Italian recommendations for the assessment of cardiovascular risk in rheumatoid arthritis: a position paper of the Cardiovascular Obesity and Rheumatic DISease (CORDIS) Study Group of the Italian Society for Rheumatology

F. Cacciapaglia[1], F.R. Spinelli[2], G.L. Erre[3], E. Gremese[4], A. Manfredi[5], M. Piga[6,7], G. Sakellariou[8,9], O. Viapiana[10], F. Atzeni[11], E. Bartoloni[12]

[1]Rheumatology Unit, Department of Precision and Regenerative Medicine and Ionian Area (DePReMeI), Università degli Studi di Bari; [2]Reumatologia, Dipartimento di Medicina Interna e Specialità Mediche, Università degli Studi di Roma La Sapienza, Rome; [3]Dipartimento di Scienze Mediche, Chirurgiche e Sperimentali, Università degli Studi di Sassari; [4]Department of Geriatrics, Orthopaedics, and Rheumatology, Policlinico Universitario A. Gemelli-IRCCS, Università Cattolica del Sacro Cuore, Rome; [5]Rheumatology Unit, Azienda Ospedaliera Universitaria Policlinico of Modena; [6]Rheumatology Unit, AOU Cagliari; [7]Department of Medical Sciences and Public Health, University of Cagliari; [8]Department of Internal Medicine and Therapeutics, University of Pavia; [9]Istituti Clinici Scientifici Maugeri, Pavia; [10]Rheumatology Unit, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona; [11]Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina; [12]Rheumatology Unit, Department of Medicine and Surgery, University of Perugia, Italy.

Abstract

Objective

Rheumatoid arthritis (RA) patients are at high risk of cardiovascular (CV) events. The aim of this position paper is to provide Italian rheumatologists with an easy, feasible and time-saving CV risk assessment in their daily clinical practice.

Methods

A narrative review of the literature and an assessment of the methodological strength underlying the current evidence on CV risk assessment in patients with RA were performed. The evidence-based results were shared among the members of the steering committee of the CORDIS study group of the Italian Society of Rheumatology. Subsequently, a unanimously agreed-upon algorithm was discussed and finally approved by the experts.

Results

RA patients should have their CV profile monitored using the Italian 'Progetto Cuore' chart, according to the current EULAR recommendations for CV risk management, at least every 5 years. In the presence of high disease activity, or a multi-drug failure condition, when prolonged treatment with glucocorticoids and/or NSAIDs is required, or if hypertension, dyslipidaemia, or diabetes mellitus are concomitant, a more stringent CV risk assessment should be considered. When moderate CV risk is documented, patients should undergo intima-media thickening measurement. The condition of high CV risk requires a cardiological evaluation.

Conclusion

This position paper provides five Italian recommendations for CV risk assessment in RA patients. A general and uniform approach to CV risk profiling may be useful to identify those patients who should undertake intensive preventive strategies to improve their CV outcomes.

Key words

rheumatoid arthritis, cardiovascular risk, cardiovascular algorithm, Progetto Cuore algorithm, Italian recommendations

*Fabio Cacciapaglia, MD, PhD**
*Francesca R. Spinelli, MD, PhD**
Gian Luca Erre, MD, PhD
Elisa Gremese, MD
Andreina Manfredi, MD, PhD
Matteo Piga, MD
Garifallia Sakellariou, MD, PhD
Ombretta Viapiana, MD
*Fabiola Atzeni, MD, PhD***
*Elena Bartoloni, MD, PhD***

**Contributed equally as first authors.*
***Contributed equally as senior authors.*

Please address correspondence to:
Fabio Cacciapaglia
U.O.C. di Reumatologia,
Dipartimento di Medicina di Precisione e Rigenerativa e Area Jonica (DiMePReJ),
Policlinico di Bari,
Piazza Giulio Cesare 11,
70124 Bari, Italy.
E-mail: fabio.cacciapaglia79@gmail.com

Received on August 28, 2022; accepted in revised form on December 16, 2022.

Competing interests: none declared.

Introduction

Cardiovascular disease (CVD) is the most common cause of mortality in patients with rheumatoid arthritis (RA). Traditional risk factors, such as hypercholesterolaemia, type 2 diabetes mellitus (DM), abnormal body mass index, abdominal obesity, and current smoking, do not fully explain the high rates of CVD in patients with RA. Further risk factors related to autoimmunity and inflammatory status, disease duration longer than 10 years, and use of systemic glucocorticoids (GCs) and/or non-steroidal anti-inflammatory drugs (NSAIDs) are now recognised as predictors of CVD as much as traditional risk factors in RA (1, 2).

Atherosclerosis (ATS) is more prevalent in RA than in the general population, and atherosclerotic lesions progress more rapidly and may be more prone to rupture, causing clinical events. Cells and cytokines implicated in the pathogenesis of RA are also involved in the development and progression of ATS, which is generally recognised as an inflammatory condition (3). Thus, ATS has been proposed as an extra-articular manifestation rather than comorbidity of RA.

Disease-modifying anti-rheumatic drugs (DMARDs), both conventional synthetic (cs) and biologic (b), could have a beneficial effect on CV risk. However, it is unclear whether this benefit is attributable to the effective control of inflammation or whether targeting specific cytokines implicated in ATS provides additional CV risk reduction. Further knowledge about the predictors of CV risk, the effects of early control of inflammation, and the specific effects of drugs will likely improve the recognition and management of CV risk in patients with RA (4).

The management of CV risk in RA patients still represents an unmet need, as several disease-related variables, including inflammatory background, disease activity, and anti-rheumatic therapies may affect the occurrence of CV comorbidities and strongly influence a reliable estimate of CV risk in these patients (5-7).

In addition, because CV risk should be managed by the rheumatologist, appropriate identification of RA patients at higher CV risk may allow the correct prevention strategies to be undertaken, either as appropriate lifestyle modifications and/or specific medical treatments.

