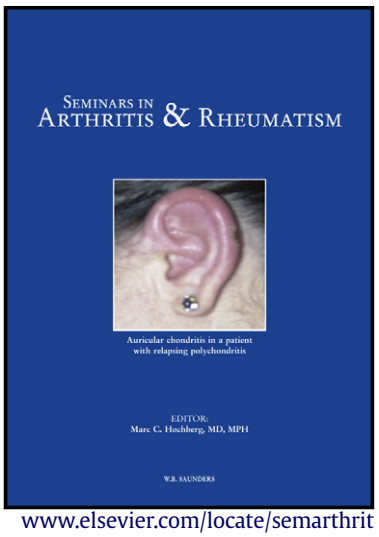


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# Recommendations for the management of cardiovascular risk in patients with rheumatoid arthritis. Scientific evidence and expert opinion

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**TITLE: Recommendations for the management of cardiovascular risk in patients with rheumatoid arthritis. Scientific evidence and expert opinion**

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## ABSTRACT

***Objectives.*** Last recommendations regarding cardiovascular risk (CVR) in Rheumatoid Arthritis (RA) patients were developed by the EULAR group in 2010. The aim is to update evidence based recommendations about this worrying health problem.

***Methods.*** We assembled a multidisciplinary workgroup (rheumatologists, endocrinologist, cardiologist, and epidemiologist) and a panel of 28 expert rheumatologists. The study was carried out in two big phases: identifying key areas in the prevention and management of CVR; and developing a set of recommendations based on a review of the available scientific evidence and use of the Delphi consensus technique. All this has been developed according to an updating process of evidence-based recommendations.

***Results.*** Twenty-five recommendations were made addressing three complementary areas: CVR assessment tools, patient eligibility for assessment, and treatment strategies for control of CVR. The grade of the recommendations was not substantially modified compared to the original EULAR recommendations, except in two of them which were upgraded from C to B. These two recommendations are the ones related to the use of corticosteroids and smoking cessation. The new developed recommendations address these two areas: CVR assessment and treatment strategies for control of CVR.

***Conclusions.*** There are substantial gaps in the current knowledge that do not allow classifying properly RA patients based on their actual CVR and to accurately identify those patients who would benefit from CVR assessment. Consequently, studies designed to determine the causal effects of RA disease characteristics on cardiovascular morbidity/mortality and to identify patients at high risk of cardiovascular disease are still needed.

**Key words:** Atherosclerosis, cardiovascular disease, cardiovascular risk factors, cardiovascular risk management, rheumatoid arthritis, risk assessment, guideline.

## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic multisystem inflammatory disease of unknown etiology affecting between 0.5 and 1% of the adult population (1, 2). Moreover, it has been associated with an increase in global mortality rates (3, 4). Meta-analyses of observational studies showed that RA patients' morbidity and mortality risks stemming from cardiovascular causes were, respectively, close to 50% and up to 60% higher than those of the general population (5-8). This excess in morbidity and mortality is mainly due to an accelerated atherogenesis process (9-11), one that cannot be fully explained by the classic atherosclerosis risk factors (12, 13). In this regard, the mechanisms leading to an elevated cardiovascular mortality rate in RA patients are complex and the presence of chronic inflammation (12, 13) and/or of a possible genetic component (14, 15) are factors likely to contribute to the increased prevalence of cardiovascular disease (CVD) in RA patients (12, 16-18). Therefore, in practical terms, comprehensive assessment and treatment of traditional and non-traditional cardiovascular risk (CVR) factors should form part of the routine care of RA patients (19).

An important aspect in managing patients with elevated CVR is the accurate assessment and grading of such a risk. Some research have shown that the tools used for risk assessment in the general population underestimate the true risk when they are applied to patients with pro-atherogenic diseases such as diabetes or chronic renal disease (20-23). Evidence suggests that this is also the case with RA (24, 25). To address this issue, the European League Against Rheumatism (EULAR) Working Group proposed the adaptation of the SCORE (Systematic Coronary Risk Evaluation) system to estimate CVR in RA patients. The EULAR task force proposed multiplying the SCORE's risk by 1.5 in those RA patients who present at least two of the following conditions: 1) disease duration > 10 years, 2) rheumatoid factor (RF) or anti-cyclic citrullinated peptide (ACCP) positivity, and 3) the presence of extra-articular manifestations (26). After reviewing the published evidence, the EULAR group suggested future research to establish the efficacy of the risk functions to assess CVR in RA, as well as to review in the near future the validity of the 1.5 weighting factor, as up to when EULAR recommendations were developed there had not been found prospective cohort studies that allowed the validation of this factor (26). Articles published in recent years show that, in daily clinical practice, it is not uncommon to see RA patients being classified as having moderate CVR, based on the adapted SCORE, who have subclinical atherosclerosis. This is especially true when non-invasive tools such as carotid ultrasonography are used (27, 28). The results from studies published after the EULAR recommendations were developed, along with an increasing amount of scientific publications and the need to address the management of CVR factors in RA patients such as: life style modification (diet control, physical activity) and control of classic CVR factors (hypercholesterolemia and hypertension, HT), which were not included in the EULAR recommendations, justify the need of the present study.

