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Subclinical atherosclerosis and history of cardiovascular events in Italian patients with rheumatoid arthritis

Results from a cross-sectional, multicenter GIRRCS (Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale) study

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Abstract

Several studies have pointed out a significant association between rheumatoid arthritis (RA) and accelerated atherosclerosis. At the best of our knowledge, no such study has been carried out in a large Italian series and, in this study, we aimed to investigate the prevalence of both subclinical atherosclerosis and history of cardiovascular events (CVEs), in patients consecutively admitted from January 1, 2015 to December 31, 2015 to Rheumatology Units throughout the whole Italy.

Centers members of GIRRCS (*Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale*) were invited to enrol patients consecutively admitted from January 1, 2015 to December 31, 2015 and satisfying American College of Rheumatology/ European League Against Rheumatism criteria for RA and to investigate each of them for: traditional cardiovascular risk factors: sex, age, smoking habit, total cholesterol, triglycerides, glycaemia, high blood pressure, metabolic syndrome (MS), type 2 diabetes (T2D); RA features: disease duration as assessed from the first symptom, disease activity as evaluated by DAS28, radiographic damage as assessed by hands and feet x-ray, and previous joint surgery; prevalence of both subclinical atherosclerosis and history of CVEs.

Eight centers participated to the study. From January 1, 2015 to December 31, 2015, the 1176 patients, who had been investigated for all the items, were enrolled in the study. They were mostly women (80.52%), with a median age of 60 years (range, 18–91 years), a median disease duration of 12 years (range, 0.8–25 years), seropositive in 69.21%. Nineteen percent were in remission; 17.51% presented low disease activity; 39.45% moderate disease activity; 22.61% high disease activity.

Eighty-two patients (6.9%) had a history for CVEs (58 myocardial infarction, 38 heart failure, 10 ischemic transitory attack, and 7 stroke). This figure appears to be lower than that reported worldwide (8.5%). After excluding the 82 patients with a history of CV events, subclinical atherosclerosis was detected in 16% of our patients, (176 patients), a figure lower than that reported worldwide (32.7%) and in previous Italian studies.

This is the first Italian multicenter study on subclinical and clinical atherosclerosis in patients with RA. We pointed out a low prevalence of both subclinical atherosclerosis and history of CV events.

Abbreviations: ACPA = anti-citrullinated protein antibody, bDMARD = biologic disease-modifying anti-rheumatic drug, CHF = congestive heart failure, CRP = C-reactive protein, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, CV = cardiovascular, CVAs = cerebrovascular accidents, CVEs = cardiovascular events, DAS28 = disease activity score in 28 joints, GIRRCS = Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale, HBP = high blood pressure, ISTAT = Italian National

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Institute of Statistics, ldCCSs = low dose corticosteroids, MI = myocardial infarction, MS = metabolic syndrome, RA = rheumatoid arthritis, RF = rheumatoid factor, T2D = type 2 diabetes.

Keywords: cardiovascular events, inflammatory process, rheumatoid arthritis, subclinical atherosclerosis, traditional cardiovascular risk factor

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by an increased risk of mortality, as compared with general population, mainly due to cardiovascular events (CVEs).[1–3] In fact, a large percentage of RA patients experience myocardial infarction (MI), cerebrovascular accidents (CVAs), and congestive heart failure (CHF) during their life.[4–6] Furthermore, an increased prevalence of subclinical atherosclerosis as evidenced by carotid artery plaques, has been observed in these patients, and this subclinical condition may allow to identify those RA patients with a higher risk to develop CVEs.[4,7] In addition, it has been pointed out that "traditional" cardiovascular (CV) risk factors, such as high blood pressure (HBP), type 2 diabetes (T2D), and metabolic syndrome (MS) are underestimated in RA patients and therefore untreated,[8–11] thus contributing to the increased CV risk, despite specific international recommendations were developed.[12,13] To date, the causes of accelerated atherosclerosis have not been fully elucidated. In fact, specific features of RA, including systemic inflammatory process and disease activity, seem to be involved in promoting CV risk in addition to traditional risk factors.[14–16]

