European Journal of Internal Medicine 96 (2022) 60–65

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original article

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

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ARTICLE INFO

Keywords:
Rheumatoid arthritis
Cardiovascular risk
Cardiovascular score
Cardiovascular algorithms
Traditional cardiovascular risk factors

ABSTRACT

Background: Several cardiovascular (CV) risk algorithms are available to predict CV events in the general population. However, their performance in patients with rheumatoid arthritis (RA) might differ from the general population. This cross-sectional multicentre study aimed to estimate the 10-year CV risk using two different algorithms in a large RA cohort and in patients with osteoarthritis (OA).

Methods: In a consecutive series of RA patients and matched OA controls without prior CV events, clinical and serologic data and traditional CV risk factors were recorded. The 10-year CV risk was assessed with the Systematic COronary Risk Evaluation (SCORE) and the "Progetto Cuore" algorithms.

Results: 1,467 RA patients and 342 OA subjects were included. RA patients were more frequently diabetic (9.9% vs 6.4%; p=0.04) and smokers (20.4% vs 12.5%; p=0.002) but had lower prevalence of obesity (15% vs 21%; p=0.003). Dyslipidaemia was more prevalent in OA (32.5% vs 21.7%; p<0.0001). The 10-year estimated CV risk was 1.6% (95%CI 1.3-1.9) in RA and 1.4% (95%CI 1.3-1.6) in OA (p=0.002) according to SCORE and 6.5% (95% CI 6.1-6.9) in RA and 4.4% (95%CI 3.9-5.1) in OA (p<0.001) according to "Progetto Cuore". Regardless of the score used, RA patients had a 3- to-4-fold increased 10-year risk of CV events compared to OA subjects.

Conclusion: RA patients have a significantly higher 10-year risk of CV events than OA subjects. In addition to effective disease control and joint damage prevention, specific protective measures targeting modifiable traditional CV risk factors should be implemented in RA.

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https://doi.org/10.1016/j.ejim.2021.10.001
Received 1 July 2021; Received in revised form 30 September 2021; Accepted 2 October 2021
Available online 14 October 2021

1. Introduction

Rheumatoid Arthritis (RA) is a chronic, systemic inflammatory disease characterized by a relatively high risk of atherosclerotic cardiovascular (CV) events. Notably, such risk has been reported to be similar to that of diabetes mellitus (DM) [1]. Large epidemiological studies suggest that a total of 70% of CV events are attributable to both traditional CV risk factors, mainly hypertension and smoking, combined with disease features [2]. In this setting, besides a genetic component, chronic inflammation may explain at least in part this CV burden by playing a dual role: a direct effect - by promoting endothelial and vessel damage and atherosclerosis progression; and an indirect effect - by modifying traditional CV risk factors such as lipid metabolism [3–5].

The European League Against Rheumatism (EULAR) recommendations for CV risk management in RA patients and other inflammatory joints disorders, firstly released in 2009 and then updated in 2015, state that clinicians should be aware of the increased CV risk in RA patients and that rheumatologists should manage this risk, including its re-assessment at least every five years and/or after significant changes in anti-rheumatic therapy [6].

A major challenge in stratifying CV risk in RA patients is defining the at-risk population and the specific contribution of disease activity. Although several screening tools are available, their performance in RA patients differs from that in the general population [7]. The available CV risk prediction algorithms include the Reynolds Risk Score (RRS), the Systematic COronary Risk Evaluation (SCORE), the "Progetto Cuore", an Italian algorithm with a similar performance to that of the SCORE chart, and the QRISK 3 [8–11]. Among these algorithms, only the QRISK 3 includes RA among the variables. In 2015, the Expanded Risk Score in RA (ERS-RA), which includes RA-specific items, was validated in RA patients included in the Consortium of Rheumatology Researchers of North America (CORRONA) registry [12]. The accurate estimation of CV risk should result in more effective prevention strategies. Unlike the general population, in RA patients, the algorithms mentioned above are suboptimal. For these reasons, EULAR suggests adapting the prediction model, using a 1.5 multiplication factor if RA is not already included in the algorithm [6,13]. However, a recent systematic review and meta-analysis showed that the available algorithms either underestimate or, sometimes, overestimate the CV risk in patients with RA, even after correcting for the 1.5 multiplier [13]. Several efforts have been attempted to improve CV risk categorization in RA patient. In this setting, carotid ultrasonography may improve the stratification of this risk when the use of a single validated algorithm, as the modified EULAR SCORE, underestimates the actual CV risk of RA patients [14]. Interestingly, in a consecutive cohort of RA patients without history of CV events, the combination of modified SCORE and QRISK3 allowed the identification of most patients with carotid plaques [15].

