Predictive Value of Arterial Stiffness and Subclinical Carotid Atherosclerosis for Cardiovascular Disease in Patients with Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We evaluated the predictive value of these vascular biomarkers for cardiovascular disease (CVD) events in patients with rheumatoid arthritis (RA): aortic pulse wave velocity (aPWV), augmentation index (AIx), carotid intima-media thickness (cIMT), and carotid plaques (CP). They are often used as risk markers for CVD.

Methods. In 2007, 138 patients with RA underwent clinical examination, laboratory tests, blood pressure testing, and vascular biomarker measurements. Occurrence of CVD events was recorded in 2013. Predictive values were assessed in Kaplan-Meier plots, log-rank, and crude and adjusted Cox proportional hazard (PH) regression analyses.

Results. Baseline median age and disease duration was 59.0 years and 17.0 years, respectively, and 76.1% were women. CVD events occurred in 10 patients (7.2%) during a mean followup of 5.4 years. Compared with patients with low aPWV, AIx, cIMT, and without CP, patients with high aPWV ($p < 0.001$), high AIx ($p = 0.04$), high cIMT ($p = 0.01$), and CP ($p < 0.005$) at baseline experienced more CVD events. In crude Cox PH regression analyses, aPWV ($p < 0.001$), cIMT ($p < 0.001$), age ($p = 0.01$), statin ($p = 0.01$), and corticosteroid use ($p = 0.01$) were predictive of CVD events, while AIx was nonsignificant ($p = 0.19$). The Cox PH regression estimates for vascular biomarkers were not significantly altered when adjusting individually for demographic variables, traditional CVD risk factors, RA disease-related variables, or medication. All patients who developed CVD had CP at baseline.

Conclusion. CP, aPWV, and cIMT were predictive of CVD events in this cohort of patients with RA. Future studies are warranted to examine the additive value of arterial stiffness and carotid atherosclerosis markers in CVD risk algorithms. Regional Ethical Committee approval numbers 2009/1582 and 2009/1583. (J Rheumatol First Release June 15 2016; doi:10.3899/jrheum.160053)

Key Indexing Terms:
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Patients with rheumatoid arthritis (RA) have increased risk of atherosclerotic cardiovascular disease (CVD)[1,2]. Increasing stiffness and remodeling of the arterial wall represent 2 important features in the development of atherosclerosis[3].

Arterial stiffness is an inevitable feature of vascular ageing

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that can be exacerbated by both traditional CVD risk factors and chronic inflammation[4,5,6]. Aortic pulse wave velocity (aPWV) and the augmentation index (AIx) are 2 common measures of arterial stiffness that have been shown to be increased in RA[7,8]. These 2 indices are frequently used as surrogate CVD endpoints in clinical research because they provide noninvasive measures that rapidly reflect the effect of various stimuli on the arterial wall[9]. The predictive values of aPWV and AIx for CVD events have been established in the general population and for patients with high CVD risk, including hypertension, renal disease, and diabetes mellitus[10,11,12]. However, the relationship between arterial stiffness and hard CVD endpoints in patients with RA has not been previously investigated.

Carotid intima-media thickness (cIMT) is a reliable marker of generalized atherosclerosis and has become a widely used indicator of subclinical atherosclerosis in rheumatology research[13,14]. Patients with RA have increased cIMT, which has been related to high levels of inflammation[15]. The predictive value of cIMT for future CVD events has previously been reported in the general population, several groups of patients with high CVD risk, and 1 small-scale RA cohort[16,17,18]. Patients with RA also have a high frequency of asymptomatic carotid artery plaques (CP)[15,19,20,21], which are considered coronary heart disease risk equivalents in the most recent European guidelines on CVD prevention[22]. The predictive value of CP for future coronary artery disease has previously been demonstrated for both the general population and patients with RA[23,24]. Several recommendations/guidelines suggest including cIMT measurements and CP detection in the evaluation of asymptomatic individuals at moderate CVD risk[22,25,26].

Since the atherosclerotic process in patients with RA is accelerated by persistent systemic inflammation, it is likely that the atherogenic mechanisms in these patients are partially different from the general population[27,28]. Therefore, extrapolating evidence regarding the predictive value of vascular biomarkers from other populations to patients with RA may prove to be futile. In our present study, we aimed to elucidate the value of arterial stiffness, assessed by aPWV and AIx, and subclinical carotid atherosclerosis, measured by cIMT and the presence of CP, as possible predictors of CVD events in patients with RA.

MATERIALS AND METHODS

The patients in our study were recruited from 2 cohorts that were established at the Department of Rheumatology, Diakonhjemmet Hospital: the European Research on Incapacitating Diseases and Social Support (EURIDISS), established in 1991, and the Oslo RA registry (ORAR), established in 1994. The cohorts have been previously described in detail[29]. They included patients of both sexes, aged 20–79 years with a diagnosis of RA classified by a rheumatologist according to the 1987 American College of Rheumatology criteria[30]. EURIDISS also had a restriction concerning disease duration (≤ 4 yrs). In 2007, patients from ORAR and EURIDISS with a disease duration ≤ 4 years were asked to participate in a followup rheumatology examination that also included a CVD risk evaluation, consisting of an evaluation of arterial stiffness and subclinical atherosclerosis. Patient data from the 2007 visit formed the baseline for our current study. All patients signed a written informed consent form prior to inclusion and both cohorts were approved by the regional ethical committee. Additional permissions to perform a followup by telephone to collect information regarding CVD events were given in May 2013 (Regional Ethical Committee approval numbers 2009/1582 and 2009/1583).

