Influence of Nonclassical Cardiovascular Risk Factors on the Accuracy of Predicting Subclinical Atherosclerosis in Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** To determine whether nontraditional risk factors increase the accuracy of predicting the presence of carotid artery plaque based on traditional cardiovascular risk factors only in patients with rheumatoid arthritis (RA).

Methods. We identified risk factors that were independently associated with ultrasonographically located plaque. In predicting carotid artery plaque, the area under the curve (AUC) of the receiver-operating characteristic (ROC) curve for the combination of traditional and nontraditional risk factors was compared to the AUC of the ROC curve for traditional risk factors and nontraditional risk factors considered separately in 91 patients with RA.

Results. Thirty-one (34%) patients had carotid artery plaque. The 3 traditional risk factors of age > 55 years, hypertension, and ever-smoking, and the 3 nontraditional risk factors of a disease duration > 8 years, polymorphonuclear cell count > 4.5×10^6/l, and hypothyroidism were each independently associated with the presence of plaque (odds ratios 2.08–8.78; p = 0.001–0.02). The percentage of patients with plaque was 0, 10%, 50%, and 83% in patients with 0–1, 2, 3, and 4–6 of these risk factors, respectively. In predicting plaque, the AUC of the ROC curve for the combination of traditional and nontraditional risk factors (0.90 ± 0.03) was greater than that for either traditional (0.80 ± 0.05; p = 0.006) or nontraditional (0.80 ± 0.04; p = 0.005) risk factors considered separately.

Conclusion. The combination of disease duration, polymorphonuclear cell counts, and thyroid status increased the accuracy of predicting subclinical atheroma in patients with RA. We believe that our findings merit external validation. (First Release April 15 2007; J Rheumatol 2007;34:943–51)

Key Indexing Terms:
RHEUMATOID ARTHRITIS ATHEROSCLEROSIS CARDIOVASCULAR RISK ASSESSMENT

Cardiovascular (CV) disease accounts for most of the increased mortality that is noted in patients with rheumatoid arthritis (RA)[1-7]. The presence of ultrasonographically identified carotid artery plaque[8-10], a reliable index of subclinical atherosclerosis that is associated with a 10-year risk for a CV event of ≥ 40%[10], has been reported to occur in up to 52% of patients with RA[11]. Previous case-control studies have indicated that a higher prevalence of traditional CV risk factors, such as smoking, hypertension, diabetes mellitus, and dyslipidemia, when considered alone, cannot explain the excess CV disease noted in RA[5,6,12]. Moreover, we have found that the median (range) 10-year risk for a CV event as calculated using the Framingham score, an equation that is based on traditional CV risk factors alone (age, sex, total cholesterol, HDL cholesterol, current smoking status, and diabetes mellitus), was only 7% (2%–24%) in patients with RA and carotid artery plaque[13]. Thus, better predictors of future CV risk are required in patients with RA.

Recently, the pathogenesis of increased CV disease in RA has been attributed to nontraditional CV risk factors that characterize RA, such as the degree of inflammation, the use of drug therapy, and concomitant hypothyroidism, that promote adverse changes in body size, blood pressure, glucose tolerance, and lipid or clotting profiles[7,11,12,14-30]. Indeed, we[13] and others[11] have shown that nontraditional CV risk factors predict the presence of carotid artery plaque as strongly as traditional CV risk factors in patients with RA. However, whether the use of nontraditional risk factors increases the accuracy of predicting CV disease has not been determined[24,30]. Therefore, our aim was to compare the accuracy of the combination of nontraditional and traditional CV risk factors with

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that of traditional risk factors used alone when predicting carotid artery plaque in patients with RA.