It has been shown that CV mortality in RA has distinct patterns among different countries; RA has been reported to present both a lower prevalence and a milder disease course in Italy and in other Mediterranean countries with respect to North European countries.[17–19] At the best of our knowledge, no study has been carried out in a large Italian series of RA patients in order to evaluate the risk of CVEs and subclinical atherosclerosis in Italian RA patients. In this work, we investigated the presence of CVEs and subclinical atherosclerosis in a cohort of RA patients enrolled in the multicenter GIRRCS (*Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale*) observational study (RA-GIRRCS Study), evaluating the possible associations among both traditional CV risk factors and disease specific features and the evidence of CVEs and subclinical atherosclerosis. Furthermore, due to the differences pointed out in RA populations across different Worldwide nations, mainly in comorbidities and long-term outcome,[20] an evaluation between our data of prevalence of both subclinical atherosclerosis and history of CVEs, and the available RA literature was performed in order to discuss possible differences.

2. Patients and methods

2.1. Study design, inclusion criteria, and data collection

Eight tertiary Rheumatologic units, throughout the whole Italy, with high experience in management of RA patients as well as in observational studies were involved. The reports of the first scheduled visit of each patient, satisfying the American College of Rheumatology/ European League Against Rheumatism criteria for RA,[21,22] and visited from January 1, 2015 to December 31, 2015 were reviewed. The patients were evaluated for traditional CV risk factors, history of CVEs and subclinical atherosclerosis. CVEs were defined as history of MI and/or CHF and/or CVAs. The prevalence of each condition and their cumulative prevalence was compared with those registered in Italian general population matched for sex and age by the Italian National Institute of Statistics (ISTAT, www.istat.it). Subclinical atherosclerosis was defined as the presence of carotid plaque as assessed by carotid and/or peripheral arteries ultrasound imaging. Its prevalence was compared with that registered in control subjects from 3 studies on subclinical atherosclerosis in Italian patients with RA, Sjogren syndrome, or systemic lupus erythematosus.[23–26] Smoking habit, evidence of HBP, T2D, and MS as well as serum levels of total cholesterol and triglycerides were recorded, at the first visit. Disease activity was assessed by Disease Activity Score in 28 joints (DAS28).[27] Furthermore, disease duration from the first disease symptom, radiographic damage evaluated as the presence of erosions/joint narrowing at hands or feet, history of joint surgery, C reactive protein (CRP) and rheumatoid factor (RF), and/or anti-citrullinated protein antibody (ACPA) were also registered. Extra-articular features were assessed, the diagnosis of these disease manifestations was based on those used in previous studies.[19] The extra-articular manifestations considered were: secondary Sjögren syndrome with clinical evidence of dry eyes/mouth, rheumatoid nodules, vasculitis, pulmonary involvement, cutaneous, and neurologic manifestations. The patients were divided in 5 groups, according with their therapeutic regimen: single conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) + low dose corticosteroids (ldCCSs); combination of ≥2 csDMARDs without CCSs; csDMARD(s) + ldCCSs + Biologic DMARD (bDMARD); sDMARD(s) + DMARD (bDMARD) without corticosteroids (CCSs); other therapeutic regimens.

Both international and national recommendations for the management of RA patients were strictly followed. The local ethics committee (*Comitato Etico Azienda Sanitaria Locale 1 Avezzano/Sulmona/L'Aquila*, L'Aquila, *Italy; protocol number 000331/17*) approved the study, that was performed according to the Good Clinical Practice guidelines and the Declaration of Helsinki. Written informed consent was obtained from all patients.

2.2. Statistical analysis

Associations between subclinical atherosclerosis and CVEs and any other demographic or clinical feature were assessed by calculating the respective ORS. Covariates were selected from 2 main areas: traditional CV risk factors: sex, age, smoking habit, serum levels of total cholesterol and triglycerides presence of MS, T2D, and HBP; RA-related risk factors: DAS28 values, duration of the disease, presence of extra-articular disease, evidence of radiographic damage, and history of joint surgery. We modeled different statistical analyses, adjusted for sex and age, by performing a logistic regression, to evaluate the possible associations between each of these among these covariates and both history of CVEs and presence of subclinical atherosclerosis. Furthermore, we performed the same analysis in order to evaluate the possible associations between the same set of variables and the evidence of MI, CHF, and CVAs singularly considered. Models fitting has been assessed carrying out a log-likelihood ratio Sidak test, adjusted for multiple tests, with type I error set at 0.05. Due to

Table 1

Demographic and clinical features of the evaluated patients.