At the visit in 2007, participants completed questionnaires regarding RA disease characteristics, smoking status, comorbidities, and medication use. A clinical examination that included anthropometric measurements and tender and swollen joint counts was performed by trained rheumatology nurses, and the Disease Activity Score based on 28 joints including erythrocyte sedimentation rate (DAS28-ESR) was calculated[31].

Inflammatory biomarkers, such as C-reactive protein, ESR, lipids [total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol], and triglycerides, were examined consecutively by the COBAS 6000 (Roche Diagnostics). ESR was measured by the Westergren method, IgM rheumatoid factor was assessed using the in-house ELISA method, and LDL-C was calculated by Friedewald formula[32].

Blood pressure (BP) was measured in a supine position by the OMRON M7 device after 5 min of rest. Several measurements were made and the mean of 2 measurements that differed by ≤ 5 mmHg (systolic and diastolic) was used. AIx and aPWV were measured according to expert consensus[33] using the Sphygmocor apparatus (AtCor). Several recordings were made in each patient and the quality was evaluated according to predetermined requirements (AtCor Medical, Technical Notes).

To measure aPWV, pulse pressure waveforms were recorded transcutaneously at the right carotid and femoral artery. Applying the R waves in a simultaneously recorded electrocardiogram as a reference frame, the pulse wave transit time from the heart to these 2 recording sites was calculated (Δt). The distances covered by the waves to either recording site were assimilated to the difference in surface distance, obtained by a measuring tape, between the sternal notch and the 2 respective recording sites. Finally, the Sphygmocor software calculated aPWV as the distance divided by Δt, expressed as m/s.

Reflected pressure waves are generated when forward pressure waves, created by ventricular contraction, meets peripheral arterial branch points and sites of impedance mismatch. In stiffer arteries, the reflected waves will return to the central arteries early, adding to the forward waves and augmenting the systolic pressure. This phenomenon can be quantified by applying a validated transfer system to arterial pressure wave forms recorded in the radial artery. The AIx represents the change in pressure between the second and first systolic peaks as a percentage of the pulse pressure. The recordings were standardized to a heart rate of 75 bpm[34].

B-mode ultrasonography examinations of the carotid arteries were performed using a GE Vivid 7 ultrasound scanner (GE Vingmed ultrasound) with a 12 MHz (9–14) linear matrix array transducer[20] by an experienced sonographer. Measurement of cIMT was done bilaterally on a 5-mm segment of the far wall of the common carotid artery, about 10 mm proximal to the carotid bulb. To avoid overestimation of cIMT, both the near and the far walls were visualized with sharp edges, indicating an insonation angle of about 90° to the vessel wall. Images (JPEG format) of cIMT measurements were read offline by 2 experienced vascular physiologists (ES and JH) using the AMS analysis (Artery Measurement System, T. Gustavsson) software[35]. A good interreader correlation coefficient for cIMT measurements had previously been reported[36]. Mean values were calculated from about 50 cIMT measurements generated from each 5-mm segment.

CP were defined as ≥ 1.5-mm protrusions into the lumen of the common carotid artery, carotid artery bulb, and/or the internal carotid artery, or at least 2× the surrounding cIMT. The presence of CP was evaluated bilaterally in the longitudinal view and verified by a cross-sectional image obtained by rotating the probe 90°.

A CVD event was defined as an acute myocardial infarction (AMI), percutaneous coronary intervention (PCI), coronary artery bypass graft surgery, ischemic stroke, transitory ischemic attack, or peripheral artery disease (PAD) occurring after the examination date in 2007. Patients for

whom data on lipids and BP had been recorded in 2007 were contacted by telephone in May 2013. In a standardized manner, they were asked (by EI) to answer a questionnaire on the occurrence of CVD events, developed by a cardiologist (AGS; a copy of the questionnaire is available online at jrheum.org as Supplementary Data 1). The questionnaire was completed by telephone and any medical language was clarified to the patient. All patient-reported CVD events were confirmed by reviewing hospital discharge summaries for each patient. If a patient had experienced multiple CVD events, the date of the first event was used for censoring.

Statistical analyses. Baseline patient characteristics, including demographic variables, anthropometric measures, rheumatic disease activity, CVD risk factors, comorbidities, and medication were presented as mean ± SD, median with interquartile range (IQR), and number (%), as appropriate.

Baseline levels of the vascular biomarkers that were analyzed as continuous variables (aPWV, AIx, cIMT) in patients who experienced a CVD event and those who remained CVD event-free were compared using independent samples Student t tests.

