception and design of the study, data analysis, and substantial contributions to the elaboration of the

manuscript. AC performed the US study, contributed to the elaboration of the protocol of study, and helped in the interpretation of data. AZ performed data analysis and helped to draft the manuscript. JR and RB recruited patients for the study. CGJ contributed to the elaboration of the protocol of study, and helped in the interpretation of data. AC, JR, RB and CGJ took part in the elaboration of the manuscript. JL participated in the design of the study, data analysis and helped to draft the manuscript. MAGG has made substantial contributions to conception and design of the study, acquisition of data, coordination of the study, and helped to draft the manuscript and was responsible of the final drafting and elaboration of the manuscript. All authors read and approved the final version of the manuscript for publication. CGV, JL and MAGG share senior authorship of this manuscript.

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