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Original article

The effect of rheumatoid arthritis–associated autoantibodies on the incidence of cardiovascular events in a large inception cohort of early inflammatory arthritis

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Abstract

Objective. RA is associated with an increased risk of cardiovascular events (CVEs). The objective was to estimate independent effects of RA autoantibodies on the incident CVEs in patients with early RA.

Methods. Patients were enrolled in the Canadian Early Inflammatory Arthritis Cohort, a prospective multicentre inception cohort. Incident CVEs, including acute coronary syndromes and cerebrovascular events, were self-reported by the patient and partially validated by medical chart review. Seropositive status was defined as either RF or ACPA positive. Multivariable Cox proportional hazards survival analysis was used to estimate the effects of seropositive status on incident CVEs, controlling for RA clinical variables and traditional cardiovascular risk factors.

Results. A total of 2626 patients were included: the mean symptom duration at diagnosis was 6.3 months (S.D. 4.6), the mean age was 53 years (S.D. 15), 72% were female and 86% met classification criteria for RA. Forty-six incident CVEs occurred over 6483 person-years [incidence rate 7.1/1000 person-years (95% confidence interval 5.3, 9.4)]. The CVE rate did not differ in seropositive *vs* seronegative subjects and seropositivity was not associated with incident CVEs in multivariable Cox regression models. Baseline covariates independently associated with incident CVEs were older age, a history of hypertension and a longer duration of RA symptoms prior to diagnosis.

Conclusion. The rate of CVEs early in the course of inflammatory arthritis was low; however, delays in the diagnosis of arthritis increased the rate of CVEs. Hypertension was the strongest independent risk factor for CVEs. Results support early aggressive management of RA disease activity and co-morbidities to prevent severe complications.

Key words: rheumatoid arthritis, ACPA, RF, seropositive, cardiovascular disease, complications

CLINICAL SCIENCE

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Rheumatology key messages

- The incidence rate of cardiovascular events in an early RA population was 7.1/1000 person-years.
- The rate of cardiovascular events was similar for seropositive compared with seronegative patients.
- Age, hypertension and delays in diagnosis were independently associated with a higher rate of cardiovascular events.

Introduction

RA is associated with a >50% increase in cardiovascular morbidity and mortality compared with the general population [1, 2]. It is unclear at which point during the course of disease the risk of cardiovascular disease (CVD) increases [3–5]. Rate differences in cardiovascular events (CVEs) have been reported to occur after a disease duration of 2 years [3]; however, the increased plaque burden seen in RA patients may occur sooner [6, 7].

The cause of accelerated atherosclerosis in RA is unknown, but can be partially attributed to a higher prevalence of traditional risk factors for CVD, including smoking, hypertension, diabetes mellitus and obesity [8]. Chronic inflammation and RA disease-specific factors have also been associated with an increased risk of CVD [9–12]. RA is characterized by the production of autoantibodies, RF and ACPA, which coexist in the majority of patients. These autoantibodies are associated with more severe disease and worse outcomes [13]. Evidence from animal models suggests that ACPA is pathogenic [14–16]. ACPA targets citrullinated peptides/proteins, which have been identified in the plaque of patients with CVD [17] and is strongly associated with cigarette smoking, a major risk factor for CVD [18]. Several studies have reported higher rates of CVD mortality and/or events in seropositive patients [11, 12, 19–26]. However, many of these studies included RA patients with very long-standing disease, with onset prior to the current treatment paradigms. In the era of aggressive early management with synthetic and biologic DMARDs, it is unclear whether the incidence of CVE remains high in RA early in the disease course and whether antibodies increase the rate. There is a lack of early RA studies examining the association of RF and ACPA with CVEs that also take into account the effects of other RA clinical variables and traditional CVD risk factors [11, 12]. The aims of this study were to estimate the incidence of CVEs in early RA and determine whether RF or ACPA is independently associated with incident CVEs in a large prospective inception cohort of patients with early inflammatory arthritis.

Methods

Study population

Study subjects were enrolled in the Canadian Early Arthritis Cohort (CATCH), a multicentre inception cohort of subjects with ongoing follow-up of early RA or undifferentiated inflammatory arthritis [27]. Study subjects for this article were enrolled between July 2003 and November 2014. Inclusion criteria for CATCH are as follows: age >18 years, persistent synovitis for 6 weeks–12 months and two or more swollen joints or one swollen MCP or proximal IP joint with one or more of the following: positive RF, positive anti-CCP2, morning stiffness >45 min, response to NSAIDs or painful MTP squeeze test. Subjects are excluded or withdrawn from the study if they are diagnosed by the treating rheumatologist with another rheumatologic condition other than undifferentiated inflammatory arthritis or RA; >90% of enrolled subjects met the 1987 ACR or 2010 ACR/EULAR criteria for RA over the course of the study. Enrolled subjects are followed by a rheumatologist using a standard protocol every 3 months for the first year, at 18 months and then yearly. Treatment is based on physician discretion. The study was approved by the Health Sciences Research Ethics Board of the University of Western Ontario and written informed consent was obtained according to the Declaration of Helsinki.