This cross-sectional, multicentre study aimed to investigate the prevalence of traditional and disease-related CV risk factors and estimate the 10-year CV-risk, using two different algorithms, in patients with RA and subjects with osteoarthritis (OA). The analysis is based on patients included in the database of the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group of the Italian Society of Rheumatology, a collaborative initiative to improve the knowledge of the interplay between rheumatic, metabolic and CV diseases [16].

2. Patients and methods

Consecutive RA patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR classification criteria [17], and regularly followed-up at Rheumatology centers, were prospectively included in a cross-sectional study. A cohort of age and sex-matched patients with peripheral joint OA was enrolled as a control population. The following clinical and serologic data were collected on enrollment: age, sex, smoking status (current, former, never), body mass index (BMI), systolic and diastolic blood pressure, lipids (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides), presence of DM and hypertension. Dyslipidaemia was defined as the use of lipid-lowering medications and/or low-density lipoprotein (LDL) cholesterol target according to their CV risk as defined by ESC/EAS Guidelines for the management of dyslipidaemias [18]. Hypertension was defined either as a history of hypertension or current use of blood pressure lowering drugs. DM was defined based on previous medical history and/or use of oral hypoglycaemic medications or insulin. Moreover, prior history of CV events was recorded, including acute coronary syndrome (ST- and non-ST elevation myocardial infarction, coronary revascularization and unstable angina), stable angina pectoris, ischemic stroke and peripheral artery disease (with or without revascularization procedures). All CV events were retrieved by review of medical charts, and all subjects with previous CV events were excluded. Disease-specific factors collected at baseline included disease duration, Health Assessment Questionnaire (HAQ) disability index as function index, and Disease activity index 28 (DAS28) by C reactive protein (CRP) and Clinical Disease Activity Index (CDAI) as measures of disease activity [18]. Serologic status included rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) as determined according to local assays. Finally, ongoing anti-hypertensive and lipid-lowering therapies and anti-rheumatic drugs, including conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), biologic (b) DMARDs and corticosteroids (mean weekly dose since diagnosis and current daily dose of prednisone or equivalent) were recorded.

Two different algorithms were used to estimate the individual 10-year risk of CV disease: the "Systematic COronary Risk Evaluation" (SCORE) and the "Progetto Cuore".

The SCORE project was initiated to develop a risk scoring system for use in the clinical management of cardiovascular risk in European clinical practice and assembled a pool of datasets from 12 European cohort studies, mainly carried out in general population settings. The SCORE risk estimation system offers direct estimation of total fatal cardiovascular risk in a format suited to the constraints of clinical practice. The SCORE equation estimates the mortality risk for the first fatal atherosclerotic event based on age, gender, smoking habits, total cholesterol and systolic blood pressure [9]. It stratifies the risk as low (score $< 1\%$), moderate ($\geq 1\%$ and $< 5\%$), high ($\geq 5\%$ and $< 10\%$) and very high ($\geq 10\%$) [8]. This algorithm recognizes Italy as a "low-risk country", and an adapted chart was used.

The "Progetto Cuore" is a project funded by the Italian Ministry of Health devoted to estimate the impact of cardiovascular diseases in the general population through a board of indicators like prevalence, incidence and mortality rates. The indicators included in the "Progetto Cuore" algorithm are defined according to the Italian population characteristics and is structured in a set of continuous variables representing the risk of macrovascular event at 10 years from when the set of clinical measures are taken. Considering age, sex, diabetes, smoking, total cholesterol and systolic blood pressure, all values are discretized since the thresholds indicated by the project [http://www.cuore.iss.it/valutazione/carte.asp], and the 10-year risk of major fatal and non-fatal CV events is stratified as low (score $< 10\%$), intermediate ($\geq 11\%$-19%) and high ($\geq 20\%$) [10,19].

