The estimated 10-years cardiovascular risk in a large cohort of Italian patients with rheumatoid arthritis: data from the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group.

Authors:

Cacciapaglia Fabio + 2, Spinelli Francesca Romana, Piga Matteo +2, Erre Gianluca +2, Sakellariou Garifallia +1, Manfredi Andreina+1, Viapiana Ombretta+1, ~~collaborators~~Alberto Floris, …….. , Alberto Cauli, Gremese Elisa, Atzeni Fabiola, Bartoloni Elena +1.

Affiliations:

[1] Rheumatology Unit - Department of Emergency Medicine and Transplantation (DETO), Università degli Studi di Bari Facoltà di Medicina e Chirurgia, Bari, Puglia, Italy.
[2] Dipartimento di Medicina Interna e Specialità Mediche - Reumatologia, Universita degli Studi di Roma La Sapienza, Roma, Italy.
[3] Rheumatology Unit, Department of Medical Sciences and Public Health, University of Cagliari, University Clinic AOU, Cagliari, Italy.~~Chair and Rheumatology Unit, University Clinic AOU Cagliari, Monserrato, CA, Italy.~~
[4] Specialità Mediche - Azienda Ospedaliero Universitaria di Sassari, UOC Reumatologia, Sassari, Italy.
[5] Division of Rheumatology, University of Pavia, IRCCS Policlinico San Matteo Foundation, Pavia, Italy.
[6] Internal Medicine, University of Modena and Reggio Emilia, Modena, Italy.
[7] Division of Rheumatology, Department of Medicine, University and Azienda Ospedaliera Universitaria Integrata of Verona, Verona, Italy.
[8] Division of Rheumatology, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy.
[9] Institute of Rheumatology, Università Cattolica del Sacro Cuore.
[10] Rheumatology Unit, University of Messina Faculty of Medicine and Surgery, Messina, Sicilia, Italy.
[11] Department of Medicine, University of Perugia, Rheumatology Unit, Perugia, Italy.

Corresponding author:
Fabio Cacciapaglia, MD PhD
Rheumatology Unit
Department of Emergency Medicine and Transplantation (DETO)
Università degli Studi di Bari
Email: fabio.cacciapaglia79@gmail.com.

ha formattato: Italiano (Italia)

ha formattato: Italiano (Italia)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Italiano (Italia)

ABSTRACT

Objectives Several cardiovascular (CV) risk algorithms are available to estimate CV morbidity and mortality risk in rheumatoid arthritis (RA) patients. However, their performance in RA differs in comparison with general population. This cross-sectional multicentre study aimed to estimate 10-years CV risk by two different algorithms in a large RA cohort compared to osteoarthritis (OA) patients.

Methods RA patients and matched OA controls were consecutively enrolled. Clinical and serologic data and traditional CV risk factors were recorded. Systematic COronary Risk Evaluation (SCORE) and "Progetto Cuore" algorithms were used to estimate the 10-years CV risk.

Results 1467 RA patients and 342 OA subjects without prior CV events 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). Dyslipidemia was more prevalent in OA (32.5% vs 21.7%; p<0.0001). The 10-years 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". RA patients had a 3- to-4-fold increased risk of 10-years fatal or non-fatal CV events compared to OA subjects according to both scores.

Conclusions RA patients display significant higher 10-years risk of CV events in comparison to OA subjects. In addition to effective disease control and joint damage prevention, specific protective measures acting on modifiable traditional CV risk factors should be implemented in these patients.

ha formattato: Inglese (Stati Uniti)

INTRODUCTION

Rheumatoid Arthritis (RA) is a chronic, systemic inflammatory disease at high risk of atherosclerotic cardiovascular (CV) events, similarly to that of diabetes mellitus (DM).[1] Chronic inflammation may explain this CV burden and plays a dual role: a direct effect - by contributing to the endothelial and vessel damage and atherosclerosis progression - and an indirect one - by modifying traditional CV risk factors such as lipid metabolism.[2]

