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Rheumatoid arthritis

Inflammation rather than anticitrullinated protein antibodies is associated with cardiovascular mortality in RA: insights from rheumatoid arthritis and coronary artery disease cohorts

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ABSTRACT

Objectives: Anticitrullinated protein antibodies (ACPAs) are associated with increased mortality in patients with rheumatoid arthritis (RA). Previous data suggest ACPAs might be associated with worse disease outcomes in patients without RA with coronary artery disease (CAD). Therefore, we investigated ACPA prevalence and its association with mortality in patients with CAD without RA. Furthermore, the role of systemic inflammation in the relation between ACPAs and mortality was investigated in RA.

Methods: The prevalence of ACPAs in patients with CAD without RA was investigated in 2 CAD cohorts (LUdwigshafen Risk and Cardiovascular Health n = 2189 patients and 656 controls; CLARIthromycin for patients with stable CORonary heart disease n = 959 patients) using a commercial enzyme-linked immunosorbent assay. Multivariable Cox proportional hazards models were performed to investigate the association between ACPAs and all-cause mortality. In 2 RA cohorts (Early Arthritis Clinic [EAC] n = 764; Better Anti-rheumatic Farmaco-therapy [BARFOT] n = 794), joint models were applied to investigate the role of C-reactive protein (CRP) on the association between ACPAs and (cardiovascular) mortality.

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Results: Average follow-up time in the cohorts ranged between 8.2 and 11.8 years. In both CAD cohorts, ACPA prevalence was low (0.9% and 4.6%), and no association was found between seropositivity and all-cause mortality. In patients with RA, the association between ACPA positivity and all-cause mortality was no longer significant after adjustment for CRP. In contrast, CRP was significantly associated with all-cause and cardiovascular mortality in RA (indirect effect hazard ratio [95% CI]: EAC 1.24 [1.14-1.34], BARFOT 1.33 [1.24-1.42]).
Conclusions: ACPA prevalence is not increased in patients with CAD without RA. In RA, the association between ACPA positivity and increased (cardiovascular) mortality was primarily explained by CRP. This highlights the impact of chronic inflammation on cardiovascular outcomes in RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Anticitrullinated protein antibodies (ACPAs) are specific for rheumatoid arthritis (RA), and a relationship between ACPAs and increased cardiovascular mortality has been described in patients with RA. However, 2 previous studies have suggested an increased prevalence of ACPAs in patients with coronary artery disease (CAD) without RA, and in these patients, ACPAs were associated with worse disease outcomes.

WHAT THIS STUDY ADDS

- We found that ACPA prevalence was not increased in 2 large cohorts of patients with CAD without RA, and no association between ACPA seropositivity and mortality was identified. In RA, the association between ACPAs and all-cause mortality seems to be explained by higher C-reactive protein (CRP) levels over time observed in ACPA-seropositive patients.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- Inflammation might be more important for increased all-cause and cardiovascular mortality rates in RA than the presence of ACPAs in itself, making therapies targeting continuous inflammation key to improving long-term outcomes for patients with ACPA-positive RA.

INTRODUCTION

Rheumatoid arthritis (RA) is a prevalent autoimmune disease characterised not only by chronic synovial inflammation, but also by an increased risk of cardiovascular disease (CVD) [1,2]. Epidemiological evidence indicates that patients with RA have a 43% increased risk of myocardial infarction and a 55% increased risk of experiencing any major adverse cardiac event compared to the general population [3,4]. Approximately half of this excess risk appears to be attributable to traditional cardiovascular risk factors [5], some of which are also risk factors for the development of RA, such as smoking [6] and obesity [7]. About one-third of the excess cardiovascular risk in RA is thought to result directly from the disease itself [5].

Systemic inflammation is known to contribute to accelerated atherosclerosis and increased cardiovascular events [8–10]. However, there are also indications that RA-specific autoantibodies, especially anticitrullinated protein antibodies (ACPAs), might play a direct role in the increased incidence of CVD in patients with RA. Several disease-specific autoantibodies can be detected in the serum of patients with RA, including rheumatoid factor (RF), ACPAs and antibodies against carbamylated proteins (anti-CarP) [11]. ACPAs are routinely determined in clinical practice and are specific for RA. These autoantibodies are detected in approximately two-thirds of patients with RA and can be present in serum years before the onset of arthritis [12]. Although their role in RA pathophysiology remains incompletely understood, ACPAs are believed to contribute to chronic inflammation, as ACPAs are able to activate the complement system [13] and trigger Fc-receptors leading to proinflammatory cytokine production [14]. Several studies have indicated that ACPAs may be independently associated with increased all-cause mortality in patients with RA, particularly from cardiovascular causes [15–18], although findings remain inconsistent [1,19–23]. Histological studies have identified citrullinated proteins within atherosclerotic plaques [24] and experimental data demonstrated that ACPAs can activate platelets via FcγRIIa-dependent pathways [25]. Taken together, these findings might indicate that ACPAs can contribute directly to the increased cardiovascular risk observed in RA.

There is also evidence that ACPAs may augment cardiovascular risk in individuals who do not have RA. Two clinical studies reported increased ACPA seropositivity in non-RA cohorts: 10.4% (15/144) of patients with coronary artery disease (CAD) compared to 3.8% (11/288) of healthy controls were ACPA-positive in 1 cohort [26], and 11% (29/275) of patients with ST-elevation myocardial infarction (STEMI) were seropositive compared with 2% (3/160) in healthy controls in another cohort [27]. In the latter study, ACPAs were independently associated with worse long-term mortality in patients with STEMI during a median follow of 9.4 years [27]. Notably, none of the 29 ACPA-positive patients developed RA during follow-up. These findings point to a potential direct role for ACPAs in cardiovascular risk in individuals without RA, but require confirmation in larger well-characterised cardiovascular cohorts. Furthermore, it remains unclear whether other RA-associated autoantibodies such as RF or anti-CarP are also present in patients with CAD, and how the presence of autoantibodies is related to cardiovascular mortality in both non-RA and RA populations. Especially, anti-CarP is of interest in this context, as carbamylation has been found in atherosclerotic plaques and increased systemic protein carbamylation was associated with a higher risk of major adverse cardiac events in a population at risk for CVD [28].