A recent survey showed that about one third of Italian rheumatologists, although recommended, do not routinely assess CV risk in their daily clinical practice (8). In this context, it is important to provide an easy, feasible, and time-sparing tool to assess CV risk during rheumatology visits.

Therefore, the aim of this paper was to propose 5 evidence-based recommendations to help rheumatologists correctly assess CV risk in patients with RA during daily clinical practice.

Methods

The task force was composed of members of the steering committee of the CORDIS Study Group of the Italian Society for Rheumatology. The group consists of ten rheumatologists with recognised expertise in the field of cardiovascular comorbidity in the course of rheumatic diseases.

The list of proposed recommendations was discussed and refined during a teleconference with all members of the study group. The principles guiding the proposed recommendations were based on a narrative review of the literature and an assessment of the methodological strength underlying the current evidence in the literature on CV risk in patients with RA. Subsequently, during the teleconference, all task force members unanimously defined a shared algorithm containing the final approved document. The proposed algorithm stratifies patients according to disease characteristics that influence CV risk (Fig. 1). All seronegative RA patients, with nonerosive disease lasting less than 10 years, without extra-articular manifestations, with preserved physical function (defined as Health Assessment Questionnaire score ≤0.5), in remission for at least one year defined by standardised disease activity score 28 and/or clinical disease activity index cut-off, were to be considered with a favourable CV risk profile. Patients who do not meet all these character-

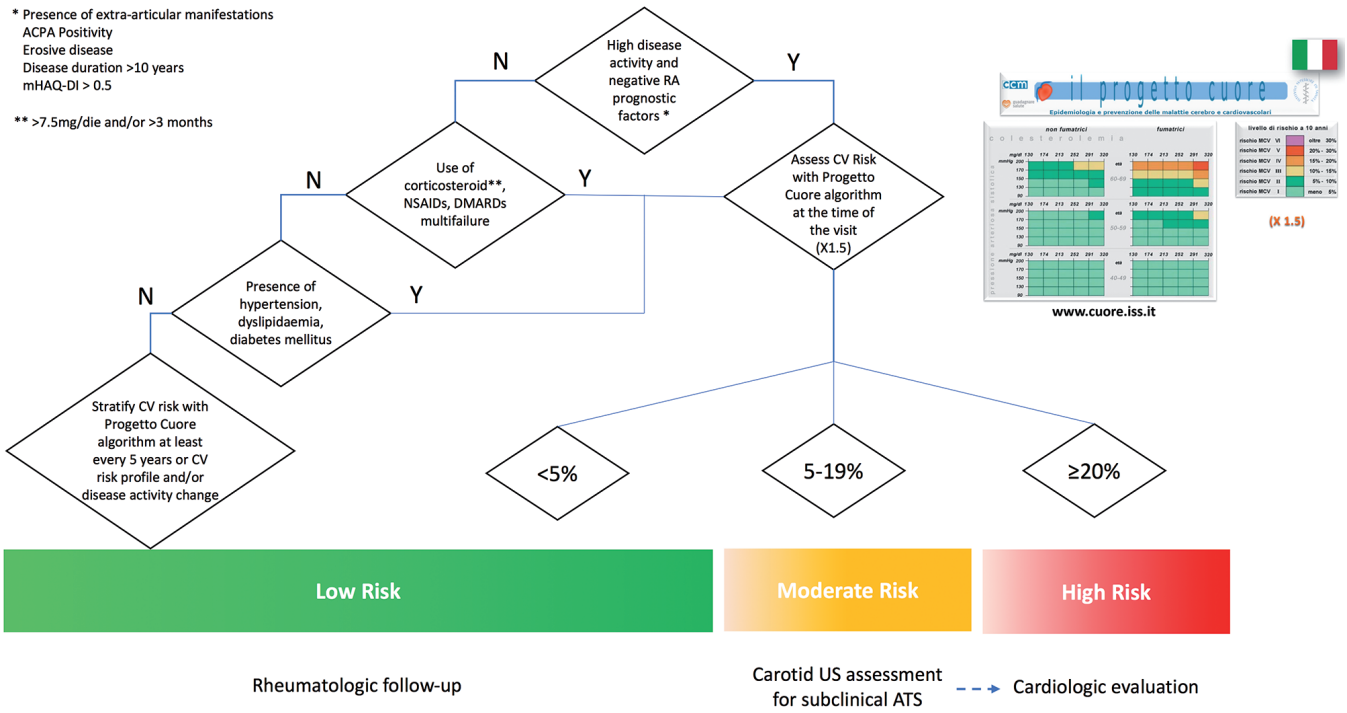

Fig. 1. Recommended algorithm as flowchart for the evaluation of CV risk in RA patients in clinical practice.
ACPA: anti-citrullinated peptides antibodies; CV: cardiovascular; DMARDs: disease-modifying anti-rheumatic drugs; mHAQ-DI: modified Health Assessment Questionnaire Disability Index; NSAIDs: non-steroidal anti-inflammatory drugs; RA: rheumatoid arthritis.

istics should be considered to have an adverse CV risk profile. The algorithm of the *Progetto Cuore*, an Italian project founded by the Istituto Superiore di Sanità in 1998 and aimed at studying the distribution of CV risk factors and CV risk in a representative sample of the Italian population (9), was proposed to evaluate the CV risk score for Italian patients with RA. This algorithm was chosen based on the updated EULAR Recommendation No. 3 to "use validated risk scores proposed by national guidelines for CVD risk assessment", while Systematic Coronary Risk Evaluation (SCORE) should only be used if no national guidelines are available (10). This algorithm stratifies patients into low (<5%), moderate (5–19%) or high (≥20%) risk of presenting with a nonfatal or fatal CV event in the next 10 years. The *Progetto Cuore* score, which does not already account for RA among the algorithm items, should be multiplied by a factor of 1.5 to better reflect the increased CVD risk in these patients, according to EULAR Recommendation No. 5 (10). Thickening of the carotid intima media and/or plaques allow identification of most patients who meet the definitions of high CV risk. Therefore, subclinical atherosclerosis assessed by carotid ultrasonography should be performed by the same rheumatologist or cardiologist to correctly reclassify patients found to be at moderate CV risk according to the *Progetto Cuore* algorithm (11).

