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ORIGINAL RESEARCH

Biological use influences the impact of inflammation on risk of major adverse cardiovascular events in rheumatoid arthritis

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ABSTRACT

Objectives Chronic inflammation promotes cardiovascular risk in rheumatoid arthritis (RA). Biological disease-modifying antirheumatic drugs (bDMARDs) improve disease activity and cardiovascular disease outcomes. We explored whether bDMARDs influence the impact of disease activity and inflammatory markers on long-term cardiovascular risk in RA.

Methods We studied 4370 participants without cardiovascular disease in a 10-country observational cohort of patients with RA. Endpoints were (1) major adverse cardiovascular events (MACE) encompassing myocardial infarction, stroke and cardiovascular death; and (2) any ischaemic cardiovascular events (iCVE) including MACE plus revascularisation, angina, transient ischaemic attack and peripheral arterial disease.

Results Over 26 534 patient-years, 239 MACE and 362 iCVE occurred. The interaction between 28-joint Disease Activity Score with C-reactive protein (DAS28-CRP) and bDMARD use was significant for MACE (p=0.017), suggesting the effect of DAS28-CRP on MACE risk differed among bDMARD users (n=515) and non-users (n=3855). DAS28-CRP (per unit increase) is associated with MACE risk in bDMARD non-users (HR 1.21 (95% CI 1.07 to 1.37)) but not users (HR 0.69 (95% CI 0.40 to 1.20)). The interaction between CRP (per log unit increase) and bDMARD use was also significant for MACE (p=0.011). CRP associated with MACE risk in bDMARD non-users (HR 1.16 (95% CI 1.04 to 1.30)), but not users (HR 0.65 (95% CI 0.36 to 1.17)). No interaction was observed between bDMARD use and DAS28-CRP (p=0.167) or CRP (p=0.237) for iCVE risk.

Conclusions RA activity and inflammatory markers associated with risk of MACE in bDMARD non-users but not users suggesting the possibility of biological-specific benefits locally on arterial wall independently of effects on systemic inflammation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Rheumatoid arthritis activity associates with increased atherosclerosis and cardiovascular risk.
⇒ Biological disease-modifying antirheumatic drugs reduce disease activity, arterial wall inflammation, atherosclerosis progression and cardiovascular event risk.

WHAT THIS STUDY ADDS

⇒ Biological use modified the effect of C-reactive protein and 28-joint Disease Activity Score using C-reactive protein on major adverse cardiovascular event risk.
⇒ C-reactive protein and 28-joint Disease Activity Score associated with major adverse cardiovascular event risk in biological non-users but not in users.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Biological disease-modifying antirheumatic drugs may reduce cardiovascular risk in rheumatoid arthritis, even if the goal of remission is not attained.

INTRODUCTION

Cardiovascular disease is a major comorbidity in rheumatoid arthritis (RA).[1] Coronary atherosclerosis burden and progression is greater in patients with RA than age-matched and gender-matched controls.[2 3] RA activity is linked to arterial wall inflammation.[4 5] RA-related inflammation also contributes to plaque progression and cardiovascular risk above and beyond traditional risk factors.[3 6] In contrast, comprehensive control of inflammation decreases both atherosclerosis progression

and cardiovascular risk.[3 7–9] The role of inflammation as an independent cardiovascular risk factor was prospectively interrogated in randomised controlled trials of interleukin-1 (IL-1) blockade and colchicine, showing a reduction in inflammation and cardiovascular risk in general patients with established coronary artery disease.[10]

Biological disease-modifying antirheumatic drugs (bDMARDs) used in RA were shown to decrease inflammation, radiographic progression[11 12] and cardiovascular risk.[13–15] Cardiovascular risk reduction in the context of ongoing bDMARD use associated with decreased coronary atherosclerosis progression and plaque stabilisation, independently of cumulative inflammation.[9] Tumor Necrosis Factor (TNF-α) inhibitors lowered both RA activity and arterial wall inflammation, particularly in areas with the greatest atherosclerosis burden.[4 5] Importantly, improvements in arterial wall inflammation are associated with decreased arterial stiffness.[5] Yet, reduction in arterial wall inflammation did not correlate with improvements in clinical measures of RA activity.[4] These observations from small-scale studies raise the possibility that the benefit of bDMARDs may additionally relate to local effects on arterial wall inflammation and atherosclerosis independently of systemic inflammatory control.[9]