To address these questions, we examined the prevalence of ACPAs and other RA-associated antibodies in 2 large, independent non-RA CAD cohorts and evaluated the association between seropositivity and all-cause mortality. In parallel, 2 early RA cohorts were analysed to assess whether systemic inflammation plays a role in the relationship between ACPAs and all-cause or cardiovascular mortality. We hypothesised that the observed association between ACPAs and adverse cardiovascular outcomes in RA might (partly) reflect underlying inflammatory burden instead of a consequence of autoantibody presence by itself.

METHODS

Study design

For the analyses reported here, we used baseline laboratory data, patient demographics and characteristics, and mortality

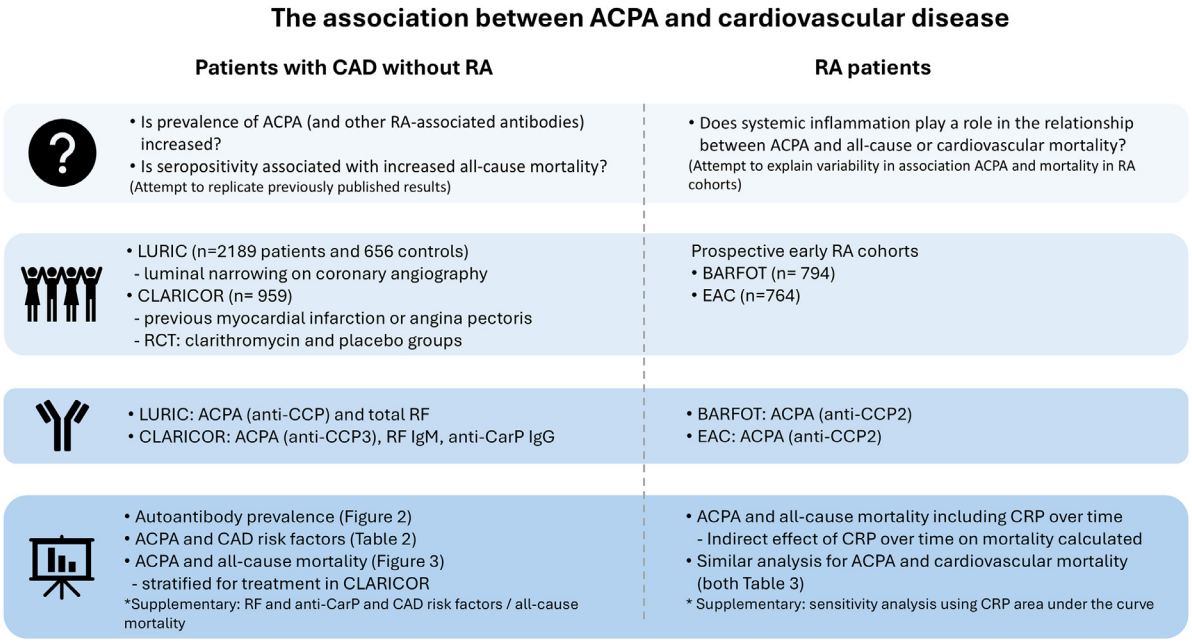

Figure 1. Overview of the study design. Research question, cohorts, autoantibody measurements and analyses are stated in both patients with CAD without and with RA. ACPA, anticitrullinated protein antibody; anti-CarP, antibodies against carbamylated proteins; BARFOT, Better Anti-rheumatic Farmaco-therapy; CAD, coronary artery disease; CCP, cyclic citrullinated peptide; CLARICOR, CLARIthromycin for patients with stable CORonary heart disease; CRP, C-reactive protein; EAC, Early Arthritis Clinic; LURIC, LUdwigshafen Risk and Cardiovascular Health; RA, rheumatoid arthritis; RCT, randomised controlled trial; RF, rheumatoid factor.

data collected from 2 large cardiovascular and 2 RA cohorts (see cohort descriptions below). For the cardiovascular cohorts, participants with a reported comorbidity of RA were excluded based on the data available to allow more accurate comparisons between the cardiovascular and RA cohorts. In all 4 original studies, written informed consent was obtained from all participants, and the studies were approved by local ethics committees [29–32]. An overview of the methodology is provided in Figure 1.

CAD non-RA cohorts

To investigate the prevalence of ACPAs and other autoantibodies and their association with mortality in non-RA populations with CAD, autoantibodies were measured specifically for the current study in stored baseline samples from 2 large independent cohorts of patients with CAD: the CLARIthromycin for patients with stable CORonary heart disease (CLARICOR) trial (959 patients analysed) [32] and the LUdwigshafen Risk and Cardiovascular Health (LURIC) study (2189 patients and 656 controls analysed) [29].

CLARICOR is a Danish, randomised multicentre trial that enrolled patients with a previous diagnosis of acute myocardial infarction or angina pectoris between 1993 and 1999 (detailed information is described elsewhere [32]). Enrolled patients were randomised to receive clarithromycin or a placebo for a period of 2 weeks between October 1999 and April 2000 [32]. A total of 959 randomly selected patients from both the intervention and control arms were analysed. Ten years follow-up data on cardiovascular outcomes, comorbidities, and mortality were obtained from the Danish National Patient Register, which records diagnoses using the International Statistical Classification of Diseases) with a coverage of almost 100%.