Patients	1176
Gender (female/male)	80.52%/19.48%
ACR 1987 classificative criteria	74.1%
ACR/EULAR 2010 classificative criteria	93.5%
Age, y	
Mean ± SD	60.38 ± 12.84
Median (range)	60 (range, 18–91)
RA clinical features	
Disease duration, y	
Mean ± SD	12.35 ± 9.61
Median (range)	12 (range, 0.8–25)
<1 y	5.50%
between 1 and 5 y	21.50%
between 5 and 10 y	22.00%
≥10 y	46.00%
RF and/or ACPA	69.21% (1176 pts)
Radiologic damage	46.10% (1165 pts)
Joint surgery	10.12% (1176 pts)
Extra-articular disease	16.32%
Disease activity_DAS28_first visit	4.83 ± 17.48 (1118 pts)
Remission	19.40%
Low disease activity	17.51%
Moderate disease activity	39.45%
High disease activity	22.61%
HAQ-DI	0.94 ± 0.78 (891 pts)
Traditional CV risk evaluation	
Cholesterol, mg/dL	196.31 ± 48.82 (998 pts)
Cholesterol >200 mg/dL	49.54% (493 pts)
Triglycerides, mg/dL	117.25 ± 51.79 (982 pts)
Triglycerides, mg/dL >130 mg/dL	31.46% (309/982 pts)
Blood glucose, mg/dL	92.60 ± 33.36 (1015 pts)
Blood glucose >110 mg/dL	13.40% (136/1015 pts)
Smoking habit	32.90% (387/1176)
High blood pressure	45.74% (538/1176 pts)
Type 2 diabetes	13.09% (154/1176 pts)
Metabolic syndrome	24.06% (283/1176 pts)
RA therapeutic strategies	
csDMARD(s) + ldCCSs	24.60%
csDMARDs combination without CCSs	11.70%
csDMARD(s) + ldCCSs + bDMARD	34.70%
csDMARD(s) + bDMARD without CCSs	17.39%
Other therapeutic strategies	11.51%
csDMARD	96.68%
MTX	78.38%
Other_csDMARDs	17.30%
bDMARDs	49.27%
TNF inhibitors	36.19%
Other bDMARDs	13.08%

ACPA = anti-citrullinated protein antibody, bDMARD = biologic disease-modifying anti-rheumatic drug, CCSs = corticosteroids, csDMARD = conventional synthetic disease-modifying anti-rheumatic drug, DAS28 = Disease Activity Score in 28 joints, HAQ-DI = health assessment questionnaire disability Index, MTX = methotrexate, RF = rheumatoid factor, ld = low dose, SDAI = simplified disease activity index, TNF = tumor necrosis factor.

the relative simple design and the expertise of the recruiting centers, we had a low percentage of missing data, that could impair our analyses. The analysis was performed using SPSS software (SPSS for Windows, version 17.0, SPSS Inc., Chicago, IL).

3. Results

3.1. Baseline characteristics of evaluated RA patients

From January 1, 2015 to December 31, 2015, 1176, admitted to 8 GIRRCS centers, were enrolled in the study; the demographic features of our cohort are shown in Table 1. They were mostly women (80.52%), with a median age of 60 years (range, 18–91 years), a median disease duration of 12 years (range, 0.8–25 years), seropositive in 69.21%. Nineteen percent were in remission; 17.51% presented low disease activity; 39.45% moderate disease activity; 22.61% high disease activity. The most common RA therapeutic strategies were csDMARD + ldCCSs (24.60%) and sDMARD(s) + ldCCSs + bDMARD (34.70%). Methotrexate (MTX) and TNF inhibitors were the most common sDMARD and bDMARD prescribed, respectively.