bDMARD use attenuated radiographic progression in RA regardless of attainment of clinical remission.[16] Less is known, however, regarding the ability of bDMARDs to influence the relationship between systemic inflammation and hard cardiovascular outcomes in large RA cohorts. One large registry study reported that cardiovascular risk was reduced in patients with RA responding to TNF inhibitors but not in non-responders.[17] This might indicate that comprehensive control of inflammation is necessary for protection against cardiovascular risk. We previously reported that disease activity was associated with cardiovascular risk in a large international consortium of patients with RA without cardiovascular disease on registration.[18] In the present study we interrogated whether bDMARD use may modify the impact of disease activity and systemic inflammation on long-term cardiovascular risk in RA.

MATERIALS AND METHODS

Patient recruitment

The sample included 4370 patients with RA registered in An inTernationAl Cardiovascular Consortium for people with Rheumatoid Arthritis from 13 centres across 10 countries (Canada, Greece, Mexico, Netherlands, Norway, South Africa, Spain, Sweden, UK and USA). These cohorts have been described in previous publications.[18 19] Patients were followed prospectively or via retrospective chart review. Participants were 18 years or older, met 1987 or 2010 classification criteria for RA and carried no formal cardiovascular disease diagnosis such as acute coronary syndrome, stable angina, stroke, transient ischaemic attack, peripheral arterial disease, revascularisation or heart failure. Patients with overlapping autoimmune disease diagnoses except for Sjogren's were excluded. The study was approved by the regional institutional review boards of the respective participating centres and in compliance with the Declaration of Helsinki. Of 4537 potential participants, patients were excluded from this study for missing bDMARD data (n=46), being over 85 years old (n=20) and missing all data regarding RA disease activity (n=101).

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting or dissemination plans of this research.

Covariates and outcomes

Data collected at baseline included age, sex, duration of RA, rheumatoid factor positivity, anti-citrullinated peptide antibody status, tender joint count, swollen joint count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and 28-joint Disease Activity Score based on CRP (DAS28-CRP). Traditional cardiac risk factors were smoking, family history of coronary artery disease, diabetes, hypertension, systolic blood pressure, diastolic blood pressure, body mass index and lipid levels. Baseline medication use including conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), bDMARDs, non-steroidal anti-inflammatory drugs, corticosteroids, antihypertensives and lipid-lowering medications was recorded.

The prespecified endpoints were (1) time to first major adverse cardiovascular events (MACE) defined as a composite of cardiovascular death, myocardial infarction and stroke; and (2) time to first ischaemic cardiovascular event (iCVE) defined as a composite of cardiovascular death, myocardial infarction, stroke, stable and unstable angina, coronary revascularisation, transient ischaemic attack and symptomatic peripheral arterial disease with or without revascularisation. Endpoint data were collected using standardised definitions, however there was no central adjudication of cardiovascular events.

Statistical analysis

Continuous variables were reported as means and SD and categorical variables as numbers and percentages. bDMARD users and non-users were compared using t-tests for continuous variables and χ^2 test for categorical variables. Variables with non-normal distributions were natural logarithm transformed. Multiple imputation by chained equations with 10 repetitions was used to impute missing data. Multivariable Cox regression models evaluated the effects of bDMARD use, DAS28-CRP and their interaction on MACE and iCVE risk. Cox regression also tested the effects of bDMARD use, CRP and their interaction on MACE and iCVE. The significance of interaction terms was assessed using likelihood ratio tests. All Cox models were stratified by centre cardiovascular risk[19] and covaried for age, gender, hypertension, diabetes,

smoking, total cholesterol to high-density lipoprotein cholesterol ratio and RA duration.

In sensitivity analyses, the multivariable Cox models were weighted using inverse probability of treatment weighting weights. Stabilised weights were estimated with propensity scores. Propensities for bDMARD treatment were derived from a logistic regression model including all aforementioned Cox regression covariates as well as family history of cardiovascular disease, seropositivity, prednisone and csDMARD use. bDMARD user and non-user groups were considered balanced on covariates with a standardised mean difference <0.10. A second set of sensitivity analyses assessed unweighted multivariable Cox models limited to follow-up on or after 1 January 2000 when bDMARD use began in the cohort. In a third set of sensitivity analyses, the primary unweighted models were evaluated additionally adjusting for methotrexate use. All analyses were performed in Stata V.15.0 and two-tailed p values<0.05 were significant.