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 between the overarching principles that clinicians should be aware for the increased CV risk in RA patients and rheumatologists should manage this risk, specifying to assess it at least every 5 years and/or after major changes in anti-rheumatic therapy.[3]

A major challenge in stratifying RA patients for their CV risk is defining the at-risk population and the contribution of disease activity. Several screening tools are available but their performance in RA patients differs in comparison with general population.[4] The CV risk prediction algorithms include the Reynolds Risk Score (RRS), the Systematic COronary Risk Evaluation (SCORE), the "Progetto Cuore", an Italian algorithm whose performance reflects that of the SCORE chart, and the QRISK 3.[5-8] Among these algorithms, only the QRISK 3 includes RA among the variables. In 2015 the Expanded Risk Score in RA (ERS-RA), that includes RA-specific items, was validated on RA patients included in the Consortium of Rheumatology Researchers of North America (CORRONA) registry.[9] The definite estimation of CV risk should result in correction of modifiable risk factors and reduction of morbidity and mortality. However, unlike in general population, in RA patients the performance of the aforementioned algorithms is suboptimal and EULAR suggests adapting the prediction model by a 1.5 multiplication factor, if RA is not already included.[3 10] But even after correcting for the 1.5 multiplier, the results of a recent literature review with metanalysis showed that

the available algorithms either underestimate or sometimes overestimate the CV risk in patients with RA.[10]

The aim of this cross-sectional, multicentre study was to investigate the prevalence of traditional and disease-related CV risk factors and to estimate the 10-years CV-risk using two different algorithms in patients with RA compared to subjects with osteoarthritis (OA). The analysis reflects the baseline data of the cohort of 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 knowledge on interrelationship between rheumatic, metabolic and CV diseases.[11]

PATIENTS AND METHODS

Consecutive RA patients fulfilling the 2010 American College of Rheumatology (ACR)/EULAR classification criteria,[12] and regularly followed-up at Rheumatology centers were prospectively included in a cross-sectional study. A cohort of age and sex-matched patients with OA was enrolled as control population. For the purpose of the study, specific clinical and serologic data were collected at enrollment using standardized definitions and included: age, sex, smoking status (current, former, never), body mass index (BMI), systolic and diastolic blood pressure values, lipid levels (total cholesterol, high density lipoprotein cholesterol, low density lipoprotein cholesterol and triglycerides), DM and hypertension. Hyperlipidaemia was defined as use of lipid-lowering medications and/or total cholesterol ≥ 200 mg/dl (i.e. 5.7 mmol/L). Hypertension was defined as either a former medical history of hypertension or current use of blood pressure lowering drugs according to guidelines for the management of hypertension. DM was defined based on previous medical history and/or use of oral hypoglycaemic medications or insulin. Moreover, previous medical history of CV events was recorded including acute coronary syndrome (ST- and non-ST elevation myocardial infarction, coronary revascularization and instable angina), stable angina pectoris, ischemic stroke and peripheral artery disease (with and without revascularization procedures). All

CV events were retrieved by review of medical charts. 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.[13] 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 risk of 10-years CV disease. The SCORE equation estimates the mortality risk for first fatal atherosclerotic event at 10 years based on age, gender, smoking habits, total cholesterol and systolic blood pressure and stratifies the risk as low (score < 1%), moderate (≥ 1% and < 5%), high (≥ 5% and < 10%) and very high (≥ 10%).[5] This algorithm recognizes Italy as a "low-risk country" and adapted chart was used.

The "Progetto Cuore" algorithm, validated in Italian subjects and suggested by the national guidelines for CV risk assessment, evaluates the 10-years risk of major fatal and non-fatal CV events based on age, sex, DM, smoking, total cholesterol and systolic blood pressure and stratifies the risk as low (score < 3%), intermediate (≥ 3%-19%) and high (≥ 20%).[7 14]

According to EULAR recommendations,[3] being RA not already included in both used algorithms, the estimated CV risk in RA patients was adapted by 1.5 multiplication factor.

