Traditional and Nontraditional Cardiovascular Risk Factors Are Associated with Atherosclerosis in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine the association between cardiovascular (CV) risk factors and atherosclerosis in patients with rheumatoid arthritis (RA).

Methods. The common carotid artery intima-media thickness (IMT) and plaque were evaluated by high resolution B-mode ultrasound in 74 consecutive patients with RA. Patients with an IMT ≥ 0.60 mm and plaque were considered to have atherosclerosis and advanced atherosclerosis, respectively. Traditional risk factors as well as an extensive range of other clinical and laboratory variables were recorded. Methods used to analyze the data included logistic regression, classification and regression tree (CART), and factor analyses.

Results. Fifty-three (72%) patients had atherosclerosis, 23 (31%) had plaque, and 21 (28%) were free of atherosclerosis. In multivariable analysis, age and hypertension were independently associated with atherosclerosis and plaque ($p \leq 0.04$). Radiographic scores and polymorphonuclear cell counts were also strongly associated with plaque ($p \leq 0.008$). Uric acid concentrations were associated with atherosclerosis, and hypothyroidism was associated with plaque, both with borderline significance ($p = 0.078$ and 0.052, respectively). In CART analysis, age, polymorphonuclear cell counts, and joint space narrowing in the hands were considered to be the most important determinants of plaque, and 62% of patients could be classified correctly after cross-validation. Factor analysis (varimax rotation) revealed that age and uric acid levels were related to low glomerular filtration rates, polymorphonuclear cell counts to disease activity, and radiographic scores to disease duration, and hypertension was associated with high cholesterol levels. The 10-year risk for a coronary event estimated using the Framingham risk equation (calculated from traditional risk factors) was only 7% in patients with plaque.

Conclusion. Atherosclerosis in RA is associated with the traditional CV risk factors age and hypertension, as well as nontraditional risk factors comprising current inflammation as reflected by polymorphonuclear cell counts, cumulative inflammation as disclosed by radiographic scores, and, to a lesser extent, with uric acid levels and hypothyroidism. Multiple risk factor assessment equations that are based on traditional risk factors only are likely to be insufficient to capture CV risk extent in RA. (J Rheumatol 2005;32:435–42)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ATHEROSCLEROSIS RISK FACTORS

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The high incidence of cardiovascular (CV) disease in rheumatoid arthritis (RA) is now well documented[1-3]. In the general population, age, male sex, total or low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, hypertension, diabetes, and smoking are the most recognized CV risk factors and are widely recommended in the prediction of CV events by their use in multiple risk factor assessment equations[4]. Systemic inflammation is also increasingly implicated in CV disease[5].

In RA, cytokine induced inflammation and insulin resistance were recently proposed as pivotal factors in RA atherogenesis[6]. Indeed, investigations have revealed that systemic inflammation is associated with CV disease and that acute-phase response related insulin resistance is common in RA[7]. Glucocorticoid use is also associated with insulin resist-

ance[8], diabetes mellitus[9], and CV events[10] in RA, while methotrexate (MTX) use was shown to be protective[11].

The search for CV risk factors has only started in RA. Apart from systemic inflammation, other potential nontraditional risk factors including subclinical hypothyroidism[12], elevated homocysteine concentrations[13], and cyclooxygenase-2 inhibitor use[14] have been implicated. Further, the prevalence of traditional risk factors may be increased in RA[8,15].

We evaluated the association between ultrasonographically identified markers of common carotid artery atherosclerosis and traditional as well as nontraditional CV risk factors in 74 unselected patients with RA.

MATERIALS AND METHODS

Patients. Seventy-four consecutive RA patients who were seen at one of our clinics (Milpark Hospital, Johannesburg) were enrolled. All patients met the American College of Rheumatology criteria for RA[16]. Only patients taking lipid-lowering or antidiabetic medications were excluded. Some patients had also participated in previous studies[8,12]. The study was approved by the Ethics Committee for Research on Human Subjects (Medical) of the University of Witwatersrand and the Milpark Hospital.

Methods. Using previously reported methods[4,8,17-22], we recorded a total of 99 patient characteristics as potential CV risk factors. These comprised demographic features, lifestyle factors, disease activity, duration and severity, drug therapy, clinical and biochemical features of the metabolic syndrome and other characteristics.