RESULTS

Patients were mostly middle-aged women with seropositive and moderately-to-severely active disease (table 1). A quarter used corticosteroids at baseline, one-third received methotrexate and 12% used bDMARDs. Of 4370 patients, 515 (11.8%) used bDMARDs at baseline. bDMARD users had longer disease duration, lower disease activity, serological inflammation, blood pressure and low-density lipoprotein-cholesterol compared with

Table 1 Sample characteristics at baseline (N=4370)

	Available n	Total sample		bDMARD non-user (n=3855)		bDMARD user (n=515)		P value
Age, years	4370	55.0	±13.9	55.0	±14.1	55.1	±12.2	0.956
Male gender	4370	1143	(26.2)	1057	(27.4)	86	(16.7)	<0.001
RA duration, years	4348	4.7	±7.4	3.9	±6.9	10.8	±8.2	<0.001
Age at RA diagnosis	4347	50.4	±14.2	51.2	±14.2	44.5	±13.0	<0.001
ACPA positive	3928	2357	(60.0)	2042	(59.6)	315	(63.0)	0.143
RF positive	4317	2886	(66.9)	2561	(67.1)	325	(65.3)	0.423
ESR, mm/hour	4328	24.7	±21.4	25.4	±21.8	20.1	±17.4	<0.001
Log CRP, mg/L	3356	1.7	±1.9	1.8	±2.0	1.2	±1.4	<0.001
Swollen joint count	3131	6.0	±5.8	6.5	±5.9	2.7	±3.6	<0.001
Tender joint count	3131	5.6	±6.0	5.9	±6.0	3.5	±4.9	<0.001
DAS28-CRP	2942	3.8	±1.4	4.0	±1.4	3.0	±1.2	<0.001
Hypertension	4369	1873	(42.9)	1670	(43.3)	203	(39.4)	0.092
Systolic BP, mm Hg	4219	138.1	±22.5	138.7	±22.8	133.6	±19.1	<0.001
Diastolic BP, mm Hg	4218	80.4	±11.1	80.6	±11.3	79.0	±9.8	0.002
Total cholesterol, mmol/L	3958	5.2	±1.1	5.2	±1.1	5.2	±1.1	0.366
LDL-c, mmol/L	3888	3.1	±1.0	3.1	±1.0	3.0	±0.9	0.01
HDL-c, mmol/L	3907	1.5	±0.4	1.4	±0.4	1.6	±0.5	<0.001
Triglycerides, mmol/L	3940	1.4	±0.8	1.4	±0.8	1.4	±0.8	0.129
Current smoker	4240	1043	(24.6)	934	(25.1)	109	(21.2)	0.054
Ever smoker	4240	2279	(53.8)	2016	(54.1)	263	(51.1)	0.193
Diabetes mellitus	4370	317	(7.3)	265	(6.9)	52	(10.1)	0.008
Family history of CVD	3359	817	(24.3)	705	(24.8)	112	(21.8)	0.146
Body mass index, kg/m^2	3981	27.1	±5.3	27.0	±5.2	27.6	±5.5	0.009
Methotrexate	4355	1376	(31.6)	1012	(26.4)	364	(70.7)	<0.001
Other csDMARDs	4198	943	(22.5)	792	(21.4)	151	(30.4)	<0.001
Corticosteroid	4361	1170	(26.8)	970	(25.2)	200	(38.9)	<0.001
Antihypertensive therapy	4368	938	(21.5)	790	(20.5)	148	(28.7)	<0.001
Lipid-lowering therapy	4364	465	(10.7)	366	(9.5)	99	(19.2)	<0.001

Values in table are mean±SD or n (%).
ACPA, anti-citrullinated protein antibody; bDMARD, bDMARD, biological disease-modifying antirheumatic drug; BP, blood pressure; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CVD, cardiovascular disease; DAS28, 28-joint Disease Activity Score; ESR, erythrocyte sedimentation rate ; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; log CRP, natural logarithm transformed C-reactive protein; RA, rheumatoid arthritis; RF, rheumatoid factor.