RA-associated antibody assays

RF was reported by physicians based on testing performed either at their site or in outpatient commercial laboratories. The different types of RF tests performed at these laboratories were not reported but cut-off values were indicated. For anti-CCP2, two different commercial assays were used (Euroimmune, Lübeck, Germany; and Inova Diagnostics, San Diego, CA, USA). Subjects were considered seropositive if they were positive for either RF or anti-CCP2 at any time during the course of follow-up. Seronegative patients were defined as never being positive for RF or anti-CCP2 at any time during the course of follow-up. Autoantibody status was not available for 155 (6%) subjects and these subjects were analysed separately.

Study variables and outcomes

Demographic information, including age, sex, income and education (self-reported from a questionnaire) were collected at baseline. Symptom duration was defined as the time in months from the patient-reported initiation of persistent arthritic symptoms until CATCH enrolment. Other baseline variables were collected by the study staff. Disease activity was determined using the 28-joint DAS (DAS28); moderate to severe disease activity was defined as a DAS28 score >3.2. Physical function was evaluated using the HAQ Disability Index; moderate to severe functional impairment was defined as an HAQ score ⩾1. Inflammatory markers included ESR and CRP. Erosions were determined using plain radiographs of the hands and feet. Erosive disease (binary outcome) was defined as the presence of any erosion. Rheumatologic medications were recorded by the physician assessor at each visit. There were <15% missing data for all variables

Table 1 Baseline characteristics of the study population

Variable		All (n = 2626)	Seronegative (n = 785)	Seropositive (n = 1686)	Antibody status unknown (n = 155)	P-value[b]
Demographics						
Age, mean (S.D.), years	2574	53 (15)	55 (16)	52 (15)	50 (16)	<0.0001
Female, n (%)	2575	1857 (72)	521 (67)	1240 (74)	96 (70)	0.0010
Income, n (%)	1715					
<$20 000		332 (19)	103 (22)	210 (19)	19 (17)	
$20 000–50 000		633 (37)	155 (33)	434 (38)	44 (39)	
$50 000–100,000		501 (29)	144 (31)	322 (28)	35 (31)	0.4369
>$100 000		249 (15)	68 (14)	166 (15)	15 (13)	
RA disease factors						
Symptom duration, months, mean (S.D.)	2604	6.3 (4.6)	5.9 (3.8)	6.3 (4.1)	8.1 (10.1)	<0.0001
RA criteria, n (%)[a]	2555	2191 (86)	537 (60)	1557 (94)	97 (75)	<0.0001
DAS28, mean (S.D.)	2275	4.87 (1.50)	4.73 (1.48)	4.95 (1.50)	4.59 (1.33)	0.0015
HAQ, mean (S.D.)	2498	0.88 (0.69)	0.86 (0.67)	0.90 (0.70)	0.78 (0.67)	0.0751
Erosions, n (%)	2029	473 (23)	133 (22)	333 (24)	7 (12)	0.0596
CRP, mean (S.D.), mg/l	2367	13.8 (17.8)	13.4 (17.1)	14.1 (18.3)	12.4 (15.8)	0.5339
ESR, mean (S.D.)	2375	26.4 (22.7)	23.9 (22.3)	27.8 (22.8)	22.2 (19.7)	0.0002
CVD risk factors						
Smoker, n (%)						
Never	2564	1145 (45)	377 (43)	715 (43)	53 (39)	0.0025
Current		469 (18)	106 (14)	321 (19)	31 (23)	
Past		982 (38)	283 (37)	626 (38)	52 (38)	
Diabetes, n (%)	2564	206 (8)	75 (10)	126 (8)	5 (4)	0.0279
Hypertension, n (%)	2564	686 (27)	219 (29)	436 (26)	31 (23)	0.2677
Dyslipidaemia, n (%)	2564	417 (16)	130 (17)	264 (16)	23 (17)	0.7792
BMI, mean (S.D.)	1672	28.0 (6.1)	28.4 (6.1)	28.0 (6.1)	26.9 (6.2)	0.1367
BMI >30, n (%)	1672	515 (31)	157 (30)	344 (31)	14 (19)	0.0424
Prior CV events, n (%)						
ACS	2621	174 (7)	54 (7)	105 (6)	15 (10)	0.1953
CVA	2621	45 (2)	10 (1)	31 (2)	4 (3)	0.8744
Medications, n (%)						
DMARDs	2621	2152 (82)	593 (76)	1458 (86)	101 (67)	<0.0001
MTX	2621	1692 (65)	427 (54)	1186 (70)	79 (53)	<0.0001
Biologics	2454	54 (2)	11 (2)	41 (3)	2 (2)	0.2810
Corticosteroids	2621	1272 (49)	391 (50)	824 (49)	57 (38)	0.0266
Naproxen	2621	510 (19)	134 (17)	351 (21)	25 (17)	0.0610
Other NSAID	2621	236 (9)	66 (8)	157 (9)	13 (9)	0.7570

[a]Meets 1987 ACR RA criteria or 2010 ACR/EULAR RA criteria. [b]$P < 0.01$ considered significant (Bonferroni correction for multiple comparisons). ACS: acute coronary syndrome; CVA: cerebrovascular accident.

except income, BMI and radiographic data, which were missing in 33, 53 and 21% of subjects, respectively (Table 1). Complete case analyses were performed.