Statements and Recommendations

1. Patients with favourable CV risk profile and without traditional CV risk factors, including hypertension, dyslipidaemia and DM should be assessed at least every 5 years with Progetto Cuore algorithm according to EULAR recommendations (10).

2. Patients with high disease activity, anti-citrullinated peptide antibody (ACPA) positivity, and/or negative prognostic factors for disease should be assessed for CV risk at the time of visit according to the Progetto Cuore algorithm.

Among RA-specific variables on CVD outcome, data from large international cohorts of RA patients have shown that disease activity and seropositivity for rheumatoid factor (RF) and ACPA are comparable in magnitude to male sex, high blood pressure, higher total cholesterol, and smoking in inducing CVD (12). A total of 70% of CV events were attributable to all CV risk factors and RA characteristics combined (separately 49% CV risk factors and 30% RA characteristics). This result indicates that controlling for modifiable RA characteristics play an important role in efforts to reduce the risk of CVD among patients with RA. Over the past two decades, several studies have examined the relationship between ACPA, their specific sub specificities, RF isotypes, and CVD in RA patients. In RA patients, a high prevalence and severity of carotid plaques has been demonstrated in high titre ACPA-positive patients (13). Evidence of citrullinated proteins within the atherosclerotic plaque supported the hypothesis of a potential target of ACPA autoantibodies, forming immune complexes that enhance ATS progression. Therefore, ACPA could be associated with atherosclerotic burden, and targeting citrullinated epitopes, particularly Cit-fibrinogen, within atherosclerotic plaques could provide a mechanism for the acceleration of ATS observed in RA patients (14). In 2009, Lopez-Long *et al.* showed that anti-CCP antibody positivity (>25 units/ml) was not associated with CV

risk factors such as smoking, hypertension, dyslipidaemia, overweight or DM. However, ACPA-positive patients had more frequent ischaemic heart disease (OR 2.58, 95%CI 1.17–5.65) and had higher mortality rates (OR 1.72, 95%CI 1.01–2.91). Multivariable analysis showed that ischaemic heart disease was independently associated with ACPA positivity (OR 2.8, 95%CI 1.19–6.56; p=0.009). The authors concluded that ACPA in RA patients were independently associated with the development of ischaemic heart disease (15).

Citrullination is a post-translational modification that is detectable in many chronic inflammatory conditions, even in the absence of RA. For this reason, in their retrospective study, Cambridge *et al*. evaluated sera from a cohort of 3052 healthy subjects followed later for the development of coronary artery disease (16). For each CV event recorded after 5 years, during an average of 15 years of follow-up, 2 matched controls were assigned. The authors recorded 144 CV events (98 acute coronary artery disease, 44 coronary interventions, and 2 silent myocardial infarctions), and 10.4% of the cases were ACPA positive compared with only 3.8% of the 288 matched controls with no CV events (OR 3.26, 95%CI 1.36–7.80; p=0.008). This result remained statistically significant after adjustment for classic CV risk factors, including smoking and CRP (OR 4.23, 95%CI 1.22–14.61); p=0.02) (16). After detecting the positivity of ACPAs in a cohort of patients without RA but with coronary artery disease (CAD), to understand whether ACPAs can be found consistently in patients with CAD and whether ACPAs are associated with mortality in these patients, Hermans *et al*. sought to study the relationship between ACPAs and long-term outcomes, including mortality in patients with ST elevation myocardial infarction (STEMI) without RA. They analysed all non-RA patients with STEMI enrolled in the MISSION intervention study (17), examining the association between ACPA (anti-CCP3) at baseline and 10-year mortality and reinfarction. Twenty-nine (11%) of the 275 included patients were ACPA-positive, and higher cumulative cardiac mortality was observed in ACPA-positive patients than in ACPA-negative patients. Moreover, even after adjusting for other associated factors, ACPA positivity was associated with long-term mortality (HR 3.1, 95%CI 1.4–7.1; p=0.01) and the combined long-term endpoint of re-infarction and death (HR 2.4, 95%CI 1.2–4.6; p=0.01). Therefore, in STEMI patients without RA, the presence of ACPA was independently associated with long-term mortality and the combined endpoint of re-infarction and death. The authors concluded that ACPA positivity in patients with and without RA could act as an independent pro-atherogenic factor. More recently, Westerlind *et al*. studied the relationship between ACPA sub-specificities and RF isotypes and incident CV events in patients with RA. They included 2814 patients with RA diagnosed within 1 year of symptom onset, typed for anti-citrullinated peptide 2 (anti-CCP2) antibodies, 20 different ACPA sub-specificities and RF isotypes, and followed longitudinally for 13 years in Swedish registries to monitor the occurrence of major adverse CV events (MACE) and CV-related death (18). The presence and levels of anti-CCP2 were associated with risk of incident acute coronary syndrome (HR 1.46, 95%CI 1.03–2.06), stroke (HR 1.47, 95%CI 1.03–2.10), CV-related death (p=0.024 for association with anti-CCP2 levels) and generally MACE (HR 1.34, 95% CI 1.06–1.70). Similarly, an association between MACE and the number of ACPA sub-specificities was observed; however, this could not be attributed to any individual or group of ACPA sub-specificities. The presence of IgM-RF was associated with all CV endpoints except acute coronary syndrome, while IgA-RF was exclusively associated with CV-related death. Adjustment for smoking status, income, and DAS28 scores decreased most of the HRs, whereas IgA-RF remained associated with CV-related death (HR 1.61, 95% CI 1.05-2.48). The RF isotypes and ACPA levels were associated with future CV events in patients with RA (18).