In addition to the laboratory variables noted in Table 1, fasting blood samples were obtained from all patients between 8:00 and 10:00 AM for the determination of a complete blood count (Celldyne flow cytometry with confirmation of abnormal results by light microscopy), rheumatoid factor (latex), LDL cholesterol, homocysteine (fluorescence polarization immunoassay; Abbott Diagnostics Division, Oslo, Norway), thyrotropin, and free thyroxine (2-site sandwich immunoassay using direct chemiluminometric technology; Bayer Corp., Tarrytown, NY, USA). Antithyroid peroxidase and antithyroglobulin antibodies (competitive immunoassay using chemiluminescence technology; Bayer) were measured in patients who had thyrotropin levels above the reference range (> 4 µIU/ml) and those who were taking thyroid hormone replacement therapy.

The 10-year risk for coronary events as determined by the traditional risk factors sex, age, total cholesterol, HDL cholesterol, systolic blood pressure, smoking status, and diabetes was estimated by the Framingham risk equation[4]. The glomerular filtration rate was calculated using the Cockcroft-Gault equation[22]. In accord with our previous study, patients with a Quantitative Insulin Sensitivity Check Index of < 0.393 were considered to be insulin resistant[8].

The common carotid arteries were evaluated with high resolution B-mode ultrasound (Image Point, Hewlett Packard, Andover, MA, USA) using a linear array 7.5-MHz probe (L7535) with a standardized setup. Patients were examined in the supine position. Both common carotid arteries were scanned longitudinally to visualize the intima-media complex of the far wall of the artery. The intima-media thickness (IMT) was measured at multiple sites more than 1 cm proximal to the common carotid artery flow divider. Multiple IMT measurements were made by computer analysis (M'ATH® Version 2.01, Metris, Argenteuil, France). The IMT was calculated for both the left and the right common carotid artery, and the common carotid artery intima-media thickness (CCA-IMT) was defined as the mean of these. Plaque was considered to be present when there was a localized irregular thickening of at least 1.5 mm[23]. All measurements were made by the same ultrasonographer (BS), who was blinded to the clinical history and risk factor profile of the patients. The coefficient of variation for the intraobserver variability was previously found to be 5.7% (r = 0.87; 95% confidence interval ± 0.06 of the observed value)[23].

Table 1. Baseline clinical and laboratory characteristics in 74 patients with RA. Methods used to evaluate the characteristics as reported[4,8,17-22].

Age, yrs	57 (27–81)
Women, n (%)	64 (86)
Caucasian: Asian (n:n)	68:6
Lifestyle	
Pack-year history of smoking*	0 (0–74)
Alcohol, units per week	0 (0–35)
Exercise, hours per week	0 (0–7)
Disease activity	
HAQ	0.625 (0–3)
VAS pain	3.2 (0–10)
VAS patient disease activity	3.2 (0–10)
VAS doctor disease activity	3.2 (0–10)
Tender joints	7 (0–36)
Swollen joints	2 (0–32)
ESR, mm/h	20 (1–111)
Hs-CRP, mg/l	10.8 (0.3–256)
Disease duration, yrs	11 (0.3–60)
Disease severity	
Deformed joints	9 (0–32)
Radiographic score**	24 (0–173)
Rheumatoid factor, IU/ml	94 (0–1286)
Rheumatoid factor positive, n (%)	60 (81)
Drug therapy	
Estrogen users, n (%)	24 (32)
Cumulative oral steroids, mg***	575 (0–107,263)
Cumulative pulsed steroids, mg†	1314 (0–23,299)
DMARD users, n (%)	56 (76)
Aspirin users, n (%)	6 (8)
Metabolic syndrome features	
Waist circumference, cm	85 (66–120)
Hypertension, n (%)	36 (49)
Systolic BP, mm Hg	124 (98–164)
Diastolic BP, mm Hg	82 (67–109)
HDL cholesterol, mmol/l	1.6 (0.8–2.6)
Triglycerides, mmol/l	1.2 (0.5–2.6)
QUICKI	0.373 (0.267–0.481)
Diabetes, n (%)	5 (7)
Uric acid, mmol/l	0.28 (0.12–0.58)
Other	
Hypothyroidism, n (%)	18 (24)
Homocysteine, µmol/l	11.7 (5.4–24.7)
Polymorphonuclear cell count, n × 10^6/l	4.3 (0.41–10.3)
Glomerular filtration rate, ml/min	79 (30–143)
Total cholesterol, mmol/l	5.1 (3.5–7.5)
LDL cholesterol, mmol/l	2.9 (1.5–5.0)
Urinary albumin/creatinine, mg/mmol	8.3 (2.7–421)
10-year risk for coronary event, %	6 (0–31)