Table 1 shows all variables considered to estimate the CV risk by the SCORE and "Progetto Cuore" algorithms respectively.

According to EULAR recommendations [6], as RA was not included in either algorithm, the estimated CV risk in RA patients was adapted using a 1.5 multiplication factor.

This study, conforming to the ethical guidelines of the Declaration of Helsinki, was approved by the local Ethical Committee as part of the GISEA Registry protocol (approval number DG-624/2012). Written informed consent was obtained from all patients at start of the observational period.

Table 1
Variables needed to calculate the different CV risk scores with related outcomes.

Variables	Systematic COronary Risk Evaluation (SCORE)(age 40-65)	"Progetto Cuore" algorithm(age 35-69)
Age	✔	✔
Gender	✔	✔
Smoking status	✔	✔
Systolic blood pressure (mmHg)	✔	✔
Total cholesterol/ hyperlipidemia	✔	✔
High Density Lipoprotein cholesterol		✔
Diabetes status		✔
On blood pressure treatment/ hypertension		✔
Outcome	Future fatal cardiovascularevent in the next 10 years	Future heart attack, stroke, or other major heart disease in the next 10 years

2.1. Statistical analysis

Data were expressed as mean ± standard deviation (SD) or 95% confidence intervals (95%CI) when appropriate. Differences in continuous variables were evaluated using the paired *t*-test and/or repeated analysis of variance (ANOVA) with Bonferroni. For categorical data, the Fisher' exact test was used to assess differences between the two groups. The odd ratio (OR) was then calculated with 95% confidence interval (CI). A *p-value* < 0.05 was considered statistically significant. The Statistical System Prism (Graphpad Instat, version 8.0.2 - GraphPad Software, San Diego CA USA) was used for all analyses.

3. Results

Overall, 1,467 RA patients without previous CV events and 342 age- and sex-matched patients with OA were enrolled. Demographic, clinical and laboratory findings are reported in Table 2. RA patients were more frequently diabetic (9.9% vs 6.4%; p=0.04) but had lower prevalence of dyslipidemia (21.7% vs 32.5%; p<0.0001) when compared to OA subjects. The prevalence of hypertension (40% vs 39.2%) was similar in both groups. The BMI was significantly lower (25.6±4.8 vs 26.6±4.4; p<0.0001), and obesity was less prevalent in RA patients (15% vs 21%; p=0.003). Moreover, RA patients were more frequently smokers (20.4% vs 12.5%; p=0.002).

As for serologic features, RF was positive in 67%, and ACPA were detected in 65% of RA patients. According to DAS28-CRP and CDAI, 34.7% and 30% of RA patients were in disease remission. Regarding treatment, 998 (68%) RA patients were on csDMARD treatment (of those 83% on methotrexate), 616 (42%) on biologic therapy and 630 (43%) on low dose glucocorticoids (<10 mg prednisone-equivalent/day). Two hundred twenty-seven OA patients (66.4%) were on NSAIDs or other analgesic agents.

As shown in Fig. 1 A, according to the SCORE chart, the mean 10-year estimated risk of the first fatal CV event was 1.6% (95%CI 1.3-1.9) in RA patients and 1.4% (95%CI 1.3-1.6) in OA patients, respectively (p=0.002). According to the "Progetto Cuore" algorithm, the 10-year risk of fatal and non-fatal CV events was 6.5% (95%CI 6.1-6.9) for RA patients, and 4.4% (95%CI 3.9-5.1) for OA controls, respectively (p<0.0001) (Fig. 1 B).