3. Patients on GCs therapy (prednisone dose or equivalent ≥7.5 mg/day or ≥3 months of continuous therapy) and/or regularly taking NSAIDs and/or who have failed multiple DMARDs should be assessed for CV risk at the time of the visit according to the Progetto Cuore algorithm.

Glucocorticoid (GC) therapy exerts a well-documented detrimental CV effect, being associated with a higher prevalence of hypertension, dyslipidaemia, obesity, and DM, both in the general population and in patients with RA (19). Furthermore, GC therapy has been associated with a higher incidence of subclinical ATS, and its adverse effects appear to occur even in the preclinical phase (20). Despite conflicting results, consistent evidence suggests that an average daily GC above a prednisone-equivalent dose of 7.5 mg, increased cumulative dose, and long-term exposure are associated with a higher risk of CV events, including cerebrovascular events and MI, and CV mortality in RA. Indeed, a 25-year follow-up study, prednisone use at an average dose of 5 mg per day was associated with a significantly increased risk of all-cause mortality in a large cohort of RA patients, even after accounting for potential bias in treatment selection (21). However, the potential for unmeasured confounders, such as failure to account for disease activity as an independent variable in many of these studies, may explain the existing conflicting evidence. Certainly, chronic inflammation increases the risk of CVD, and the use of GC therapy in these patients may reflect high disease activity and more severe disease. Therefore, the reduction of chronic inflammation by low-dose GC therapy may, to some extent, counterbalance its harmful CV effects (20, 22). In this context, the EULAR recommendations state that GCs should be used at the lowest possible dose and for the shortest duration, based on the risk-benefit analysis for the patient (10). However, which low-dose GC therapy is considered safe is still a matter of debate. In this regard, in a systematic review that included RA patients taking less than 10 mg per day of prednisone, this low-dose prednisone had no sig-

nificant detrimental effects on CV risk factors, including lipid profile and subclinical atherosclerosis (23). However, for a prednisone dose of 6-10 mg daily an increased risk of major CV events, including MI, stroke, and CVD mortality was observed in most studies (23). Recently, a population-based analysis of a large cohort of patients with immune-mediated and inflammatory diseases demonstrated a twofold overall absolute risk of CVD at 1 year even in patients using less than 5 mg prednisolone daily compared with those not using it, after accounting for disease activity at baseline (24). Furthermore, an analysis of the long-standing CorEvitas registry cohort showed that the introduction of GC therapy in GC-naive patients in the previous 6 months to 1 year was associated with an increased risk of CV events at doses ≥5 mg prednisone daily, and the risk increased with cumulative dose and duration of use (25). If further confirmed, these preliminary results suggest the importance of reducing GC therapy to a prednisone dose of less than 5 mg per day as soon as possible, especially in patients with long-term GC use. Otherwise, RA patients on stable, long-term GC therapy should undergo careful CVD risk assessment at least once a year, and patients at high CV risk according to the *Progetto Cuore* algorithm should be referred for cardiology evaluation.

Similarly, the extensive use of NSAIDs has been associated with an increased risk of CVD in the general population, with a clear dose- and time-dependent effect (26). On the other hand, the evidence for the selective and non-selective CV effects of NSAIDs in RA patients is more mixed as many factors, including baseline inflammatory status, differences in the comparison cohort (osteoarthritis patients *vs*. ankylosing spondylitis patients) and drug choice (naproxen, ibuprofen or celecoxib), duration of use, prescribed dose (anti-inflammatory or analgesic indication), and pre-existing CV comorbidities, greatly hinder interpretation of the data (27).

The PRECISION trial, the largest clinical trial that included about 24,000 RA and osteoarthritis patients to evaluate the effects of selective and non-selective NSAIDs on major CV events, showed that celecoxib had similar CV safety at moderate doses compared with ibuprofen and naproxen (28). However, the lack of a control group as a comparator and the high rate (70%) of study dropouts mean that the net effects of NSAIDs on major CV outcomes cannot be confirmed. In addition, NSAIDs may act differently in patients with RA, as the negative vascular effects of cyclooxygenase-2 (COX-2) inhibition may be offset by the reduction in systemic inflammatory burden. A systematic review and meta-analysis showed that NSAIDs may increase the risk of CV events in RA, although the effect was mainly determined by rofecoxib, a withdrawn product, compared with nonselective NSAIDs or celecoxib (29). In this context, a recent large study in the National Health Insurance Database showed that exposure to NSAIDs, particularly non-selective ones, in the previous 30 days was associated with a significantly increased risk of hospitalisation for stroke and acute MI in patients with RA (30). Interestingly, the risk of events was further increased in high-dose non-selective NSAID users compared with low-dose users and remained statistically significant after stratification for comorbidities and concomitant antiplatelet therapy. (30).

Although celecoxib appears to be associated with lower CV mortality than nonselective NSAIDs in patients with RA (31), current evidence does not allow definitive conclusions to be drawn about the CV safety of NSAIDs in this population, especially in patients with pre-existing CV or CVD risk factors. Therefore, it is recommended that the CV risk profile be evaluated annually in patients with RA who regularly take selective or non-selective NSAIDs for pain control, especially when in combination with chronic GC therapy. Regarding GC therapy, patients at high CV risk according to the *Progetto Cuore* algorithm should be referred for cardiologic evaluation. Finally, failure of several conventional and/or biologic DMARDs reflects uncontrolled disease activity and persistent inflammatory burden, which is a recognised pathogenetic mechanism underlying the increased CVD risk in these patients (32). In a recent cross-sectional study including more than 1,200 patients with RA without previous CV events, reclassification of CV risk according to the SCORE algorithm into very high risk was reported in more than half of the patients after carotid ultrasound evaluation, and disease activity was significantly associated with reclassification on multivariate analysis (33). Although the mechanisms are still poorly understood, observational studies and clinical trials have shown positive effects of DMARDs, such as methotrexate, tumour necrosis factor (TNF) inhibitors, and anti-interleukin (IL)-6 agents, on surrogate markers of CVD and increased CV outcomes in patients with RA in remission or low disease activity, probably due to better control of systemic inflammation or yet unexplored drug-specific mechanisms (3, 34). Given the close interaction between systemic inflammation, disease activity, and ATS, failure of several cs and/or b DMARDs should be considered a negative prognostic factor for increased CV risk in patients with RA.