The LURIC study is a German prospective cohort study that enrolled patients with CAD defined as luminal narrowing on angiography between 1997 and 2000 (detailed information is described elsewhere [29]). Clinical indications for angiography were suspected CAD based on symptoms such as acute chest pain or noninvasive tests consistent with myocardial ischaemia. Follow-up mortality data for this cohort were available until 2010. Although severe chronic disease was an exclusion criterion in LURIC [29], additional screening using baseline comorbidity- and medication data, as well as self-reported (incomplete) follow-up comorbidity surveys, was performed to identify and exclude RA cases from the analyses reported here, leading to the exclusion of 29 patients with CAD and 4 controls. Of the included participants, 2189 patients with CAD and 656 controls (family members and patients who underwent angiography, but did not have CAD) were tested for ACPAs and RF.

RA cohorts

To evaluate the role of systemic inflammation in the relation between ACPAs and mortality in RA, data from 2 prospective early RA cohorts were examined: the Leiden Early Arthritis Clinic (EAC) [30] and the Better Anti-rheumatic Farmaco-therapy (BARFOT) cohort [31]. In both cohorts, antirheumatic drug treatment was initiated by the treating rheumatologist based on the accepted treatment strategies at that time.

In the EAC, 764 patients with early RA, enrolled between 1993 and 2010, were studied (detailed information is described elsewhere [30]). Seventy-nine patients were excluded due to missing data on smoking status. In EAC, between 1993 and 1995 patients were initially treated with nonsteroidal anti-inflammatory drugs. In 1996 to 1998, hydroxychloroquine or sulfasalazine were used early in the disease course, and from 1999 onwards, treatment with methotrexate (MTX) was initiated. C-reactive protein (CRP) levels were measured annually for up to a maximum of 10 years. All-cause mortality data were available through April 2012, while cause-specific mortality could only be assessed through 2008 due to changes in privacy legislation, limiting the scope of the cardiovascular mortality subanalyses to 575 patients [15].

The Swedish BARFOT cohort included 803 patients with newly diagnosed early RA recruited between 1993 and 1999. Nine patients were excluded because of missing smoking status, 6 patients because of missing causes of death. In BARFOT between 1993 and 1996, most patients were initially treated with mild disease-modifying antirheumatic drugs such as sulfasalazine or auranofin, and from 1996 onwards, most patients received early treatment with MTX. CRP was measured at baseline and at follow-up visits at 6, 12, 24, 60, and 96 months. Mortality data were available until December 2010 (detailed information is described elsewhere [31]).

Autoantibody measurements

In CLARICOR, ACPAs were measured in stored baseline serum using the QUANTA Lite cyclic citrullinated peptide (CCP) 3 immunoglobulin (Ig)G enzyme-linked immunosorbent assay (ELISA) (Inova Diagnostics). Positivity was calculated according to the manufacturer's instructions using the standard-curve method. RF IgM and anti-CarP IgG were determined using validated in-house ELISAs, and 78 healthy individuals from the Leiden area aged 20 to 70 years were taken along as controls to determine the cut-off (Supplementary Methods S1). In LURIC, ACPA and RF positivity were assessed in samples (either heparin plasma, citrated plasma, or acidified citrated plasma [Stabilyte]) using the Alinity i anti-CCP IgG and Alinity c total RF assays (Abbott), according to manufacturer protocols. In both EAC and BARFOT, ACPAs were measured at baseline using the anti-CCP2 ELISA (Euro-Diagnostica) with a cut-off >25 units.

Statistical analysis

In CLARICOR and LURIC, baseline characteristics and risk factors were compared between autoantibody-positive and autoantibody-negative patients using the appropriate statistical tests (chi-square, Fisher's exact, Student's t test, or Mann-Whitney U test). Associations between autoantibodies and all-cause mortality were evaluated using Kaplan-Meier curves and log-rank tests. Furthermore, Cox proportional hazards analyses with adjustment for age and sex were performed, with the autoantibody-negative patient group as reference. In CLARICOR, all-cause mortality analyses were performed separately for the clarithromycin and placebo groups, as previous research indicated higher mortality in the clarithromycin group [32]. A meta-analysis based on a random-effects model was performed using R package metafor. The small number of antibody-positive patients prohibited meaningful analyses concerning cause-specific mortality outcomes.

In EAC and BARFOT, previous analyses showing an association between ACPA positivity and both higher all-cause and cardiovascular mortality [15] were extended to explore the role of systemic inflammation on this relation. CRP repeatedly measured over time was used as a proxy for inflammation. As depicted in Supplementary Figure S1, inflammation might be a potential mediating factor in the association between ACPAs and mortality in RA. The relationship between ACPAs and CRP trajectories was analysed using linear mixed-effects models (LMMs) with random intercept and random slope using restricted maximum likelihood estimation. In all analyses, CRP is log-transformed. Joint models, which incorporate both an LMM and a Cox regression model, were employed to simultaneously use the repeatedly measured CRP values for each patient and the time-to-event (mortality) data, with the Cox model adjusted for age, sex, smoking status, and year of inclusion as proxy of changed treatment strategy over time, in line with previous analyses [15]. Mediation effects were assessed by calculating the indirect effect of CRP on mortality in these joint models [33–35]. As a sensitivity analysis, a joint model with a nonweighted cumulative association structure was calculated, using the CRP area under the curve. Hazard ratios (HRs) with 95% CIs are reported. Further details are provided in Supplementary Methods S2.