* Average number of cigarettes smoked daily × years smoked ÷ 20; ** evaluated using the Sharp/van der Heijde method; *** comprising cumulative prednisone dose; † comprising cumulative prednisone equivalent dose used intraarticularly, intramuscularly, and/or intravenously. VAS: visual analog scale; ESR: erythrocyte sedimentation rate; hs-CRP: high sensitivity C-reactive protein; DMARD: disease modifying agent for rheumatic disease; QUICKI: Quantitative Insulin Sensitivity Check Index; HAQ: Health Assessment Questionnaire.

Statistical analysis. Results were expressed as median (range) unless indicated otherwise. In accord with previous reports, patients with a CCA-IMT < 0.60 mm and no plaque were considered to be free of atherosclerosis[23,24]. A CCA-IMT ≥ 0.60 mm is a marker of atherosclerosis and plaque indica-

tive of advanced atherosclerosis[23,24]. Patient characteristics were compared between patients with and without atherosclerosis and between patients with and without plaque with Mann-Whitney U and chi-square tests. Associations between patient characteristics and atherosclerosis and plaque, respectively, were further analyzed by simple logistic regression analysis. Subsequently, the most explanatory multivariable models for atherosclerosis and plaque were constructed based on considering the strength of associations in univariate analysis, interactions, and causality. The correlation between radiographic scores and joint deformities was determined by the Spearman correlation coefficient.

To determine whether alternative models existed, the data were assessed by classification and regression tree (CART) analysis[25]. Plaque was entered as the dependent variable and all 99 recorded patient characteristics (other than the outcome variables) were used. CART analysis is a multivariable analysis that also performs a 10-fold cross-validation, providing an estimate of the expected correct classification of cases if the model was derived from samples taken from the community at large in contrast to one's own center.

Finally, factor analysis with varimax rotation[26] was used to elucidate whether the patient characteristics that were associated with the carotid artery findings in previous analyses reflected different RA features or not. Varimax rotation results in an orthogonal analysis that reveals uncorrelated factors, and in which factor loadings are equivalent to bivariate correlations between the observed variables and the components[26]. Five factors were retained and variables with factor loadings ≥ 0.44 were considered to contribute to the factor. Statistical computations were made using Stata v. 8.2 (Stata Corp., College Station, TX, USA) and CART v. 4.0 (Salford Systems, San Diego, CA, USA). P values < 0.05 and ≥ 0.05 to < 0.1 were considered significant and borderline significant, respectively.

RESULTS

Patient characteristics. The most relevant baseline characteristics are presented in Table 1. Ten patients were undergoing thyroxine replacement therapy. Another 8 were found to have subclinical hypothyroidism (thyroid-stimulating hormone > 4 μIU/ml and normal thyroxine levels)[12]. Fifteen (83%) of these patients had elevated thyroid antibody titers. The glomerular filtration rate (GFR) was < 90 ml/min in 52 (70%) patients and < 60 ml/min in 16 (22%) patients.

Common carotid artery atherosclerosis. Twenty-one (28%) patients had no atherosclerosis, 53 (72%) had atherosclerosis, and 23 (31%) had plaque. The median CCA-IMT was 0.654 (range 0.496–1.15) mm.

Univariate analysis of atherosclerosis and plaque. The CV risk factors that differed between the subgroups are shown in Table 2. Age, the prevalence of hypertension, systolic blood pressure, uric acid levels, waist circumference, and the GFR were markedly higher in patients with atherosclerosis compared to those without atherosclerosis. Patients with plaque were also significantly older and more often hypertensive than those without plaque. In addition, they had longer disease duration, higher joint deformity counts and radiographic scores, higher triglyceride levels, lower insulin sensitivity, and higher polymorphonuclear cell counts, and they were more often hypothyroid than patients without plaque. In other words, several nontraditional and RA related CV risk factors were associated with plaque. The 10-year risk for a coronary event according to the Framingham risk equation[4] was only 7% in patients with plaque.