4. Patients with more than one traditional CV risk factor, including hypertension, dyslipidaemia, and DM, should be assessed for CV risk at the time of the visit, according to the Progetto Cuore algorithm.

Traditional CV risk factors are more prevalent in RA patients than in the general population and explain, at least in part, the excess CVD in these patients (12, 35). Among traditional CV risk factors, hypertension has been associated with the greatest impact on CV outcome in RA. The prevalence of hypertension in patients with RA is widely variable, ranging from 3% to 78%, and is higher than that observed in the general population (36). A recent systematic literature review showed that lack of regular exercise, use of GC therapy, and Cox-2 inhibitors may be responsible for the increased risk of hypertension in RA patients, whereas MTX appears to exert a protective role (37). Among csDMARDs and bDMARDs, only leflunomide was clearly

associated with an increased risk of hypertension (38). As in the general population, studies in RA patients have confirmed the association between hypertension and major CV events, including MI and stroke (39-42). More importantly, in RA patients, hypertension is a strong independent risk factor for CVD. Hypertensive RA patients are characterised by more than double the risk of CV events, especially MI, compared with non-hypertensive RA patients (35, 36). Thus, a regular control of blood pressure is highly advisable in these patients, and blood pressure should be managed in RA patients as in the general population. The COMORA study showed that an annual assessment of CV risk factors, including blood pressure, was performed in 59% of 3920 patients, and systematic blood pressure assessment identified hypertension in 18% of 2489 previously undiagnosed patients (43). Moreover, considering all patients with an indication for antihypertensive therapy, the rate of attainment of target pressure is relatively low, about 50 percent, and comparable to that of the general population, thus reinforcing the urgent need to improve regular blood pressure monitoring in these patients (44, 45).

Like hypertension, dyslipidaemia is a not negligible CV risk factor in inflammatory rheumatic diseases, particularly in RA. It is well established that patients with RA, especially with active disease, have a peculiar lipid profile, characterised by a paradoxical decrease in total and LDL cholesterol and impaired HDL cholesterol function, both of which are responsible for an increased risk of CV events (46, 47). An altered lipid profile doubles the risk of CV events in patients with RA, regardless of disease activity, and the impact of the inflammatory burden of the disease should not overlook the importance of lipid management in these patients (4). Currently, there is no general validated recommendation on when and how often lipid profile monitoring should be performed, due to limited evidence as well as confounding effect of inflammation. Annual lipids monitoring should be recommended in *high-risk* RA patients, regardless of age, especially in the *high CV risk* subgroup, and should be reconsidered if there are changes in concomitant conditions, including the introduction of high-dose GC and some b/tsDMARD therapies, such as IL-6 and JAK inhibitors, and reduction in disease activity. Evaluation of the lipid profile in the low activity/remission phases of disease can provide a more reliable estimate and calculation of the atherogenic index and may be considered a better marker for CV risk assessment. However, as with hypertension, lipid target attainment is very low even in RA patients at higher CVD risk who meet the treatment indications of the general population (44), thus suggesting the need to improve optimal management of CV risk factors. Moreover, considering the beneficial effect of lipid-lowering therapy in reducing CV risk in these patients (48), early dentification of those at increased risk and referral of RA patients for introduction of statin therapy according to suggested recommendations should be considered in all patients in order to reduce CV risk (49).

Diabetes mellitus is reported as a comorbidity in about 20% of RA patients, and RA is associated with an increased risk of developing DM, arguing that systemic inflammation is the link between the two diseases (50, 51). Overall, the prevalence of DM in RA has been reported to be higher than in osteoarthritis patients (52) and in general population, suggesting that systemic inflammation and concomitant GC therapy may play a key role. It is well established that the risk of developing CVD in patients with RA is similar to that of diabetic patients, suggesting that appropriate treatment is critical to prevent CV events (53). However, DM is underdiagnosed and inadequately treated in diabetic patients with RA, as found in a recent retrospective study that showed baseline HbA1c levels ≥7 in about one-third of patients with RA (54). This implies the importance of awareness and proper management of glycometabolic profile in RA patients. In this setting, diabetic RA patients should be included in high-risk CV profile regardless of age, disease activity and concomitant CV risk factors and should be treated according to current recommendations similar to the general population.

5. Patients with high CV risk should be referred for cardiologic evaluation.

Given the increase in CV morbidity and mortality in RA patients at high CV risk and the lack of specific recommendations for CV treatment in these patients, we believe that the management of high-risk patients should be shared with a cardiologist for proper assessment and management of CVD and initiation of preventive measures to reduce CV risk according to specific guidelines as for the general population. In our opinion, close collaboration with cardiologists to implement and optimise CV risk stratification, assessment, and management in RA is highly advisable in this category of patients (55).

Conclusions

These statements represent the first Italian recommendations on CV risk assessment in patients with RA, aimed at providing a general and uniform approach to CV risk profile assessment in these individuals according to 10-year CV risk estimation. Indeed, in association with lifestyle modifications, including smoking cessation and regular physical activity, and adequate control of disease activity-which is a cornerstone of CV risk management in RA-we believe that 10-year CV risk assessment at least every 5 years is necessary in these patients and should be reconsidered following any change in CV risk factors, disease activity, or modification of DMARD or GC therapy. Multiplied by 1.5, the *Progetto Cuore* algorithm, which has just been validated in a large Italian cohort of RA (52), can be considered a reliable and reproducible tool for estimating the CV risk profile in patients with RA; patients who show at least moderate CV risk should also be evaluated for subclinical ATS with carotid ultrasound.