RESULTS

Baseline demographics and mortality outcomes across patient populations in all CAD and RA cohorts are shown in Table 1. The mean follow-up time was approximately 9 years. Mortality rates during follow-up ranged from 16% (105/656) in the LURIC control group to nearly 39% (372/959) in CLARICOR.

Autoantibody prevalence in patients with CAD

In CLARICOR, 4.6% (44/959) of patients with CAD without RA tested positive for ACPAs (Fig 2A), which is lower than the 10% to 11% ACPA seropositivity described previously in other patients with CAD populations [26,27]. RF IgM and anti-CarP were detected in 8.6% (82/959) and 3.0% (26/959) of patients, respectively (Fig 2B,C). In contrast to what is commonly observed in patients with RA [36], dual autoantibody positivity was rare in patients with CAD without RA with only 5 patients being ACPAs and RF double positive, and no patients who were ACPAs and anti-CarP double positive. No triple-positive patients with CAD were identified.

In the LURIC cohort, 0.9% (19/2189) of patients with CAD and 0.3% (2/656) of controls were positive for ACPAs (Fig 2D) and 1.1% (24/2189) of patients with CAD and 0.6% (4/656) of controls were positive for RF (Fig 2E). There were no significant differences in the frequency of autoantibody positivity between patients with CAD and controls (anti-CCP: $P = .19$; RF: $P = .38$). Dual autoantibody positivity was low with only 2 patients with CAD being both RF- and ACPA-double positive.

To investigate whether traditional cardiovascular risk factors might be less present in patients with CAD who are ACPA-positive compared to seronegative patients with CAD, for example, due to differences in underlying atherosclerotic processes, cardiovascular risk factors at baseline were compared between ACPA-positive and ACPA-negative individuals in both CLARICOR and LURIC. Age, sex, smoking status, diagnosis of hypertension, low-density lipoprotein (LDL) levels, and percentage of patients with previous myocardial infarction did not significantly differ between ACPA-positive and ACPA-negative patients in either cohort (Table 2). Similar findings were observed for RF (CLARICOR and LURIC, Supplementary Tables S1, S2, respectively) and anti-CarP (CLARICOR only, Supplementary Table S3), with the exception of RF-positive individuals in LURIC being significantly older than RF-negative individuals. Overall, autoantibody-positive and autoantibody-negative patients were comparable concerning cardiovascular risk factors.

Autoantibodies and mortality in patients with CAD

Kaplan-Meier curves for all-cause mortality showed no differences between ACPA-positive and ACPA-negative patients in the clarithromycin and placebo arms of CLARICOR (Fig 3A,B) and in LURIC (Fig 3C) (log-rank tests not significant). Age- and sex-adjusted Cox regression analyses confirmed these findings

Table 1
Demographic data at baseline and information on deaths during follow-up in coronary artery disease and rheumatoid arthritis cohorts

	CAD cohorts			RA cohorts	
	CLARICOR	LURIC		BARFOT	EAC
Demographics	CAD (n = 959)	CAD (n = 2189)	Controls (n = 656)	RA (n = 794)	RA (n = 764)
Baseline					
Age (y), mean ± SD	65.3 ± 10.4	63.6 ± 10.0	58.3 ± 12.1	57.5 ± 15.6	56.8 ± 15.7
Female, n (%)	293 (30.6)	532 (24.3)	313 (47.7)	524 (66.0)	514 (67.3)
Smoking ever, n (%)	814 (84.9)	1503 (68.7)	319 (48.6)	469 (59.1)	415 (54.3)
BMI in kg/m^2, mean ± SD	-	27.5 ± 3.9	27.5 ± 4.4	25.4 ± 5.0	25.8 ± 3.9
Myocardial infarction, n (%)	630 (65.7)	1157 (52.9)	-	-	-
Follow-up					
Follow-up (y), mean ± SD	8.2 ± 2.9	8.7 ± 3.1	9.5 ± 2.4	11.8 ± 3.7	9.0 ± 4.8
Death, n (%)	372 (38.8)	694 (31.7)	105 (16.0)	228 (28.7)	137 (17.9)
Death from cardiac cause, n (%)	170 (17.7)	394 (18.0)	49 (7.5)	141 (17.8)	40 (5.2)

BARFOT, Better Anti-rheumatic Farmaco-therapy; BMI, body mass index; CAD, coronary artery disease; CLARICOR, CLARIthromycin for patients with stable CORonary heart disease; EAC, Early Arthritis Clinic; LURIC, LUdwigshafen Risk and Cardiovascular Health; RA, rheumatoid arthritis.