Table 2 Individual components of prespecified composite outcomes of interest stratified by bDMARD use

	bDMARD users	bDMARD non-users
First MACE	10	229
Cardiovascular death	1	39
Non-fatal myocardial infarction	3	112
Non-fatal stroke	6	78
First iCVE	15	347
Cardiovascular death	–	31
Non-fatal myocardial infarction	3	108
Non-fatal stroke	6	76
Stable angina	1	54
Transient ischaemic attack	1	22
Peripheral arterial disease	3	29
Revascularisation	1	27

bDMARDs, biological disease-modifying antirheumatic drugs ; iCVE, ischaemic cardiovascular event; MACE, major adverse cardiovascular event.

non-users. In contrast, a greater proportion of bDMARD users received methotrexate, alternate csDMARDs, antihypertensive and lipid-lowering medication, were diabetic and had greater high-density lipoprotein-cholesterol compared with non-users (table 1).

There were 239 first MACE over 26 534 patient-years of follow-up and 362 first iCVEs over 26 275 patient-years (table 2). The overall crude incidence rates per 1000 patient-years were 9.0 (95% CI 7.9 to 10.2) for MACE and 13.8 (95% CI 12.4 to 15.3) for iCVE. Incidence rates (per 1000 patient-years) for MACE did not significantly differ between bDMARD non-users (9.3 (95% CI 8.2 to 10.6)) and users (5.4 (95% CI 2.9 to 10.1), p=0.078). For iCVE, crude incidence rates were higher in bDMARD non-users (14.2 (95% CI 12.8 to 15.8)) compared with bDMARD users (8.2 (95% CI 5.0 to 13.6), p=0.027). Figure 1 shows the cumulative hazard of MACE and iCVE in bDMARD non-users and users at low (1 SD below the mean, coinciding with DAS28-CRP=2.4) and high (1 SD above the mean, coinciding with DAS28-CRP=5.1) levels of disease activity.

In multivariable Cox models, the main effects of DAS28-CRP (per unit increase) associated with both risk of MACE (HR 1.19 (95% CI 1.06 to 1.34), p=0.004) and iCVE (HR 1.18 (95% CI 1.07 to 1.30), p=0.002). In contrast, CRP (per log unit increase) predicted risk of MACE (1.15 (95% CI 1.02 to 1.28), p=0.017) but not iCVE (HR 1.06 (95% CI 0.97 to 1.16), p=0.166). The interaction of DAS28-CRP with bDMARD use was significant for MACE (p=0.017), indicating that the effect of DAS28-CRP on MACE risk was different among bDMARD non-users and users (figure 2). DAS28-CRP associated with MACE in bDMARD non-users (HR 1.21 (95% CI 1.07 to 1.37), p=0.002) but not users (p=0.191). bDMARD use also