MATERIALS AND METHODS

Patients. The study was approved by the Ethics Committees for Research on Human Subjects (Medical) of the University of Witwatersrand and Milpark Hospital, Johannesburg. We studied 91 patients that met the American College of Rheumatology criteria for RA[31] and were seen at a clinic at the Milpark Hospital. These comprised the 74 consecutive patients that were enrolled in our previous investigation on atherosclerosis[13] and endothelial dysfunction[22] in RA together with another 17 consecutive patients that were evaluated during August 2006. Only patients taking lipid-lowering agents were excluded. Six patients had diabetes[32], but these were not using glucose-lowering agents and were treated with dietary intervention only. The lowest recorded glomerular filtration rate as estimated by the Cockroft-Gault equation[33] was 30 ml/min. Only 14 patients were prednisone users and the prednisone dose was only 2, 2.5, 3, 4, 5, and 10 mg/day in 3, 2, 3, 2, 3, and 1 patient, respectively. Twenty-four patients were not using disease modifying antirheumatic drugs (DMARD) and 16 (67%) of these were seen for the first time at our clinic. The DMARD used were methotrexate (n = 56), chloroquine (n = 30), minocycline (n = 14), leflunomide (n = 11), sulfasalazine (n = 7), and azathioprine (n = 6). In patients on DMARD, the number of the respective agents used was 1, 2, 3, and 4 in 25, 29, 11, and 2 patients, respectively. Thus, 42 (46%) patients were on combination DMARD. Only 3 patients were treated with a biological agent (infliximab) for ≤ 2 years.

Demographic, clinical, and laboratory data. These data (Table 1) were obtained through patient interview, physical examination, medical record review, and laboratory tests performed on fasting blood samples. We recorded demographic characteristics and lifestyle factors. Physical disability was assessed by the Health Assessment Questionnaire[34]. We recorded the 36-joint counts for tenderness, swelling, and deformities[35,36]. In addition, we determined the 28-joint count for tenderness and swelling (data not shown) to allow for calculation of the Disease Activity Score 28 (DAS28)[37] using the formula $0.56 \times \sqrt{}$(tender joint count 28) + $0.28 \times \sqrt{}$(swollen joint count 28) + 70 × ln (erythrocyte sedimentation rate) + 0.014 × visual analog scale (VAS) patient disease activity. Patients with DAS28 ≤ 2.4 were considered to have inactive disease (disease remission)[37]. The other disease activity markers that were evaluated consisted of the VAS for physician-evaluated disease activity and high sensitivity C-reactive protein [immunoturbidimetric assay performed on Olympus OSR 6185 (Olympus Diagnostics, Lismeehan, Ireland)]. We did not evaluate radiographic scores in the last 17 patients since, in our previous investigation[13], these correlated strongly with the joint counts for deformities ($r_s = 0.808$, $p < 0.0001$), and the number of deformed joints was an equally strong predictor of atherosclerosis as were radiographic scores. Apart from the oral corticosteroids and DMARD noted above, we recorded the use of parenteral (intraarticular, intramuscular, or/and intravenous) corticosteroids, estrogen, and antihypertensive agents. Blood pressure measurements were determined in accord with reported guidelines on the evaluation and treatment of hypertension[38]. Hypertension was diagnosed in patients with a blood pressure ≥ 140/90 mm Hg (as compared to 130/85 mm Hg in our previous report[13]) and in those employing antihypertensive agents. We measured lipid levels, fasting plasma glucose concentrations, serum insulin, and uric acid levels[13]. Insulin resistance was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR) using the formula (insulin (μU/ml) × glucose (mmol/l))/22.5. Diabetes was diagnosed in accord with the recent recommendations of the American Diabetes Association[32]. The 10-year risk for a coronary event was calculated using the Framingham score[39]. We measured serum homocysteine levels, total leukocyte and polymorphonuclear (PMN) cell counts, and thyrotropin and free thyroxine levels[40]. Seventeen patients had known hypothyroidism on thyroid replacement therapy. Another 8 patients had a raised thyrotropin level (> 4 μIU/ml) and normal free thyroxine levels, and were therefore diagnosed as having subclinical hypothyroidism[40].