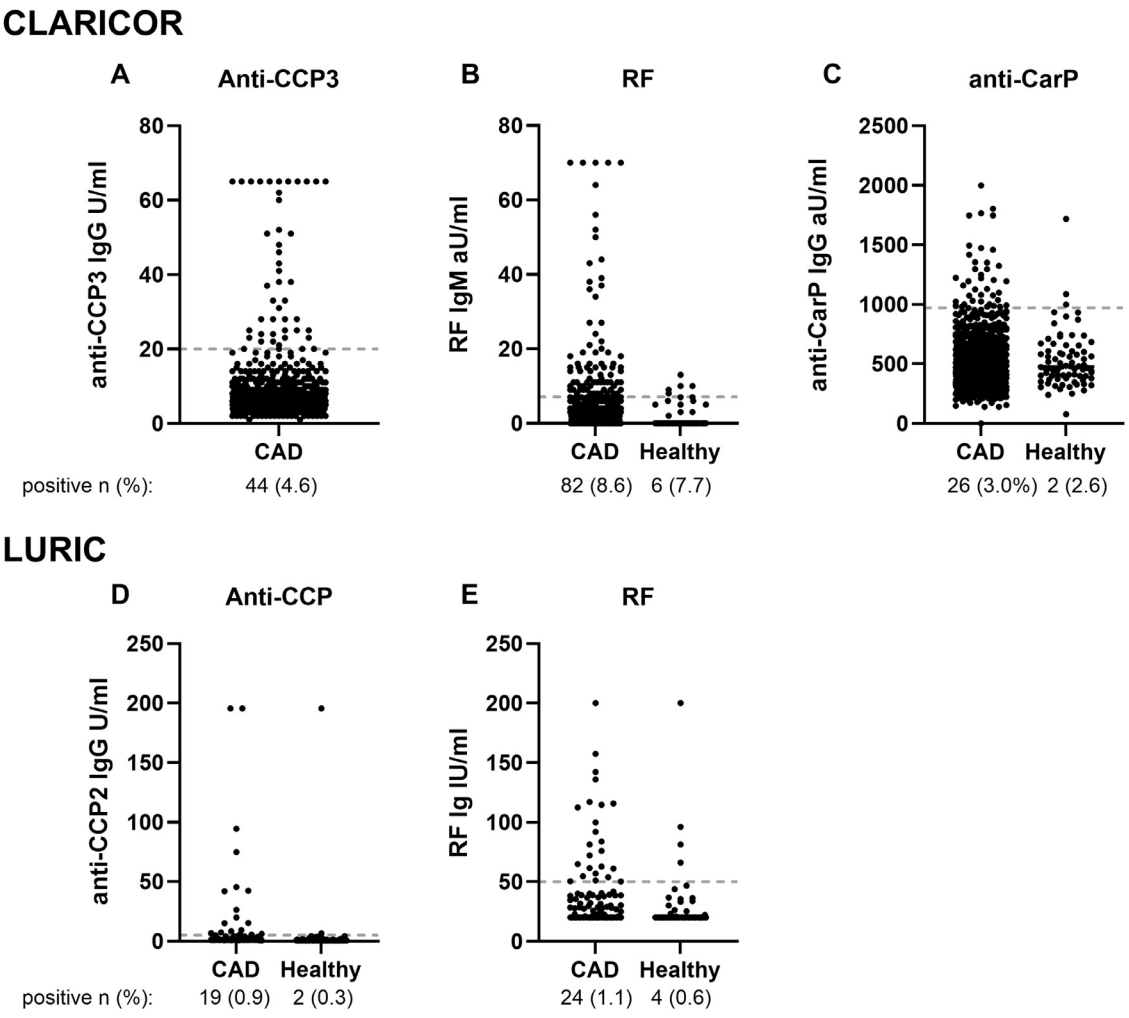

Figure 2. Autoantibody measurements in CAD cohorts. CLARICOR: (A) anti-CCP3 IgG in patients with CAD only, (B) RF IgM in patients with CAD and Leiden healthy controls, (C) anti-CarP IgG in patients with CAD and Leiden healthy controls. LURIC: (D) anti-CCP IgG and (E) total RF in patients with CAD and LURIC controls. Dashed lines represent assay cut-offs. anti-CarP, antibodies against carbamylated proteins; CAD, coronary artery disease; CLARICOR, CLARIthromycin for patients with stable CORonary heart disease; CCP, cyclic citrullinated peptide; Ig, immunoglobulin; LURIC, LUdwigshafen Risk and Cardiovascular Health; RF, rheumatoid factor.

(CLARICOR clarithromycin group HR 0.94 [95% CI: 0.52-1.68]; CLARICOR placebo group HR 0.63 [95% CI: 0.26-1.53]; LURIC HR 0.87 [95% CI: 0.39-1.94]; Supplementary Table S4), which were pooled using meta-analysis (HR 0.84 [95% CI: 0.55-1.27]). Similar results were obtained for RF and anti-CarP in CLARICOR (Supplementary Fig S2A-D), which were further confirmed with adjusted Cox regression analyses (Supplementary Table S4). In the LURIC study, RF-positive patients displayed worse survival

Table 2
Cardiovascular risk factors at baseline in CLARICOR and LURIC by ACPA status

Patient characteristics	CLARICOR			LURIC		
	anti-CCP3– (n = 915)	Anti-CCP3+ (n = 44)	*P* value	Anti-CCP– (n = 2170)	anti-CCP+ (n = 19)	*P* value
Age (y), mean ± SD	65.2 ± 10.4	67.1 ± 9.6	.20	63.6 ± 10.0	62.7 ± 11.1	.72
Female, n (%)	281 (30.7)	12 (27.3)	.75	527 (24.3)	5 (26.3)	.79
Smoking ever, n (%)	775 (84.7)	39 (88.6)	.62	1489 (68.6)	14 (73.7)	.82
Clarithromycin group, n (%)	452 (49.4)	28 (63.6)	.091	-	-	-
BMI (kg/m^2), mean ± SD	-	-	-	27.5 ± 3.9	25.9 ±3.7	.073
Hypertension, n (%)	371 (40.5)	19 (43.2)	.85	1623 (74.8)	15 (78.9)	.80
LDL cholesterol in mmol/L, median (IQR)	2.5 (2.1-3.0)	2.5 (2.0-3.1)	.90	2.9 (2.4-3.5)	2.8 (2.3-3.2)	.36
Previous myocardial infarction, n (%)	597 (65.2)	33 (75.0)	.24	1144 (52.7)	13 (68.4)	.26

ACPA, anticitrullinated protein antibody; BMI, body mass index; CLARICOR, CLARIthromycin for patients with stable CORonary heart disease; CCP, cyclic citrullinated peptide; LDL, low-density lipoprotein; LURIC, LUdwigshafen Risk and Cardiovascular Health.
In CLARICOR, ACPA is measured using anti-CCP3 tests, in LURIC using anti-CCP tests.