The relevant significant and nonsignificant associations between CV risk factors and atherosclerosis and plaque, respectively, as determined in logistic regression analysis, are presented in Table 3. These results confirm the associations between the CV risk factors disease duration, joint deformities, radiographic scores, hypothyroidism, polymorphonuclear cell counts, and plaque. They also show that apart from age and hypertension, the other traditional risk

Table 2. Cardiovascular risk factors in patients without versus with atherosclerosis and without versus with plaque.

Variable	No Atherosclerosis, n = 21	Atherosclerosis, n = 53	p	No Plaque, n = 51	Plaque, n = 23	p
Age, yrs	46 (27–74)	59 (40–81)	< 0.0001	55 (27–75)	60 (47–81)	0.002
Disease duration, yrs	7.8 (0.4–25)	12 (0.3–60)	0.381	8 (0.3–29)	14 (0.4–60)	0.016
Disease severity						
Deformed joints	1 (0–31)	10 (0–32)	0.076	5 (0–31)	14 (0–32)	0.002
Total radiographic score	18 (0–143)	28 (0–173)	0.684	15 (0–173)	54 (0–159)	0.010
Metabolic syndrome						
Waist, cm	80 (66–106)	88 (69–120)	0.015	84 (66–114)	91 (70–120)	0.144
Hypertension, n (%)	3 (14)	33 (62)	0.002	19 (37)	17 (74)	0.004
Systolic BP, mm Hg	120 (102–140)	130 (98–164)	0.002	122 (98–164)	132 (102–160)	0.195
Triglycerides, mmol/l	0.9 (0.7–2.5)	1.3 (0.5–2.6)	0.094	1.1 (0.5–2.6)	1.3 (0.6–2.5)	0.038
QUICKI	0.384 (0.333–0.481)	0.371(0.267–0.400)	0.099	0.384 (0.267–0.481)	0.359 (0.268–0.460)	0.040
Uric acid, mmol/l	0.26 (0.15–0.34)	0.30 (0.12–0.58)	0.005	0.28 (0.12–0.47)	0.32 (0.13–0.58)	0.064
Other						
Hypothyroidism, n (%)	2 (10)	16 (30)	0.062	8 (16)	10 (43)	0.010
Polymorphonuclear count, n × 10^6/l	4.2 (2.6–8.8)	4.3 (0.4–10)	0.577	4.1 (1.3–8.8)	4.9 (0.4–10.3)	0.024
Glomerular filtration rate, ml/min	88 (55–137)	74 (30–143)	0.003	83 (32–143)	65 (30–135)	0.111
10-year risk for coronary event, %	2 (0–13)	7 (2–31)	< 0.0001	5 (0–31)	7 (2–24)	0.005

QUICKI: Quantitative Insulin Sensitivity Check Index. Analysis by Mann-Whitney U and chi-square tests.

Table 3. Univariate logistic models for atherosclerosis and plaque.