Future steps will be to establish validated protocols and standard operating procedures to improve CV risk prediction in RA and to evaluate preventive strategies and joint management of CV comorbidities in patients with RA.

References

1. AMAYA-AMAYA J, SARMIENTO-MONROY JC, MANTILLA RD, PINEDA-TAMAYO R, ROJAS-VILLARRAGA A, ANAYA JM: Novel risk factors for cardiovascular disease in rheumatoid arthritis. *Immunol Res* 2013; 56: 267-86. https://doi.org/10.1007/s12026-013-8398-7
2. FERGUSON LD, SATTAR N, MCINNES IB: Managing cardiovascular risk in patients with rheumatic disease. *Rheum Dis Clin North Am* 2022; 48: 429-44. https://doi.org/10.1016/j.rdc.2022.02.003
3. KEROLA AM, ROLLEFSTAD S, SEMB AG: Atherosclerotic cardiovascular disease in rheumatoid arthritis: Impact of inflammation and antirheumatic treatment. *Eur Cardiol* 2021; 16: e18. https://doi.org/10.15420/ecr.2020.44
4. SKEOCH S, BRUCE IN: Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol* 2015; 11: 390-400. https://doi.org/10.1038/nrrheum.2015.40
5. MARTÍN-GONZÁLEZ C, MARTÍN-FOLGUERAS T, QUEVEDO-ABELEDO JC, DE ARMAS-RILLO L, GONZÁLEZ-GAY MÁ, FERRAZ-AMARO I: Disease activity in patients with rheumatoid arthritis increases serum levels of apolipoprotein C-III. *Clin Exp Rheumatol* 2022; 41(1): 67-73. https://doi.org10.55563/clinexprheumatol/fe4go6
6. RUSCITTI P, CIPRIANI P, LIAKOULI V *et al*: Occurrence and predictive factors of high blood pressure, type 2 diabetes, and metabolic syndrome in rheumatoid arthritis: findings from a 3-year, multicentre, prospective, observational study. *Clin Exp Rheumatol* 2021; 39: 995-1002. https://doi.org/10.55563/clinexprheumatol/5r53em
7. CAFARO G, PERRICONE C, RICCUCCI I *et al*.: Traditional and disease-related non-computed variables affect algorithms for cardiovascular risk estimation in Sjögren's syndrome and rheumatoid arthritis. *Clin Exp Rheumatol* 2021; 39 (Suppl. 133): S107-13. https://doi.org/10.55563/clinexprheumatol/xef8uz
8. SPINELLI FR, CACCIAPAGLIA F, ATZENI F *et al*.: Cardiovascular risk assessment in patients with autoimmune rheumatic diseases: an Italian rheumatologists' survey. *Ann Rheum Dis* 2020; 79 (Suppl. 1): 980. https://dx.doi.org/10.1136/annrheumdis-2020-eular.6093
9. PALMIERI L, PANICO S, VANUZZO D *et al*.: Evaluation of the global cardiovascular absolute risk: the Progetto CUORE individual score. *Ann Ist Super Sanita* 2004; 40: 393-99.
10. AGCA R, HESLINGA SC, ROLLEFSTAD S *et al*.: EULAR recommendations for cardiovascular disease risk management in patients with rheumatoid arthritis and other forms of inflammatory joint disorders: 2015/2016 update. *Ann Rheum Dis* 2017; 76: 17-28. https://doi.org/10.1136/annrheumdis-2016-209775
11. RUEDA-GOTOR J, QUEVEDO-ABELEDO JC, CORRALES A *et al*.: Reclassification into very-high cardiovascular risk after carotid ultrasound in patients with axial spondyloarthritis. *Clin Exp Rheumatol* 2020; 38: 724-31.
12. CROWSON CS, ROLLEFSTAD S, IKDAHL E *et al*.: A Trans-Atlantic Cardiovascular Consortium for Rheumatoid Arthritis (ATACC-RA). Impact of risk factors associated with cardiovascular outcomes in patients with rheumatoid arthritis. *Ann Rheum Dis* 2018; 77: 48-54. https://doi.org/10.1136/annrheumdis-2017-211735
13. OKANO T, INUI K, SUGIOKA Y *et al*.: High titer of anti-citrullinated peptide antibody is a risk factor for severe carotid atherosclerotic plaque in patients with rheumatoid arthritis: the TOMORROW study. *Int J Rheum Dis* 2017; 20: 949-59. https://doi.org/10.1111/1756-185x.13106
14. SOKOLOVE J, BRENNAN MJ, SHARPE O *et al*.: Brief report: citrullination within the atherosclerotic plaque: a potential target for the anti-citrullinated protein antibody response in rheumatoid arthritis. *Arthritis Rheum* 2013; 65: 1719-24. https://doi.org/10.1002/art.37961
15. LÓPEZ-LONGO FJ, OLIVER-MIÑARRO D, DE LA TORRE I *et al*.: Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. *Arthritis Rheum* 2009; 61: 419-24. https://doi.org/10.1002/art.24390
16. CAMBRIDGE G, ACHARYA J, COOPER JA, EDWARDS JC, HUMPHRIES SE: Antibodies to citrullinated peptides and risk of coronary heart disease. *Atherosclerosis* 2013; 228: 243-46. https://doi.org/10.1016/j.atherosclerosis.2013.02.009