The continuous vascular biomarkers were dichotomized to facilitate exploratory analyses of differences in CVD event rates. Established cutoff values were used to divide the cohort into high and low aPWV (m/s) and cIMT (mm) groups (> 9.9 m/s and ≥ 0.9 mm, respectively)[16,22,37,38]. No consensus exists regarding cutoff values for AIx (%) and previous studies have used tertiles to divide patients into groups[10,39]. Accordingly, the cutoff for high/low AIx was defined between the upper (AIx ≥ 31%) and middle/lower (AIx < 31%) tertiles. For CP, the cohort was divided by presence/absence of CP. Subsequently, the groups were compared using Kaplan-Meier time-to-event plots and corresponding log-rank tests.

Crude Cox proportional hazard (PH) regression was applied to evaluate whether the occurrence of CVD events was predicted by vascular biomarkers, demographic variables, traditional CVD risk factors, RA disease-related variables, or antirheumatic or cardioprotective medication. The number of CVD events limited our ability to perform adjusted analyses to assess the effect of potential confounders[40]. In adjusted Cox PH regression models with CVD events as the dependent variable and each vascular biomarker as the independent variable, we limited our adjustments to 1 covariate to avoid inflated risk of Type I error and increased bias. Adjusting covariates included demographic variables, traditional CVD risk factors, cardiovascular comorbidities, RA disease–related variables, and anti-rheumatic or cardioprotective medication. PH assumptions were tested and confirmed both graphically (log-log curves) and by applying time-dependent covariates.

Patients who were lost to followup were included in the main analyses as CVD event-free, i.e., censored at study end. Additional analyses were also performed in which these patients were treated as if (1) they had been censored at baseline (i.e., not participated in our study); and (2) they had all experienced CVD events at study end. In addition, separate analyses were undertaken in which the patients who had previously experienced a CVD event were withdrawn from our analyses.

Statistical analyses were performed using SPSS statistics version 21 (IBM Corp.).

RESULTS

The CVD questionnaire was completed for 161 of the 169 patients who were contacted in 2013. Of these, 134 patients had vascular biomarker measurements at baseline (Figure 1). In addition, 4 of the 8 patients who were lost to followup had available vascular biomarker data.

Baseline characteristics of the 138 patients, including vascular biomarker measurements, are shown in Table 1. There was a female preponderance of 76.1%, and median (IQR) age and disease duration were 59.0 years (51.0–66.9) and 17.0 (15.0–19.0) years, respectively. The mean ± SD followup time was 5.4 ± 0.8 years. Ten patients experienced a total of 11 CVD events during the followup: 5 AMI, 3 PCI, 1 ischemic stroke, and 2 PAD; only 1 of these events occurred in the 18 patients who had established CVD at baseline.

Apart from the vascular biomarkers, age (p = 0.01) and corticosteroid use (p = 0.01) were significantly correlated with CVD outcomes in the crude Cox PH regression analyses (Table 2). Statin use was also correlated with increased risk of CVD events (p = 0.01); however, this association was not statistically significant when adjusting for age, indicating that the age of the statin user was a confounder (data not shown).

Patients with CVD events had significantly higher aPWV

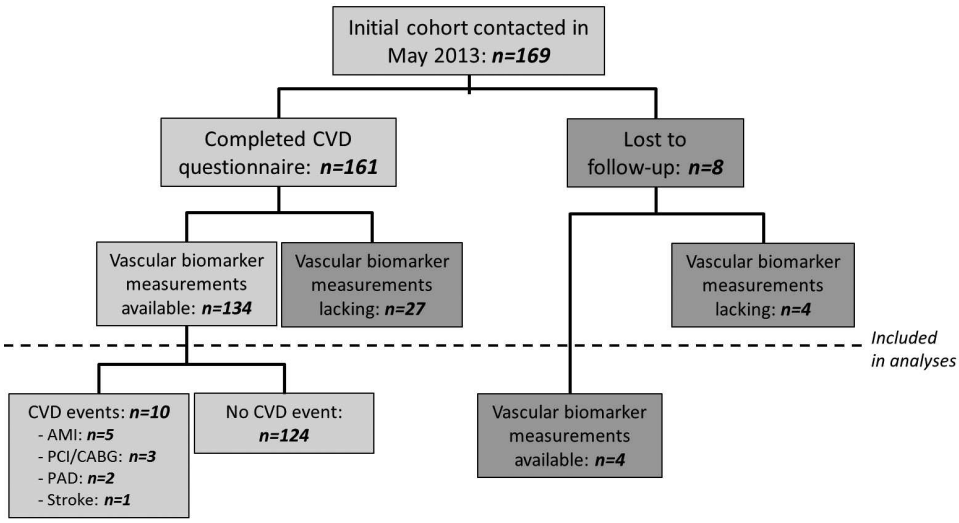

Figure 1. Flowchart of the study. The initial cohort consisted of 169 eligible patients. Eight patients were lost to followup, of whom 4 had available data on vascular biomarker measurements. Of the 161 patients who completed the CVD questionnaire, 134 patients had available vascular biomarkers, and 10 of these had experienced a CVD event during the followup. CVD: cardiovascular disease; AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; CABG: coronary artery bypass graft; PAD: peripheral artery disease.

Table 1. Baseline patient characteristics (entire cohort n = 138).