This updated evidence review goes in line with current recommendations regarding the update of Clinical Practice Guidelines (CPG) or any other type of evidence-based recommendations, which state that evidence should be reviewed at least every three-five years in order to keep its validity (29, 30). Therefore the aim if this study is to update evidence based recommendations for the assessment and CVR management in RA patients, taking as reference the 2010 EULAR Recommendations for CVR management.

## METHODS

### Review - Study Design

A qualitative synthesis of the scientific evidence currently available was performed. The Delphi technique of consensus methodology was used to collect and consolidate expert opinion based on the participants' clinical experience when only no or low quality scientific evidence was available. All this was developed according to an updating CPG process.

### Work group

The work group includes a seven person expert group (EG) composed of 4 rheumatologists, 1 endocrinologist, 1 cardiologist, and 1 epidemiologist, with substantial experience in controlling CVR in RA patients, and on the other hand, 28 rheumatologists selected by the EG to participate as the Delphi technique panel

members (PMs). All work was coordinated and supervised by an experienced epidemiologist specially trained in scientific literature reviews relating to CVR prevention and management.

**Study stages**

This study has been developed according to the different stages for updating CPG in the Spanish National Health System, methodology proposed by the main institutions involved in the elaboration and updating of CPG based on scientific evidence: literature search, critical appraisal and synthesis and updating recommendations (31-34).

The study process was divided into four different stages: a) identification of the key areas for assessment and management of CVR in RA patients; b) analysis of the scientific evidence relevant to those key areas; c) Delphi consensus; and d) qualitative synthesis of the scientific evidence and actualization and formulation of final recommendations.

*Identification of key areas for the assessment and management of CVR in RA patient:*

*Updated recommendations*

The EG defined the main objectives of the recommendations, the key concepts, and the target audience. They identified those clinical questions expected to have the greatest impact on RA patient care and outcomes vis-à-vis the assessment and management of CVR. The latest recommendations from EULAR on CVR management were taken as reference. As its search strategy ran up to May 2008, this study has updated the literature search up to August 2012.

The recommendations of this study have been divided in three sections. The first section gathers information regarding CVR assessment in RA. The second section includes updated EULAR recommendations about the characteristics of the RA patient candidate to be assessed for CVR and the frequency at which that assessment should take place. Finally, the last section gathers information about the management of classic CVR factors and about the control of chronic inflammatory activity.

*Analysis of scientific evidence regarding the key areas of interest*

A precise search strategy was designed to locate CPG, systematic reviews (SR), and meta-analysis (MA) published between January 2008 and August 2012 in the Medline and Cochrane Library databases, using terms from the United States National Library of Medicine thesaurus (Medical Subject Headings, MeSH) when available, with descriptors and Boolean operators (AND, OR, NOT) clearly defined. The following MeSH terms were included: "rheumatoid arthritis", "cardiovascular system", and "risk assessment". The search was filtered by: species (human), language (English and Spanish), age (18 years or older) and type of publication. This search was complemented by queries performed through meta-search engines (e.g., Sumsearch and Tridatebase) using as free text the following terms: “Cardiovascular Risk Assessment”, “Cardiovascular Disease”, and “Rheumatoid Arthritis”. In addition, we checked both domestic and international websites related to scientific societies of rheumatology and cardiology and of agencies responsible for developing and compiling CPGs. Three criteria were used to determine whether original recommendation warranted submission for SR: the scientific evidence available related to the question of interest was either outdated, contradictory, or of low quality (e.g., cross-sectional studies, case series).

As the located CPG, RS and MA did not provide evidence about the RA characteristics associated with increased CVR or evidence on the frequency of CVR assessments the EG developed two specific and separate SRs in search of primary studies. We designed search strategies for MEDLINE, EMBASE, and Cochrane for each SR. Selection criteria included the type of study (SR, MA, and cohorts), adult Caucasian patients with RA, and studies published in English or Spanish from 1 January 2008 to 1 August 2012 (available in Supplementary Material).