Carotid artery plaque. Carotid artery plaque was defined as a localized irregular thickening ≥ 1.5 mm identified by high resolution B-mode ultrasonography (Image Point, Hewlett Packard, Andover, MA, USA). We also measured the common carotid artery intima-media thickness (CCA-IMT) more than 1 cm proximal to the common carotid artery flow divider. All ultrasonographic evaluations were performed by the same investigator, who was unaware of CV risk factor profiles of the patients. Further details of carotid artery ultrasonography in our unit have been reported[13].

Data analysis. Results are expressed as mean (95% confidence interval) or number (%) unless indicated otherwise. For non-normally distributed data, the geometric means (95% CI) are given, and these data were also logarithmically transformed prior to statistical analysis. Most variables recorded in patients with plaque were compared with those recorded in patients without plaque using the unpaired Student t test (continuous variables) and either the Fisher exact test or chi-square test as appropriate (dichotomous variables); the association of individual DMARD therapy (methotrexate, chloroquine, minocycline, leflunomide, sulfasalazine, or azathioprine) with the presence of plaque was assessed in univariate logistic regression models, plaque being entered as the dependent variable and the individual DMARD as independent variables.

In view of the large number of assessed CV risk factors, many comparisons were made. Therefore and instead of setting significance lower than the conventional < 0.05, we verified associations of CV risk factors with plaque in multivariable regression models with consideration of interactions, collinearity, and causality. Since 31 patients had plaque, we also took into account that entering more than 3 independent variables in logistic regression models may result in overfitting[41]. For the purpose of these multivariable analyses, CV risk factors that constituted continuous variables and for which threshold values for increased CV risk in RA are unavailable at this stage were dichotomized using the 95% CI of the respective characteristics in patients without plaque. The association between the presence or absence of plaque and the number of CV risk factors was determined by Fisher's exact test and in logistic regression models with the number of traditional or/and nontraditional CV risk factors considered as independent variables. To assess the accuracy of predicting carotid artery plaque, the areas under the curves (AUC) of the receiver-operating characteristic (ROC) curves were compared[42]. The AUC for the ROC curves for traditional CV risk factors together with nontraditional CV risk factors was compared to that of either traditional or nontraditional CV risk factors considered separately.

RESULTS

Characteristics of patients with and without plaque. The recorded characteristics in patients with (n = 31, 34%) and without plaque are shown in Table 1. With regard to traditional CV risk factors, patients with plaque were older, had a higher pack-year history of smoking, higher uric acid levels and HOMA-IR values, had a more frequent history of ever smoking, and were more often hypertensive and using antihypertensives (Table 1). Also, the 10-year risk for a coronary event, as calculated using the Framingham score, was higher in patients with plaque compared to those without plaque. With regard to nontraditional risk factors, patients with plaque had a longer RA disease duration, more deformed joints, and higher PMN cell and total leukocyte counts, and they were more often hypothyroid. The CCA-IMT was 0.106 mm higher in patients with plaque compared to those without plaque ($p < 0.0001$).

The HOMA-IR was associated with hypertension [1.56 (1.25–1.95) μU.mmol/ml.l in hypertensives (n = 34) and 1.01 (0.84–1.21) μU.mmol/ml.l in nonhypertensives (n = 60); p = 0.004], whereas uric acid levels were associated with age (R

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Table 1. Recorded characteristics in RA patients with and without plaque.