As far as the traditional CV risk factors are concerned, 45.20% presented a HBP, 32% reported smoking habit, 24.30% were affected by MS, and 13.10% by T2D. Serum total cholesterol resulted 196.31 ± 48.82 mg/dL (mean ± SD), serum triglycerides 117.25 ± 51.79 mg/dL; blood glucose 92.60 ± 33.36 mg/dL. In particular, 49.54% displayed a serum total cholesterol >200 mg/dL; 31.46% triglycerides >130 mg/dL; 13.43% out of patients displayed a glycaemia >110 mg/dL. Furthermore, 5.4% were affected by osteoporosis, 4.3% by thyroid diseases, 1.1% by HBV infection, and 0.9% by HCV infection.

3.2. History of CVEs and related risk factors

Eighty-two patients (6.9%) had a history for CVEs (58 patients myocardial infarction, 38 patients heart failure, 10 patients ischemic transitory attack, 7 patients stroke). This prevalence is higher than that reported in Italian National Institute of Statistics (ISTAT, www.istat.it) (Table 2).

Univariate analyses (Table 3) pointed out significant associations between both some traditional CV risk factors and some RA-related factors and history of CVEs. In particular, among the former, older age (odds ratio [OR]: 1.06, 95% confidence interval [CI]: 1.04–1.08, $P < .001$), male sex (OR: 2.73, 95% CI: 1.71–4.37, $P < .001$), MS (OR: 6.72, 95% CI: 4.20–10.77, $P < .001$), T2D (OR: 5.71, 95% CI: 3.54–9.18, $P < .001$), HBP (OR: 11.37, 95% CI: 5.63–22.95, $P < .001$) were each significantly associated with previous CVEs. Among the latter, a high disease activity (DAS28 >5.1) only was significantly associated with the presence of CVEs (OR: 1.50, 95% CI: 1.27–1.97, $P = .042$). Therefore, smoking habit, total cholesterol values, disease duration, RF, ACPA, extra-articular disease, joint surgery, and radiographic were not statistically associated with history of CVEs. Of note, in multivariate analysis (Table 3), the evidence of MS (OR: 2.54, 95% CI: 1.29–4.52, $P = .005$), T2D (OR: 2.32, 95% CI: 1.29–4.29, $P = .007$), and HBP (OR: 4.92, 95% CI: 2.14–11.45, $P < .001$) as well as the high disease activity (DAS28 >5.1) (OR: 1.31, 95% CI: 1.15–1.68, $P = .003$) were significantly associated with previous CVEs, in our cohort of RA patients. Furthermore, by univariate and multivariate analyses, we evaluated the possible association among the identified variables and evidence of MI, CHF, and CVAs (additional Table 1, http://links.lww.com/MD/B905 additional Table 2, http://links.lww.com/MD/B905 additional Table 3, http://links.lww.com/MD/B905).

3.3. Subclinical atherosclerosis and its associations

After excluding the 82 patients with a history of CV events, subclinical atherosclerosis was detected in 16% of our patients, (176 patients), it resulted higher than those observed in control groups from Italian studies on other diseases reported in those studies.[23–26]

Table 2

Specific prevalence rate ratios in RA GIRRCS cohort.

Age	RA patients, number	Subclinical atherosclerosis, number	Specific prevalence rate (*10,000 people)
35–44	94	0	0
45–54	210	19	90.5
55–64	383	54	161.0
65–74	304	78	258.6
35–74	991	151	158.4
Age	**RA patients, number**	**CVEs, number**	**Specific prevalence rate (*10,000 people)**
35–44	94	2	31.2
45–54	210	3	61.2
55–64	383	19	97.6
65–74	304	36	130.4
35–74	991	60	83.6

CVEs = cardiovascular events, GIRRCS = Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale, RA = rheumatoid arthritis