*Delineation of Systematic Reviews*

The first SR was designed to respond to the question: Are RA patients with metabolic syndrome or who are RF-positive, or ACCP-positive, or who suffer from either extra-articular disease or prolonged inflammatory disease at a greater risk for a cardiovascular event than RA patients with none of these factors? The main outcome of interest was a cardiovascular event, either fatal or non-fatal, quantified as a Mortality Ratio (MR) due to CV causes, a Hazard Ratio (HR), an Odds Ratio (OR), and a Relative Risk (RR).

The second SR aimed to answer the following question: How frequently should CVR be assessed in RA patients? The main outcome of interest was time from RA onset to appearance of an excessive level of CVR. Literature search strategies, along with the flowchart used for the identification and selection process for both the first and the second RS, are available in Supplementary Material.

The quality of the studies was evaluated using the critical reading template developed by SIGN, the SIGN evidence scale (35) (Table 1). Tables summarizing the main study

characteristics were created, to include an evaluation of the quality of each study reviewed.

*Delphi Consensus*

Based on the results from the scientific evidence analysis, we selected those statements with either no supporting evidence or those based on scientific data of low quality level (<2++) on the SIGN evidence scale. We developed a 12-item questionnaire for the first round of the Delphi process, organized into 4 key areas: risk assessment tools, RA disease characteristics that increase CVR, risk assessment frequency, and therapeutic strategies to control and manage CVR. Items consisted of Likert Scale-type brief independent statements and degree of agreement was scored from 1 (strongly disagree) to 5 (strongly agree). Additionally, PMs could include free text comments on each of the proposed items, based either on scientific evidence or on their own clinical experience.

The questionnaire (first round) was sent to all 28 PMs and 7 EG members via group email. Following analysis of the first questionnaire, a second one was sent (second round) via individual email. This latter questionnaire followed the same structure as the first, but included the 7 statements with lowest level of agreement from the first round. For each statement, this report gave the total score given by the PMs during the first round. Data were expressed as median and interquartile range (IR) and the high degree of agreement (DA) $\geq 4$ as a percentage. During this second round, all panel members were asked to assign a level of agreement to each statement, this time taking into account the overall group results from the first round.

*Summary of scientific evidence and formulation of recommendations*

When evaluating and summarizing the scientific evidence, we took into account the internal validity of the studies, any data of statistical significance, how precisely findings were reported (e.g., confidence intervals (CI), size of the estimates), and the applicability of such findings to the whole. We chose the system proposed by SIGN to classify both the evidence level (EL) and the recommendation grade (RG) (35). Accordingly, all recommendations were developed in light of the EL and the consensus reached by the PM.

**RESULTS**

The results presented in this article are drawn from six CPG - two RA-specific (36, 37), and four reports on CVR management in the general population (38-41) -, nine SR and MA (42-50), and four SR without MA (51-54). Of those SR performed specifically for this analysis, we included seven original articles (55-61) from 438 studies compiled (not counting duplicates). A total of 25 recommendations (Table 2), divided in three sections, were formulated for the evaluation and management of CVR in RA patients.

***Cardiovascular risk assessment***

EULAR recommendations for the management of CVR in RA patients and other inflammatory diseases have suggested adapting RA patient CVR estimates by multiplying the SCORE function by a correction factor of 1.5 (26). To the best of our knowledge, there are to date no studies supporting the accuracy of this modified

SCORE model in terms of correctly discriminating between high and low CVR in RA patients. In this regard, a recent study has shown that use of the EULAR formula may result in underestimates of the true CVR in RA patients (62).

A few studies have proposed the use of non-invasive tools, such as a carotid ultrasound or a brachial-ankle index, in order to establish the presence of subclinical atherosclerosis in those asymptomatic individuals with an intermediate risk level based on CVR prediction tables (38, 40, 47, 63). Although of high quality, these studies were performed in the general population. Nevertheless, meta-analyses performed in the general population (64) and in patients with RA (46, 65) indicate that an increase in the carotid artery intima-media wall thickness determined by carotid ultrasound is associated with an increment in the risk of having of cardiovascular events. Similarly, a meta-analysis in general population demonstrated that the ankle brachial index is a good predictor of cardiovascular events (47). Recent studies indicate that carotid ultrasound may also represent a useful diagnostic tool for identifying subclinical atherosclerosis in RA (66). Further to this end, a recent study that assessed coronary artery calcium scores, based on a multi-detector coronary artery scan, and the presence of carotid plaques in the common carotid artery (via a carotid ultrasound), revealed that carotid ultrasound is more sensitive than the coronary artery calcium score in determining the presence of subclinical atherosclerosis in RA patients (67). Regrettably, despite evidence of an increased frequency of subclinical atherosclerosis in these carotid ultrasound studies (46), there exists only a single prospective study on RA with a 5-year follow-up showing that carotid intima-media thickness (cIMT) is a good predictor of CVD (28). In this small study (n=47 patients without classic risk factors or CVD at recruitment), RA patients with cIMT < 0.77 mm did not experience CVD events, whereas 6 of the 10

patients with cIMT thickness > 0.9 mm suffered CVD events by the end of the five-year follow-up period ($p<0.001$) (28).