Statistical analysis

Data are expressed as mean ± standard deviation (SD) or 95% confidence intervals 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 Fisher' exact test was used to assess any difference between two groups. The odd ratio (OR) was then calculated with 95% 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 analysis.

RESULTS

Overall, 1467 RA patients without prior CV events and 342 age and sex matched patients with OA were enrolled in this multicenter cross-sectional study.

Demographic, clinical and laboratory findings are reported in Table I. Notably, 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) as compared to OA subjects. The prevalence of hypertension (40% vs 39.2%) was similar in both groups. Mean BMI was significantly lower in RA patients (25.6±4.8 vs 26.6±4.4; p<0.0001) and obesity was less prevalent (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 patients. According to DAS28-CRP and CDAI, 34.7% and 30% respectively of patients were in disease remission at inclusion, 68% were on csDMARD treatment and 42% of patients were on biologic therapy. Moreover, 43% of RA patients were currently taking low dose glucocorticoids (<10 mg prednisone-equivalent/day). Two hundred twenty-seven (66.4%) of OA patients were taking NSAIDs or analgesic agents.

As shown in Figure 1 A, according to the SCORE chart the mean 10 years estimated risk of 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 (p=0.002). According to the “Progetto Cuore” algorithm, the 10-years 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 (p<0.0001) (Figure 1 B).

Stratifying patients at high CV-risk with the specific cutoff of 5% for the SCORE or 20% for the “Progetto Cuore” algorithm, we observed that 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).

DISCUSSION

The present study analyzed the performance of the SCORE and the “Progetto Cuore” algorithms for predicting fatal and non-fatal CV events in a large Italian cohort of RA patients in comparison to an age and sex-matched OA population. According to both scores, RA patients are characterized by a significant increased risk of 10-years fatal and non-fatal CV events in comparison to the OA cohort. Moreover, RA patients are characterized by a significant three to four-fold higher probability to be categorized in the highest CV risk.

The reliable estimation of CV disease risk in RA patients represents an undeniable challenge in order to optimize preventive strategies and pharmacological interventions aiming at reducing CV morbidity and mortality. In this setting, CV risk scores are an important and universally validated tool to estimate the long-term risk of major fatal and non-fatal CV events in the general population. However, the complex and still unexplored pathogenesis of CV risk in RA, only partly explained by concomitant traditional CV risk factors, hinder the correct application of CV risk scores in this population.[15] The EULAR recommendations suggest to apply a 1.5 multiplier to any CV algorithm if RA is not already included in the model, based on few case control studies and expert opinion. Whereas some scores, as FRS, SCORE and RRS, seem to underestimate, QRISK2 has been demonstrated to overestimate CV disease risk, especially in the high-risk subgroups.[3 16] Moreover, several approaches aimed to increase predictive performance of these scores (i.e., use of multipliers, biomarkers, disease-specific variables, or modified scores) failed to significantly improve reclassification of CV risk in RA.[9] The magnitude of the problem is further amplified by the lack of large studies comparing the value of CV algorithms in estimating the risk of CV events in RA patients in comparison with general population. In this setting, our study included the largest Italian RA cohort evaluated to date, to explore the performance of two validated CV risk scores in predicting CV risk

in comparison to a control population. To the best of our knowledge, this is the first study assessing the value of "Progetto Cuore" algorithm in a wide cohort of Italian patients with RA having a comparator age and sex matched group.

The SCORE model is recommended by EULAR to classify the risk of CV disease in RA patients if not national guidelines are available. However, the SCORE chart underestimate the 10-year risk of fatal and non-fatal CV events in low- and moderate-risk cohorts of European early RA patients and overestimate the risk in high risk groups.[16 17] 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 QRISK3 algorithm in a five-year prospective RA inception cohort. [3 18] In our RA cohort, the estimated fatal and non-fatal 10-years 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, identifies more patients in the high-risk group. Very few studies explored the performance of "Progetto Cuore" algorithm 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.[19] 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 significant different distribution of observed events compared to predicted ones.[19]