Information on prevalent (at baseline) and incident physician-diagnosed CVEs was ascertained by patient self-report. More specifically, patients were instructed to indicate if they had ever received a diagnosis by a physician for the following: angina, heart attack, stroke or mini-stroke. Physician-diagnosed diabetes, hypertension and hyperlipidaemia were similarly obtained by patient reports. Cigarette smoking status was categorized as current, past or never smoker. Height and weight were measured by site staff and used to calculate BMI as follows: weight (kg)/height (m^2). BMI was measured at each visit by the study staff. Follow-up questionnaires ask that the subject specify any new diagnoses, hospitalizations and reasons for hospitalizations, as well as the dates associated with these events. Reporting of cardiovascular risk factors and events was validated using a sample of 141 subjects. Agreement between self-reported CVEs and the medical record was good ($\kappa = 0.66$).

Statistical analyses

Continuous variables were reported as means (S.D.) and values for the three antibody groups (seropositive, seronegative and antibody status unknown) were compared using analysis of variance (ANOVA) with Bonferroni correction for multiple comparisons. Categorical data were compared using the Fisher's exact test. Differences in values for the three groups were considered significant if $P < 0.01$.

Incident CVEs were reported as an incidence rate (IR) with 95% confidence intervals (CIs) per 1000 person-years at risk. The log-rank test was used to determine significance of differences in survivor functions by antibody groups and results were shown using Kaplan–Meier survival curves. Cox proportional hazards regression models were performed to determine the risk of CVEs associated with CVD risk factors and RA-associated factors: unadjusted, adjusted for age and sex and multivariable adjustment. The following baseline variables were selected *a priori* to test for multivariable model fit based on score criterion using the Akaike's information criterion: sex, age, income category, smoking history, antibody status, symptom duration, presence of erosions, more than moderate disease activity by DAS28 score, more than moderate functional impairment by HAQ score, CRP level, BMI, diagnosis of hypertension, diabetes, dyslipidaemia and treatment with DMARDs, corticosteroids, naproxen or other NSAIDs. Variables were selected for the model to maximize the score statistic, accounting for the penalty for model complexity with each additional variable included. Using Martingale residuals, the proportional hazards assumption was met for all the models. For all the survival analyses, $P < 0.05$ was considered significant. All statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 2626 subjects were enrolled in CATCH at the time of data analysis: 1686 (64%) were seropositive, 785 (30%) were seronegative and for 155 (6%) the antibody status was unknown. Baseline characteristics of the study population are shown in Table 1. The majority of patients (86%) met classification criteria for RA. The mean age of the study population was 53 years (S.D. 15) and 72% were female. The duration of symptoms prior to enrolment was 6.3 months (S.D. 4.6) and they had moderate disease activity with a DAS28 score of 4.9 (S.D. 1.5). A significant proportion of subjects (23%) had erosive disease at baseline. The majority of patients were taking a DMARD at baseline (82%) (either started prior to enrolment or at the first CATCH visit). Corticosteroid use was frequent (49%) and 28% were also taking an NSAID. Seropositive compared with seronegative subjects were younger, had higher ESR levels, were more likely to be female, met RA classification criteria, were current smokers and were treated with DMARDs ($P < 0.01$). Subjects with unknown antibody status were similar to seronegative subjects except they were more likely to be current smokers and had longer symptom duration ($P < 0.01$).

Cardiovascular risk factors and events at baseline

Cardiovascular risk factors at baseline were common (Table 1), with the most prevalent being a history of cigarette smoking (44% were current or past smokers). Hypertension was reported in 713 (27%), dyslipidaemia in 432 (16%) and diabetes in 213 (8%). The average BMI of 28.0 (S.D. 6.1) was in the overweight category and 31% were obese. Prior CVEs were reported in 222 (8%) subjects. There was no statistically significant difference in baseline CV risk factors or prior CV events between seropositive and seronegative subjects.

