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Original Article

Adherence to the 2019 ESC/EAS guidelines for dyslipidaemia management in a large rheumatoid arthritis cohort: Data from the CORDIS Study Group of the Italian Society of Rheumatology

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ABSTRACT

Background/aim: Lipid-lowering therapy prescription is low in rheumatoid arthritis (RA) patients, often not achieving lipid threshold target despite treatment. However, evidence derives from small, monocentric cohorts. We assessed adherence to lipid-lowering treatment for primary cardiovascular (CV) prevention in a RA cohort according to international guidelines.

Methods: A cross-sectional analysis of an Italian RA cohort was performed. Disease-related features and traditional CV risk factors were collected. The 10-year CV risk was estimated by Systematic COronary Risk Evaluation 2 (SCORE-2) algorithm. The primary preventive dyslipidaemia strategy was assessed according to 2019 European Society of Cardiology/European Atherosclerosis Society guidelines.

Results: 1.133 RA patients (78.2% female, aged 60.6±10.2 years) free from CV events were included. According to SCORE-2, 42.9% of patients were at moderate risk (1–5-%), 33.3% at high risk (5–10%) and 23.7% at very high risk (>10%). In the whole cohort, 12.9% of patients with <5%, 23.6% with 5–10% and 32.3% with >10% risk were on statin, respectively ($p<0.001$). According to 2019 ESC/EAS guidelines, 51.5% of patients had LDL-c at target. Among patients with LDL-c not at target, 76% were not on lipid-lowering treatment. At multivariate analysis, patients with higher CV risk had significantly lower probability of LDL-c at target.

Conclusion: In a wide Italian RA cohort, more than 50% of patients had high or very high CV risk. In these, lipid-lowering treatment prescription is suboptimal leading to not achievement of LDL-c target. Physicians should improve lipid screening and primary prevention therapy to reduce CV risk and improve CV comorbidity in RA patients.

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1. Background

The evidence that several variables, including inflammation, autoimmunity and traditional cardiovascular (CV) risk factors, closely interact to enhance atherosclerotic risk burden in rheumatoid arthritis (RA) has been well established over the past decade [1]. However, the actual contribution of each parameter is still to be clarified. In this context, among the traditional CV risk factors, the impact of dyslipidaemia on the CV risk of RA patients is the most controversial. Indeed, disease-related inflammatory mechanisms accounting for the "lipid paradox" may be associated with altered lipid profile that make the lipid profile assessment unreliable in RA patients, particularly during the active stages of the disease [2,3]. Moreover, RA treatments can affect cholesterol metabolism, further contributing to lipid fluctuations [4]. All these factors prevent reliable estimation of long-term CV risk in RA patients and partly explain the suboptimal performance of CV risk algorithms in individuals with inflammatory joint diseases [5].

In 2019, the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) updated the guidelines for the management of dyslipidaemia in the general population, identifying different low-density lipoprotein-cholesterol (LDL-c) thresholds to be achieved based on patient individual CV risk, suggesting the different primary and secondary CV prevention strategies [6]. However, a considerable proportion of patients at high or very high CV risk, as patients with diabetes mellitus or with recent myocardial infarction, are unlikely to achieve LDL-c targets in routine clinical practice, thus requiring optimization or intensification of lipid lowering therapy [7–9]. To the best of our knowledge, to date no studies have evaluated the adherence and performance of these guidelines in patients with RA.

Therefore, the specific aim of the study was to estimate the proportion of RA patients eligible to lipid lowering therapy and its actual prescription as primary prevention according to 2019 ESC/EAS guidelines in a large Italian RA cohort.

1.1. Patients and methods

In this cross-sectional study, data from a cohort of consecutive RA patients fulfilling the 2010 American College of Rheumatology/European League Against Rheumatism classification criteria [10] included in the Cardiovascular Obesity and Rheumatic DISease (CORDIS) dataset and evaluated in 10 Italian University Rheumatologic Centers, were extracted in December 2020. The CORDIS is a non-profit study group established within the Italian Society of Rheumatology on the initiative of academic rheumatologists interested in the study of CV risk in rheumatic diseases aimed to improve knowledge and awareness of CV disease impact on patients with musculoskeletal rheumatic diseases [11].