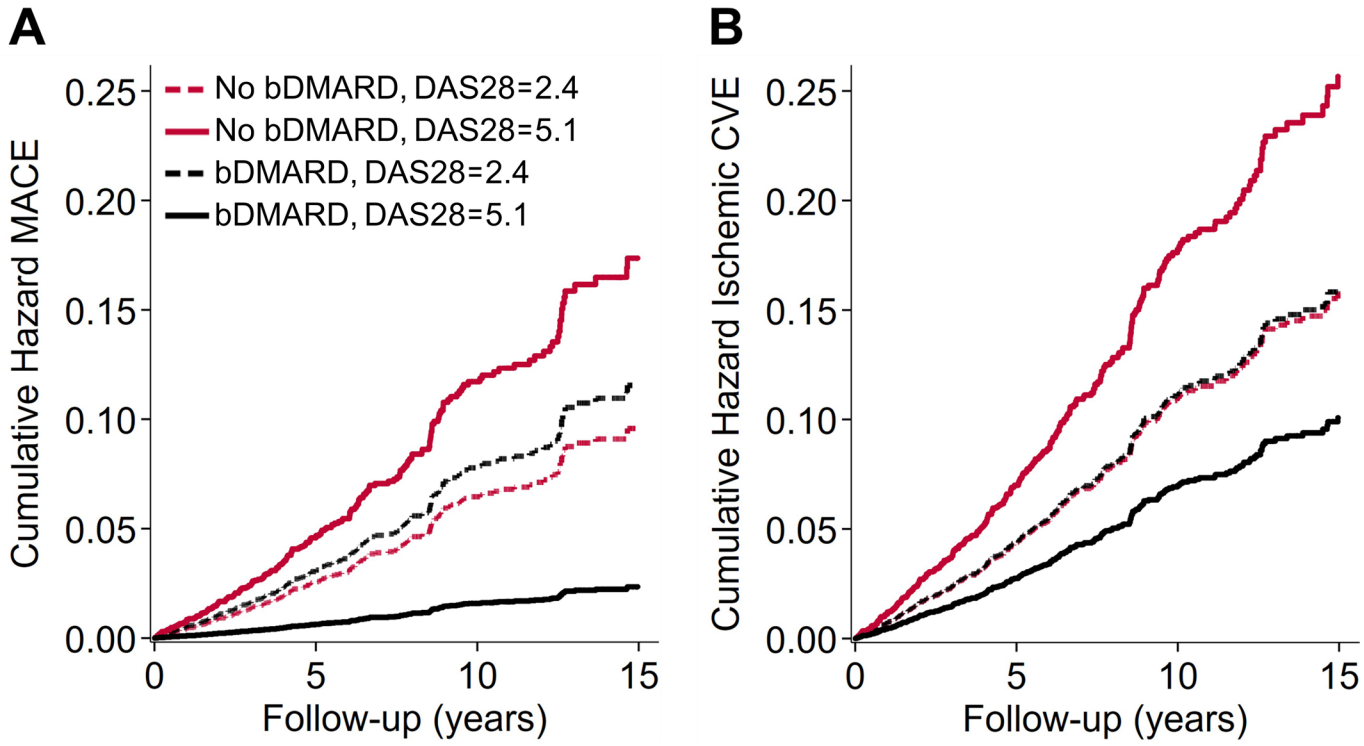


Figure 1 Cumulative hazard plots of (A) MACE and (B) any ischaemic CVE in bDMARD users and non-users at low DAS28-CRP (1 SD below the mean, coinciding with DAS28-CRP=2.4) and high DAS28-CRP (1 SD above the mean, coinciding with DAS28-CRP=5.1). bDMARD, biological disease-modifying antirheumatic drug; CVE, cardiovascular event; DAS28-CRP, 28-joint Disease Activity Score with C-reactive protein; MACE, major adverse cardiovascular event.