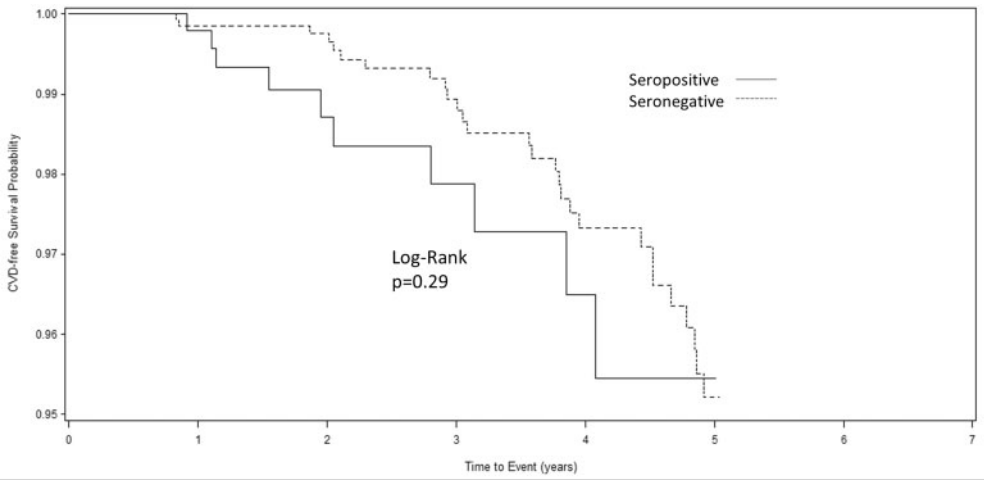
Incident CVEs

Forty-six new CVEs in 46 subjects, including two deaths attributable to CVD were observed over 6483 person-years [overall IR 7.1 (95% CI 5.3, 9.4) per 1000 person-years; female IR 5.6 (95% CI 3.8, 8.2) per 1000 person-years; male IR 12.0 (95% CI 7.7, 18.6) per 1000 person-years]. The median time to incident CVE was 1.99 years (range 0.5–10). Of the 46 incident CVEs, the majority were acute coronary syndromes ($n = 38$) and the remainder were cerebrovascular events ($n = 8$). CVE IRs per 1000 person-years were similar across antibody groups: 7.7 (95% CI 4.3, 13.9) for seronegative subjects, 7.1 (95% CI 5.1, 10.0) for seropositive subjects and 7.7 (95% CI 1.1, 54.6) for subjects with missing antibody status (Fig. 1). Of the 1694 (65%) subjects with both RF and anti-CCP2 measured, 705 (42%) were positive for both, 244 (14%) for RF alone and 185 (11%) for ACPA alone. There was no difference in incident CVEs for the above antibody groups (data not shown); in RF-negative subjects, ACPA was not significantly associated with CVE [hazard ratio (HR) 0.79 (95% CI 0.23, 2.85)]. There was also no difference in the CVE IR for coronary *vs* cerebrovascular events (data not shown). Results were unchanged in sensitivity analyses stratified by age >65 years and by sex (data not shown). Adjusting for age and sex as well as other covariates did not significantly change the effect of antibody status on incident CVEs (Tables 2 and 3).

Table 2 shows the unadjusted HRs for incident CVEs for various baseline demographics, RA disease factors, CVD risk factors and medications. The following factors were significantly associated with an increased rate of CVEs: older age [HR 1.57 (95% CI 1.24, 1.99) per decade], longer duration of RA symptoms [HR 1.10 (95% CI 1.04, 1.15) per month], hypertension [HR 3.98 (95% CI 2.20, 7.16)], dyslipidaemia [HR 2.87 (95% CI 1.55, 5.32)] and NSAID use other than naproxen [HR 2.47 (95% CI 1.25, 4.87)]. Socio-economic status (SES) assessed using income was not significantly associated with incident CVEs. Results were similar for the impact of education level on CVE rate (data not shown). Smoking and RA disease factors (disease activity, erosions, functional scores, inflammatory markers, use of synthetic or biologic DMARDs, MTX dose or corticosteroids) were not significantly associated with the rate of CVEs. Females had a lower risk of new CVEs [HR 0.47 (95% CI 0.26, 0.84)] when not adjusting for age (Table 2).

By multivariable Cox proportional hazards modelling (Table 3), increasing age, RA symptom duration and a history of hypertension were independently associated with an increased rate of incident CVEs. Hypertension, dyslipidaemia, diabetes and the use of non-naproxen NSAIDs were highly associated with each other

Fig. 1 Incident CVEs in the Canadian Early Inflammatory Arthritis Cohort



	Year	0	1	2	3	4	5	6	7
Seropositive	Events	0	2	3	10	20	28	32	34
	Persons at risk	1670	1264	961	730	501	284	116	53
Seronegative	Events	0	1	5	7	9	10	11	11
	Persons at risk	772	466	280	180	97	47	7	0

Kaplan–Meier survival curves for the comparison of incident cardiac event rates between seropositive patients (solid line) and seronegative patients (dotted line).

($P < 0.0001$). No significant effect modification was detected for the variables in the regression model (data not shown).

Discussion

In this study we investigated the relationship between RA-associated autoantibodies and incident CVEs in the CATCH cohort. The CATCH cohort is a large early RA inception cohort with moderately severe disease and early initiation of DMARDs (>80% treated at a mean symptom duration of 6 months). In this population with a mean follow-up time of <4 years, we found that the incidence of CVEs was 7.1 (95% CI 5.3, 9.4) per 1000 person-years and not significantly different for RF- or ACPA-positive subjects (seropositive) compared with antibody-negative subjects (seronegative).

The role of RA-associated autoantibodies in CVD remains unclear. ACPA is associated with cigarette smoking, a major risk factor for CVD and in our cohort, both RF- and ACPA-positive patients were more likely to be current smokers [18]. ACPA and RF are also poor prognostic markers, associated with erosive joint disease and extra-articular manifestations [13]. Therefore, seropositive patients may have a higher inflammatory burden, which can contribute to accelerated atherosclerosis [9–12, 28]. Because RF and ACPA frequently coexist, it is difficult to determine whether one or both of these antibodies contribute to CVD risk. In a recent study combining multiple cohorts of early RA with long-term follow-up, ACPA but not RF was associated with CV mortality adjusted for age, sex and smoking status [26]. During the observation period for our study, early in the course of disease, RF or ACPA alone or in combination was not independently associated with an increased rate of CVEs. Other studies have shown an association between RF and/or ACPA with CVEs and mortality [11, 12, 19–26]. Most of these studies were of established disease with long follow-up times and/or did not account for potential confounders [19–24]. Some of these studies only included hospital-based RA populations with more severe disease than our population of community and outpatient hospital practices [21, 22]. The Better Anti-Rheumatic FarmacOTherapy project (BARFOT) study, with a study population similar to CATCH, showed an association of ACPA and RF with CVE only in RA patients <65 years of age [15]; however, we did not find that stratifying by age changed our results. We had shorter follow-up with fewer events, which may account for the difference. Our findings are consistent with those from Innala *et al.* [12] that reported no significant association of antibody-status with CVEs in the first 5 years from RA onset.