For the specific purpose of this study, all patients with the following available baseline clinical and serological data were included: age, sex, smoking status, body mass index (BMI), systolic and diastolic blood pressure, lipid profile, including total cholesterol (TC), LDL-c, high density (HD) L-c and triglycerides, history of diabetes mellitus and hypertension. Diabetes mellitus was defined as previous medical history and/or the use of oral or parenteral hypoglycaemic medications or insulin, and hypertension as either a history of hypertension or the use of blood pressure lowering agents.

Patients with missing data, a history of myocardial infarction, coronary revascularization, unstable or stable angina, ischemic stroke and peripheral artery disease (with or without revascularization procedures) retrieved by retrospective review of medical charts, were excluded. Data on current treatments, such as anti-hypertensive, lipid-lowering therapies and anti-rheumatic drugs, including conventional synthetic (cs) disease-modifying anti-rheumatic drugs (DMARDs), biologic (b) and targeted synthetic (ts) DMARDs and glucocorticoids (mean weekly dose since diagnosis and the current daily dose of prednisone or equivalent), were recorded. In addition, rheumatoid factor (RF) and anti-citrullinated peptide antibodies (ACPA) were recorded. Finally, disease-specific factors such as disease duration, C reactive protein (CRP), disease activity index based on 28-joint evaluation (DAS28) and Clinical Disease Activity Index (CDAI) as measures of disease activity and the Health Assessment Questionnaire (HAQ) disability index as the function index were evaluated [12–14].

Each patient was stratified according to the individual 10-year CV risk using the updated Systematic COronary Risk Evaluation 2 (SCORE-2) algorithm for CV risk corrected for 1.5 multiplicator factor as recommended by the European Alliance of Associations for Rheumatology (EULAR) [15,16].

The condition of dyslipidaemia and the individual indication to lipid-lowering therapy as well as LDL-c targets were defined according to the 2019 ESC/EAS guidelines for the management of dyslipidaemia [6]. These guidelines identify LDL-c thresholds to be achieved based on individual CV risk: <100 mg/dL for patients with a 10-year CV risk of 1–5%; <70 mg/dL for those with a CV risk >5% and <10%; <55 mg/dL for those with a CV risk >10%.

The present study was conducted according to the ethical guidelines of the Declaration of Helsinki and was approved by the local Ethical Committee as part of the GISEA Registry protocol (approval number DG-624/2012), and written informed consent was obtained from all patients.

1.2. Statistical analysis

Data were expressed as mean ± standard deviation (SD) or 95% confidence intervals (95% CI), when appropriate. The distribution of data was assessed with the Shapiro-Wilk test. Differences in continuous variables were evaluated using the one-way analysis of variance (ANOVA) for parametric and the Kruskall-Walis test for non-parametric variables. The Chi-square test was used for categorical data to assess differences among the three groups. A p-value < 0.05 was considered statistically significant, while variables with a p-value < 0.1 in descriptive statistical analysis were evaluated with a logistic regression model and univariate analysis. Subsequently, variables that achieved statistical significance ($p < 0.05$) in univariate analysis were included in a multivariate logistic regression model adjusted for age, sex, and disease duration. All analyses were performed using the SPSS statistic program (version 21—IBM software, New York, NY, USA).

2. Results

Overall, a cohort of 1133 RA patients (78.2% female) with a mean age of 60.6±10.2 years and with no previous CV events was included in the analysis. Demographics and clinical features of the cohort are reported in Table 1. Median (IQR) disease duration was 120 (136–149) months. Among traditional CV risk factors, 431 (38%) patients were on anti-hypertensive agents, 205 (22.1%) were current smokers, and 240 (21.2%) were on lipid-lowering agents. One-hundred and two (9%) patients were diabetic, 174 (15.4%) were obese, and 397 (35%) were overweight.

The 10-year CV risk stratification, adjusted for a multiplier factor of 1.5 for RA, showed that no patients were at low CV risk (<1%), 487 (42.9%) patients were at moderate CV risk (1–5%), 377 (33.3%) were at high CV risk (5–10%) and 269 (23.7%) at very high CV risk (>10%). The comparison of the three patient groups classified according to their estimated 10-year CV risk (<5%, 5–10%, and >10%) demonstrated that patients with CV risk <5% were significantly younger, more frequently female, with lower systolic and diastolic blood pressure, less frequently on antihypertensive treatment, diabetic, smoker and with chronic kidney disease in comparison to the other groups (Table 2). Although there were no statistically significant differences in absolute BMI values among the three CV risk classes, the percentage of overweight and obese RA patients was significantly lower among patients with an estimated CV risk of <5%. Of note, patients with an estimated 10-year CV risk >10% had significantly lower levels of TC, LDL-c and HDL-c, but higher

Table 1
Demographic and clinical features of RA patients.