Based on these data, the EG recommends to follow EULAR recommendation about assessing CVR in those RA patients without clinically evident CVD by using the modified EULAR SCORE risk formula (Table 2; R1; RG: D, EL: 3), and adds a new recommendation: Carotid ultrasound or ankle-brachial index as methods to rank CVR are indicated in asymptomatic RA patients with intermediate CVR (1%-4%). The experience of the professional or equipment availability will determine the use of either method (Table 2; R2; RG: B, EL: 1+). The experts concluded that the choice of one of these tools over the other would depend upon the experience of the clinician and the equipment available at each site.

***Patients eligible for cardiovascular risk assessment and frequency for CVR assessment***

Well-designed cohort studies have shown that patients with extra-articular manifestations who are RF-or ACCP-positive have a greater risk for CVD (58, 60, 61). Using the Hazard Ratio (HR), Inhala and colleagues (58) estimated that the risk of developing a new cardiovascular event in the five-year period after symptom onset was 3.3 (95%CI: 1.4-7.9), which is consistent with the magnitude of effect reported by Myasoedova et al. (61) regarding the risk of cardiac failure in RA patients (HR: 3.1; 95%CI: 1.9-5.1). This study further found that RF-positive patients were at higher risk for cardiac failure than their RF-negative counterparts (HR: 1.6; 95%CI: 1.0-2.5). With respect to the relationship between ACCP and CVD, Lopez Longo and colleagues found almost three-fold increased risk of ischemic heart disease in RA patients who were

ACCP-positive versus those who were ACCP-negative (OR: 2.8; 95%CI: 1.2-6.6) (60). It is worth noting, however, that despite the excellent design of this study, it did include hospitalized patients with a 10 years average of disease duration.

On the subject of metabolic syndrome and disease duration, we did not find enough information supporting the notion that such patients had a greater CVR. We found only one well-designed case-control study with a low risk for bias; here, no association was noted between metabolic syndrome in RA patients and higher levels of coronary artery calcification after adjusting for years of smoking and inflammatory activity measures (OR:1.7; 95%CI: 0.9-3.5) (68). The available scientific evidence examining the correlation between duration of RA and the risk of CVD development remains inconclusive. In the SR for this study, we included a cohort study that identified a link between the amount of time a patient has lived with RA and heart failure (61). Patients with RA for less than a year were at a higher risk of heart failure after adjusting for classic CVR factors and ischemic heart disease (HR: 2.1; 95%CI: 1.1-3.8)**.** However, this result should be interpreted with caution as it may reflect a higher inflammatory burden at the time of disease diagnosis, as well as a lack of proper adjustment for confounding factors, such as the use of medication for controlling the disease.

Given the lack of scientific evidence on the role of metabolic syndrome and on the impact that the duration of an inflammatory disease can have on CVR in RA patients, a Delphi consensus was used to determine the panel's agreement based only on their clinical experience. The level of agreement reached among the PMs was high (DA ≥4), and these recommendations were included in the final version. The experts recommend making an assessment of CVR in RA patients if at least one of the following criteria

was met: the patient exhibits extra-articular manifestations (Table 2; R3; RG: C, EL: 2+), is RF-positive (Table 2; R4; RG: C, EL: 2+), is ACCP-positive (Table 2; R5; RG: D, EL: 2+), presents some metabolic syndrome features (Table 2; R6; RG: D, EL: 4) or is suffering a long-standing chronic inflammatory disease (Table 2; R7; RG: D, EL: 4).

In contrast to EULAR recommendations, the present study establishes one new recommendation for each of the clinical characteristics associated with a higher CVR (extra-articular manifestations, RF+, ACCP+, metabolic syndrome and disease duration) which allows differentiating those with a higher grade of recommendation from those ones with a low grade of recommendation. None of these recommendations present a higher grade of recommendation to those included in the EULAR guideline ("*The CVR scoring models should be adapted to RA patients, introducing a 1.5 weighting factor, this multiplying factor should be used when the patients complies with 2 out of the 3 following risk factors: duration of the disease > 10 years, RF+ or ACCP+, presence of extra-articular manifestations*". Grade of Recommendation: C) (26).