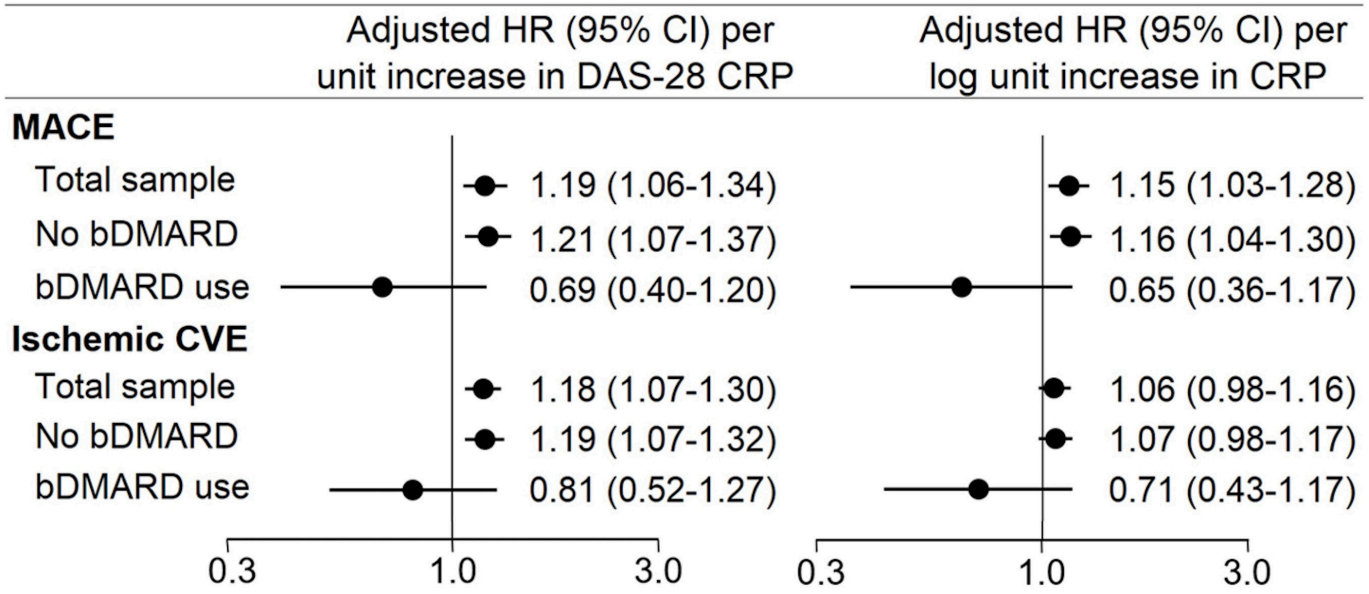


Figure 2 Effect of inflammation on cardiovascular event risk overall and stratified by bDMARD use. Models adjust for age, gender, hypertension, diabetes, smoking, total cholesterol/high-density lipoprotein cholesterol ratio and disease duration. bDMARD, biological disease-modifying antirheumatic drug; CVE, cardiovascular event; DAS28-CRP, 28-joint Disease Activity Score with C-reactive protein; MACE, major adverse cardiovascular event.

moderated the effect of CRP on MACE (p=0.011), with log CRP associating with MACE in bDMARD non-users (HR 1.16 (95% CI 1.04 to 1.30), p=0.009), but not users (p=0.151). For iCVE, the interactions of DAS28-CRP with bDMARD use (p=0.167) and CRP with bDMARD use (p=0.237) were not significant (figure 2). The effects of DAS28-CRP or CRP and covariates on cardiovascular event risk in bDMARD non-users and users are reported in online supplemental tables S1 and S2, respectively.

Results were similar in sensitivity analyses of inverse probability of treatment weighting weighted Cox models, unweighted Cox models restricted to follow-up on or after 01 January 2000 and unweighted Cox models further adjusted for methotrexate use (table 3).

DISCUSSION

We here explored whether bDMARD use influenced the association between clinical measures of disease activity or biomarkers of RA-related inflammation and cardiovascular risk in a large, international, longitudinally followed cohort of patients with RA. A prior study reported lower cardiovascular risk exclusively in TNFi responders but not in non-responders.[17] Another found no significant difference in risk of MACE among patients with RA with residual disease activity compared with those in remission on treatment with TNFi or Janus Kinase (JAK) inhibitors.[6] However, to our knowledge, previous reports have not tested bDMARD treatment as a moderator of the effect of inflammation on cardiovascular outcomes. Patients with RA presenting with acute myocardial infarction may exhibit similar DAS28 values prior to the index event but significantly higher CRP and ESR versus matched case controls.[20] It is therefore possible that RA activity as described in a composite index might not be sensitive enough to a predictor in patients at high risk.[20] Hence, CRP was evaluated as an additional inflammatory marker and predictor of outcomes of interest.

We found that clinical disease activity measured as DAS28-CRP was associated with both risk of MACE and any iCVE—the latter consistent with our prior report[18]—whereas CRP was associated only with the risk of MACE. Since CRP secretion is TNF-α and IL-6 dependent, biologics such as TNF inhibitors, tocilizumab and targeted synthetic DMARDs such as JAK inhibitors may intercept this pathway leading to low CRP without necessarily achieving clinical disease target.[21] DAS28-CRP incorporating tender and swollen joint counts as additional qualifiers of disease activity may in fact constitute a more comprehensive descriptor of articular inflammation than CRP. Indeed, DAS28-CRP was most sensitive in identifying synovial inflammation histologically (92%) compared with CRP (71%) and ESR (48%).[21] In a registry of almost 9000 patients with RA, more than half did not have elevated ESR and/or CRP despite ongoing disease activity by joint counts and global measurements.[22] Likewise, 76% of our patients with at least moderate disease activity (DAS28-CRP>3.2) had CRP<30 mg/L—considered as a cardiovascular risk threshold—and 61% had normal age and sex-adjusted ESR.