RA patients (all Caucasian)	n. 1133
Sex (female), n (%)	886 (78.2)
Age, years - mean (SD)	60.6 (10.2)
Weight, Kg - mean (SD)	67.8 (13.9)
Height, cm - mean (SD)	162 (10)
BMI (Kg/m^2) - mean (SD)	25.7 (4.6)
BMI, Overweight (25–29.9 kg/m^2), n. (%)	397 (35.0)
BMI, Obese (≥30 Kg/m^2), n. (%)	174 (15.4)
Disease duration, months - median (95%CI)	120 (136–149)
RF, n (%)	738 (65.1)
ACPA, n (%)	718 (63.4)
CDAI, median (95%CI)	7 (6–7)
DAS28, median (95%CI)	3.2 (3.0–3-3)
CRP, mg/L - median (95%CI)	2.9 (2.7–3)
HAQ-DI, median (95%CI)	0.75 (0.6–0,9)
TC, mg/dL - mean (SD)	204 (38)
LDL-c, mg/dL - mean (SD)	122 (33)
LDL-c on target, n. (%)	583 (51.5)
HDL-c, mg/dL - mean (SD)	62 (17)
Triglycerides, mg/dl - mean (SD)	103 (50)
Systolic BP, mmHg - mean (SD)	128 (17)
Diastolic BP, mmHg - mean (SD)	77 (11)
Diabetes mellitus, n. (%)	102 (9)
Current Smokers, n. (%)	250 (22.1)
Chronic Kidney Disease, n. (%)	11 (0.9)
csDMARDs, n (%)	806 (71.1)
b/tsDMARDs, n (%)	490 (43.2)
Corticosteroids, n (%)	464 (40.9)
Daily Prednisone, mg - median (95%CI)	2 (1.25–2.5)
Statins, n (%)	240 (21.2)
Aspirin, n (%)	67 (5.9)
Anti-hypertensive agents, n (%)	431 (38.0)

Note: ACPA, anti-citrullinated protein antibodies; b, biologic; BMI, body mass index; BP, blood pressure; CDAI, clinical disease activity index; CRP, C-reactive protein; cs, conventional synthetic; DAS28, disease activity score on 28 joints; DMARDS, disease-modifying anti-rheumatic drug; HAQ-DI, health assessment questionnaire disability index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; RF, rheumatoid factor; TC, total cholesterol; ts, target synthetic.

levels of triglycerides ($p<0.001$). Furthermore, patients with an estimated 10-year CV risk >10% were significantly more frequently on treatment with csDMARDs ($p=0.002$), whereas patients with a CV risk of 5–10% were significantly less frequently on bDMARDs ($p=0.004$).

According to the 2019 ESC/EAS guidelines, only 51.5% (583) of patients had LDL-c at target. Although significantly more patients with an estimated CV risk >10% were taking lipid-lowering drugs, the probability of being on target for LDL-c was inversely associated with the individual estimated 10-year CV risk. Specifically, 63 (12.9%) patients with a CV risk of <5%, 89 (23.6%) patients with a CV risk of 5–10% and 87 (32.3%) patients with a CV risk >10% were on statin treatment, respectively ($p<0.001$). As reported in Fig. 1, the proportion of patients with an estimated 10-year CV risk <5% (97.5%) who reached the target for LDL-c was significantly higher than patients with a CV risk of 5–10% (22.3%) and >10% (8.9%), respectively ($p<0.001$). Of note, among the 48.5% of patients with LDL-c levels not at target according to individual CV risk thresholds, 417 (76%) patients were not on lipid-lowering treatment, while 132 (24%) patients were already taking hypolipidemic agents, in particular 62 (16%) among patients with an estimated 10-year CV risk of 5–10% and 70 (26%) among those with an estimated 10-year CV risk >10%.