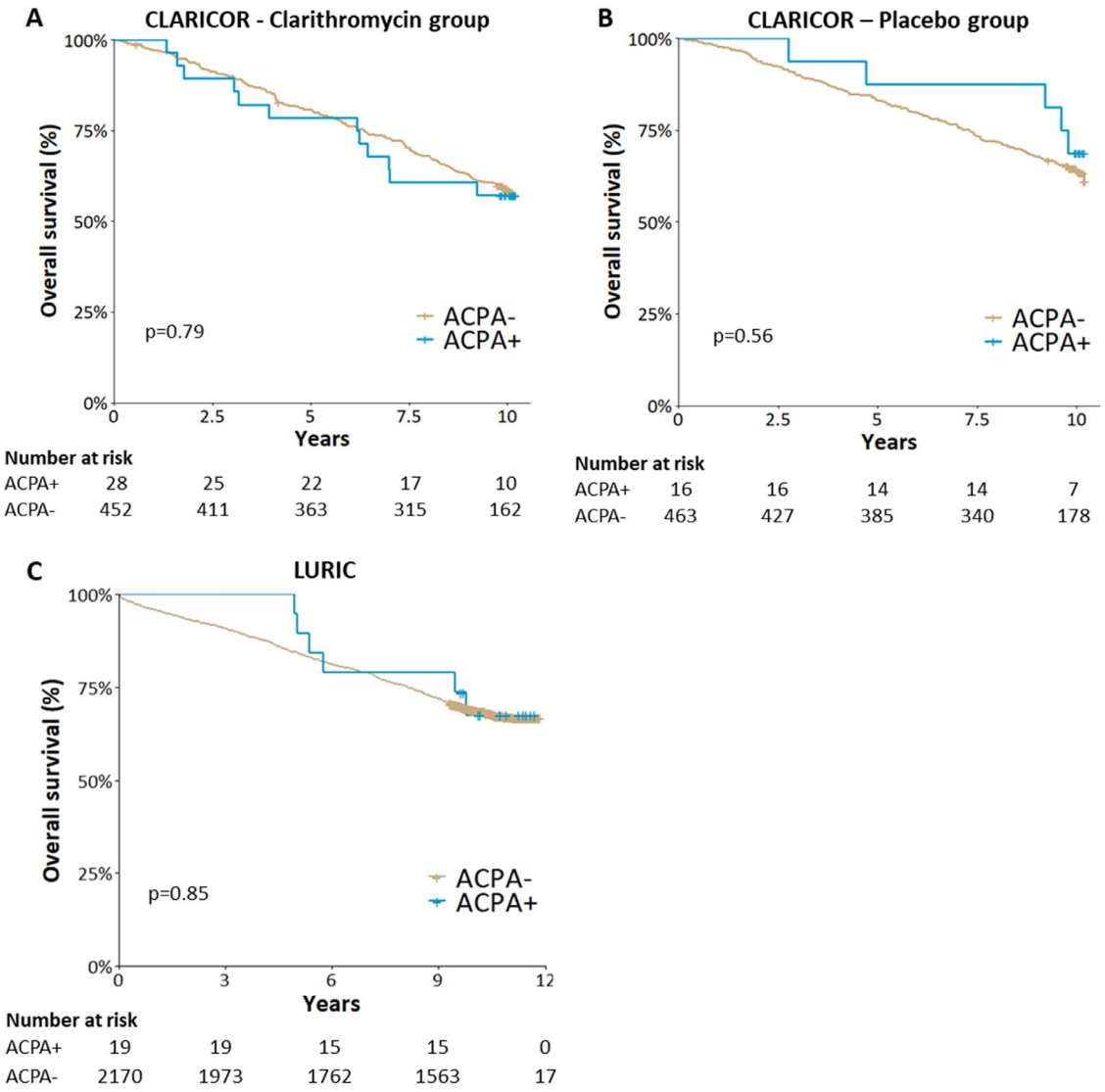

Figure 3. Association between ACPA positivity and all-cause mortality depicted using Kaplan-Meier curves. (A) CLARICOR clarithromycin treatment group, (B) CLARICOR placebo group, (C) LURIC. *P* values calculated with log-rank tests. Number of patients at risk in both strata over time is listed below each graph. ACPA, anticitrullinated protein antibody; CLARICOR, CLARIthromycin for patients with stable CORonary heart disease; LURIC, LUdwigshafen Risk and Cardiovascular Health.

compared to their RF-negative counterparts (log-rank test $P = .011$; Supplementary Fig S2E), but after correction for age and sex this difference was no longer significant (HR 1.40 [95% CI: 0.81-2.43]; Supplementary Table S4). Based on these results, it seems that the presence of ACPAs does not associate with worse all-cause mortality in patients with CAD.

Table 3
Association between ACPA and mortality in 2 RA cohorts

Model	HR (95% CI) in EAC	HR (95% CI) in BARFOT
All-cause mortality		
Adjusted Cox regression	1.66 (1.17-2.37)	1.50 (1.13-1.99)
Joint model including CRP	1.22 (0.70-2.17)	1.14 (0.73-1.75)
Cardiovascular mortality		
Adjusted Cox regression	1.57 (0.82-2.99)	2.10 (1.46-3.01)
Joint model including CRP	0.92 (0.31-2.53)	1.65 (0.95-2.92)

ACPA, anticitrullinated protein antibody; BARFOT, Better Anti-rheumatic Farmaco-therapy; CRP, C-reactive protein; EAC, Early Arthritis Clinic; HR, hazard ratio; RA, rheumatoid arthritis.
HRs with 95% CI for ACPA in both adjusted Cox regression (without CRP) and joint models (including CRP) in EAC and BARFOT are given. Outcome was either all-cause mortality or cardiovascular death. Survival analysis was adjusted for age, sex, inclusion period and smoking status.