Stratifying patients at high CV-risk with the specific cutoff of ≥5% for the SCORE or ≥20% for the "Progetto Cuore" algorithm, 35 (2.4%) RA and 2 (0.6%) OA patients were at high CV-risk according to the SCORE (OR 4.1, 95%CI 1.1-17.6; p=0.03), while 52 (3.5%) RA and 4 (1.2%) OA patients were characterized by high CV risk according to the "Progetto Cuore" algorithm (OR 3.0, 95%CI 1.1-8.0; p=0.02). The SCORE algorithm and the "Progetto Cuore" chart ponder at moderate CV risk those patients with an estimated 10-years CV risk between 1% and 5% and between 10% and 20%, respectively. Unpredictably, using the SCORE this condition was estimated in 498 (34%) of RA patients and 158 (46.2%) of OA patients (OR 0.72, 95%CI 0.57-0.91; p=0.007), while using the "Progetto Cuore" 213 (14.5%) RA patients and 40 (11.7%) OA patients (OR 1.71, 95%CI 1.23-2.39; p=0.001) were stratified as at moderate CV risk. Along with these findings the SCORE algorithm estimated RA patients at moderate risk of CV events 2.5 times more frequently than "Progetto Cuore" chart. On the contrary, in OA patients the moderate risk for CV events was 2 times higher using the "Progetto Cuore" chart than the SCORE algorithm.

Table 2
Demographic and clinical features of RA and OA patients.

	RA (n.1467)	OA (n.342)	*p*-value
Age, years – mean (SD)	59.8 (11.5)	58.7 (11.5)	0.15
Female, n. (%)	1149 (78.3)	273 (79.8)	0.54
BMI, kg/m2 – mean (SD)	25.6 (4.8)	26.6 (4.4)	<0.0001
BMI > 30 kg/m2, n. (%)	220 (15)	72 (21)	0.003
Weight, Kg – mean (SD)	68 (14)	76 (11)	<0.0001
Height, m – mean (SD)	173 (13)	168 (15)	<0.0001
Diabetes, n. (%)	145 (9.9)	22 (6.4)	0.04
Dyslipidaemia, n. (%)	318 (21.7)	111 (32.5)	<0.0001
Hypertension, n. (%)	587 (40)	134 (39.2)	0.80
Smoking, n. (%)	299 (20.4)	43 (12.6)	0.0007
Antiplatelet drugs, n. (%)	126 (8.5)	36 (10.5)	0.25
Anticoagulant agents, n. (%)	54 (3.7)	10 (2.9)	0.62
RF positivity, n. (%)	983 (67)		
ACPA positivity, n. (%)	954 (65)		
HAQ, mean (95%CI)	0.82 (0.77-0.87)		
Disease duration, months - mean (95% CI)	135 (129-140)		
csDMARDs, n. (%)	998 (68)		
bDMARDs, n. (%)	617 (42)		
Corticosteroids, n. (%)	631 (43)		
Prednisone dose (mg/day), mean (95%CI)	4.5 (3.5-7.8)		
DAS28-CRP, mean (95%CI)	4.7 (3.5-5.9)		
CDAI, mean (95%CI)	8.8 (8.3-9.4)		
DAS28-CRP <2.6, n. (%)	509 (34.7)		
CDAI ≤2.8, n. (%)	441 (30)		

ACPA, anti-citrullinated peptides antibody; BMI, body mass index; b, biologic; cs, conventional synthetic; DMARD, disease modifying anti-rheumatic drugs; SD, standard deviation; RF, rheumatoid factor.

4. Discussion

The present study assessed the 10-year cardiovascular risk using the SCORE and the "Progetto Cuore" algorithms in a large Italian cohort of RA patients and age- and sex-matched OA subjects. Regardless of the tool used, RA patients had a relatively higher CV risk than the OA cohort and a three to four-fold higher probability of being in the highest CV risk category. These data deserve considerations as the comparator disease is, by itself, associated with a significant increased risk of CV disease, namely heart failure and ischemic heart disease, and CV mortality in comparison to healthy population [20]. Low grade inflammation, increased prevalence of DM and metabolic syndrome, reduced physical activity with consequent obesity and use of non-steroidal anti-inflammatory drugs represent independent risk factors for CV disease in OA patients. Interestingly, our RA patients were more frequently diabetic but had lower prevalence of obesity and dyslipidemia, thus reinforcing the strong independent contribution of the disease in CV risk. In the same line it could be explained the surprising finding of different prevalence of "moderate" condition depending on which algorithm is