Also consistent with prior studies is the high prevalence of traditional risk factors for CVD [8, 28]. Despite being common in the CATCH cohort, smoking and obesity were not significant predictors of CVEs. The association between traditional CVD risk factors and CVEs does not appear as strong in RA compared with healthy controls [29]. It has also been shown that higher BMI may be

Table 2 Risk of incident CVEs

Baseline variable	Unadjusted HR (95% CI)	HR adjusted for age and sex (95% CI)
Demographics		
Age	1.57 (1.24, 1.99)/decade	1.52 (1.20, 1.93)/decade[a]
Female gender	0.47 (0.26, 0.84)	0.59 (0.33, 1.07)[b]
Income	0.99 (0.69, 1.43)/category	1.07 (0.73, 1.56)
RA disease factors		
Seropositive	0.69 (0.35, 1.38)	0.86 (0.43, 1.73)
Symptom duration	1.10 (1.04, 1.15)/month	1.11 (1.06, 1.16)/month
DAS28 >3.2	1.06 (0.50, 2.27)	0.94 (0.44, 2.01)
HAQ >1	0.79 (0.43, 1.44)	0.76 (0.42, 1.39)
CRP, mg/l	1.0 (0.98, 1.02)/unit	0.99 (0.98, 1.01)
ESR	1.0 (0.99, 1.01)/unit	1.0 (0.98, 1.00)
Presence of erosions	1.49 (0.78, 2.84)	1.20 (0.62, 2.33)
CVD risk factors		
Current smoker	1.48 (0.75, 2.92)	1.70 (0.85, 3.38)
Diabetes	2.22 (0.99, 4.96)	1.53 (0.67, 3.49)
Hypertension	3.98 (2.20, 7.16)	2.98 (1.58, 5.61)
Dyslipidaemia	2.87 (1.55, 5.32)	2.01 (1.05, 3.82)
BMI	1.02 (0.97, 1.08)	1.02 (0.97, 1.08)
Medications		
DMARD	0.95 (0.37, 2.40)	0.91 (0.36, 2.31)
MTX	0.80 (0.42, 1.49)	0.74 (0.39, 1.39)
Corticosteroids	1.14 (0.64, 2.04)	0.96 (0.40, 2.33)
Naproxen	0.33 (0.12, 0.91)	0.40 (0.14, 1.13)
Other NSAID	2.47 (1.25, 4.87)	2.31 (1.17, 4.57)

[a]Controlled for sex only. [b]Controlled for age only.

Table 3 Cox proportional hazards model for risk of incident CVEs[a]

Baseline variables	Adjusted HR (95% CI)
Seropositive	0.81 (0.40, 1.64)
Age	1.32 (1.00, 1.72)/year
Female gender	0.64 (0.35, 1.16)
Symptom duration	1.11 (1.05, 1.65)/month
DAS28	1.03 (0.47, 2.28)
Hypertension	2.71 (1.42, 5.19)
Dyslipidemia	1.51 (0.77, 2.96)
Other NSAID	1.80 (0.89, 3.64)

[a]All variables listed in Table 2 were tested to determine the best model fit; variables were selected based on score criterion using the Akaike's information criterion.

protective for CVEs in RA, with the highest CVD risk occurring in patients who were underweight [30]. This trend was not observed in the CATCH cohort (data not shown) nor in another inception cohort from Sweden [12]. We found hypertension to be the strongest predictor of CVEs (HR >2.71), which is consistent with findings from other studies [8].

The contribution of dyslipidaemia to CVD risk in RA has been contradictory in the literature. The lipid paradox seen in RA (higher total cholesterol levels associated with fewer CVEs) complicates the diagnosis of dyslipidaemia [31]. An abnormal atherogenic index [total cholesterol:high-density lipoprotein (HDL) cholesterol ratio] may be a better predictor of CVE given that in the presence of inflammation, HDL levels decrease more profoundly than total cholesterol [28, 32–35]. Depending on the definition of dyslipidaemia used by the various studies, the association between dyslipidaemia and CVEs could vary. In CATCH, dyslipidaemia at baseline was reported by the treating rheumatologist and could be based on either a history of elevated low-density lipoprotein cholesterol or atherogenic index and/or treatment with a lipid-lowering agent. Consistent with a prior study of early RA, we found a significant association between dyslipidaemia and CVEs when accounting for age and sex. However, the association was not independent of other traditional CVD risk factors. Low SES increases CVD risk, but is infrequently studied in RA. We did not find any significant association with SES. In CATCH, low SES was found to be associated with worse disease activity only in the first year after diagnosis, which may partly explain this finding [36].