Variable	Atherosclerosis OR	Atherosclerosis p	Atherosclerosis 95% CI	Plaque OR	Plaque p	Plaque 95% CI
Age/10, yrs	5.41	< 0.0001	2.31, 12.69	2.43	0.004	1.30, 4.54
Female, yes/no	0.59	0.531	0.12, 3.05	0.63	0.515	0.16, 2.50
Asian, yes/no	0.17	0.049	0.03, 0.99	0.42	0.439	0.05, 3.80
Lifestyle						
Pack-year history of smoking, 0–74	1.02	0.320	0.98, 1.05	2.49	0.341	0.81, 7.63
Disease activity						
HAQ, 0–3	1.17	0.604	0.65, 2.09	1.29	0.365	0.75, 2.22
Pain, 0–10	1.00	0.807	0.99, 1.02	1.00	0.796	0.99, 1.02
Tender joints, 0–36	1.00	0.901	0.95, 1.06	1.02	0.400	0.97, 1.07
Swollen joints, 0–32	1.05	0.310	0.96, 1.14	1.06	0.102	0.99, 1.14
ESR, 1–111 mm/h	1.00	0.954	0.98, 1.02	1.00	0.462	0.98, 1.01
Hs-CRP, 0.3–256 mg/l	1.01	0.430	0.99, 1.01	1.00	0.711	0.99, 1.01
Disease duration, 0.3–60 yrs	1.04	0.232	0.99, 1.10	1.07	0.013	1.01, 1.13
Disease severity						
Deformed joints, 0–32	1.05	0.124	0.99, 1.11	1.09	0.002	1.03, 1.15
Total radiographic score, 0–173	1.00	0.479	0.99, 1.02	1.01	0.009	1.00, 1.02
RF positive, yes/no	3.29	0.053	0.98, 10.00	1.16	0.822	0.32, 4.17
Drug therapy						
COX-2 inhibitor use, yes/no	0.99	0.851	0.29, 2.77	0.67	0.493	0.21, 2.13
Estrogen use, yes/no	1.79	0.322	0.57, 5.65	1.54	0.410	0.55, 4.33
Cumulative oral steroids, 0–107,263 mg	1.00	0.178	1.00, 1.00	1.00	0.288	1.00, 1.00
Cumulative pulse steroids, 0–23,299 mg	1.00	0.960	1.00, 1.00	1.00	0.479	1.00, 1.00
DMARD use, yes/no	1.37	0.593	0.44, 4.29	1.23	0.728	0.38, 3.98
Metabolic syndrome						
Waist circumference, 66–120 cm	1.06	0.019	1.01, 1.11	1.03	0.098	0.99, 1.07
Hypertension, yes/no	9.90	0.001	2.59, 37.90	4.77	0.005	1.60, 14.20
Systolic BP, 98–164 mm Hg	1.06	0.006	1.02, 1.11	1.02	0.210	0.99, 1.05
Diastolic BP, 67–109 mm Hg	1.07	0.060	1.00, 1.14	0.98	0.550	0.93, 1.04
Triglycerides, 0.5–2.6 mmol/l	2.71	0.096	0.84, 8.73	2.38	0.077	0.91, 6.21
HDL cholesterol, 0.8–2.6 mmol/l	1.19	0.771	0.37, 3.81	1.33	0.622	0.43, 4.09
QUICKI × 10, 2.67–4.81	0.25	0.042	0.06, 0.95	0.27	0.051	0.07, 1.01
Uric acid × 10, 1.2–5.8 mmol/l	2.91	0.006	1.36, 6.25	1.85	0.034	1.05, 3.25
Other						
Hypothyroidism, yes/no	4.11	0.078	0.85, 19.76	4.13	0.013	1.35, 12.64
Homocysteine, 5.4–24.7 µmol/l	1.09	0.253	0.94, 1.26	0.98	0.779	0.86, 1.12
Polymorphonuclear count, 0.41–10.3 × 10^6/l	1.03	0.864	0.76, 1.40	1.39	0.043	1.01, 1.90
Glomerular filtration rate, 30–143 ml/min	0.97	0.0009	0.95, 0.99	0.98	0.090	0.96, 1.00
Total cholesterol, 3.5–7.5 mmol/l	0.74	0.274	0.43, 1.27	0.97	0.923	0.58, 1.65
LDL cholesterol, 1.48–4.96 mmol/l	0.82	0.562	0.42, 1.60	1.07	0.840	0.55, 2.06
10-year risk for coronary event, 0–31%	1.47	< 0.0001	1.19, 1.81	1.11	0.034	1.01, 1.22

QUICKI: Quantitative Insulin Sensitivity Check Index.

factors (sex, total cholesterol, HDL cholesterol, and smoking) were not associated with atherosclerosis or plaque. All 5 diabetic patients had atherosclerosis and 2 had plaque.

Multivariable analysis of atherosclerosis and plaque. The "best" explanatory models for atherosclerosis and plaque are shown in Table 4. Age and hypertension were the most important predictors of atherosclerosis. When age was replaced by GFR, this model was not materially altered (results not shown). By contrast, the strongest predictors of plaque were the radiographic score and polymorphonuclear cell counts. Radiographic scores and joint deformities were strongly correlated (r_s = 0.808, p < 0.0001). When radiographic scores were replaced by deformed joints, this model was also not materially altered (results not shown). Uric acid contributed to atherosclerosis and hypothyroidism to plaque, both with borderline significance. According to these models, 87.8% of patients could be classified correctly for atherosclerosis and 82.4% for plaque.

The data for plaque were then assessed using CART analysis. Plaque was best predicted by age, joint space narrowing in the hands, and polymorphonuclear cell counts. Other alternative predictors of importance in CART analysis included total radiographic scores, pain, disease duration, 10-year risk for a coronary event, GFR, white cell counts, pulse pressure, microalbuminuria, and Health Assessment Questionnaire (HAQ) result. With all 99 patient characteristics entered, again a high percentage of patients were correctly classified: 85.1%. When age, joint space narrowing in

Table 4. Multivariable logistic models for atherosclerosis and plaque.