Characteristic	No Plaque, n = 60	Plaque, n = 31	p
Age, yrs	52 (49–55)	60 (57–63)	0.0004
Women, n (%)	52 (87)	24 (77)	0.3
Caucasian: Asian	54:6	30:1	0.3
Lifestyle factors			
Pack-year history of smoking*,**	1.5 (0.7–2.7)	5.5 (2.5–11.0)	0.01
Current smokers, n (%)	10 (17)	9 (29)	0.2
Ever smokers, n (%)	18 (30)	18 (58)	0.009
Current alcohol users, n (%)	22 (37)	12 (39)	0.9
Current exercisers, n (%)	17 (28)	7 (23)	0.6
Health Assessment Questionnaire disability	0.796 (0.578–1.013)	1.057 (0.706–1.407)	0.2
Disease activity			
Swollen joint count**	4 (2–5)	5 (2–9)	0.1
Tender joint count	9 (7–12)	12 (7–17)	0.3
Patient disease activity VAS	4.0 (3.1–4.8)	4.9 (3.4–6.3)	0.3
Physician disease activity VAS	3.3 (2.6–4.0)	4.0 (2.7–5.2)	0.4
Erythrocyte sedimentation rate, mm/h**	16 (11–22)	14 (9–21)	0.7
C-reactive protein, mg/l**	6.9 (4.7–10.1)	11.4 (7.1–18.1)	0.1
Disease activity score 28	3.7 (3.2–4.2)	3.8 (3.0–4.6)	0.9
Disease activity score 28 ≤ 2.4, n (%)	20 (33)	11 (35)	0.8
Disease duration**	6 (4–8)	10 (7–16)	0.04
Disease severity			
Deformed joint count**	3 (2–5)	8 (5–12)	0.01
Rheumatoid factor positive, n (%)	49 (82)	25 (81)	0.9
Drug therapy			
Cumulative oral corticosteroids, mg**†	106 (36–309)	142 (26–766)	0.2
Cumulative pulsed corticosteroids, mg**‡	343 (151–777)	713 (255–1993)	0.3
DMARD users, n (%)	44 (73)	23 (74)	0.9
Estrogen users, n (%)	15 (25)	9 (29)	0.7
Antihypertensive users, n (%)	10 (17)	17 (55)	0.002
Other traditional CV risk factors			
Hypertension, n (%)	15 (25)	19 (61)	0.0007
Systolic blood pressure, mm Hg	126 (122–130)	130 (123–137)	0.3
Diastolic blood pressure, mm Hg	83 (80–85)	81 (78–84)	0.4
Total cholesterol, mmol/l	5.1 (4.8–5.3)	5.0 (4.6–5.3)	0.7
LDL cholesterol, mmol/l	2.9 (2.7–3.1)	2.8 (2.5–3.1)	0.8
HDL cholesterol, mmol/l	1.6 (1.5–1.7)	1.6 (1.4–1.8)	0.9
Body mass index, kg/m^2	24.6 (23.4–25.8)	25.3 (23.5–27.0)	0.5
Waist circumference, cm	85 (82–88)	91 (86–96)	0.08
Diabetes, n (%)	3 (5)	3 (10)	0.3
HOMA-IR, μU.mmol/ml.l**	1.09 (0.92–1.29)	1.58 (1.20–2.08)	0.02
Uric acid, mmol/l	0.28 (0.16–0.30)	0.33 (0.29–0.37)	0.04
10-year risk for coronary event, %**¶	4 (3–5)	7 (5–9)	0.0006
10-year risk for CV event > 20%, n (%)	1 (2)	1 (3)	0.6
Other nontraditional CV risk factors			
Homocysteine, μmol/l	11.8 (10.8–12.7)	11.8 (10.2–13.3)	1.0
Total leukocyte count, × 10^6/l**	6.5 (6.1–7.0)	7.6 (6.7–8.5)	0.03
Polymorphonuclear cell count, × 10^6/l**	4.1 (3.8–4.5)	5.1 (4.4–5.8)	0.015
Glomerular filtration rate, ml/min	87 (80–94)	79 (69–88)	0.2
Overt or subclinical hypothyroidism, n (%)	11 (18)	14 (45)	0.007
CCA-IMT, mm**	0.622 (0.604–0.641)	0.728 (0.688–0.771)	< 0.0001

* Average number of cigarettes smoked daily by years smoked/20; ** geometric means (95% CI); † cumulative prednisone dose; ‡ cumulative prednisone equivalent dose used intraarticularly, intramuscularly, or/and intravenously; ¶ Framingham score. VAS: visual analog scale; DMARD: disease modifying antirheumatic drugs; CV: cardiovascular; LDL: low-density lipoprotein; HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; CCA-IMT: common cartoid artery intima-media thickness.