In addition to items included in SCORE chart, the "Progetto Cuore" algorithm encompass DM as traditional CV risk factor. Concomitant DM in RA patients is associated with higher prevalence of history of major CV events.[20] Moreover, among traditional CV risk factors, DM represents the best predictor of subclinical atherosclerosis progression at one year of follow-up, in association with hypertension.[21] In this setting, it should be considered that in our study DM was significantly more prevalent in RA patients in comparison to OA controls. Undoubtedly, concomitant glucocorticoid therapy – assumed by 43% of RA patients even if at low-dose – may partially account for the higher

risk of DM in this population. However, this result deserves consideration; indeed, the prevalence of some comorbidities strongly associated with increased risk of DM, including obesity and dyslipidemia, is significantly higher in the comparator group included in our study. Previous studies estimating DM prevalence in RA patients in comparison to non-RA general population reported inconsistent results and the selection of the comparator group, which included general population, OA subjects or subjects with other CV comorbidities, may partly explain such inconsistency.[22] Taken together, these results suggest that DM represents an important variable which should be considered in algorithms evaluating CV comorbidity in RA patients.

In the "Progetto Cuore" algorithm, prescription of anti-hypertensive therapy by physician is included as a separate item in addition to the registration of a single value of systolic blood pressure. In this setting, an established diagnosis of hypertension has surely greater weight in predicting CV risk compared to recording systolic blood pressure at a single time point. The prevalence of hypertension in patients with chronic inflammatory rheumatic disorders is significantly increased in comparison to healthy age and sex-matched subjects and, among all traditional CV risk factors, hypertension considerably increase the risk of major CV events in RA patients as compared to control subjects.[23] [24] These data reflect the importance to include hypertensive condition, and not only the measured blood pressure, as adjunctive issue in algorithms evaluating the risk of CV events and mortality in RA patients.

The observed low prevalence of obesity and dyslipidemia in our RA cohort compared to OA subjects may be the result of metabolic effects and "lipid paradox", as previously reported as result of chronic inflammation on lipid metabolism that should dampen the lipid effect on CV risk of RA patients.[25] [26]

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 and contributes to a 50% higher CV disease comorbidity risk in comparison to non-smoker RA subjects.[27] [28] Moreover, in association with inflammatory status and high blood pressure, smoking significantly contributed to predict coronary atherosclerosis progression in patients

with early RA.[29] Interestingly, in a large cohort of RA patients, smoking cessation was associated with lower disease activity and improvement of lipid profile and predicted of lower risk of future CV events, including acute coronary syndrome, chronic ischemic heart disease, cerebrovascular events or death for coronary events.[30] Indeed, smoking still represent a strong 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 as single point parameter, the RA-related variables cant reflect the natural fluctuation of inflammatory burden observed in these patients.

The strength of this study is the large sample size which included cohorts of RA patients from different geographical areas. This makes the results of relevant value as they mirror different genetic background and different environmental settings, thus providing a reliable estimate of CV risk in Italian RA patients not just limited to a specific geographical area. Moreover, the cohorts included all consecutive patients, thus reducing the risk of selection bias.

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

In conclusion, the results of this study highlight that, 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. Compared to OA patients, RA patients have a higher probability to fall in the highest CV risk category and have a significantly higher 10-years risk of CV events. Therefore, besides controlling RA disease

activity, in order to reduce CV morbidity and mortality, specific preventive measures should be implemented to control of some traditional risk factors, as DM or hypertension, strongly associated to the risk of CV events.