Variable	Atherosclerosis OR	p	95% CI	Plaque OR	p	95% CI
Age/10, yrs	4.32	0.001	1.81, 10.26	2.56	0.025	1.12, 5.81
Hypertension, yes/no	5.63	0.031	1.18, 26.95	4.30	0.038	1.09, 17.00
Uric acid × 10, mmol/l	2.38	0.078	0.91, 6.26			
Radiographic score				1.02	0.007	1.01, 1.03
Polymorphonuclear cell count, n × 10^6/l				1.84	0.008	1.17, 2.88
Hypothyroidism, yes/no				4.02	0.052	0.99, 16.39
	Sensitivity = 94.4 %; specificity = 71.4% PPV = 89.3%; NPV = 83.3% Correctly classified = 87.8%			Sensitivity = 69.6%; specificity = 88.2% PPV = 72.7%; NPV = 86.5% Correctly classified = 82.4%		

PPV: positive predictive value; NPV: negative predictive value.

Table 5. Multivariable logistic model for plaque based on the most important predictors in classification and regression tree (CART) analysis.

Variable	OR	p	95% CI
Age, yrs	1.11	0.007	1.03, 1.19
Polymorphonuclear count, n × 10^6/l	1.60	0.014	1.10, 2.31
Joint space narrowing in hands	1.03	0.011	1.01, 1.06
	Sensitivity = 47.8% specificity = 88.2% PPV = 64.7%; NPV = 79.0% Correctly classified = 75.7%		

PPV: positive predictive value; NPV: negative predictive value.

the hands, and polymorphonuclear cell counts were entered into a logistic regression analysis, 75.7% of patients were correctly classified (Table 5). However, in the CART 10-fold cross-validated model, correct classification was 62%. Cross-validated models incorporate information regarding uncertainty in the population and yield more conservative results. Taken together, the series of logistic and CART analyses indicate that several predictive models exist.

Factor analysis of the CV risk factors. Table 6 shows the factor analysis of the 99 recorded patient characteristics other than the outcome variables. Only the 54 variables that had loadings ≥ 0.44 for the first 5 factors are shown. The first factor represents the metabolic syndrome, the second disease duration, the third disease activity, the fourth hypertension and high cholesterol, and the fifth age. Hypothyroidism did not appear in any of the first 5 factors. The other previously identified variables that were strongly associated with atherosclerosis or plaque, namely age, hypertension, radiographic scores, and polymorphonuclear cell counts, were found in different factors. In other words, they were each associated with different RA characteristics.

DISCUSSION

In our study on unselected patients with RA, univariate and multivariable analyses revealed that age and hypertension were strongly associated with atherosclerosis, and that age, hypertension, radiographic scores, and polymorphonuclear cell counts were strongly associated with advanced atherosclerosis or the presence of plaque. For example, compared to normotensive patients, hypertensive patients were 9.9-fold more likely to have atherosclerosis and 4.8-fold more likely to have plaque, and a one unit (n × 10^6/l) increase in polymorphonuclear cell count was associated with an odds ratio of 1.39 for plaque (Table 3). High uric acid concentrations were associated with atherosclerosis and hypothyroidism was associated with plaque, both with borderline significance. Hyperuricemia as well as hypothyroidism are recognized independent CV risk factors in the general population[12,27,28]. Factor analysis disclosed that these risk factors represented different aspects of RA. Thus, age and high uric acid levels were associated with renal impairment, hypertension was related to hypercholesterolemia, radiographic scores were related to disease duration or cumulative inflammation, and polymorphonuclear cell counts to disease activity or current inflammation. Hypothyroidism did not appear in the first 5 factors and was also not considered important in the CART analysis.

Renal impairment was as strongly predictive of atherosclerosis as was age, and both variables were collinear. Indeed, age is used in the Cockcroft-Gault equation for GFR[22]. The GFR was also less important than age in CART analysis. Accordingly, the GFR was not shown in multivariable models. Renal impairment, even of mild severity (GFR < 90 ml/min), is reportedly an important independent CV risk factor[22]. Joint deformity counts predicted plaque as strongly as radiographic scores, but again both risk factors were collinear and hence the joint deformity score was not shown in multivariable models. When radiographic scores are not available, joint deformity counts could also be used as a predictor of plaque.