At univariate analyses (Table 4), it was suggested that both some traditional CV risk factors and some RA-related risk factors resulted to be associated with the presence of subclinical atherosclerosis. As far the traditional CV risk factors are concerned, older age (OR: 1.08, 95% CI: 1.07–1.18, $P < .001$), higher serum values of total cholesterol (OR:1.02, 95% CI: 1.01–1.16, $P < .001$), and triglycerides (OR: 1.01, 95% CI: 1.00–1.02, $P < .001$), MS (OR: 7.35, 95% CI: 5.35–10.13, $P < .001$), T2D (OR: 5.71, 95% CI: 1.83–3.88, $P < .001$), HBP (OR:10.82, 95% CI: 7.24–16.18, $P < .001$), were each significantly associated with subclinical atherosclerosis. Concerning the RA related risk factors, high disease activity (DAS28 >5.1) (OR: 2.85, 95% CI: 2.07–3.92, $P < .001$), and longer disease duration (OR: 1.02, 95% CI: 1.01–1.04, $P = .001$) were significantly associated with presence of subclinical atherosclerosis. To date, remission (DAS28 <2.6) (OR: 0.45, 95% CI: 0.29–0.714, $P = .001$) was negatively associated with subclinical atherosclerosis. Therefore, smoking habit, RF, ACPA, extra-articular disease, joint surgery, and radiographic damage were not associated with subclinical atherosclerosis. Interestingly, in multivariate analysis, older age (OR: 1.069, CI 95%: 1.05–1.09, $P < .001$), MS (OR: 3.41, CI 95%: 2.16–5.40, $P < .001$), and HBP (OR: 3.71, CI 95%: 2.23–6.17, $P < .001$) and high disease activity (DAS28 >5.1) (OR: 2.11, CI 95%: 1.35–3.32, $P = .001$) were all significantly associated with the presence of subclinical atherosclerosis.

Table 3

CVEs univariate and multivariate analyses.

Univariate analyses	OR	SE	*P*	CI 95%
Gender	2.73	0.24	**<.001**	1.71–4.37
Age	1.06	0.01	**<.001**	1.04–1.08
Smoking habit	0.95	0.24	.85	0.21–4.60
Total cholesterol	0.99	0.03	.47	0.99–1.03
Triglycerides	1.01	0.02	**.017**	1.00–1.09
Metabolic syndrome	6.72	0.24	**<.001**	4.20–10.77
Type 2 diabetes	5.71	0.24	**<.001**	3.54–9.18
High blood pressure	11.37	0.36	**<.001**	5.63–22.95
Rheumatoid factor	1.15	0.25	.578	0.70–1.90
Anti-citrullinated protein antibodies	1.11	0.23	.628	0.71–1.75
Disease duration	0.97	0.01	.10	0.97–1.05
Remission	1.07	0.28	.803	0.62–1.87
Low disease activity	1.05	0.29	.856	0.59–1.89
Moderate disease activity	1.36	0.23	.156	0.88–2.17
High disease activity	1.50	0.33	**.042**	1.27–1.97
Joint surgery	0.44	0.52	.12	0.16–1.25
Radiographic damage	1.03	0.23	.87	0.66–1.63
Extra-articular disease	1.63	0.27	.07	0.94–2.77
Multivariate analysis	**OR**	**SE**	***P***	**CI 95%**
Gender	3.46	0.29	**<.001**	1.94–6.18
Age	1.01	0.01	.202	0.99–1.04
Triglycerides	1.00	0.02	.159	0.99–1.08
Type 2 diabetes	2.32	0.31	**.007**	1.29–4.29
Metabolic syndrome	2.54	0.39	**.005**	1.29–4.52
High blood pressure	4.92	0.43	**<.001**	2.14–11.45
High disease activity	1.31	0.38	**.003**	1.15–1.68

Bolded values indicate statistically significant results ($P < .05$).

CI = confidence interval, OR = odds ratio.

Table 4

Subclinical atherosclerosis univariate and multivariate analyses.