ACPAs, CRP, and mortality in patients with RA

In contrast to the results in the CAD cohorts, ACPA positivity has been associated with increased all-cause mortality in multiple cohorts of patients with RA [15,18,37]. This raises the question whether the increase in mortality rates in ACPA-positive patients with RA can be solely attributed to the presence of autoantibodies or whether other factors, such as systemic inflammation, are involved. If so, CRP over time, as a proxy for systemic inflammation, could be a mediator in the association between ACPAs and mortality in patients with RA (as depicted in Supplementary Fig S1). To investigate this hypothesis, we reanalysed data from 2 early RA cohorts, the EAC and the BARFOT cohort. During follow-up, 137/764 patients (17.9%) died in EAC and 228/794 (28.7%) in BARFOT. Multivariable Cox models on the association between ACPAs and all-cause mortality, including age, sex, smoking status, and year of inclusion as covariates, were repeated and provided results consistent with previous findings (EAC HR 1.66 [95% CI: 1.17-2.37]; BARFOT HR 1.50 [95% CI: 1.13-1.99]; Table 3) [15]. Furthermore, CRP over time was significantly associated with ACPA positivity (EAC β = 0.13 [95% CI: 0.08-0.18]; BARFOT β = 0.16 [95% CI: 0.12-0.20]), a prerequisite for CRP to be a potential mediator. When CRP was added using a joint model, the association between ACPAs and all-cause mortality was attenuated and became nonsignificant (EAC HR 1.22 [95% CI: 0.70-2.17]; BARFOT HR 1.14 [95% CI: 0.73-1.75]; Table 3, for complete models see Supplementary Tables S5, S6). In contrast, there was a significant indirect effect of logCRP on mortality (EAC HR 1.24 [95% CI: 1.14-1.34]; BARFOT HR 1.33 [95% CI: 1.24-1.42]). Thus, the association between ACPAs and all-cause mortality found earlier in BARFOT and EAC is most likely largely explained by CRP.

Analyses were repeated using cardiovascular mortality instead of all-cause mortality as the outcome measure. A total of 40/575 patients (7.0%) in EAC and 141/788 (17.9%) in BARFOT died from cardiovascular causes. A significant association between ACPA positivity and cardiovascular mortality was observed in BARFOT (HR 2.10 [95% CI: 1.46-3.01]), but not in EAC (HR 1.57 [95% CI: 0.82-2.99]) in multivariable Cox regression. Adjustment for CRP in the joint model reduced the HRs, now being nonsignificant in both cohorts (EAC HR 0.92 [95% CI: 0.31-2.53]; BARFOT HR 1.65 [95% CI: 0.95-2.92]; Table 3, for complete models see Supplementary Tables S7, S8). The calculated indirect effect for logCRP over time on cardiovascular mortality was significant in both cohorts (EAC HR 1.45 [95% CI: 1.27-1.66]; BARFOT HR 1.42 [95% CI: 1.31-1.54]). Sensitivity analysis using the cumulative CRP model yielded similar results (Supplementary Table S9).

DISCUSSION

In this study, the relationship between ACPA positivity and mortality was investigated in 2 large cohorts of patients with CAD without RA as well as in 2 cohorts of patients with RA. In contrast to previous findings [26,27], the prevalence of ACPAs in individuals with CAD without RA was not significantly higher compared to controls without CAD. In both CLARICOR and LURIC, the presence of ACPAs was not associated with worse all-cause mortality in patients with CAD. Additional analyses investigating other RA-associated autoantibodies similarly showed no significant association between RF and anti-CarP and mortality in patients with CAD without RA. Regarding RA, on the other hand, multiple studies have reported a significant association between ACPA positivity and increased all-cause mortality [15,17,18,37]. However, using joint modelling analyses, we found that the HR for the effect of ACPAs on all-cause and cardiovascular mortality became nonsignificant after the addition of CRP over time, while increased CRP levels were significantly associated with mortality. Thus, high inflammation over time seems to be a more important factor for mortality and CVD in patients with RA than the presence of ACPAs in itself.

The prevalence of ACPAs in patients with CAD in LURIC and in CLARICOR was lower than the 10% to 11% ACPA positivity previously described in 2 other CAD non-RA cohorts [26,27]. There might be several explanations for this disparity. Test characteristics might vary between different commercial assays, but this seems unlikely to fully explain the different findings. Differences in size and inclusion criteria between cohorts may further explain differences in ACPA frequencies and outcomes. For example, in CLARICOR, 959 patients with a previous diagnosis of myocardial infarction or angina pectoris were included, a diagnosis which could have been established several years before, while 1 of the previous studies included 275 patients at the time of STEMI diagnosis [27]. In the other study by Cambridge et al [26], 3052 healthy middle-aged men without clinical CAD were included with a follow-up of 5 years, whereas in LURIC 2189 patients with CAD were included. Moreover, using the Danish National Patient Register, we could reliably exclude patients with a concomitant diagnosis of RA from the patients with CAD in CLARICOR, whereas in the other studies, there might have been unidentified patients with RA left in CAD groups, skewing the results. The low number of patients with CAD without RA positive for multiple RA-related autoantibodies further supports the successful exclusion of patients with RA from our investigation.