17. HERMANS MPJ, VAN DER VELDEN D, MONTERO CABEZAS JM *et al*.: Long-term mortality in patients with ST-segment elevation myocardial infarction is associated with anti-citrullinated protein antibodies. *Int J Cardiol* 2017; 240: 20-24. https://doi.org10.1016/j.ijcard.2017.04.046
18. WESTERLIND H, RÖNNELID J, HANSSON M *et al*.: Anti-citrullinated protein antibody specificities, rheumatoid factor isotypes, and incident cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2020; 72: 1658-67. https://doi.org/10.1002/art.41381
19. ATZENI F, RODRÍGUEZ-CARRIO J, POPA CD *et al*.: Cardiovascular effects of approved drugs for rheumatoid arthritis. *Nat Rev Rheumatol* 2021; 17: 270-90. https://doi.org/10.1038/s41584-021-00593-3
20. BARTOLONI E, ALUNNO A, SANTOBONI G, GERLI R: Beneficial cardiovascular effects of low-dose glucocorticoid therapy in inflammatory rheumatic diseases. *J Rheumatol* 2012; 39: 1758-60; author reply 1761. https://doi.org/10.3899/jrheum.120192
21. CHESTER WASKO M, DASGUPTA A, ILSE SEARS G, FRIES JF, WARD MM: Prednisone use and risk of mortality in patients with rheumatoid arthritis: moderation by use of disease-modifying antirheumatic drugs. *Arthritis Care Res* 2016; 68: 706-10. https://doi.org/10.1002/acr.22722
22. SAKELLARIOU G, SCIRÈ CA, RUMI F *et al*.: Influence of initial glucocorticoid co-medication on mortality and hospitalization in early inflammatory arthritis: an investigation by record linkage of clinical and administrative databases. *Arthritis Res Ther* 2022; 24: 144. https://doi.org/10.1186/s13075-022-02824-8
23. RUYSSEN-WITRAND A, FAUTREL B, SARAUX A, LE LOËT X, PHAM T: Cardiovascular risk induced by low-dose corticosteroids in rheumatoid arthritis: a systematic literature review. *Joint Bone Spine* 2011; 78: 23-30. https://doi.org/10.1016/j.jbspin.2010.02.040
24. PUJADES-RODRIGUEZ M, MORGAN AW, CUBBON RM, WU J: Dose-dependent oral glucocorticoid cardiovascular risks in people with immune-mediated inflammatory diseases: A population-based cohort study. *PLoS Med* 2020; 17: e1003432. https://doi.org/10.1371/journal.pmed.1003432
25. OCON AJ, REED G, PAPPAS DA, CURTIS JR, KREMER JM: Short-term dose and duration-dependent glucocorticoid risk for cardiovascular events in glucocorticoid-naive patients with rheumatoid arthritis. *Ann Rheum Dis* 2021; 80: 1522-29. https://doi.org/10.1136/annrheumdis-2021-220577
26. Coxib and traditional NSAID Trialists' (CNT) Collaboration, BHALA N, EMBERSON J, MERHI A *et al*.: Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. *Lancet* 2013; 382: 769-79. https://doi.org/10.1016/S0140-6736(13)60900-9
27. BRAUN J, BARALIAKOS X, WESTHOFF T: Non-steroidal anti-inflammatory drugs and cardiovascular risk - a matter of indication. *Semin Arthritis Rheum* 2020; 50: 285-88. https://doi.org/10.1016/j.semarthrit.2019.07.012
28. SOLOMON DH, HUSNI ME, WOLSKI KE, WISNIEWSKI LM, BORER JS; PRECISION TRIAL INVESTIGATORS: Differences in safety of non-steroidal anti-inflammatory drugs in patients with osteoarthritis and patients with rheumatoid arthritis: A randomized clinical trial. *Arthritis Rheumatol* 2018; 70: 537-46. https://doi.org/10.1002/art.40400
29. ROUBILLE C, RICHER V, STARNINO T *et al*.: The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2015; 74: 480-89. https://doi.org/10.1136/annrheumdis-2014-206624
30. CHEN YR, HSIEH FI, CHANG CC, CHI NF, WU HC, CHIOU HY: Effect on risk of stroke and acute myocardial infarction of nonselective non-steroidal anti-inflammatory drugs in patients with rheumatoid arthritis. *Am J Cardiol* 2018; 121: 1271-77. https://doi.org/10.1016/j.amjcard.2018.01.044
31. CHENG BR, CHEN JQ, ZHANG XW *et al*.: Cardiovascular safety of celecoxib in rheumatoid arthritis and osteoarthritis patients: a systematic review and meta-analysis. *PLoS One* 2021; 16: e0261239. https://doi.org/10.1371/journal.pone.0261239
32. FRAGOULIS GE, SOULAIDOPOULOS S, SFIKAKIS PP, DIMITROULAS T, D KITAS G: Effect of biologics on cardiovascular inflammation: mechanistic insights and risk reduction. *J Inflamm Res* 2021; 14: 1915-31. https://doi.org/10.2147/jir.S282691
33. FERRAZ-AMARO I, CORRALES A, QUEVEDO-ABELEDO JC *et al*.: Disease activity influences the reclassification of rheumatoid arthritis into very high cardiovascular risk. *Arthritis Res Ther* 2021; 23: 162. https://doi.org/10.1186/s13075-021-02542-7