The apparent ability of bDMARDs to mitigate the effect of disease activity and CRP on MACE may point to benefits locally on the arterial wall inflammation and plaque composition offsetting the influence of joint-derived inflammation. Indeed, TNF inhibitors attenuated aortic and carotid wall inflammation in RA, particularly in areas with the greatest plaque burden; yet reduction in vessel

Table 3 Sensitivity analyses for the effect of inflammation on cardiovascular event risk in bDMARD non-users and users

	Adjusted HR (95% CI) per unit increase in DAS-28 CRP			Adjusted HR (95% CI) per log unit increase in CRP		
	HR (95% CI)	P value	P-int.	HR (95% CI)	P value	P-int.
MACE						
Inverse probability weighting						
No bDMARD	1.18 (1.06 to 1.32)	0.002	0.048	1.16 (1.04 to 1.30)	0.011	0.020
bDMARD use	0.76 (0.44 to 1.31)	0.317		0.65 (0.35 to 1.22)	0.177	
Follow-up after 01 January 2000						
No bDMARD	1.21 (1.02 to 1.43)	0.031	0.022	1.20 (1.01 to 1.43)	0.039	0.007
bDMARD use	0.69 (0.39 to 1.23)	0.206		0.60 (0.34 to 1.08)	0.086	
Adjusted for methotrexate						
No bDMARD	1.21 (1.07 to 1.36)	0.002	0.017	1.16 (1.03 to 1.29)	0.010	0.011
bDMARD use	0.70 (0.39 to 1.25)	0.228		0.65 (0.35 to 1.20)	0.173	
Any ischaemic CVE						
Inverse probability weighting						
No bDMARD	1.17 (1.05 to 1.29)	0.003	0.166	1.06 (0.96 to 1.17)	0.245	0.167
bDMARD use	0.80 (0.54 to 1.18)	0.261		0.67 (0.40 to 1.12)	0.128	
Follow-up after 01 January 2000						
No bDMARD	1.09 (0.93 to 1.28)	0.263	0.309	1.03 (0.89 to 1.18)	0.717	0.293
bDMARD use	0.81 (0.52 to 1.29)	0.378		0.70 (0.42 to 1.18)	0.180	
Adjusted for methotrexate						
No bDMARD	1.19 (1.07 to 1.32)	0.002	0.165	1.07 (0.98 to 1.17)	0.147	0.234
bDMARD use	0.83 (0.51 to 1.34)	0.436		0.73 (0.43 to 1.23)	0.236	

All models adjusted for age, gender, hypertension, diabetes, smoking, total cholesterol/high-density lipoprotein cholesterol ratio and rheumatoid arthritis duration.
bDMARD, biological disease-modifying antirheumatic drug; CRP, C-reactive protein; CVE, cardiovascular event; DAS28, 28-joint Disease Activity Score; MACE, major adverse cardiovascular event; P-int., P value for interaction with bDMARD use.

wall inflammation did not correlate with improvements in disease activity measured as DAS28.[4 5] Maximally diseased aortic segments in RA exhibited significantly higher glucose uptake on positron emission tomography/CT (PET/CT) than that in corresponding segments of stable patients with coronary artery disease. After treatment with TNF inhibitors, uptake decreased to levels significantly lower than that in stable patients with coronary artery disease and despite residual moderate disease activity by DAS28.[5] Moreover, patients with RA in clinical remission exhibited similar aortic glucose uptake on PET/CT with normal controls despite significantly higher serum CRP.[23]

In atherosclerosis-prone mice, labelled adalimumab bound in plaque and inhibited monocyte influx, reducing atherogenesis and plaque inflammation.[24] Accordingly, in patients with RA without or with only early atherosclerosis, bDMARDs attenuated new plaque formation independently of cumulative systemic inflammation.[9] In advanced disease, progressively inefficient removal of apoptotic cells from plaques by activated macrophages (efferocytosis) leads to secondary necrosis and necrotic lipid core formation increasing plaque vulnerability.[25] TNF inhibitors restored efferocytosis through macrophage low-density lipoprotein receptor-related protein 1 and reduced necrosis in atherosclerotic lesions of mice.[26] Accordingly, treatment with bDMARDs in RA associated with the loss of low-attenuation plaques in a duration-dependent manner, reflecting resorption of the necrotic lipid core of high-risk lesions and transition to stable fibrous or heavily calcified plaques.[9 27 28] Moreover, bDMARDs decreased cholesterol loading onto human macrophages independently of specific immunoinflammatory effects.[29] Importantly, cholesterol loading onto macrophages associated with both atherosclerosis burden and cardiovascular risk in RA and bDMARD use mitigated its relationship with both outcomes.[30] Furthermore, bDMARD use optimised cholesterol efflux out of macrophages, corresponding to lipid removal out of atherosclerotic lesions, further attenuating coronary atherosclerosis progression.[31]