CVEs and mortality for both RA patients and the general population have been declining in recent decades; however, the rate of this decline is the same for RA patients compared with the general population, resulting in the continued higher CVD risk for patients with RA [37–39]. The rate of CVEs in our study is similar to what has been reported in the general population for the same age group [40]. Preliminary data from large administrative databases have also reported similar CVE rates for RA

patients compared with age- and sex-matched controls in the last two decades [41, 42].

The decline in CVD in RA may be attributable to better disease control. In CATCH, subjects were started early on DMARDs, mostly MTX, which has been shown to decrease CVEs [43]. In addition, the introduction of biologic DMARDs may also be contributing to the decline in the risk of CVD [44, 45]. We found that delays in the diagnosis of inflammatory arthritis were independently associated with CVEs. These delays were within 1 year of symptom onset as per the inclusion criteria of the CATCH cohort. Delays >1 year may have a more significant impact on CVEs. This supports the importance of early treatment initiation with DMARDs in preventing CVEs. Better RA disease control allows for the decreased use of corticosteroids and NSAIDs, medications known to increase CVD risk [43]. Our study aligned with a recent meta-analysis showing that NSAIDs other than naproxen increase the risk of CVEs [43]; limiting the use of NSAIDs for RA is recommended [46–48], and if NSAIDs are required, it may be preferable to use naproxen. Corticosteroids, which are also known to be associated with CVD [43], did not increase the rate of new CVEs in our study. We only investigated medications taken by patients at enrolment; it is possible that the duration of NSAID treatment prior to study enrolment was longer than that for corticosteroids, given that NSAIDs are available over the counter.

The timing of the increased risk for CVD relative to RA disease onset is unclear. It may continue to increase over time or it may be highest in the first 7 years after diagnosis and then decline [37, 49]. Nevertheless, numerous studies using various imaging modalities have shown an increased atherosclerotic burden in RA patients with <1 year disease duration [5, 6]. Measures of atherosclerosis, such as ultrasound Doppler for carotid intima-media thickness, CT for coronary calcium, modalities to assess endothelial dysfunction or serum surrogate markers were not available in CATCH. The lower rates of CVEs reported here may not reflect atherosclerotic burden and longer follow-up may be necessary to determine the long-term impact of RA on CVD, particularly in those patients with delayed diagnosis.

The strengths of this study are that it is a large, multicentre inception cohort, including patients from both community and hospital-based rheumatology practices. The subjects enrolled have early disease with 6 months duration of symptoms and the majority were treated with DMARDs. Details of co-morbidities at baseline, including CVD risk factors and pre-existing CVEs, as well as medications were systematically collected, allowing for the ability to account for multiple possible confounders. New CVEs were collected prospectively and, although self-reported, were validated by chart review (L.J.B., unpublished results).

Limitations include missing data for autoantibodies and erosive disease, which reflects the current practice in some centres in Canada where access to ACPA testing is not uniformly available and X-rays are not routinely performed. The population enrolled in this study consists mostly of Caucasian subjects with high rates of obesity; our findings may not be generalizable to other populations with different racial groups or exposures, including diet related to geographic location. This study focused on CVEs early in the disease course and therefore follow-up times are relatively short (<4 years) with a small number of events. The findings may not be generalizable to patients with longer disease duration. Time-varying factors (disease and functional scores, inflammatory markers, hypertension, lipid levels and treatments) were not tested as potential predictors of incident CVEs; future work will involve investigating the effect of these variables over the course of disease on new CVEs.

Conclusions

The rate of incident CVEs early in the course of RA is low and not significantly higher in seropositive patients. It appears that early treatment with DMARDs contributes to the low rates of CVEs given that delays in diagnosis were significantly and independently associated with an increased rate of events. With longer follow-up of this inception cohort, the rates of CVEs may increase. In addition, the contribution of RA disease factors to CVD risk may change over the course of the disease. Traditional CV risk factors were significantly associated with an increased rate of incident CVEs. These risk factors are modifiable, but have been shown to be poorly managed in RA [50]. Our results suggest that better management of blood pressure and lipid control may lower the risk for CVEs in RA.

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References

1 Aviña-Zubieta JA, Choi HK, Sadatsafavi M *et al*. Risk of cardiovascular mortality in patients with rheumatoid arthritis: a meta-analysis of observational studies. Arthritis Rheum 2008;59:1690–7.

2 Avina-Zubieta JA, Thomas J, Sadatsafavi M, Lehman AJ, Lacaille D. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2012;71:1524–9.

3 Maradit-Kremers H, Crowson CS, Nicola PJ *et al*. Increased unrecognized coronary heart disease and sudden deaths in rheumatoid arthritis: a population-based cohort study. Arthritis Rheum 2005;52:402–11.

4 Holmqvist ME, Wedrén S, Jacobsson LT *et al*. No increased occurrence of ischemic heart disease prior to the onset of rheumatoid arthritis: results from two Swedish population-based rheumatoid arthritis cohorts. Arthritis Rheum 2009;60:2861–9.

5 Kerola AM, Kauppi MJ, Kerola T, Nieminen TV. How early in the course of rheumatoid arthritis does the excess cardiovascular risk appear? Ann Rheum Dis 2012;71:1606–15.