Characteristics	Values
Demographic variables	
Age, yrs, median (IQR)	59.0 (51.0–66.9)
Female, n (%)	105 (76.1)
BMI, kg/m^2, mean ± SD	26.1 ± 5.1
Vascular biomarkers, mean ± SD	
aPWV	8.40 ± 1.91
AIx	27.2 ± 9.9
cIMT	0.78 ± 0.19
CP, n (%)	79 (57.2)
Rheumatic disease variables	
Disease duration, yrs, median (IQR)	17.0 (15.0–19.0)
DAS28, mean ± SD	2.65 ± 1.01
CRP, mg/l, median (IQR)	3.00 (1.00–8.00)
ESR, mm/h, mean ± SD	16.3 ± 13.0
RF, IgM, n (%)	68 (53.5)
CV risk factors, mean ± SD	
Total cholesterol, mmol/l	5.66 ± 1.20
LDL-C, mmol/l	3.29 ± 1.03
Triglycerides, mmol/l, median (IQR)	1.09 (0.79–1.53)
HDL-C, mmol/l	1.75 ± 0.56
SysBP, mmol/l	134.2 ± 19.6
DiaBP, mmol/l	80.5 ± 9.4
Current smoking, daily, n (%)	29 (21.0)
Ever smoked, daily, n (%)	89 (65.9)
Comorbidities, n (%)	
Hypertension	75 (54.3)
Diabetes mellitus	14 (10.1)
CV disease	18 (13.0)
Carotid artery plaque(s)	79 (57.2)
Medication, n (%)	
Anti-HT	49 (35.5)
Statins	25 (18.1)
bDMARD	30 (21.7)
sDMARD	90 (65.2)
Corticosteroids	42 (30.4)
NSAID	43 (31.2)

IQR: interquartile range; BMI: body mass index; aPWV: aortic pulse wave velocity; AIx: augmentation index; cIMT: carotid intima-media thickness; CP: carotid plaques; DAS28: Disease Activity Score in 28 joints; CRP: C-reactive protein; ESR: erythrocyte sendimentation rate; RF: rheumatoid factor; IgM: immunoglobulin M; CV: cardiovascular; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; sysBP: systolic blood pressure; diaBP: diastolic blood pressure; CV disease: acute myocardial infarction, ischemic stroke, transitory ischemic attack, peripheral artery disease, percutaneous coronary intervention, coronary artery bypass graft surgery; anti-HT: antihypertensive medication (diuretics, calcium channel inhibitors, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β blockers); DMARD: disease-modifying antirheumatic drugs; bDMARD: biologic DMARD; sDMARD: synthetic DMARD; NSAID: nonsteroidal antiinflammatory drugs.

Table 2. Crude Cox proportional hazards regression of possible predictors of CVD events. The HR with 95% CI for each potential predictor variable are estimated from a proportional hazards model including only that variable in the model.

Variables	HR (95% CI)	p
Vascular biomarkers		
aPWV, per m/s	1.85 (1.33–2.57)	< 0.001
AIx, per %	1.05 (0.98–1.13)	0.19
cIMT, per 0.1 mm	1.65 (1.27–2.13)	< 0.001
CP	—	NR
Demographic variables		
Female vs male	0.30 (0.09–1.03)	0.06
Age, per yr	1.10 (1.02–1.18)	0.01
BMI, per kg/m^2	1.08 (0.97–1.19)	0.15
Traditional CVD risk factors		
Total cholesterol, per mmol/l	1.51 (0.91–2.48)	0.11
LDL-C, per mmol/l	1.23 (0.67–2.27)	0.50
HDL-C, per mmol/l	1.22 (0.39–3.81)	0.73
Triglycerides, per mmol/l	1.04 (0.27–3.96)	0.95
SysBP, per mmHg	1.02 (0.99–1.05)	0.11
DiaBP, per mmHg	1.03 (0.97–1.10)	0.36
Smoking, daily vs non-smoke	2.20 (0.27–17.6)	0.46
Smoking, ever vs never	1.87 (0.39–9.02)	0.43
Comorbidities, yes vs no		
Hypertension	3.47 (0.74–16.34)	0.12
Diabetes mellitus	1.00 (1.13–7.93)	0.99
Previous CVD	0.71 (0.09–5.63)	0.75
RA disease variables		
Disease duration, per yr	0.99 (0.74–1.34)	0.97
CRP, per mg/dl	1.11 (0.64–1.92)	0.72
ESR, per mm/h	1.03 (0.99–1.07)	0.21
DAS28-ESR, per unit	0.68 (0.34–1.36)	0.27
Medication		
Anti-HT, non-user vs user	0.82 (0.23–2.92)	0.76
Statins, non-user vs user	0.20 (0.06–0.69)	0.01
bDMARD, non-user vs user	0.63 (0.16–2.43)	0.50
sDMARD, non-user vs user	0.20 (0.03–1.57)	0.13
sDMARD only, non-user vs user	0.50 (0.14–1.78)	0.29
Corticosteroids, non-user vs user	0.17 (0.04–0.67)	0.01
NSAID, non-user vs user	1.05 (0.27–4.06)	0.95