By a binary logistic analysis, we observed that a higher 10-year CV risk was associated with a lower probability of having LDL-c levels at target. In particular, as shown in Table 3, after multivariate analysis adjusted for age, sex and the different RA-related covariates (disease duration, corticosteroid therapy, b/tsDMARD treatment, CDAI, CRP, HAQ, RF/ACPA seropositive status), the groups of patients with a 10-year CV risk >10% and 5–10% had OR=0.001 (95%CI 0.00–0.002; $p<0.001$) and OR=0.003 (95%CI 0.001–0.007; $p<0.001$) of being at

Table 2
Demographic and clinical features stratified according to the estimated 10-year CV risk.

	Estimated 10-years CV risk			
	<5%	5–10%	>10%	p
1133 RA patients, all Caucasian, n. (%)	487 (42.9)	377 (33.3)	269 (23.7)	<0.001
Female, n. (%)	419 (86)	276 (73.2)	191 (71)	<0.001
Age, years (SD)	53 (6.6)	62.4 (6.5)	72 (7.1)	<0.001
Weight, Kg (SD)	67.3 (14.9)	67.9 (13.1)	68.8 (13.1)	0.35
Height, cm (SD)	163 (8)	162 (9)	162 (8)	0.28
BMI, Kg/mq (SD)	25.4 (5.2)	25.8 (4.2)	26.2 (4.1)	0.06
BMI 25–30 kg/mq, n. (%)	140 (28.7)	142 (37.6)	115 (42.7)	<0.001
BMI > 30 kg/mq, n. (%)	68 (13.9)	60 (15.9)	46 (17.1)	0.03
TC, mg/dL (SD)	205 (36)	208 (37)	199 (42)	0.03
LDL-c, mg/dL (SD)	121 (30)	126 (33)	119 (35.7)	0.03
LDL-c on-Target, n. (%)	475 (97.5)	84 (22.3)	24 (8.9)	<0.001
HDL-c, mg/dL (SD)	65 (17)	60 (16)	58 (16)	<0.001
Triglycerides, mg/dL (SD)	97 (49)	105 (49)	111 (51)	<0.001
Treatment with Statin, n. (%)	63 (12.9)	89 (23.6)	87 (32.3)	<0.001
Systolic BP, mmHg (SD)	120 (13)	132 (16)	139 (18)	<0.001
Dyastolic BP, mmHg (SD)	75 (10)	78 (10)	79 (13)	<0.001
Anti-Hypertensive agents, n. (%)	116 (23.8)	154 (40.8)	161 (59.8)	<0.001
Diabetes mellitus, n. (%)	27 (5.5)	39 (10.3)	36 (13.4)	<0.001
Current Smoker, n. (%)	64 (13.1)	109 (28.9)	77 (28.6)	<0.001
Aspirin Therapy, n. (%)	17 (3.4)	26 (6.9)	24 (8.9)	0.006
Chronic Kidney Disease, n. (%)	0	5 (1.3)	6 (2.2)	0.007
Disease Duration, mo - median (95%CI)	120 (129–148)	120 (114–132)	120 (97.7–132)	0.49
RF, n. (%)	301 (61.8)	250 (66.3)	187 (69.5)	0.08
ACPA, n. (%)	300 (61.6)	237 (62.8)	181 (67.3)	0.29
CRP, mg/L - median (95%CI)	2.2 (2–2.9)	2.9 (2.5–3.1)	4.0 (3–4.7)	<0.001
CDAI - median (95%CI)	7 (5.5–8)	7 (6.5–8)	6 (5–7)	0.26
DAS28 - median (95% CI)	3.1 (2.9–3.2)	3.3 (3.1–3.5)	3.2 (2.9–3.4)	0.22
HAQ-DI - median (95% CI)	0.62 (0.5–0.75)	0.75 (0.6–1)	0.75 (0.5–1)	0.003
Corticosteroids, n. (%)	191 (39.2)	156 (41.4)	117 (43.5)	0.50
Daily PDN, mg - median (95%CI)	2 (0–2.5)	2 (1–2.5)	2.5 (2–2.5)	0.29
csDMARDs, n. (%)	320 (65.7)	279 (74)	207 (76.9)	0.002
b/tsDMARDs, n. (%)	232 (47.6)	138 (36.6)	120 (44.6)	0.004

Note: ACPA, anti-citrullinated protein antibodies; b, biologic; BMI, body mass index; BP, blood pressure; CDAI, clinical disease activity index; CRP, C-reactive protein; cs, conventional synthetic; DAS28, disease activity score on 28 joints; DMARDS, disease-modifying anti-rheumatic drug; HAQ-DI, health assessment questionnaire disability index; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; PDN, prednisone; RF, rheumatoid factor; TC, total cholesterol; ts, target synthetic.