6 Hannawi S, Marwick TH, Thomas R. Inflammation predicts accelerated brachial arterial wall changes in patients with recent-onset rheumatoid arthritis. Arthritis Res Ther 2009;11:R51.

7 Chung CP, Oeser A, Raggi P *et al*. Increased coronary-artery atherosclerosis in rheumatoid arthritis: relationship to disease duration and cardiovascular risk factors. Arthritis Rheum 2005;52:3045–53.

8 Baghdadi LR, Woodman RJ, Shanahan EM, Mangoni AA. 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.

9 Mantel Ä, Holmqvist M, Nyberg F *et al*. Risk factors for the rapid increase in risk of acute coronary events in patients with new-onset rheumatoid arthritis: a nested case-control study. Arthritis Rheumatol 2015;67:2845–54.

10 Solomon DH, Reed GW, Kremer JM *et al*. Disease activity in rheumatoid arthritis and the risk of cardiovascular events. Arthritis Rheumatol 2015;67:1449–55.

11 Ajeganova S, Andersson ML, Frostegård J, Hafström I. Disease factors in early rheumatoid arthritis are associated with differential risks for cardiovascular events and mortality depending on age at onset: a 10-year observational cohort study. J Rheumatol 2013;40:1958–66.

12 Innala L, Möller B, Ljung L *et al*. Cardiovascular events in early RA are a result of inflammatory burden and traditional risk factors: a five year prospective study. Arthritis Res Ther 2011;13:R131.

13 Taylor P, Gartemann J, Hsieh J, Creeden J. A systematic review of serum biomarkers anti-cyclic citrullinated peptide and rheumatoid factor as tests for rheumatoid arthritis. Autoimmune Dis 2011;2011:815038.

14 Hill JA, Bell DA, Brintnell W *et al*. Arthritis induced by posttranslationally modified (citrullinated) fibrinogen in DR4-IE transgenic mice. J Exp Med 2008;205:967–79.

15 Kinloch AJ, Alzabin S, Brintnell W *et al*. Immunization with *Porphyromonas gingivalis* enolase induces autoimmunity to mammalian α-enolase and arthritis in DR4-IE-transgenic mice. Arthritis Rheum 2011;63:3818–23.

16 Petkova SB, Konstantinov KN, Sproule TJ *et al*. Human antibodies induce arthritis in mice deficient in the low-affinity inhibitory IgG receptor FcγRIIB. J Exp Med 2006;203:275–80.

17 Sokolove J, Brennan MJ, Sharpe O *et al*. Brief report: citrullination within the atherosclerotic plaque: a potential target for the anti-citrullinated protein antibody response in rheumatoid arthritis. Arthritis Rheum 2013;65:1719–24.

18 Lundström E, Källberg H, Alfredsson L, Klareskog L, Padyukov L. Gene-environment interaction between the DRB1 shared epitope and smoking in the risk of anti-citrullinated protein antibody-positive rheumatoid arthritis: all alleles are important. Arthritis Rheum 2009;60:1597–603.

19 Gonzalez A, Icen M, Kremers HM *et al*. Mortality trends in rheumatoid arthritis: the role of rheumatoid factor. J Rheumatol 2008;35:1009–14.

20 Farragher TM, Goodson NJ, Naseem H *et al*. Association of the HLA-DRB1 gene with premature death, particularly from cardiovascular disease, in patients with rheumatoid arthritis and inflammatory polyarthritis. Arthritis Rheum 2008;58:359–69.

21 López-Longo FJ, Oliver-Miñarro D, de la Torre I *et al*. Association between anti-cyclic citrullinated peptide antibodies and ischemic heart disease in patients with rheumatoid arthritis. Arthritis Rheum 2009;61:419–24.

22 Goodson N, Marks J, Lunt M, Symmons D. Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with onset in the 1980s and 1990s. Ann Rheum Dis 2005;64:1595–601.

23 Maradit-Kremers H, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis: a population-based study. Arthritis Rheum 2005;52:722–32.

24 Mackey RH, Kuller LH, Deane KD *et al*. Rheumatoid arthritis, anti-cyclic citrullinated peptide positivity, and cardiovascular disease risk in the women's health initiative. Arthritis Rheumatol 2015;67:2311–22.

25 Young A, Koduri G, Batley M *et al*. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and in pulmonary fibrosis. Rheumatology 2007;46:350–7.

26 Ajeganova S, Humphreys JH, Verheul MK *et al*. Anticitrullinated protein antibodies and rheumatoid factor are associated with increased mortality but with different causes of death in patients with rheumatoid arthritis: a longitudinal study in three European cohorts. Ann Rheum Dis 2016;75:1924–32.

27 Cheng CK, McDonald-Blumer H, Boire G *et al*. Care gap in patients with early inflammatory arthritis with a high fracture risk identified using FRAX®. J Rheumatol 2010;37:2221–5.

28 Skeoch S, Bruce IN. Atherosclerosis in rheumatoid arthritis: is it all about inflammation? Nat Rev Rheumatol 2015;11:390–400.

29 Gonzalez A, Maradit Kremers H, Crowson CS *et al*. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients? Ann Rheum Dis 2008;67:64–9.