Polymorphonuclear cell counts were previously reported to predict mortality in RA, and to be related to disease activity as well as glucocorticoid use[29]. In our study, only 11 (15%) patients were taking oral prednisone. White cell counts are independently associated with coronary events[30]

Table 6. Varimax rotated factor loadings in 74 patients with RA.

Variable	Factor Loadings 1	2	3	4	5
Age	0.010	0.231	0.200	0.253	**0.666**
HAQ Disability Index	0.279	0.105	**0.743**	0.107	–0.055
Pain	0.218	–0.091	**0.822**	0.046	–0.061
Tension	–0.038	–0.160	**0.480**	0.314	–0.304
Depression	0.139	–0.122	**0.733**	0.144	–0.168
Helplessness	0.046	–0.062	**0.764**	0.078	–0.110
Fatigue	0.135	–0.031	**0.584**	0.056	–0.206
Patient disease activity	0.164	–0.061	**0.846**	0.009	–0.010
Doctor disease activity	0.162	–0.099	**0.889**	0.003	0.068
Tender joints	0.001	–0.052	**0.740**	0.137	0.096
Swollen joints	0.107	–0.024	**0.767**	–0.074	0.260
ESR	0.165	0.038	**0.655**	–0.158	0.042
High sensitivity CRP	–0.048	–0.091	**0.436**	–0.109	0.274
Disease duration	0.015	**0.773**	–0.132	0.098	0.104
Deformed joints	0.094	**0.898**	0.048	–0.013	0.112
Joint space narrowing in hands	0.059	**0.863**	–0.007	–0.023	0.056
Joint space narrowing in feet	–0.022	**0.709**	–0.215	0.082	0.125
Joint space narrowing in hands and feet	0.036	**0.896**	–0.082	0.012	0.086
Erosions in hands	–0.114	**0.726**	0.046	0.026	–0.047
Erosions in feet	–0.063	**0.684**	–0.150	–0.071	–0.143
Erosion in hands and feet	–0.096	**0.799**	–0.078	–0.035	–0.117
Total radiographic score	–0.017	**0.956**	–0.090	–0.007	0.007
Cumulative oral steroid use	0.079	**0.450**	0.086	0.136	0.122
Cumulative total steroid use	0.090	**0.456**	0.083	0.159	0.096
Current MTX use	–0.019	0.231	**–0.487**	–0.038	–0.073
Current DMARD use	0.064	0.156	**–0.565**	–0.130	–0.032
Waist circumference	**0.828**	–0.058	–0.001	0.140	0.104
Weight	**0.752**	–0.198	–0.053	0.100	–0.197
Body mass index	**0.698**	–0.137	0.119	0.227	–0.125
Hypertension	0.420	0.102	0.050	**0.608**	0.267
Systolic blood pressure	0.223	0.128	0.068	**0.761**	0.068
Diastolic blood pressure	0.392	0.010	0.015	**0.534**	–0.135
Pulse pressure	0.005	0.160	0.078	**0.606**	0.188
Mean blood pressure	0.343	0.073	0.044	**0.706**	–0.043
Glucose	**0.598**	–0.096	0.306	–0.259	0.060
Triglycerides	**0.607**	–0.117	0.282	0.293	0.009
Triglycerides/HDL cholesterol	**0.707**	0.034	0.347	0.011	0.011
Cholesterol/HDL cholesterol	**0.510**	–0.006	0.326	0.081	–0.151
Uric acid	0.410	0.041	–0.150	–0.060	**0.582**
Insulin	**0.764**	0.240	0.131	–0.080	–0.121
Homeostasis model assessment for Insulin resistance	**0.782**	0.170	0.196	–0.173	–0.102
QUICKI	**–0.824**	–0.037	–0.011	–0.089	–0.007
Insulin resistance	**0.497**	–0.088	–0.114	0.106	–0.028
Metabolic syndrome features	**0.776**	–0.005	0.286	0.193	0.154
Metabolic syndrome	**0.701**	–0.071	0.231	0.137	0.089
Diabetes	**0.487**	–0.146	0.155	–0.290	0.191
Homocysteine	0.059	–0.048	0.145	0.044	**0.454**
White blood cell count	0.059	–0.222	**0.477**	–0.148	–0.039
Polymorphonuclear cell count	0.023	–0.158	**0.470**	–0.163	0.017
Glomerular filtration rate	**0.474**	–0.136	–0.028	0.011	**–0.724**
Creatinine	0.126	–0.005	–0.143	–0.170	**0.704**
Total cholesterol	–0.015	–0.276	0.099	**0.659**	–0.264
LDL cholesterol	0.035	–0.185	0.102	**0.553**	–0.252
10-year risk for coronary event	**0.527**	–0.067	0.210	0.179	0.335