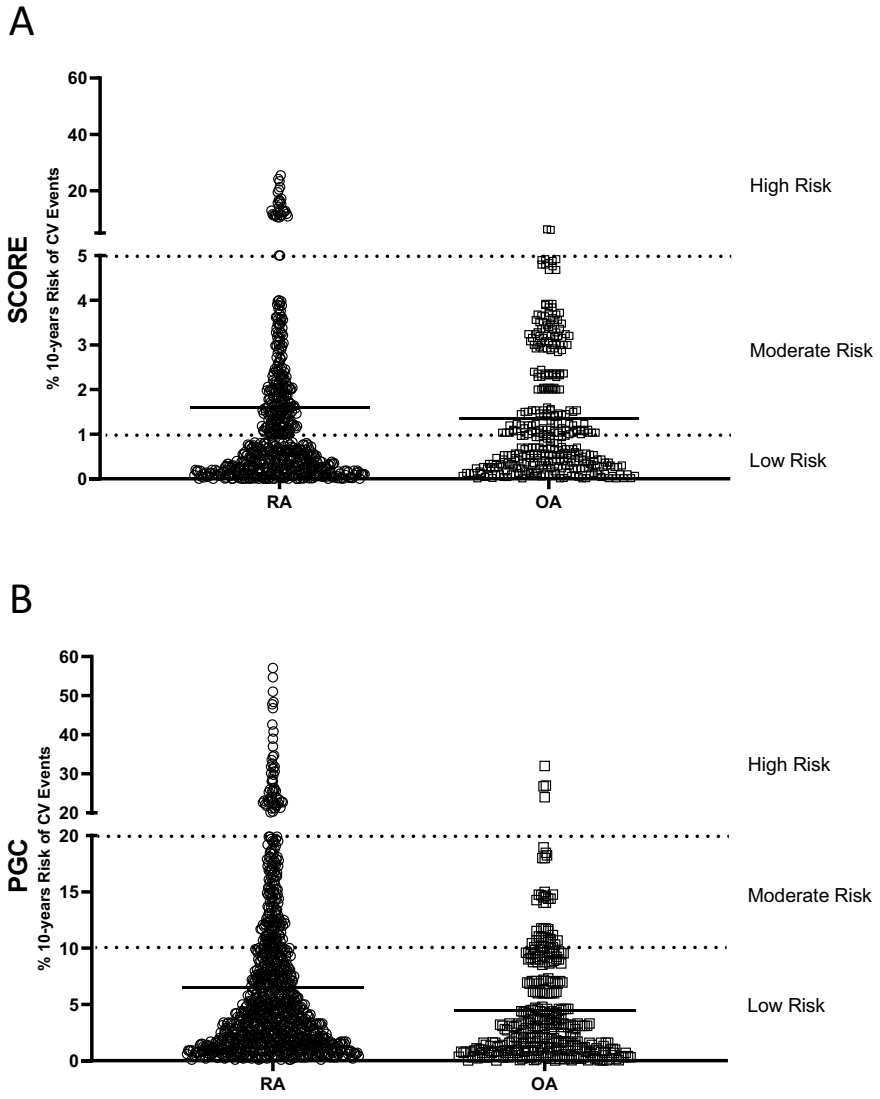

Fig. 1. Estimated 10 years CV-risk according to SCORE chart (A) and Progetto Cuore (PGC) algorithm (B) in rheumatoid arthritis (RA) and osteoarthritis (OA) patients.

used to estimate CV risk. Indeed, the observed higher prevalence of estimated moderate CV risk in OA patients using the SCORE, and the opposed condition using the "Progetto Cuore" algorithm, may be the result of different weight attributed to each traditional CV risk factor included in the algorithm, and, above all, the absence of DM among items included in the SCORE but included in the "Progetto Cuore". Moreover, this finding may suggest that traditional CV risk factors may exert a different weight in the assessment of CV risk in the two diseases and that still unexplored disease-specific pathogenic mechanisms may contribute differently to the score determination. This may have impact on the stratification of the risk with particular effect on the "moderate" condition instead of low or high risk and should be considered using alternatively the algorithms. Indeed, according to the 2019 ESC/EASD Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases, the presence of DM configures a "high" CV risk, independently of any other CV risk factor or how the CV risk has been estimated [21]. Indeed, identifying high CV risk RA patients among subjects included in the moderate risk category still represents a challenge in these patients. In this setting, the use of imaging techniques, as measurement of Coronary Artery Calcification Score or evaluation of carotid plaques, has been extensively demonstrated to identify high or very high CV risk patients among those included in the moderate category according to CV algorithms [14,22]. In this context, it is notable that reclassification of RA patients in the very high CV risk after carotid ultrasound is independently associated with dyslipidemia and disease activity, thus reinforcing the close interplay between altered lipid profile and inflammation in the pathogenesis of CV damage in RA patients [23].