REFERENCES

1. Løgstrup BB, Ellingsen T, Pedersen AB, *et al*. Cardiovascular risk and mortality in rheumatoid arthritis compared with diabetes mellitus and the general population. *Rheumatology* 2021;60:1400-09.
2. Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? *Nat Rev Rheumatol* 2015;11:390-400.
3. 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.
4. Cacciapaglia F, Fornaro M, Venerito V, Perniola S, Urso L, Iannone F. Cardiovascular risk estimation with 5 different algorithms before and after 5 years of bDMARD treatment in rheumatoid arthritis. *Eur J Clin Invest.* 2020;50:e13343.
5. Ridker PM, Buring JE, Rifai N, *et al*. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds Risk Score. *JAMA* 2007;297:611-9.
6. Conroy RM, Pyörälä K, Fitzgerald AP, *et a*l; SCORE project group. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. *Eur Heart J* 2003;24:987-1003.

ha formattato: Inglese (Stati Uniti)

ha formattato: Olandese (Paesi Bassi)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Olandese (Paesi Bassi)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

7. Donfrancesco C, Palmieri L, Cooney MT, *et al*. Italian cardiovascular mortality charts of the CUORE project: are they comparable with the SCORE charts? *Eur J Cardiovasc Prev Rehabil* 2010;17:403-9.

8. Hippisley-Cox J, Coupland C, Brindle P. Development and validation of QRISK3 risk prediction algorithms to estimate future risk of cardiovascular disease: prospective cohort study. *BMJ* 2017;357:j2099.

9. Solomon DH, Greenberg J, Curtis JR, *et al*. Derivation and internal validation of an expanded cardiovascular risk prediction score for rheumatoid arthritis: a Consortium of Rheumatology Researchers of North America Registry Study. *Arthritis Rheumatol* 2015;67:1995-2003.

10. Colaco K, Ocampo V, Ayala AP, *et al*. Predictive utility of cardiovascular risk prediction algorithms in inflammatory rheumatic diseases: A systematic review. *J Rheumatol* 2020;47:928-938.

11. Cacciapaglia F, Erre G, Sakellariou G, *et al*. Cardiovascular Risk Evaluation in Systemic Lupus Erythematosus and Rheumatoid Arthritis: Preliminary Results from the "Cardiovascular Obesity and Rheumatic DISease (CORDIS)" Study Group of the Italian Society of Rheumatology [abstract]. *Arthritis Rheumatol* 2019;71 (suppl 10):2136.

12. Aletaha D, Neogi T, Silman AJ, *et al*. 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569-2581.

13. Aletaha D, Landewe R, Karonitsch T, *et al*. Reporting disease activity in clinical trials of patients with rheumatoid arthritis: EULAR/ACR collaborative recommendations. *Ann Rheum Dis* 2008;67:1360-1364.

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Francese (Francia)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

14. Palmieri L, Donfrancesco C, Giampaoli S, *et al*. Favorable cardiovascular risk profile and 10-year coronary heart disease incidence in women and men: results from the Progetto CUORE. *Eur J Cardiov Prev* 2006;13:562-570.

15. Crowson CS, Rollefstad S, Kitas GD, *et al*. A Trans-Atlantic Cardiovascular Risk Consortium for Rheumatoid Arthritis (ATACC-RA). Challenges of developing a cardiovascular risk calculator for patients with rheumatoid arthritis. *PLoS One* 2017;12:e0174656.

16. Arts EE, Popa CD, Den Broeder AA, *et al*. Performance of four current risk algorithms in predicting cardiovascular events in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2015;74:668–74.

17. Arts EE, Popa CD, Den Broeder AA, *et al*. Prediction of cardiovascular risk in rheumatoid arthritis: performance of original and adapted SCORE algorithms. *Ann Rheum Dis* 2016;75:674-80.

18. Corrales A, Vegas-Revenga N, Rueda-Gotor J, *et al*. Carotid plaques as predictors of cardiovascular events in patients with Rheumatoid Arthritis. Results from a 5-year-prospective follow-up study. *Semin Arthritis Rheum* 2020;50:1333-1338.

19. Navarini L, Margiotta DE, Caso F, *et al*. Performances of five risk algorithms in predicting cardiovascular events in patients with Psoriatic Arthritis: An Italian bicentric study. *PLoS One* 2018;13:e0205506.

20. Costello RE, Marsden A, Movahedi M, *et al*. The effect of glucocorticoid therapy on mortality in patients with rheumatoid arthritis and concomitant type II diabetes: a retrospective cohort study. *BMC Rheumatol* 2020;4:4.