Only those variables with a loading ≥ 0.44 (bold type) in the first 5 factors are shown.
QUICKI: Quantitative Insulin Sensitivity Check Index.

and were recently shown to predict carotid artery IMT increases over time in patients with RA[31].

In our multivariable models, 76% to 88% (Tables 4 and 5) of patients could be correctly classified. These percentages are unexpectedly high, since they were based on 3 to 5 variables only. The pathogenesis of cardiovascular disease is complex and despite extensive studies, risk prediction models based on traditional CV risk factors as in the Framingham equation fail to predict coronary heart disease in 25% to 50% of cases in the population at large[32]. The 66% correct classification after cross-validation by CART is therefore more realistic. This decrease in correct classification after cross-validation may also relate to the small size of our cohort and our cross-sectional design. For example, weaker risk factors such as elevated homocysteine and variables that often change over time, such as the HAQ and insulin sensitivity, may be found to be reliable predictors of CV disease in patients with RA if studied longitudinally and in a larger cohort. As well, 10 of our 18 hypothyroid patients were already undergoing replacement therapy at the time of the study, while the latter intervention was recently shown to reverse atherosclerosis[33]. Another limitation of our study is that we did not assess menopausal status. However, menopause contributes to atherosclerosis mainly through changes in lipid metabolism and hormonal alterations[34]. Lipids and estrogen use were recorded.

To further evaluate the relative importance of traditional and nontraditional risk factors in CV disease in RA, we calculated the 10-year risk for coronary events based on the Framingham risk equation. According to this method, the median 10-year risk was only 7% in patients with atherosclerosis as well as in those with plaque (Table 2). In a 10-year prospective study on 10,000 subjects, normal CCA-IMT without plaque, mild CCA-intima thickening without plaque, and the presence of plaque were associated with 0.0001%, 8.6%, and 39.3% (non-stenosing plaque) to 81.1% (stenosing plaque) CV event incidences, respectively[24]. The 10-year risk for coronary events may be grossly underestimated particularly in RA patients with plaque when calculated on the basis of traditional risk factors only. This has the practical implication that decisions regarding the need for primary preventive measures such as statin therapy cannot be based on CV risk as predicted by multiple traditional risk factor equations only in RA.

Finally, factor analysis of CV risk factors revealed other relevant findings. While hypertension and hyperuricemia are increasingly considered to be metabolic syndrome features in non-RA subjects[7,21], in our study cohort hypertension was more strongly associated with hypercholesterolemia, and high uric acid levels were more strongly related to impaired renal function. An *increased* GFR was associated with the metabolic syndrome. This was recently reported in the general population[35,36]. Insulin reduces norepinephrine induced glomerular efferent arteriolar constriction[36]. Insulin resistance could thereby have the effect of increasing the transcapillary pressure gradient by increasing efferent arteriolar resistance[36]. Hyperinsulinemia has also been shown to stimulate the production of growth factors such as insulin-like growth factor 1 and 2, which may promote glomerular hypertrophy[36]. Elevated homocysteine levels have been reported in patients with RA[13]. MTX use, disease activity, high creatinine levels, and cobalaminopenia were implicated[37,38]. In our cohort, all patients treated with MTX were receiving folate supplementation, and homocysteine was associated not with MTX use or disease activity, but with impaired renal function.

Risk factors that are associated with atherosclerosis in RA include the traditional risk factors age and hypertension, as well as the nontraditional risk factors comprising current inflammation as reflected by circulating polymorphonuclear cells, cumulative inflammation as disclosed by radiographic scores and joint deformity counts, and, to a lesser extent, hypothyroidism and hyperuricemia. Multiple risk factor assessment equations that are calculated from traditional risk factors only are likely to be insufficient to disclose CV risk extent in patients with RA. These findings should help in the understanding, identification, and treatment of cardiovascular disease in patients with RA.

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