The complex pathogenesis of CV risk in RA, partly explained by concomitant traditional CV risk factors, hinders the correct application and performance of available CV risk scores in this population [24]. This curtails the implementation of effective preventive pharmacological and non-pharmacological strategies. The EULAR recommendations suggest applying a 1.5 multiplier to CV algorithms that do not include RA; however, this is based on a few case-control studies and expert opinion. While some scores, e.g., FRS, SCORE and RRS, seem to underestimate the risk, the QRISK2 has been shown to overestimate CV disease risk, especially in high-risk subgroups [6,25]. Moreover, several approaches aimed to increase the predictive performance of these scores (i.e., use of multipliers, biomarkers, disease-specific variables, or modified scores) failed to improve reclassification of CV risk in RA significantly [12]. The magnitude of the problem is further amplified by the lack of large studies comparing the predictive performance of CV algorithms between RA patients and the general population. In this setting, our study included the largest Italian RA cohort evaluated to date and explore the

performance of two validated CV risk scores in predicting CV risk compared to a control population. To the best of our knowledge, this is the first study assessing the value of "Progetto Cuore" algorithm in a large cohort of Italian patients with RA and age- and sex-matched comparator group.

EULAR recommends the SCORE model to classify the risk of CV disease in RA patients if national guidelines are not available. However, the SCORE chart underestimates the 10-year risk of fatal and non-fatal CV events in low- and moderate-risk cohorts of early RA European patients and overestimate the risk in high-risk groups [25,26]. Both SCORE and a modified EULAR SCORE, recently proposed to improve CV risk stratification, resulted weaker predictors of CV events or death in comparison to the QRISK3 algorithm in a five-year prospective RA inception cohort [6,27]. In our RA cohort, the estimated fatal and non-fatal 10-year CV risk assessed by the "Progetto Cuore" algorithm was approximately 5-fold higher than the risk for fatal events measured by SCORE. Moreover, the "Progetto Cuore" algorithm, considering also non-fatal events, identified more patients in the high-risk group. Very few studies explored the "Progetto Cuore" algorithm's performance in predicting CV risk in chronic inflammatory disease patients. *Navarini L et al* evaluated the performance of five algorithms, including SCORE and "Progetto Cuore", in a retrospective analysis of a cohort of Italian patients with psoriatic arthritis, showing that both scores underestimated CV risk [28]. Despite a good discriminative ability between patients with and without CV events, the "Progetto Cuore" algorithm, as well as SCORE, performed poorly in terms of calibration, with a significantly different distribution of observed events compared to predicted ones [28].

In addition to items included in the SCORE tool, the "Progetto Cuore" algorithm encompasses DM as a traditional CV risk factor. Concomitant DM in RA patients is associated with a higher prevalence of history of major CV events [29]. Moreover, among conventional CV risk factors, DM represents the best predictor of subclinical atherosclerosis progression at one year of follow-up, in association with hypertension [30]. In this setting, it should be highlighted that, in our study, DM was significantly more prevalent in RA patients than in OA controls. Concomitant glucocorticoid therapy in 43% of RA patients, albeit at low dose, may partially account for the higher prevalence of DM in this population. However, the prevalence of comorbidities strongly associated with increased risk of DM, obesity and dyslipidemia, was significantly higher in the comparator group. Previous studies estimating DM prevalence in RA patients in comparison to the non-RA general population reported inconsistent results. The different comparator group used, general population, OA subjects or subjects with other CV comorbidities, may partly explain such inconsistency [31]. Taken together, these results suggest that DM represents an important variable that should be accounted for in algorithms evaluating CV comorbidity in RA patients.