*Annual assessment of CVR in RA patients*

The available scientific evidence supporting annual assessments of CVR in RA patients stems from descriptive studies and expert opinions (26, 36). Our SR was unable to identify any study designed to determine the optimal frequency for CVR assessment taking into account the time from RA onset. A preliminary recommendation was formulated as a starting point for the Delphi process. Despite the low proportion of PMs who answered "agree" or "strongly agree" with this recommendation (GA ≥4=69%, IR: 3-4), their overall level of agreement was considered acceptable and the statement was finally included along with the other recommendations**.** The EG recommends annually

assessing CVR in RA patients (Table 2; R8; RG: D, EL: 3), therefore EULAR recommendation is not modified (26).

***Cardiovascular risk management***

*Physical exercise and control of classic cardiovascular risk factors*

The following set of recommendations addresses therapeutic strategies not considered by the EULAR recommendations (26), such as, those related to life style modifications associated with a higher CVR. Regarding physical activity, there are findings that support the inclusion of physical activity as part of a multidisciplinary care program to reduce CVR and prevent the development of CVD in RA patients (48, 51). However, two crucial aspects still need to be elucidated: 1) to establish the exercise protocols suitable for RA patients and 2) to determine when patients should do exercise (51).

High quality studies indicate that optimal management of hypercholesterolemia, arterial hypertension, smoking discontinuation, and obesity control are of main importance to successfully reducing CVR in the general population (39-41). Although there are no studies on RA patients, these recommendations are also applicable to the RA population (see Table 1).

Taken together, the experts advised following the same therapeutic strategies for the control and management of hypercholesterolemia, hypertension, smoking and obesity in RA patients as those recommended for the general population. The strength of the recommendations for the control of hypercholesterolemia, obesity and smoking was strong (B) and supported by studies with a level of evidence measuring 1 + +. The

reason for not giving a Grade A to any of these recommendations was due to the fact that these recommendations are supported by studies rated as 1 + + but in populations different from RA; it is to say different from our population. Therefore, the level of the evidence of these recommendations was maintained unchanged but the grade of recommendation was reduced to B. However, the evidence for the management of hypertension in RA patients was weaker (D). This recommendation was therefore submitted for Delphi consensus, resulting in strong level of agreement (DA ≥4) (Table 2; R9-R17). With respect to the implementation of physical activity in RA patients in order to better control CVD, the experts recommend encouraging patients to do physical exercise in accordance with their functional abilities (Table 2; R18; RG: B, EL: 2++).

*Drugs and CVR in RA patients*

Regarding the use of drug therapies to control RA-related inflammatory activity and thus, CVR, two situations should be taken into account. The use of disease-modifying anti-rheumatic drugs (DMARDs), which reduce inflammatory activity, and the prescription of drugs that actually increase CVR and that should be used with caution.

Recent studies show that the use of DMARDs, both synthetic and biologic, is associated with reductions in CVR (42, 43, 52, 53). The MA by Micha and colleagues (42) encompassed 10 observational studies of patients with RA, psoriasis, or polyarthritis treated with methotrexate. Their analyses detected a 21% reduction in the development of CVD (n=10 studies, RR: 0.79; 95%CI: 0.73-0.87), and a decrease of 18% in heart attacks (n=5 studies, RR: 0.82; 95%CI: 0.71-0.96), with no evidence of statistical heterogeneity among studies; p=0.30 and p=0.34, respectively. The SR by Westlake and

colleagues (52), which included 20 studies (1 experimental, 18 longitudinal, and 1 cross-sectional) that examined the effects of anti-TNF drugs in CVR among RA patients, concluded that most of these studies showed a reduction in CVR, though not as consistently as the study involving methotrexate. This SR also concluded that these drugs do not seem to increase the risk of heart failure. More recently, Barnabe and colleagues (43) published an SR and a MA of cohort studies and randomized controlled trials (RTCs). The MA from cohort studies showed that patients treated with anti-TNF drugs experienced a reduction in the risk of developing CVD (adjusted-RR: 0.5; 95%CI: 0.3-0.8), heart attack (adjusted-RR: 0.8; 95%CI: 0.7-1.0) and stroke (adjusted-RR: 0.7; 95%CI: 0.5-0.9). Although the MA from randomized clinical studies showed the same tendency, the difference in the risk level for CVD failed to achieve statistical significance (adjusted RR: 0.8; 95%CI: 0.2-2.6). However, it is worth noting that the MA of cohort studies showed high heterogeneity and a possible publication bias.