We showed that bDMARD use modified the effect of inflammation on MACE but not on any iCVE. Several reasons may explain this observation. First, the definition of any iCVE includes 'soft' events such as stable angina and transient ischaemic attack. 'Soft' outcomes

have been associated with lower levels of both arterial wall and systemic inflammation compared with hard MACE. Patients suffering acute myocardial infarction (MI) exhibited more vulnerable plaques on coronary angiography and denser inflammation in both non-culprit and culprit lesions compared with patients with stable angina.[32] Serum CRP was higher in patients with acute MI versus stable angina and in those who died from an MI compared with those who survived.[33–35] Differences between intraluminal temperature at the site of a culprit lesion—reflecting local inflammation—and core temperature during acute MI were higher than the respective differences between lesional and core temperatures observed in patients presenting with unstable or stable angina.[36] Importantly, those differences correlated strongly with serum CRP.[36] Accordingly, in our cohort, patients suffering were MACE had significantly greater baseline CRP compared with those with angina and transient ischaemic attacks. As patients with higher disease activity respond better to bDMARDs compared with those with lower, the same principle may extend to RA-related cardiovascular disease.[37–40]

Second, the definition of iCVE additionally considers events at alternate vascular territories such as the femoral and popliteal arteries. Atherosclerosis progression is highly heterogeneous temporally and spatially across various arterial beds.[41] Gene expression differences across vascular territories with or without atherosclerosis contribute to this mechanistic and phenotypic heterogeneity.[42] Human arteries are complex organ systems hosting strategically located immune cells, poised to participate in immune functions and dictate tissue tropism of disease.[43] The influence of risk factors on atherosclerosis progression varies across vascular beds.[44–46] Territorial differences in flow patterns, shear and mural tensile stress as well as the variable presence and function of perivascular adipose tissue further diversify the anatomic location, stenosis grade and composition of atherosclerotic plaques.[47] Prior studies indeed reported greater foam cell content and lipid-rich lesions in the carotid arteries compared with lower cholesterol, higher fibrous content and calcification in the femoral circulation, indicating differences in plaque vulnerability.[48 49] Such disparities across arterial beds may alter the influence of and sensitivity to the local atheroprotective functions of bDMARDs, culminating in variable benefits against territory-specific ischaemic event risk.[50] Accordingly, we showed that bDMARD use modified the effect of inflammation on MACE but not on any iCVE.

Our study has several limitations. Patients originated from centres with a particular interest in RA-associated cardiovascular disease. This may introduce referral bias and question the generalisability of our findings. Although standard definitions were used, differences in outcome reporting are still plausible. Events were not centrally adjudicated. Patient surveillance varied; certain centres evaluated patients prospectively while others did so retrospectively through chart review. Information on cardiovascular risk factors, disease characteristics and treatments were only available at baseline. Most patients were prevalent bDMARD users on registration and information on bDMARD class use was not available. Information on socioeconomic status which may impact bDMARD prescription practices and adherence was also not available. Enrolment to the consortium spans an older era reflecting treatment trends that differ from contemporary practices and guidelines, as exemplified by the unavailability or low use of bDMARDs prior to 2000. Nevertheless, the results of sensitivity analyses restricted to enrolment after January 2000 were similar to the results of the primary analyses. Our study was not a priori powered to explore the influence of bDMARD use on the relationship between disease activity and cardiovascular risk. The overall small number of events, specifically in bDMARD-treated patients, may therefore limit statistical power and our observations should be considered exploratory. Finally, although analyses were stratified by centre-specific cardiovascular event rate, our results may be still confounded by variations in RA treatments and cardiopreventive strategies among the various centres.

CONCLUSION

Higher disease activity and CRP at baseline are associated with a greater risk of MACE in bDMARD non-users but not in users. This may indicate additional bDMARD-specific benefits directly on arterial wall inflammation and atherosclerotic plaque anatomy, stability and biology, independently of systemic inflammation. However, the influence of bDMARD use on the relationship between inflammation and all ischaemic cardiovascular events did not reach statistical significance. This may signal heterogeneity in response to bDMARD treatments reflecting mechanistic differences, variations in atherosclerotic phenotypes across vascular territories and intensity of inflammation across the severity of outcomes.

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