CVD: cardiovascular disease; aPWV: aortic pulse wave velocity; AIx: augmentation index; cIMT: carotid intima-media thickness; CP: carotid plaques; BMI: body mass index; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; sysBP: systolic blood pressure; diaBP: diastolic blood pressure; RA: rheumatoid arthritis; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints; anti-HT: antihypertensive medication; DMARD: disease-modifying antirheumatic drugs; bDMARD: biologic DMARD; sDMARD: synthetic DMARD; NSAID: nonsteroidal antiinflammatory drugs; NR: not reported, not estimable because all events occurred in 1 group.

at baseline compared with those who did not experience CVD events during followup ($p < 0.001$; Figure 2A). The log-rank test revealed that more CVD events occurred among the patients with high aPWV than in the group with low aPWV ($p < 0.0001$), as illustrated in the corresponding Kaplan-Meier plot (Figure 3A). In the univariate Cox PH regression model, while evaluating aPWV as a continuous variable, the HR (95% CI) per unit (m/s) increase in aPWV was 1.85 (1.33–2.57, $p < 0.001$; Table 2). This estimate was moderately weakened when the model was adjusted for age ($p = 0.01$), but was not substantially altered in the remaining multivariate analyses (Table 3). Similarly, the estimates were robust in the 2 approaches (Supplementary Table 1 is available online at jrheum.org) for evaluating patients who were lost to followup and the separate analyses in which patients who had previously experienced a CVD event were

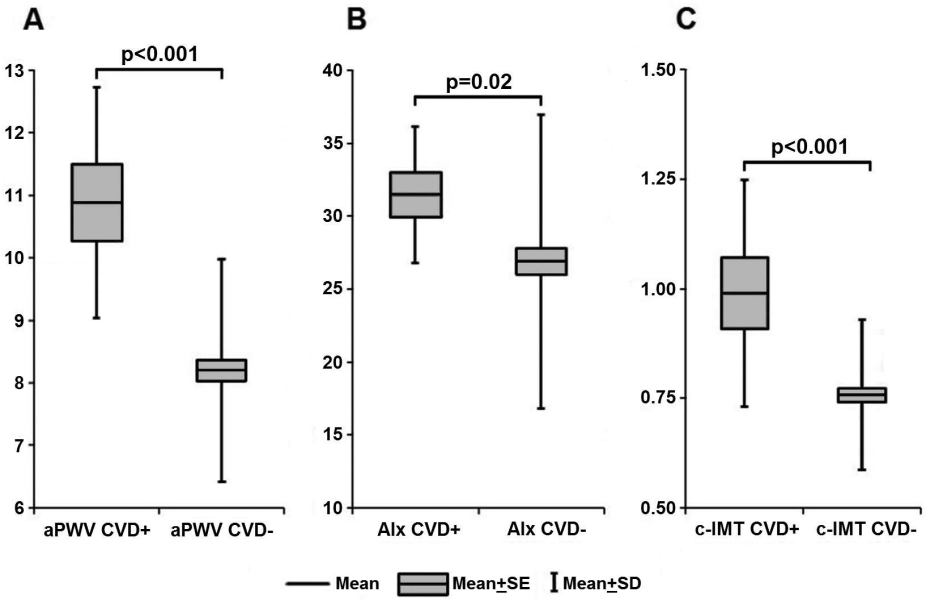

Figure 2. Levels of vascular biomarkers in patients with and without CVD events during followup. Patients with RA who have CVD events during followup (CVD+) and those who do not (CVD–). Mean ± SE and ± SD for (A) aPWV, (B) AIx, and (C) cIMT. CVD: cardiovascular disease; RA: rheumatoid arthritis; SE: standard error; aPWV: aortic pulse wave velocity; AIx: augmentation index; cIMT: carotid intima-media thickness.

excluded (Supplementary Table 1 and Supplementary Table 2 are available online at jrheum.org).

Compared with patients who remained CVD event-free, baseline AIx was significantly higher among patients with CVD events ($p = 0.02$; Figure 2B). According to the log-rank test, more CVD events occurred in the group with high AIx compared with those with low AIx ($p = 0.04$), and this is reflected in the related Kaplan-Meier plot (Figure 3B). However, when evaluating AIx as a continuous variable in Cox PH regression models, it did not reach a level of statistical significance in the univariate ($p = 0.19$; Table 2) or in the multivariate analyses ($p = 0.07$–0.61; Table 3). Again, adding or disregarding the patients who were lost to followup (Supplementary Table 1 is available online at jrheum.org) and excluding patients who had previously experienced CVD did not substantially alter the estimates (Supplementary Table 1 and Supplementary Table 2 are available online at jrheum.org).

Baseline cIMT was significantly higher in patients with CVD events compared with those who remained CVD event-free ($p < 0.001$; Figure 2C). The log-rank test for the dichotomized cIMT variable showed that patients with high cIMT experienced significantly more CVD events than those with low cIMT ($p = 0.01$), as outlined in the Kaplan-Meier plot (Figure 3C). When cIMT was analyzed as a continuous variable in univariate Cox PH regression models, a 0.1-mm increase in cIMT entailed an HR (95% CI) of 1.65 (1.27–2.13, $p < 0.001$; Table 2). This estimate was robust in all the specified adjustments (Table 3) in multivariate analyses and was not substantially changed by the additional approaches A and B (Supplementary Table 1 is available online at jrheum.org) for patients who were lost to followup or the separate analyses in which patients with preexisting CVD were excluded (Supplementary Table 1 and Supplementary Table 2 are available online at jrheum.org).