Although current scientific evidence consistently supports the use of anti-TNF drugs to reduce CVR in RA patients, the mechanisms leading to this reduction need to be elucidated. One hypothesis concerned the drug's effect on the lipid profile. Daien and colleagues published a MA (69) in which they concluded that the cardio-protective effects of anti-TNF drugs in RA patients could not be explained either by LDL quantitative changes or by the atherogenic profile. The protection should stem from the drug's effect on HDL levels, an association that warrants further examination by prospective studies involving long-term follow-up. The MA of 32 articles, including 13 prospective before/after studies, which analyzed the evidence on long-term anti-TNF treatment and its effects on blood lipid levels, showed an increase in HDL levels (+0.3 mmol/l, $p<0.0001$) and total cholesterol (+0.3 mmol/l, $p=0.03$). LDL levels and

atherogenic profiles did not vary. Triglyceride levels increased (+0.3 mmol/l, p< 0.001) and the apoB/A ratio decreased (-0.3, p<0.0001). A prospective cohort study of RA patients in which prevalent cases of diabetes mellitus were excluded, suggested that anti-TNF treatment was associated with a 51% reduced risk of developing diabetes (HR: 0.5; 95%CI: 0.2-1.0) (70). Although there are studies demonstrating that there is no association between anti-TNF drug use and increased risk of congestive heart failure (CHF) in the short-term, the use of anti-TNF agents in RA patients with CHF is not recommended.

In the present work, the experts encourage clinicians to maintain, as much as possible, the disease in clinical remission, since tight control of the disease would likely help reduce the inflammatory burden and thereby lead to a lower CVR (Table 2; R19; RG: B, EL: 2++). This recommendation does not change the grade of the original EULAR recommendation: (*R2.The disease activity should be controlled in order to reduce CVR) (26)*. In addition, the experts have established new recommendations for the management of CVR in RA patients in special situations; heart failure and acute coronary syndrome. They recommend not prescribing anti-TNF drugs to RA patients susceptible to severe heart failure or severe left ventricular systolic dysfunction (Table 2; R20: RG: D, EL: 3), or during the acute phase of an acute coronary syndrome (Table 2; R21; RG: D, EL: 2+).

*Drugs requiring caution*

Physicians prescribing non-steroidal anti-inflammatory drugs (NSAIDs) must select the best agent and therapeutic dose, taking into account the risk factors relevant to that

patient, and keeping in mind that while COX-2 inhibitors and classic NSAIDs have similar anti-inflammatory effects, their cardiovascular toxicity rates can vary greatly (36). Thus, it is advisable to assess and follow-up carefully the patient's CVR factors. Clinicians should exercise caution when prescribing such drugs to high CVR patients or to those patients already diagnosed with CVD. High-level scientific evidence has demonstrated a link between NSAIDs and COX-2 inhibitors in the management of patients with systolic cardiac failure (II-IV NYHA) (71). NSAIDs may worsen acute hypertension and cause deterioration in renal function. Therefore, the use of these drugs should be recommended only when the benefits clearly outweigh the risks. A cohort study of 22,576 hypertensive CVD patients investigated the possible link between chronic NSAID use (patient self-report) and CVD mortality. In fact, the results showed a significant increase in CVD mortality (HR: 2.3; 95%CI: 1.7-3.0) (72). Other recommendations indicate that clinicians should be extremely careful when prescribing NSAIDs and COX-2 inhibitors during the acute phase of an acute coronary syndrome (73).

On the subject of treating RA patients with corticosteroids, an SR by Ruyssen-Witrand and colleagues (49) identified only a weak association between CVR factors and low-dose corticosteroids treatment (<10 mg/day of prednisone) in RA patients. However, the review also discovered a substantial increase in CVD in 4 of the 6 studies; this included: myocardial infarction (HR: 1.7; 95%CI: 1.2-2.3), stroke in patients receiving a prednisone dose between 6 and 10 mg/day (HR: 4.4; 95%CI: 1.6-11.9), mortality (HR: 2.03; 95%CI: 1.2-3.3), and CVD composite index in RF-positive patients (HR: 2.2; 95%CI: 1.2-4.0). In contrast, the other two studies failed to find any association between low-dose corticosteroid treatment and mortality (OR: 2.2; 95%CI: 0.3-102.5) or the CVD composite index (OR: 1.3; 95%CI: 0.8-2.0).

In our study, the EG recommend that clinicians prescribe NSAIDs only over the shortest time course possible (Table 2; R22; RG: B, El: 1+) and avoid using these drugs in RA patients experiencing hypertension, renal and/or heart failure (Table 2; R23; RG: B, EL: 1+). NSAIDs should be discontinued in patients with acute coronary syndrome (Table 2; R24; RG: D, EL: 2+). For corticosteroid treatment, the experts recommend their use when clearly indicated, but only at the lowest dose possible (Table 2; R25; RG: B; EL: 2++). In this study, recommendations number 22 and 25 have changed the original EULAR grade of recommendation passing both from C to B.