LDL-c target, in comparison to patients with a CV risk <5%, respectively. However, patients with a CV risk of 5–10% and >10% had almost two-fold higher probability of being on lipid-lowering treatment in comparison to patients with a CV <5% [OR 1.64 (1.06–2.55; $p=0.02$) and 1.73 (1.04–2.89; $p=0.03$), respectively]. Finally, patients with a 10-year CV risk of 5–10% and >10% had a nearly four-fold and more than double risk, respectively, of having non-target LDL-c levels not taking lipid lowering drugs [OR 3.87 (95%CI 2.24–6.8; $p<0.001$) and OR 2.48 (1.09–5.61; $p=0.02$), respectively].

3. Discussion

The primary prevention of CV morbidity in patients with chronic inflammatory diseases, including RA, is still an unmet need despite the growing awareness of pathogenic mechanisms contributing to the increased CV risk in these patients and the availability of international

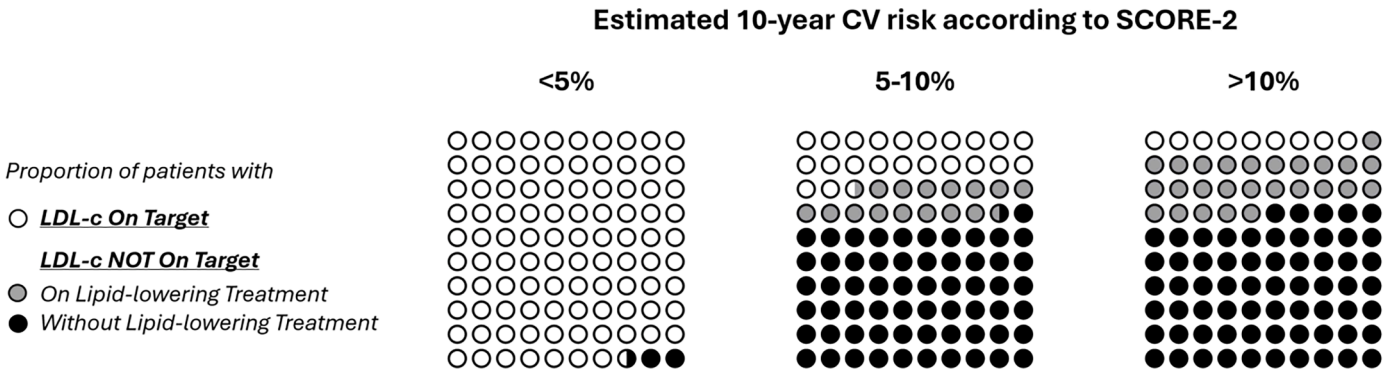

Fig. 1. Proportion of RA patients at LDL-c target according to individual moderate (<5%), high (5–10%) or very-high (>10%) estimated 10-year CV risk by SCORE-2 algorithm. White dots: proportion of patients who reached the LDL-c target. Grey dots: proportion of patients who did not reach the LDL-c target despite being on lipid treatment. Black dots: proportion of patients who did not reach the LDL-c target and are not taking therapy.
All differences among groups are statistically significant ($p<0.001$).

Table 3
Logistic regression analysis.

Dependent Variable	Univariate			Multivariate*		
	OR	95%CI	p	OR	95%CI	p
LDL at target						
<5%	1 (Ref)			1 (Ref)		
5–10%	0.007	0.003–0.1	<0.001	0.003	0.001–0.007	<0.001
>10%	0.002	0.001–0.01	<0.001	0.001	0.00–0.02	<0.001
Ongoing Statin						
<5%	1 (Ref)			1 (Ref)		
5–10%	2.08	1.45–2.97	<0.001	1.64	1.06–2.55	0.028
>10%	3.22	2.23–4.61	<0.001	1.73	1.04–2.89	0.036
Non-target LDL without lipid-lowering agents						
<5%	1 (Ref)			1 (Ref)		
5–10%	2.21	0.72–6.9	0.19	3.87	2.24–6.68	<0.0001
>10%	1.15	0.38–3.6	0.81	2.48	1.09–5.61	0.029

* Adjusted for age, sex, disease duration, steroid, b/tsDMARD, MTX, CDAI, CRP, HAQ, RF/ACPA positivity status.

recommendations for its management [1,16–18].