21. Dalbeni A, Giollo A, Bevilacqua M, *et al*. Traditional cardiovascular risk factors and residual disease activity are associated with atherosclerosis progression in rheumatoid arthritis patients. *Hypertens Res* 2020;43:922-928.

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Olandese (Paesi Bassi)

ha formattato: Inglese (Stati Uniti)

ha formattato: Olandese (Paesi Bassi)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Italiano (Italia)

ha formattato: Italiano (Italia)

ha formattato: Italiano (Italia)

22. Jin Y, Chen SK, Liu J, *et al*. Risk of Incident Type 2 Diabetes Mellitus Among Patients With Rheumatoid Arthritis: A Population-Based Cohort Study. *Arthritis Care Res* 2020;72:1248-1256.

23. Bartoloni E, Alunno A, Valentini V, *et al*. Role of Inflammatory Diseases in Hypertension. *High Blood Press Cardiovasc Prev* 2017;24:353-361.

24. Bartoloni E, Alunno A, Gerli R. Hypertension as a cardiovascular risk factor in autoimmune rheumatic diseases. *Nat Rev Cardiol* 2018;15:33-44.

25. Cacciapaglia F, Perniola S, Venerito V, *et al*. The impact of biologic drugs on high-density lipoprotein cholesterol efflux capacity in rheumatoid arthritis patients. *J Clin Rheumatol* 2020; Online Ahead of Print.

26. Fornaro M, Cacciapaglia F, Venerito V, Lopalco G, Iannone F. Influence of changes in cholesterol levels and disease activity on the 10 years cardiovascular risk estimated with different algorithms in rheumatoid arthritis patients. *Ann Rheum Dis.* 2020;79:e104.

27. Sugiyama D, Nishimura K, Tamaki K, *et al*. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2010;69:70-81.

28. Baghdadi LR, Woodman RJ, Shanahan EM, *et al*. 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.

29. Mong N, Tarjanyi Z, Tothfalusi L, *et al*. Largely accelerated arterial aging in rheumatoid arthritis is associated with inflammatory activity and smoking in the early stage of the disease. *Front Pharmacol* 2020;11:523962.

30. Roelsgaard IK, Ikdahl E, Rollefstad S, *et al*. Smoking cessation is associated with lower disease activity and predicts cardiovascular risk reduction in rheumatoid arthritis patients. *Rheumatology* 2020;59:1997-2004.

ha formattato: Francese (Francia)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Inglese (Stati Uniti)

ha formattato: Italiano (Italia)

ha formattato: Italiano (Italia)

ha formattato: Olandese (Paesi Bassi)

Table 1 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
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.

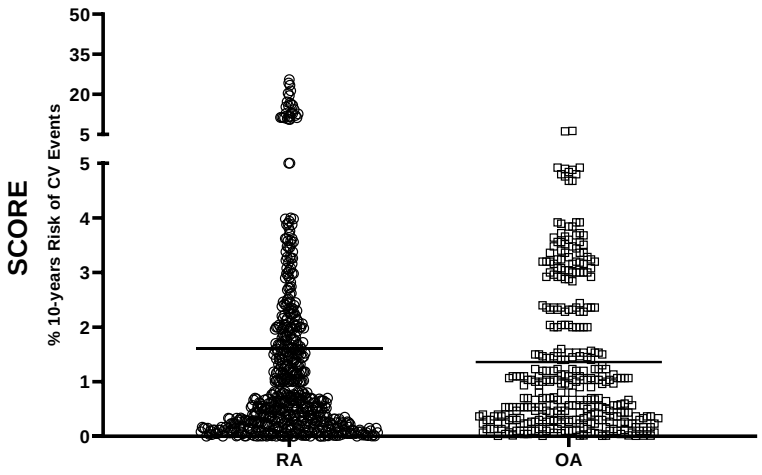
ha formattato: Italiano (Italia)

ha formattato: Italiano (Italia)

Figure 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.

ha formattato: Inglese (Stati Uniti)

A



B