## CONCLUSIONS

This study summarizes recommendations for the assessment and management of CVR in RA patients. As a whole, the updated recommendations in this study for the management of CVR in RA patients do not substantially change from the EULAR original ones, but they add new evidence based information, not included in the EULAR Guideline, about life style modifications (diet control and physical activity), control of classic CVR factors (hypercholesterolemia, HT) and therapeutic strategies in RA patients in special clinical situations such as congestive heart failure, renal failure or acute coronary syndrome. The present study also analyzes the available scientific evidence regarding key factors in the management of CVR in RA patients, not addressed by the EULAR Guideline, such as diagnostic techniques (carotid ultrasound and brachial-ankle index) which allows detecting replacing markers for CV disease and helping to reclassify patients according to their real CVR.

The value of these recommendations for the clinical practice resides in the fact that they combine two key elements: the latest available scientific evidence and the clinical experience of the rheumatologists who see such patients daily.

Having analyzed the existing evidence, there are important gaps in the knowledge related to the assessment and management of CVR in RA patients. There is extensive high-quality evidence supporting those recommendations related to the control of CVR factors, both classic as well as disease activity factors. In contrast, studies examining risk stratification, the profile of RA patients at risk of CVD, and the optimal frequency for assessment are scarce.

The current state of the field shows the need for further research to improve our understanding of this important area affecting the health of RA patients. Also needed are observational studies designed to determine the causal effects of RA disease characteristics on cardiovascular morbidity/mortality and to identify patients at high risk for CVD.



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## COMPETING INTERESTS

The authors declare that they have no conflicts of interest related to this work.

## AUTHORS' CONTRIBUTIONS

MAG-G y MAM-A made substantial contributions to the conception and design of the study, to the literature review, data analysis, and, importantly, to the elucidation and drafting of the manuscript. They also gave their approval to the final version.

CG-J, SC, JL, IF-A, BG-F, and FD-G helped in the interpretation of data and in the elaboration of the manuscript and similarly gave their approval to the version submitted for be publication.

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**Table 1.** SIGN Levels of Evidence and Grades of Recommendation.

| |
|---|
| **Levels of Evidence** |
| 1++ High-quality meta-analysis, systematic reviews of clinical trials or high-quality clinical trials with low risk of bias. |
| 1+ Well-conducted meta-analysis, systematic reviews of clinical trials, or well-conducted clinical trials with low risk of bias. |
| 1- Meta-analysis, systematic reviews of clinical trials, or clinical trials with high risk of bias. |
| 2++ High-quality systematic reviews of cohort or case-control studies.<br><br>Cohort or case-control studies with very low risk of bias and high probability of establishing a causal relationship. |
| 2+ Well-conducted cohort or case-control studies with low risk of bias and moderate probability of establishing a causal relationship. |
| 2- Cohort or case-control studies with high risk of bias and significant risk of non-causal relationship. |
| 3 Non-analytic studies such as case reports, case series or descriptive studies. |
| 4 Expert opinion. |
| **Grades of Recommendation** |
| A: At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the guide's target population, or a body of evidence comprised of studies classified as 1+ with high consistency among them. |
| B: Body of evidence comprised of studies classified 2++, directly applicable to the guide's target population and that have been shown to have high consistency among them, or evidence extrapolated from studies classified as 1++ or 1+. |
| C: Body of evidence comprised of studies classified as 2+ directly applicable to the guide's target population and that have been shown to have high consistency among them; or evidence extrapolated from studies classified as 2++. |
| D: Level 3 or 4 evidence, or evidence extrapolated from studies classified as 2+. |
| **Good clinical practice** |
| Recommended practice based on clinical experience and the consensus of the drafting team. |