Statins are the cornerstone for CV disease prevention in the general population due to their dual lipid-lowering and pleiotropic anti-inflammatory effects. Although the randomized controlled Trial of Atorvastatin for the Primary Prevention of Cardiovascular Events in RA patients (TRACE RA) failed to draw definitive results due to early discontinuation for low event rates [19], reasonable evidence supports the beneficial effects of statins, both as reduction of CV mortality and atherosclerosis progression in RA patients, particularly in those with higher inflammatory status [20–22]. Nonetheless, screening for dyslipidemia and lipid-lowering drug prescriptions in RA patients is suboptimal [23]. Primary lipid screening is reported in less than half of eligible RA patients older than 65 years and only 37% of a younger RA cohort [24,25]. When RA is the unique CV risk factor, patients have a lower probability of undergoing diabetes mellitus and hyperlipidemia screening than the non-RA population with one CV disease risk factor, despite an equivalent-to-higher CV risk [26]. These findings suggest that existing CV risk factors and comorbidities may increase the likelihood of CV risk screening prescription in RA patients while the disease itself is unacknowledged as an independent CV risk factor.

Of note, although patients with RA have a CV risk like that of patients with diabetes mellitus, prescription of primary lipid screening in RA patients was quite similar to that reported in general population and significantly lower than in diabetic patients [24,25]. Of more importance, even among RA patients with known CV disease or concomitant diabetes mellitus, only a quarter met the goal of LDL-c $\leq$ 70 mg/dl, with about 60% of patients having an annual lipid test [27,28]. In this context, the fact that, in our large Italian RA cohort, about three quarter of patients not reaching the LCL-c target do not take hypolipidemic therapy, although meeting indication according to the 2019 ESC/EAS guidelines, is relevant and indirectly reflects the difficulties in CV risk assessment and management in this population. Similarly, a retrospective evaluation of more than 20.000 Italian RA patients using the administrative healthcare databases demonstrated a significant lower rate of lipid-lowering therapy prescription in patients in comparison to matched controls [29]. Moreover, RA patients with dyslipidemia showed significantly lower persistency on treatment [29]. This may be partly a consequence of the lack of recommendations for screening and managing CV disease in RA patients. Moreover, there is still uncertainty about the boundaries of the management of CV comorbidities among rheumatologists, cardiologists and general practitioners [23]. In a recent position paper, the CORDIS study group suggested that the rheumatologist should calculate the 10-year CV risk by the Italian algorithm "Progetto Cuore" in all RA patients, especially in those with specific CV risk factors including dyslipidaemia, to provide a reliable indication for their management [30].

In a statin-naïve cohort, Myasoedova E. et al. showed that RA patients had lower LDL-c levels before statin introduction and a lower probability of achieving LDL-c target after 90 days of statin use in comparison to control subjects [31]. It is noteworthy that worse inflammatory parameters at baseline were associated with a lower probability of reaching the LDL-c target, confirming the significant impact of the disease in regulating and altering lipid metabolism [31].

Prescription of lipid-lowering therapy by both rheumatologists and primary care physicians is still consistently low across different cohorts with substantial geographical differences [23,29,32–36]. Several factors may contribute to suboptimal statin prescription in these patients, including physician unawareness of RA as an independent CV risk factor,

absence of specific recommendations on lipid management in these populations, uncertainty about prescribing primary prevention therapy in patients considered at low CV risk, concerns about side effects of statins (in particular in patients with a condition characterized by chronic pain) and their potential interference with multiple concomitant immunosuppressive therapies, and conflicts over the role of different specialists in prescribing CV preventive treatments [23,35,37]. Not least, more than half of RA patients, especially older or with shorter disease duration, are unaware of the higher CV risk associated with their disease, and only one-quarter reported a CV risk counseling from their physician or rheumatologist [38]. This highlights the importance of patient perspective and appropriate counseling to improve awareness of the higher CV risk and compliance with therapy [38]. The application of an algorithm that stratifies patient risk categories according to CV parameters and RA-related features impacting CV risk, such as disease activity, antibody profile and concomitant corticosteroid therapy, may improve the identification and proper management of eligible patients, as recently suggested [30,32]. The suboptimal assessment of CV risk factors and estimation of CV risk enhance the extent of the problem.