As illustrated in the Kaplan-Meier plot (Figure 3D), all CVD events occurred in the group with CP at baseline and none in the group that did not have CP, and this difference was statistically significant in the log-rank test ($p < 0.005$). Because of the separation of the events, CP could not be assessed as a predictor for CVD events in Cox PH regression analyses.

DISCUSSION

In our present study, we have shown that aPWV, cIMT, and CP are predictors of future CVD events in patients with RA. Further, our results indicate that AIx may have prognostic qualities regarding future CVD.

Traditional CVD risk factors and CVD risk algorithms developed for the general population cannot completely account for the high CVD morbidity and mortality in patients with RA[41,42,43]. Substantial research has been invested into evaluating noninvasive vascular biomarkers that better reflect the added CVD risk imposed by chronic inflammation[13]. Since conducting trials on hard CVD endpoints is time consuming and costly, these vascular biomarkers have become attractive as surrogate CVD endpoints in clinical trials. Taking into account the extent to which aPWV, AIx, cIMT, and CP have been applied in cross-sectional studies and clinical trials in rheumatology[13,15,44,45], it is surprising

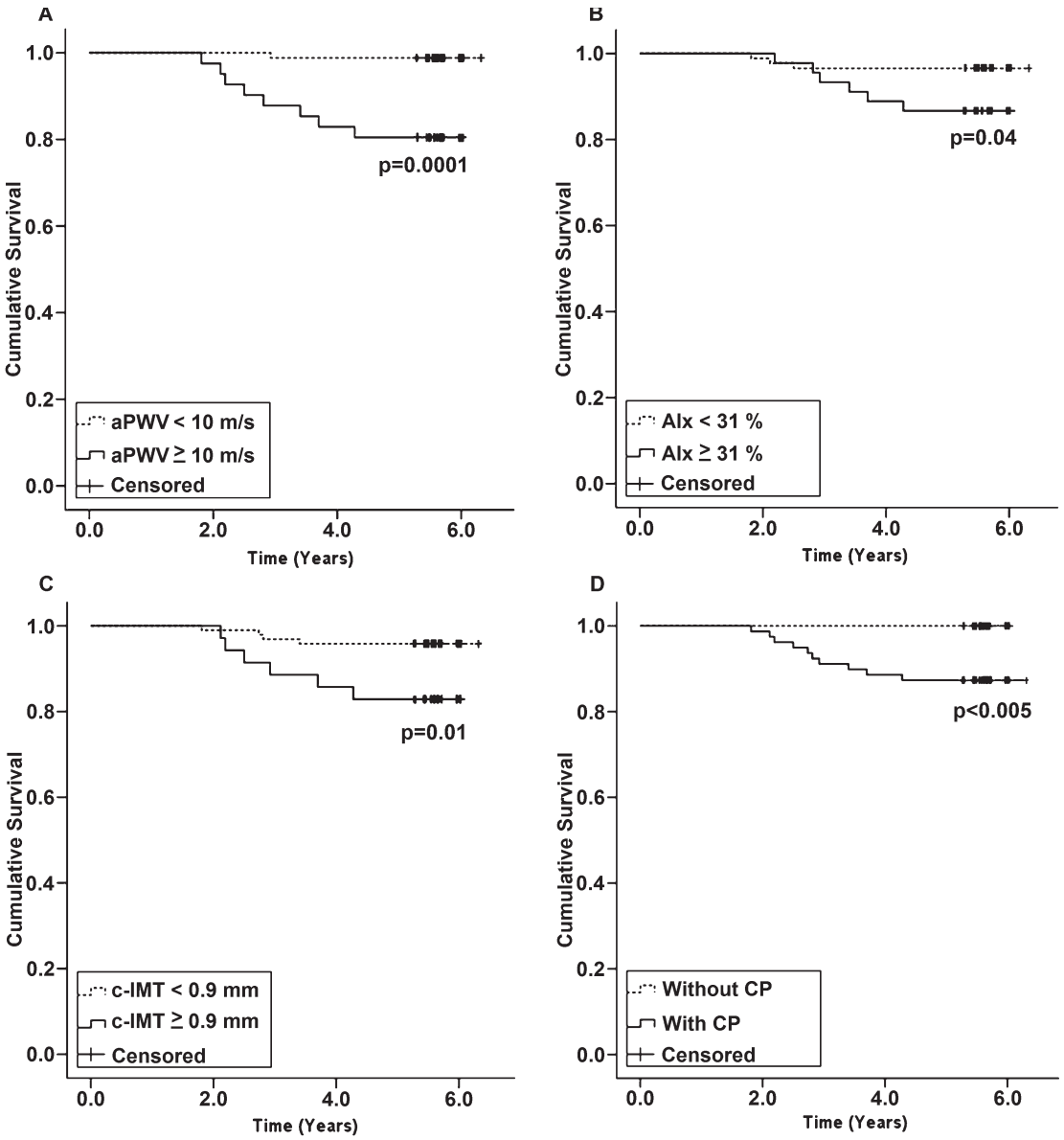

Figure 3. Occurrence of CVD events during followup. Kaplan-Meier plots with log-rank (Mantel-Cox) test HR for occurrence of CVD events in patients with RA with high and low (A) aPWV, (B) AIx, (C) cIMT, and (D) CP. CVD: cardiovascular disease; RA: rheumatoid arthritis; aPWV: aortic pulse wave velocity; AIx: augmentation index; cIMT: carotid intima-media thickness; CP: carotid plaque.