Univariate analyses	OR	SE	*P*	CI 95%
Gender	1.26	0.18	.201	0.88–1.80
Age	1.08	0.08	**<.001**	1.07–1.18
Smoking habit	0.94	0.16	.72	0.69–1.29
Total cholesterol	1.02	0.02	**<.001**	1.01–1.16
Triglycerides	1.01	0.01	**<.001**	1.00–1.02
Metabolic syndrome	7.35	0.16	**<.001**	5.35–10.13
Type 2 diabetes	5.71	0.24	**<.001**	1.83–3.88
High blood pressure	10.82	0.20	**<.001**	7.24–16.18
Rheumatoid factor	0.86	0.16	.353	0.62–1.18
Anti-citrullinated protein antibodies	0.96	0.15	.79	0.71–1.29
Disease duration	1.02	0.08	**.001**	1.01–1.04
Remission	0.45	0.23	**.001**	0.29–0.71
Low disease activity	0.68	0.21	.077	0.45–1.04
Moderate disease activity	0.79	0.16	.141	0.58–1.08
High disease activity	2.85	0.16	**<.001**	2.07–3.92
Joint surgery	0.93	0.25	.72	0.55–1.51
Radiographic damage	0.98	0.15	.88	0.72–1.31
Extra-articular disease	1.42	0.19	.07	0.98–2.07
Multivariate analysis	**OR**	**SE**	***P***	**CI 95%**
Gender	0.84	0.31	.163	0.87–2.34
Age	1.06	0.01	**<.001**	1.05–1.09
Total cholesterol	1.01	0.02	.138	0.99–1.02
Triglycerides	1.01	0.02	.116	1.00–1.01
Metabolic syndrome	3.41	0.23	<.001	2.16–5.40
Type 2 diabetes	0.57	0.29	.205	0.39–1.23
High blood pressure	3.71	0.27	**<.001**	2.23–6.17
Disease duration	1.01	0.01	.199	0.99–1.09
Remission	0.84	0.31	.587	0.46–1.55
High disease activity	2.11	0.23	**.001**	1.35–3.32

Bolded values indicate statistically significant results ($P < 0.05$).
CI = confidence interval, OR = odds ratio.

4. Discussion

CV comorbidities are frequently associated with RA, strongly influencing not only the clinical course and the outcome of these patients, but also the therapeutic strategies in order to prevent the occurrence of severe CVEs.[14,15] On this light, any study exploring this clinical setting may provide useful information about the evolution of clinical picture and the response to treatments. Of interest, taking together our data it is possible to point out a low prevalence of both subclinical atherosclerosis and history of CV events when compared with other available series.[5–7] In addition, in our multicenter GIRRCS observational study, we show that, among the traditional CV risk factors, only some of them were related with a history of CVEs, and, on other hand, highest values of the DAS28 were associated with the presence of both CVEs and/or subclinical atherosclerosis, suggesting that not only the traditional CV risk factors but also the disease activity is independently associated with the development of CV complications.

In our study, we observed a low prevalence of these CV comorbidities, both subclinical atherosclerosis and history of CVEs when compared with other series.[5–7] Subclinical atherosclerosis prevalence is lower than that reported in meta-analysis of observational studies on the topic (16% vs 32.7%).[7] In this study, an increased prevalence of carotid plaques in RA patients has been shown.[7] Specifically, the authors analyzed 59 studies and reported that 32.7% of patients displayed this feature.[7] As far as history of CVEs is concerned, several studies and meta-analyses evaluated the prevalence of CVEs in RA patients, and our prevalence seems lower than that reported in meta-analysis of observational studies (6.9% vs 8.5%).[5,7] Taking together these findings is not possible to address definitive conclusions concerning the reduced prevalence that we observed and future specific-designed studies are surely needed to fully elucidated these possible differences, in RA population, across different nations. In this context, it has been proposed that the iniquity in access to health care system and stricter eligibility criteria for treatments, such observed in countries with lower socioeconomic welfare, may strongly influence the comorbidities and long-term outcome in RA patients.[15]

Despite the well-known role of traditional CV risk factors, in inducing CVEs and subclinical atherosclerosis in general population, our analysis failed to show the expected association among some of these factors and the development of CVEs. In fact, we observed that only MS and HBP were associated with both CVEs and subclinical atherosclerosis while T2D was associated only with the evidence of CVEs. To date, multiple lines of evidence confirmed a significant association between RA and MS, T2D and HBP.[28,29] Furthermore, in this context, meta-analytic data confirmed the role of traditional CV risk factors in accelerating atherosclerosis, and thus CVEs, in RA patients.[30] In addition, it has been shown that traditional CV risk factor may not be optimally identified and treated, in RA patients, thus contributing to the increase of CVEs risk.[31,32] Finally, NSAIDs and steroids, frequently used in RA patients, may rise the systemic blood pressure.[33,34]