Interestingly, in our cohort, the very high CV risk group had a significantly higher probability of having non-target LDL-c despite a higher frequency of statin therapy than the other CV risk groups. In addition, having a higher CV risk was independently associated with a lower likelihood of LDL-c at target despite a higher likelihood of being on hypolipidemic therapy, after adjustment for disease-related confounders. In similar cross-sectional studies employing different CV risk algorithms, patients at intermediate or high CV risk had the highest probability of not achieving the LDL-c goals despite lipid-lowering therapy [36,39]. This may reflect the suboptimal performance of CV risk algorithms in these patients and the intrinsic difficulty in estimating the real contribution of disease-related inflammatory and immune mechanisms in enhancing CV risk. On the other hand, although statins have been demonstrated to exert a positive effect in primary CV risk prevention in RA patients, their effective LDL-lowering activity has not been fully ascertained [33]. In this setting, disease-related immune mechanisms, the effect of inflammation on lipid profile and composition as well as unexplored pharmacologic interferences between statins and immunomodulant therapies may explain a non-computable effect of statins on LDL-c and other lipid molecules, such as Apolipoproteins A and B [33].

Noteworthy, in our RA cohort, 56% of patients had a high or very high CV risk and no patients were in the low CV risk category. Probably, if an imaging evaluation had been performed in all moderate-risk patients, the high-risk percentage would have been further increased [40]. It should also be considered that factors potentially contributing to CV risk in these patients - disease activity, median daily corticosteroid dose and rate of patients on corticosteroid therapy at inclusion - were similar across the three risk categories, thus reinforcing the role of the disease as an independent CV risk factor [1].

Finally, in our population, patients classified in the very high-risk category were more frequently male, with older age and characterized, as expected, by a higher prevalence of traditional CV risk factors. Interestingly, the lower lipid levels, including total cholesterol, LDL-c and HDL-c, in association with higher triglycerides in this category compared to the other groups may reflect, at least in part, the effect of the inflammatory burden, as demonstrated by the higher levels of CRP at inclusion. This patient profile deserves greater attention as potentially exposed to long-term increased risk of CV disease.

We acknowledge that the cross-sectional nature of our study limits any inference on long-term CV disease outcomes. Moreover, adherence and persistence to statin as well as drug dose could not be accurately assessed nor potential confounder factors, like physical activity, socioeconomic status, education level, dietary habits and familial form of hypercholesterolemia, have been accounted in data analysis. In this setting, it was also not possible to calculate how many patients declined statin therapy despite physician prescription and differences in healthcare system in other countries may limit study generalizability. However, the study provides a representative and reliable picture of the current statin prescription habit in a wide Italian RA cohort in different geographical settings and represents one of the first evidence that lipid-lowering therapy prescription is sub-optimal in this population despite indication according to validated international recommendations. Moreover, the large sample size and absence of missing data represent the undeniable main strengths of the study.

In conclusion, the under-prescription of statins emphasizes the importance of considering other lipid-lowering strategies in eligible RA patients, including proprotein convertase subtilisin kexin 9 inhibitors in selected categories [41]. In addition to optimal management of underlying inflammatory disease, which may further improve metabolic disturbance and reduce CV event rates [42], we believe that LDL-c goal attainment for primary and secondary prevention purposes is feasible in these patients through a rational and integrated collaboration between different specialists, as demonstrated in countries where rheumatologists and general physicians close collaborate to manage the CV risk of RA patients and to implement EULAR recommendations [43]. Finally, all physicians treating RA patients should be active and aware of managing CV risk. Above all, modifiable traditional risk factors, such as dyslipidemia, should be handled appropriately to minimize the individual CV risk and also potential adverse CV events related to treatments, as recently recommended by the EULAR [44] and Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicine Agency [45].

Author contributions

All Authors contributed to the study's conception, design and data acquisition. FC and MF contributed to the statistical analysis of data. FC, EB, and FRS drafted the manuscript. All Authors critically revised it. All Authors gave final approval and agreed to be accountable for all aspects of work, ensuring integrity and accuracy.

Data availability

The data supporting the findings of this study are available from the corresponding Author upon reasonable request.

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Conflict of interest

None declared.

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