that evidence concerning their value for predicting future CVD in patients with RA has been virtually nonexistent. Our results support further use of aPWV, cIMT, and CP as surrogate CVD endpoints in rheumatology research.

The observed rate of CVD events in our cohort (1.3 events per 100 patient-yrs) was surprisingly low. There may be several reasons for this. First, the median age in our cohort was relatively low (59.0 yrs) with regard to CVD risk, especially when considering the female majority in our patients. Second, the levels of inflammatory biomarkers and rheumatic disease activity in our patients were modest, implying a lower CVD risk. Third, most traditional CVD risk factors (e.g., lipids, smoking, body mass index, and BP) were inside a normal range, suggesting that the patients were either healthy or well treated.

The gold standard measure of arterial stiffness[33] — aPWV — has a good predictive value for future CVD in several populations[10,12]. Further, aPWV retains its predictive value for CVD events after adjustments for commonly used CVD risk algorithms[46,47]. Interestingly, the predictive value of aPWV appears to be higher in conditions with high CVD risk[10], which is in line with our results.

We were unable to reach a final conclusion regarding the predictive value of AIx for future CVD events. When AIx was evaluated as a dichotomous variable, the group with higher AIx was significantly more likely to experience CVD

Table 3. Adjusted Cox proportional hazards models for vascular biomarkers as predictors of cardiovascular disease events. Because of the separation of the events, we were not able to assess CP as a predictor for CVD events using Cox proportional hazards regression. The HR with 95% CI are estimated from a proportional hazards model including the vascular biomarker in addition to 1 additional covariate.

Variables	aPWV, HR (95% CI), p	AIx, HR (95% CI), p	IMT, HR (95% CI), p
Unadjusted	1.85 (1.33–2.57), < 0.001	1.05 (0.98–1.13), 0.19	1.65 (1.27–2.13), < 0.001
Adjusted for demographic variables			
Age, yrs	1.66 (1.11–2.49), 0.01	1.02 (0.94–1.11), 0.61	1.53 (1.14–2.05), < 0.005
Male	1.82 (1.27–2.61), 0.001	1.08 (0.99–1.17), 0.07	1.57 (1.20–2.04), 0.001
BMI, kg/m^2	1.85 (1.33–2.57), < 0.001	1.05 (0.98–1.14), 0.18	1.62 (1.26–2.07), < 0.001
Adjusted for traditional CVD risk factors			
TC, mmol/l	1.83 (1.29–2.61), < 0.001	1.04 (0.96–1.13), 0.35	1.72 (1.28–2.30), < 0.001
LDL-C, mmol/l	1.91 (1.34–2.73), < 0.001	1.05 (0.97–1.13), 0.25	1.67 (1.27–2.19), < 0.001
HDL-C, (mmol/l	1.95 (1.35–2.82), < 0.001	1.05 (0.97–1.13), 0.25	1.72 (1.29–2.29), < 0.001
TG, mmol/l	1.88 (1.34–2.65), < 0.001	1.05 (0.97–1.13), 0.22	1.70 (1.29–2.22), < 0.001
SysBP, mmHg	1.84 (1.29–2.62), 0.001	1.03 (0.95–1.12), 0.53	1.62 (1.23–2.13), 0.001
DiaBP, mmHg	1.89 (1.35–2.64), < 0.001	1.05 (0.97–1.14), 0.24	1.78 (1.29–2.45), < 0.001
Smoker, daily	1.91 (1.34–2.71), < 0.001	1.06 (0.98–1.16), 0.14	1.65 (1.26–2.16), < 0.001
Former smoker, daily	1.91 (1.34–2.71), < 0.001	1.06 (0.98–1.14), 0.17	1.76 (1.28–2.42), < 0.001
Adjusted for rheumatology disease variables			
Disease duration, yrs	1.85 (1.33–2.57), < 0.001	1.05 (0.98–1.13), 0.20	1.66 (1.28–2.15), < 0.001
CRP, mg/dl	1.90 (1.33–2.72), < 0.001	1.05 (0.97–1.14), 0.22	1.68 (1.28–2.22), < 0.001
ESR, mm/h	1.91 (1.34–2.71), < 0.001	1.04 (0.97–1.13), 0.27	1.63 (1.23–2.16), 0.001
DAS28	1.87 (1.30–2.70), 0.001	1.07 (0.98–1.16), 0.13	1.82 (1.32–2.51), < 0.001
Adjusted for CV comorbidities			
Hypertension	1.89 (1.34–2.68), < 0.001	1.04 (0.96–1.12), 0.38	1.59 (1.20–2.11), 0.001
Diabetes mellitus	1.85 (1.33–2.56), < 0.001	1.05 (0.98–1.13), 0.20	1.65 (1.28–2.14), < 0.001
Previous CVD	1.88 (1.36–2.59), < 0.001	1.05 (0.98–1.13), 0.20	1.64 (1.27–2.11), < 0.001
Adjusted for medication use			
Anti-HT	1.87 (1.38–2.53), < 0.001	1.05 (0.98–1.13), 0.19	1.76 (1.31–2.37), < 0.001
Statins	1.80 (1.25–2.59), 0.002	1.06 (0.99–1.14), 0.11	1.52 (1.16–1.98), 0.002
bDMARD	1.88 (1.35–2.63), < 0.001	1.05 (0.98–1.13), 0.20	1.61 (1.25–2.07), < 0.001
sDMARD	1.79 (1.29–2.48), < 0.001	1.04 (0.97–1.12), 0.23	1.56 (1.21–2.01), 0.001
sDMARD only	1.79 (1.28–2.51), < 0.001	1.05 (0.97–1.13), 0.22	1.64 (1.26–2.14), < 0.001
Corticosteroids	1.63 (1.18–2.23), 0.003	1.04 (0.96–1.12), 0.33	1.79 (1.33–2.42), < 0.001
NSAID	1.89 (1.34–2.67), < 0.001	1.05 (0.98–1.13), 0.19	1.65 (1.28–2.12), < 0.001