**Table 2.** Recommendations for the assessement and management of cardiovascular risk in RA patients.

| RECOMMENDATIONS | RG | EL | DA ≥4* |
|---|---|---|---|
| ***1. Cardiovascular risk assesstment*** | | | |
| **R1.** Asymptomatic RA patients with no clinical evidence of CVD should be assessed for CVR using the modified SCORE system. | D | 3 | 100% |
| **R2.** Carotid ultrasound or ankle-brachial index as methods to rank CVR are indicated in asymptomatic RA patients with intermediate CVR (1%-4%). The experience of the professional or equipment availability will determine the use of either method[#]. | B | 1+ | -- |
| 2. ***Patients eligible for cardiovascular risk assessment and frequency for CVR assessment*** | | | |
| **R3**. RA patients with extra-articular symptoms should be assessed for CVR due to their higher risk of developing CVD compared to asymptomatic patients[#]. | C | 2+ | 100% |
| **R4.** RA patients who are RF-positive should be assessed for CVR due to their higher risk of developing CVD versus their RF-negative counterparts. | C | 2+ | 96% |
| **R5.** RA patients who are ACCP-positive should be assessed for CVR due to their higher risk for developing CVD compared to their ACCP-negative counterparts. | D | 2+ | 96% |
| **R6.** RA patients with metabolic syndrome should be assessed for CVR because they may be at higher risk for cardiovascular events than those without this syndrome[#]. | D | 4 | 100% |
| **R7.** RA patients with longer disease durations may be considered for CVR assessment due to their increased risk for developing CVD. | D | 4 | 100% |
| **R8.** Performing annual CVR assessments in RA patients is recommended. | D | 3 | 69% |
| ***3. Cardiovascular risk management*** | | | |
| **R9.** The use of statins is recommended in the primary prevention of cardiovascular events in RA patients with CVR ≥ 10%. Such individuals should be encouraged to lead a heart-healthy lifestyle both before and during drug treatment[#]. | B | 1++ | -- |
| **R10.** For primary prevention in cases of CVR≥10%, statin treatment should be started before treatment at low-to-medium doses even with baseline cholesterol levels LDL 70-100 mg/dl. Patient should be encouraged to lead a heart-healthy lifestyle before and during drug treatment[#]. | B | 1++ | -- |
| **R11.** Starting statin treatment at medium-to-low doses should be considered in AR patients with CVR ≥ 1% and < 5% if LDL cholesterol levels <100mg/dl cannot be achieved through lifestyle changes[#]. | B | 1++ | -- |
| **R12.** Starting statin treatment at medium-to-low doses should be considered in patients with CVR< 1%, if LDL cholesterol levels <190 are not achieved through lifestyle changes[#]. | B | 1++ | -- |
| **R13.** The main recommended lipid profile target, in the presence of hypercholesterolaemia and very high CVR (≥10%), is a LDL-cholesterol level < 70 mg/dl or a reduction of at least 50% of its plasma levels[#]. | B | 1++ | -- |
| **R14.** The recommended lipid profile target in the presence of hypercholesterolaemia and high CVR (5%-9%) is a LDL-cholesterol level < 100 mg/dl[#]. | B | 1++ | -- |
| **R15.** Patients with stage 1 hypertension (>140/90 mmHg) and CVR ≥5% should be prescribed anti-hypertension drugs[#]. | D | 4 | 100% |
| **R16**. Smokers should be encouraged to quit to prevent and control CVR by making the best effective smoking cessation interventions available to them[§]. | B | 1++ | -- |
| **R17.** Obese or overweight RA patients should be encouraged to lose weight because these factors are associated with an increase in CVR[#]. | B | 1++ | -- |
| **R18**. Physical activity, appropriate to the patient's health status, should be encouraged to prevent and control CVD development[#]. | B | 2++ | -- |
| **R19**. RA activity should be controlled with disease-modifying anti-rheumatic drugs (DMARDs) as a reduction in the inflammation burden is associated with lower CVR. | B | 2++ | -- |
| **R20**. Anti-TNF alpha treatment is not recommended in patients with uncontrolled cardiac failure or severe left ventricular systolic dysfunction[#]. | D | 3 | 96% |
| **R21.** Anti-TNF alpha treatment is not recommended during the acute phase of Acute Coronary Syndrome when signs of cardiac failure are present[#]. | D | 2+ | 96% |
| **R22.** NSAIDs with the highest safety profile should be prescribed for the shortest time period possible. | B | 1+ | -- |
| **R23**. Hypertensive or renal failure patients should be "red-flagged" if prescribed NSAIDs[#]. | B | 1+ | -- |
| **R24.** NSAIDs treatment should be suspended in patients with Acute Coronary Syndrome during its acute phase[#]. | D | 2+ | 92% |
| **R25.** Corticoids should be prescribed at the lowest dose possible[§]. | B | 2++ | -- |

*ACCP: Anticyclic citrullinated peptide antibodies; CVD: Cardiovascular disease; CVR: Cardiovascular risk; DA: Degree of agreement; EL: Evidence level; RG: Recommendation grade; NSAIDs: Nonsteroidal anti-inflammatory drugs; RF: rheumatoid factor.*

*# New Recommendation.*

*§ Modified Recommendation*

**In the absence of data, the recommendation was not submitted for Delphi consensus if the EL was greater than 2+.*