In both RA cohorts, chronic inflammation seemed to play a more important role in the increased all-cause and cardiovascular mortality risk in ACPA-positive patients with RA than the presence of ACPAs in itself. It is known that systemic inflammation can lead to atherosclerosis and CAD via increased oxidative stress and endothelial dysfunction [1,2,8,9]. Our findings are in line with previous reports that found that the risk of cardiovascular events was higher in patients with RA with higher disease activity scores (DAS) [38,39] and increased CRP levels [40,41]. ACPA positivity might reflect a disease state in which there is more ongoing inflammation, explaining why multiple studies have reported a significant association between ACPA positivity and increased all-cause mortality before [15,17,18,37].

Early intense treatment in RA was shown to normalise excess mortality rates in ACPA-negative patients with RA, but in ACPA-positive patients, mortality rates are still higher than in the general population [37]. Hence, therapies specifically targeting the continuous underlying inflammation in ACPA-positive RA might be the key to improve long-term outcomes. Several studies investigated the effect of intensifying immunosuppressive therapy on cardiovascular risk in RA, including both seropositive and seronegative patients, based on surrogate endpoints. In the treatment of early aggressive rheumatoid arthritis (TEAR) trial, total cholesterol increased after treatment initiation, regardless of treatment regimen (MTX monotherapy, MTX and etanercept duo therapy or MTX, sulfasalazine, and hydroxychloroquine triple therapy), and was inversely correlated with DAS and CRP [42]. Over time, patients receiving triple therapy had higher levels of the favourable high-density lipoprotein cholesterol and lower levels of LDL cholesterol (LDL-C) compared to patients on other treatments [42]. Addition of the interleukin-6 receptor blocker tocilizumab in patients treated with MTX led to a reduction of inflammation and other vascular risk surrogate markers such as fibrinogen, but was also associated with elevations of total cholesterol and LDL-C [43]. In contrast, a more recent study showed that in patients with RA with moderate disease activity on MTX, both add-on therapy with tumour necrosis factor α inhibitors or with sulfasalazine and hydroxychloroquine led to a reduction in arterial inflammation based on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography scans [44]. In summary, these studies using surrogate endpoints for cardiovascular risk do not allow a definitive conclusion regarding the long-term effect of specific RA treatment strategies on clinical CVD.

Our study has several limitations. The number of identified ACPA-positive patients with CAD was limited despite using large CAD non-RA cohorts, which restricted analyses, for example, on cardiovascular mortality. Furthermore, there was no uniformity in ACPA tests among cohorts and differences in specificity and sensitivity might have led to differences in positivity rates. Except for LURIC, no population-specific control groups were available. Although in CLARICOR patients with RA were excluded from the CAD non-RA group with high certainty, comorbidity registration over time was less thorough in LURIC and depended on chart review of medication at inclusion and survey data on comorbidity and medication use over time. The low number of LURIC patients that are positive for more than 1 RA-specific autoantibody indicates this approach was successful, but the possibility that a few patients with RA might have remained in the analyses cannot be excluded. Moreover, in both RA cohorts, CRP was measured on a yearly basis, providing only a rough estimate of cumulative inflammation over time. In the CAD cohorts, there was no information about inflammation over time available. In the EAC cohort cause-specific mortality data were only available for a subset of patients because of changes in privacy regulations, thereby decreasing the power of the analyses on cardiovascular mortality in this cohort.

Despite these drawbacks, our study also has considerable strengths. Two large CAD cohorts including follow-up data were used, making this, to the best of our knowledge, the most extensive study into the prevalence of ACPAs in the non-RA CAD population to date. In addition to ACPAs, we also evaluated RF and anti-CarP, which have also been indicated to potentially impact CVD and mortality [15,45]. Furthermore, findings in CAD cohorts were complemented with analyses of 2 large early RA cohorts with well-documented CRP and mortality data. Advanced joint modelling techniques, which are only rarely used in the field of rheumatology despite its appealing name, were applied to adjust mortality analyses in these patients with RA for CRP, a time-varying covariate, to optimise the modelling of inflammation over time. In this manner, we feel this study provides the most comprehensive answer to date on the question of whether ACPAs are associated with CVD in individuals with and without RA.

Taken together, our research shows that ACPA positivity is not associated with CVD in patients without RA. The association between ACPA positivity and CVD in RA, described before by others and in our cohorts, is likely explained by the higher inflammation over time in seropositive patients with RA. Therefore, in contrast to seronegative RA, in patients with ACPA-positive RA, the ongoing chronic inflammatory process seems to be especially critical in the development of CVD and is therefore an important therapeutic target to improve long-term outcomes for these seropositive patients with RA.

Competing interests

None.

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Contributors

All authors meet the 4 criteria for authorship. All authors contributed to study design/data acquisition/analyses, were involved in drafting or critically revising the manuscript, approved the final version for publication and agree to ensure that any questions related to accuracy or integrity of the work are appropriately investigated and resolved.

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Patient consent for publication

All participants provided written informed consent.

Ethics approval

All studies were performed in concordance with the Declaration of Helsinki, approved by the relevant local medical ethical committee.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data are available upon reasonable request. For the r code for the analyses, or the statistical analysis plan drafted before starting this study, please contact Veerle Derksen. Deidentified participant data belong to the respective study groups: LURIC group (prof Winfried März), CLARICOR trial group (prof Christian Gluud), the BARFOT group (Dr Sofia Ajeganova), and the EAC (prof Annette van der Helm - Van Mil). This data can only be used in collaboration with the study groups.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ard.2025.11.023.

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