34. HU S, LIN C, CAI X *et al*.: The biological disease-modifying antirheumatic drugs and the risk of cardiovascular events: A systematic review and meta-analysis. *Mediators Inflamm* 2021; 2021: 7712587. https://doi.org/10.1155/2021/7712587
35. BAGHDADI LR, WOODMAN RJ, SHANAHAN EM, MANGONI AA: The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. *PLoS One* 2015; 10: e0117952. https://doi.org/10.1371/journal.pone.0117952
36. BARTOLONI E, ALUNNO A, GERLI R: Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. *Nat Rev Cardiol* 2018; 15: 33-44. https://doi.org/10.1038/nrcardio.2017.118
37. HADWEN B, STRANGES S, BARRA L: Risk factors for hypertension in rheumatoid arthritis patients-A systematic review. *Autoimmun Rev* 2021; 20: 102786. https://doi.org/10.1016/j.autrev.2021.102786
38. BAKER JF, SAUER B, TENG CC *et al*.: Initiation of disease-modifying therapies in rheumatoid arthritis is associated with changes in blood pressure. *J Clin Rheumatol* 2018; 24: 203-9. https:/ doi.org/10.1097/rhu.0000000000000736
39. RUSCITTI P, CIPRIANI P, MASEDU F *et al*.: Increased cardiovascular events and subclinical atherosclerosis in rheumatoid arthritis patients: 1-year prospective single centre study. *PLoS One* 2017; 12: e0170108. https://doi.org/10.1371/journal.pone.0170108
40. CHEN YJ, LIU SC, LAI KL *et al*.: Factors associated with risk of major adverse cardiovascular events in patients with rheumatoid arthritis: a nationwide, population-based, case-control study. *Ther Adv Musculoskelet Dis* 2021; 13: 1759720X211030809. https://doi.org/10.1177/1759720x211030809
41. ARGNANI L, ZANETTI A, CARRARA G *et al*.: Rheumatoid arthritis and cardiovascular risk: retrospective matched-cohort analysis based on the RECORD Study of the Italian Society for Rheumatology. *Front Med* 2021; 8: 745601. https://doi.org/10.3389/fmed.2021.745601
42. GOUZE H, AEGERTER P, SAID-NAHAL R *et al*.: Rheumatoid arthritis, as a clinical disease, but not rheumatoid arthritis-associated autoimmunity, is linked to cardiovascular events. *Arthritis Res Ther* 2022; 24: 56. https://doi.org/10.1186/s13075-022-02722-z
43. DOUGADOS M, SOUBRIER M, ANTUNEZ A *et al*.: Prevalence of comorbidities in rheumatoid arthritis and evaluation of their monitoring: results of an international, cross sectional study (COMORA). *Ann Rheum Dis* 2014; 73: 62-68. https:// doi.org/10.1136/annrheumdis-2013-204223
44. ROLLEFSTAD S, IKDAHL E, WIBETOE G, SEXTON J, CROWSON CS, VAN RIEL P: An international audit of the management of dyslipidaemia and hypertension in patients with rheumatoid arthritis-results from 19 countries. *Eur Heart J Cardiovasc Pharmacother* 2022; 8: 539-48. https://doi.org/10.1093/ehjcvp/pvab052
45. IKDAHL E, WIBETOE G, ROLLEFSTAD S *et al*.: Guideline recommended treatment to targets of cardiovascular risk is inadequate in patients with inflammatory joint diseases. *Int J Cardiol* 2019; 274: 311-18. https://doi.org/10.1016/j.ijcard.2018.06.111
46. ROBERTSON J, PETERS MJ, MCINNES IB, SATTAR N: Changes in lipid levels with inflammation and therapy in RA: a maturing paradigm. *Nat Rev Rheumatol* 2013; 9: 513-23. https://doi.org/10.1038/nrrheum.2013.91
47. PLUTZKY J, LIAO KP: Lipids in RA: is less not necessarily more? *Curr Rheumatol Rep* 2018; 20: 8. https://doi.org/10.1007/s11926-018-0715-7
48. KITAS GD, NIGHTINGALE P, ARMITAGE J, SATTAR N, BELCH JJF, SYMMONS DPM; TRACE RA CONSORTIUM. A multicenter, randomized, placebo-controlled trial of atorvastatin for the primary prevention of cardiovascular events in patients with rheumatoid arthritis. *Arthritis Rheumatol* 2019; 71: 1437-49. https://doi.org/10.1002/art.40892
49. HOLLAN I, RONDA N, DESSEIN P *et al*.: Lipid management in rheumatoid arthritis: a position paper of the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J Cardiovasc Pharmacother* 2020; 6: 104-14. https://doi.org/10.1093/ehjcvp/pvz033
50. ALBRECHT K, LUQUE RAMOS A, HOFFMANN F, REDEKER I, ZINK A: High prevalence of diabetes in patients with rheumatoid arthritis: results from a questionnaire survey linked to claims data. *Rheumatology* 2018; 57: 329-36. https:// doi.org/10.1093/rheumatology/kex414
51. TIAN Z, MCLAUGHLIN J, VERMA A, CHINOY H, HEALD AH: The relationship between rheumatoid arthritis and diabetes mellitus: a systematic review and meta-analysis. *Cardiovasc Endocrinol Metab* 2021; 10: 125-31. https:// doi.org/10.1097/xce.0000000000000244
52. CACCIAPAGLIA F, SPINELLI FR, PIGA M *et al*.: Estimated 10-year cardiovascular risk in a large Italian cohort of rheumatoid arthritis patients: Data from the Cardiovascular Obesity and Rheumatic DISease (CORDIS) Study Group. *Eur J Intern Med* 2022; 96: 60-65. https://doi.org/10.1016/j.ejim.2021.10.001
53. LOGSTRUP BB, ELLINGSEN T, PEDERSEN AB *et al*: Cardiovascular risk and mortality in rheumatoid arthritis compared with diabetes mellitus and the general population. *Rheumatology* 2021; 60: 1400-409. https:// doi.org/10.1093/rheumatology/keaa374
54. MANTRAVADI S, GEORGE M, BRENSINGER C, DU M, BAKER JF, OGDIE A: Impact of tumor necrosis factor inhibitors and methotrexate on diabetes mellitus among patients with inflammatory arthritis. *BMC Rheumatol* 2020; 4: 39. https://doi.org/10.1186/s41927-020-00138-3
55. SEMB AG, IKDAHL E, WIBETOE G, CROWSON C, ROLLEFSTAD S: Atherosclerotic cardiovascular disease prevention in rheumatoid arthritis. *Nat Rev Rheumatol* 2020; 16: 361-79. https://doi.org/10.1038/s41584-020-0428-y