30 Escalante A, Haas RW, del Rincón I. Paradoxical effect of body mass index on survival in rheumatoid arthritis: role of comorbidity and systemic inflammation. Arch Intern Med 2005;165:1624–9.

31 Myasoedova E, Crowson CS, Kremers HM *et al*. Lipid paradox in rheumatoid arthritis: the impact of serum lipid measures and systemic inflammation on the risk of cardiovascular disease. Ann Rheum Dis 2011;70:482–7.

32 Rantapää-Dahlqvist S, Wållberg-Jonsson S, Dahlén G. Lipoprotein (a), lipids, and lipoproteins in patients with rheumatoid arthritis. Ann Rheum Dis 1991;50:366–8.

33 Boers M, Nurmohamed MT, Doelman CJ *et al*. Influence of glucocorticoids and disease activity on total and high density lipoprotein cholesterol in patients with rheumatoid arthritis. Ann Rheum Dis 2003;62:842–5.

34 Hahn BH, Grossman J, Chen W, McMahon M. The pathogenesis of atherosclerosis in autoimmune rheumatic diseases: roles of inflammation and dyslipidemia. J Autoimmun 2007;28:69–75.

35 Georgiadis AN, Papavasiliou EC, Lourida ES *et al*. Atherogenic lipid profile is a feature characteristic of patients with early rheumatoid arthritis: effect of early treatment—a prospective, controlled study. Arthritis Res Ther 2006;8:R82.

36 Yang G, Bykerk VP, Boire G *et al*. Does socioeconomic status affect outcomes in early inflammatory arthritis? Data from a Canadian multisite suspected rheumatoid arthritis inception cohort. J Rheumatol 2015;42:46–54.

37 Widdifield J, Bernatsky S, Paterson JM *et al*. Trends in excess mortality among patients with rheumatoid arthritis in Ontario, Canada. Arthritis Care Res 2015;67:1047–53.

38 Humphreys JH, Warner A, Chipping J *et al*. Mortality trends in patients with early rheumatoid arthritis over 20 years: results from the Norfolk Arthritis Register. Arthritis Care Res 2014;66:1296–301.

39 Meune C, Touzé E, Trinquart L, Allanore Y. Trends in cardiovascular mortality in patients with rheumatoid arthritis over 50 years: a systematic review and meta-analysis of cohort studies. Rheumatology 2009;48:1309–13.

40 Wielgosz A, Arango M, Bancej C *et al*. Tracking heart disease and stroke in Canada. Ottawa, ON, Canada: Public Health Agency of Canada, 2009.

41 Lacaille D, Sayre EC, Abrahamowicz M. Improvement in mortality in RA compared to the general population – closing the mortality gap [abstract]. Arthritis Rheumatol 2015;67(Suppl 10):abstract 1999.

42 Myasoedova E, Crowson CS, Matteson EL *et al*. Decreased cardiovascular mortality in patients with incident rheumatoid arthritis (RA) in recent years: dawn of a new era in cardiovascular disease in RA? Arthritis Rheumatol 2015;67(Suppl 10):abstract 3237.

43 Roubille C, Richer V, Starnino T *et al*. The effects of tumour necrosis factor inhibitors, methotrexate, non-steroidal anti-inflammatory drugs and corticosteroids on cardiovascular events in rheumatoid arthritis, psoriasis and psoriatic arthritis: a systematic review and meta-analysis. Ann Rheum Dis 2015;74:480–9.

44 Barnabe C, Martin BJ, Ghali WA. Systematic review and meta-analysis: anti-tumor necrosis factor α therapy and cardiovascular events in rheumatoid arthritis. Arthritis Care Res 2011;63:522–9.

45 Provan SA, Berg IJ, Hammer HB *et al*. The impact of newer biological disease modifying anti-rheumatic drugs on cardiovascular risk factors: a 12-month longitudinal study in rheumatoid arthritis patients treated with rituximab, abatacept and tociliziumab. PLoS One 2015;10:e0130709.

46 Roubille C, Richer V, Starnino T *et al*. Evidence-based recommendations for the management of comorbidities in rheumatoid arthritis, psoriasis, and psoriatic arthritis: expert opinion of the Canadian Dermatology-Rheumatology Comorbidity Initiative. J Rheumatol 2015;42:1767–80.

47 Martín-Martínez MA, González-Juanatey C, Castañeda S *et al*. Recommendations for the management of cardiovascular risk in patients with rheumatoid arthritis: scientific evidence and expert opinion. Semin Arthritis Rheum 2014;44:1–8.

48 Peters MJ, Symmons DP, McCarey D *et al*. EULAR evidence-based recommendations for cardiovascular risk management in patients with rheumatoid arthritis and other forms of inflammatory arthritis. Ann Rheum Dis 2010;69:325–31.

49 Kremers HM1, Crowson CS, Therneau TM, Roger VL, Gabriel SE. High ten-year risk of cardiovascular disease in newly diagnosed rheumatoid arthritis patients: a population-based cohort study. Arthritis Rheum 2008;58:2268–74.

50 van Breukelen-van der Stoep DF, van Zeben D, Klop B, van de Geijn GM *et al*. Marked underdiagnosis and undertreatment of hypertension and hypercholesterolaemia in rheumatoid arthritis. Rheumatology 2016;55:1210–6.