Although the well-known role of the smoking habit in RA pathogenesis, its impact on CVEs and subclinical atherosclerosis, during RA, have still not been identified and the "smoking paradox" has been proposed.[35–37] The weaker association between smoking habit and both CVEs and subclinical atherosclerosis might be related with an "index event" bias, in which causal factors appear not to apply to disease complications, during observational and epidemiological studies.[38] We did not observe any role of hypercholesterolemia in RA CVEs. In fact, despite of the increased CV risk observed during this disease, the rheumatoid pro-inflammatory process may induce a decrease of serum total cholesterol, the so called RA lipid paradox.[39] This result confirms that quantitative analyses might not identify the real impact of cholesterol on CV comorbidities in RA. In fact, the systemic inflammation modulates specific qualitative changes in lipoproteins, mainly affecting the HDL fraction, which loses its anti-inflammatory activity and its skill to reverse cholesterol transport function.[40,41] On these bases, further studies are needed to fully clarify the role of lipoproteins in inducing CVEs in RA patients.

The inflammatory process strongly modulates all stages of the atherosclerosis, including endothelial damage, plaque formation, destabilization, and, finally, the thrombogenic events leading to occlusion.[42] Many pathogenic pathways are activated in this complex process including, endothelial cell dysfunction, oxidative stress, pro-thrombotic phenotype, and pro-atherogenic metabolic effects.[15,16] Taken together all these data confirm that the pro-inflammatory process, associated with a dysregulation of immune system, is strongly involved in the development of accelerate atherosclerosis in RA.[43–47] In our observational study, we observed that the high disease activity was significantly associated with the evidence of both CVEs and subclinical atherosclerosis. In fact, it has been shown that patients with history of MI had more tender joints, worse fatigue, and higher ESR levels.[37] As far as the relationship between disease duration and CVEs are concerned, our study did not find any statistical association. Although conflicting data are reported in available literature, concerning the association between disease duration and CV risk,[48,49] our results show that inflammatory burden more than duration of the disease, contributes to the development of CVEs. Taking together our data, we may suggest that not only the management of traditional CV risk factor but also a good control of disease activity, may play an important role in preventing the CVEs and thus premature death in RA patients.[43,48,50]

Our multicenter study carries out some limitations. The specific design of our study, in which the different therapeutic strategies of RA patients were not randomized, did not allow us to analyze the possible association between treatments and outcomes, to avoid the risk of a "confounding by indication" bias.[51–53] However, it must be pointed out that a large percentage of our patients were treated with CCSs. Although the available data are conflicting, because of deleterious effects of CCSs, such as disturbances of lipid and glucose metabolism and increase in blood pressure, might be, at least in this setting, counteracted by the anti-inflammatory properties of this family of medications, the possible pro-atherogenic role of such drugs should be taken into account in the management of these patients.[54,55] In fact, it has been reported that a sustained exposure to CCSs was significantly associated with cardiometabolic comorbidities in rheumatic diseases, thus contributing to increased CV risk.[56–60] Although a growing body of evidence suggests new possible therapeutic targets in rheumatic diseases,[61–64] future specific designed studies are needed to entirely elucidate this issue, considering, even today, the central role of CCSs "bridging" therapy in management of these patients.[65] Furthermore, due to a higher value of missing data concerning body mass index (BMI), we could not evaluate its impact on CVEs and subclinical atherosclerosis. However, it has been shown that during RA, in which sarcopenia may alter the body composition, BMI may not be considered a valid predictor of CVEs and subclinical atherosclerosis, as in normal population.[66–68]

In conclusion, in our knowledge, this is the first multicenter study on subclinical and clinical atherosclerosis in patients with RA, throughout the whole country and not limited to some specific geographic area. We pointed out a low prevalence of both subclinical atherosclerosis and history of CV events when compared with other available series. Nonetheless, a high disease activity and presence of cardiovascular risk factors were found to play a role to RA patients similarly from other countries. Our results show that high values of DAS28 are associated with CVEs and subclinical atherosclerosis, confirming the need of optimal control of the disease activity in order to decrease the burden of CV comorbidities. Furthermore, the presence of HBP and MS were significantly associated with CVEs and subclinical atherosclerosis, confirming the some traditional CV risk factors may play a specific role in modulating CV complications, during RA, and showing that the risk for CVEs in Italian population parallels what observed in other countries. Future longitudinal analyses, on larger cohorts of patients, with longer follow-up, are surely needed in order to reinforce these data and suggest new research fields.

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