In the "Progetto Cuore" algorithm, prescription of anti-hypertensive therapy is included as a separate item in addition to systolic blood pressure. In this setting, an established diagnosis of hypertension is likely to carry more weight in terms of CV risk prediction than an isolated systolic blood pressure recording. The prevalence of hypertension in patients with chronic inflammatory rheumatic disorders is significantly increased compared to healthy age and sex-matched subjects. Among all traditional CV risk factors, hypertension considerably increases the risk of major CV events in RA patients compared to control subjects [32,33]. These data reflect the importance of including hypertension, and not only a blood pressure value, in algorithms evaluating the risk of CV events and mortality in RA patients.

Surely, the observed low prevalence of obesity and dyslipidemia in our RA cohort may be the result of the "lipid paradox", thus reflecting the effect of chronic inflammation on lipid metabolism [34,35]. Indeed, EULAR recommendations suggest that lipid profile should be ideally measured when disease activity is stable or in remission. We acknowledge that only about one third of our patients were in remission. However, previous evidence demonstrated that CV algorithms that not include inflammatory markers or disease activity indices, as SCORE and "Progetto Cuore", are not influenced by changes in cholesterol levels and disease activity [35].

Finally, in our cohort, smoking was significantly more prevalent in RA patients compared to OA subjects. Smoking represents a recognized causative factor contributing to RA development and joint damage progression. It contributes to a 50% higher CV disease comorbidity risk in comparison to non-smoking RA subjects [36,37]. Moreover, in association with inflammatory status and high blood pressure, smoking significantly predicts coronary atherosclerosis progression in patients with early RA [38]. Interestingly, in a large cohort of RA patients, smoking cessation was associated with lower disease activity and improvement of lipid profile and predicted a lower risk of future CV events, including acute coronary syndrome, chronic ischemic heart disease, cerebrovascular events or death for coronary events [39]. Indeed, smoking remains a solid contributor to CV morbidity and mortality in RA and current evidence suggests that smoking cessation should be strongly recommended in these patients.

The main limitation of this study is its cross-sectional design, limiting the possibility to evaluate the contribution of modifiable disease-related variables (as inflammatory markers or disease activity) on the risk of CV events; indeed, as they were collected at a single timepoint, the RA-related variables do not adequately reflect the natural fluctuation of inflammatory burden observed in these patients.

Strength of the study is the large sample size, which included cohorts of RA patients from different geographical areas. This allows result generalization as they reflect different genetic factors and environmental settings, providing a robust estimate of CV risk in Italian RA patients across different regions. Moreover, the cohorts included consecutive patients, reducing the risk of selection bias.

The development and validation of CV risk algorithms in RA patients remain challenging as several variables, including both traditional CV risk factors and inflammatory parameters, contribute differently to increase CV morbidity in these patients. However, the present study results highlight that RA patients are characterized by a significantly higher risk of future CV morbidity and mortality compared to age and sex-matched OA patients.

In conclusion, compared to age and sex-matched OA controls, RA patients have a different distribution of traditional CV risk factors with a higher prevalence of DM and a lower prevalence of obesity and dyslipidemia and are more often smokers. Furthermore, they have a significantly higher probability of being in the highest CV risk category and a higher 10-year risk of CV events.

Therefore, besides controlling RA activity, the application of SCORE and/or "Progetto Cuore" models in RA patients, to stratify individual CV risk is mandatory in clinical practice, eventually also with the application of imaging techniques to correctly classify high risk patients. Subsequently, specific preventive measures should be implemented to control traditional risk factors, particularly avoiding smoking and improving blood pressure and glycaemic levels, to reduce CV morbidity and mortality of RA patients.

Author contribution

Fabio Cacciapaglia: Data analysis. **Elena Bartoloni, Fabio Cacciapaglia, Francesca Romana Spinelli**: Writing original draft. **All Authors** equally contributed to data collection and curation, conceptualization, methodology, review and editing original draft.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Declaration of Competing Interest

Authors have no specific competing interests to declare related to this work.

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