CP: carotid plaques; CVD: cardiovascular disease; aPWV: aortic pulse wave velocity; AIx: augmentation index; IMT: intima-media thickness; BMI: body mass index; TC: total cholesterol; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TG: triglycerides; sysBP: systolic blood pressure; diaBP: diastolic blood pressure; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: Disease Activity Score in 28 joints; anti-HT: antihypertensive medication; DMARD: disease-modifying antirheumatic drugs; bDMARD: biologic DMARD; sDMARD: synthetic DMARD; NSAID: nonsteroidal antiinflammatory drugs.

events. However, nonsignificant estimates were yielded when AIx was evaluated as a continuous variable. In a metaanalysis, Vlachopoulos, *et al* found that AIx has a predictive value for CVD events, although there was significant heterogeneity among the included studies[11]. Moreover, a study consisting of over 3000 subjects from the general population reported that AIx predicted CVD events in men, but not in women[39]. This could have possible implications for the RA population, in which there exists a female preponderance[48]. However, the low number of CVD events in our study prohibited further investigation of this hypothesis.

Our results support the conclusion of a small study (n = 47) by Gonzalez-Juanatey, *et al* that cIMT has a good predictive value for future CVD events in patients with RA[16]. There is a current debate concerning the usefulness of cIMT measurement as a clinical tool in CVD risk evaluation. In the 2013 American College of Cardiology/American Heart Association guideline on the assessment of CVD risk, cIMT measurements were no longer recommended in risk assessment for a first CVD event[49]. The strongest evidence for downgrading this recommendation was the results from a 2012 metaanalysis, in which cIMT had minimal predictive value when added to the Framingham Risk Score[18,49,50]. However, the authors of a 2013 metaanalysis concluded that the heterogeneity of current evidence precludes a conclusion on whether the addition of cIMT to CVD risk algorithms will have incremental value for CVD risk assessment in specific subgroups[17]. Taking into account that most CVD risk algorithms inaccurately predict future CVD events in patients with RA, the cIMT involvement in CVD risk prediction calculators for patients with RA has yet to be determined.

CP at baseline were predictive of future CVD events in our cohort. However, because of the complete separation of the events, we were not able to estimate the HR with Cox PH regression. Our results are in line with previous evidence showing that CP in patients with RA are associated with

future acute coronary syndromes and poor CVD-free survival[24,51].

Because the CVD outcomes in our study were collected by telephone questionnaires, recall bias could have affected the observed CVD event rate. The possibility that recall bias could have augmented the event rate was excluded by collecting medical discharge summaries. Even so, some CVD events may have been missed. The relatively low number of CVD events represents a limitation to our study. Strict adherence to the rule of 10 events per variable would preclude fitting additional covariates into the Cox PH regression models. However, there is room for relaxing this rule, albeit increasing the risk of Type I error and relative bias[40]. The adjusted results in our paper should be considered with this limitation in mind. Also, the low number of events may explain why AIx was not significant in the Cox PH regression analyses. A further limitation is that the low number of CVD events prohibited the evaluation of the additive value of the vascular biomarkers to estimation of CVD risk using traditional risk calculators. One should also be aware that the relatively long disease duration in this patient cohort may limit the generalizability to populations with shorter disease duration.

To our knowledge, our present study provides the first evidence that aPWV has an independent predictive value for future CVD events in patients with RA. The study also substantiates the existing evidence concerning the predictive value of cIMT and CP for CVD in this population. Future studies are warranted to examine the additive value of arterial stiffness and carotid artery atherosclerosis in estimation of CVD risk by current risk algorithms.

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ONLINE SUPPLEMENT

Supplementary data for this article are available online at jrheum.org.

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