= 0.286, p = 0.006). HOMA-IR and uric acid levels were therefore not included in the subsequent multivariable analyses. Antihypertensive therapy was also not entered in multivariable analyses since the respective agents were only prescribed in patients with hypertension.

All patients receiving methotrexate were taking folic acid

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supplementation. Homocysteine levels were 11.1 (10.3–11.9) μmol/l in methotrexate users and 12.8 (11.2–14.4) μmol/l in non-methotrexate users (p = 0.06). Methotrexate [OR 0.65 (95% CI 0.27–1.60), p = 0.3], chloroquine [OR 0.76 (95% CI 0.29–1.97), p = 0.6], minocycline [OR 0.74 (95% CI 0.21–2.63), p = 0.6], leflunomide [OR 1.12 (95% CI 0.30–4.25), p = 0.9], sulfasalazine [OR 2.82 (95% CI 0.58–13.76), p = 0.2], or azathioprine use [OR 0.37 (95% CI 0.04–3.40), p = 0.4] was not associated with plaque.

Independent relationships between nontraditional CV risk factors and plaque. Independent associations of nontraditional CV risk factors with plaque are shown in Figure 1. These data include the crude associations of nontraditional CV risk factors with plaque; those adjusted for the number of traditional CV risk factors (age > 55 yrs as determined from the 95% CI for age in patients without plaque, ever-smoking, and hypertension); and those adjusted for the log-transformed 10-year risk for a coronary event calculated using the Framingham score. Importantly, a disease duration > 8 years, PMN cell count > 4.5 n × 10^6/l, and hypothyroidism were strong independent predictors of plaque. A disease duration > 8 years was also independently associated with plaque when age was adjusted for as a continuous variable [OR 4.02 (95% CI 1.41–11.44), p = 0.008].

In keeping with the results of a factor analysis in our previous investigation[13], the PMN cell count was associated with disease activity variables including the DAS28 (R = 0.26, p = 0.01), patient VAS for disease activity (R = 0.23, p = 0.03), physician VAS for disease activity (R = 0.33, p = 0.001), log swollen joint count (R = 0.28, p = 0.006), log C-reactive protein (R = 0.38, p = 0.0002), and log erythrocyte sedimentation rate (R = 0.21, p = 0.04). The PMN cell count and leukocyte count were strongly correlated (R = 0.93, p < 0.0001). The PMN cell count was 4.7 (3.3–6.1) and 4.4 (4.1–4.8) n × 10^6/l in current prednisone users (n = 14) and current non-prednisone users (n = 77), respectively (p = 0.5). The PMN cell count was not associated with the log current prednisone dose (R = 0.04, p = 0.7), the log cumulative oral corticosteroid dose (R = 0.10, p = 0.4), and the log cumulative pulsed corticosteroid dose (R = 0.03, p = 0.2). The log disease duration correlated with the log number of deformed joints (R = 0.54, p < 0.0001).

Independent relationships between traditional CV risk factors and plaque. Independent associations of traditional CV risk factors with plaque are shown in Figure 2. These data include the crude associations of traditional CV risk factors with plaque as well as those adjusted for the number of nontraditional CV risk factors. Age > 55 years, hypertension, and ever-smoking were strong independent predictors of plaque. A pack-year history of smoking > 2.7 was less strongly associated with plaque than was a history of ever smoking in multivariable logistic regression analysis (p = 0.04 vs p = 0.006, respectively).

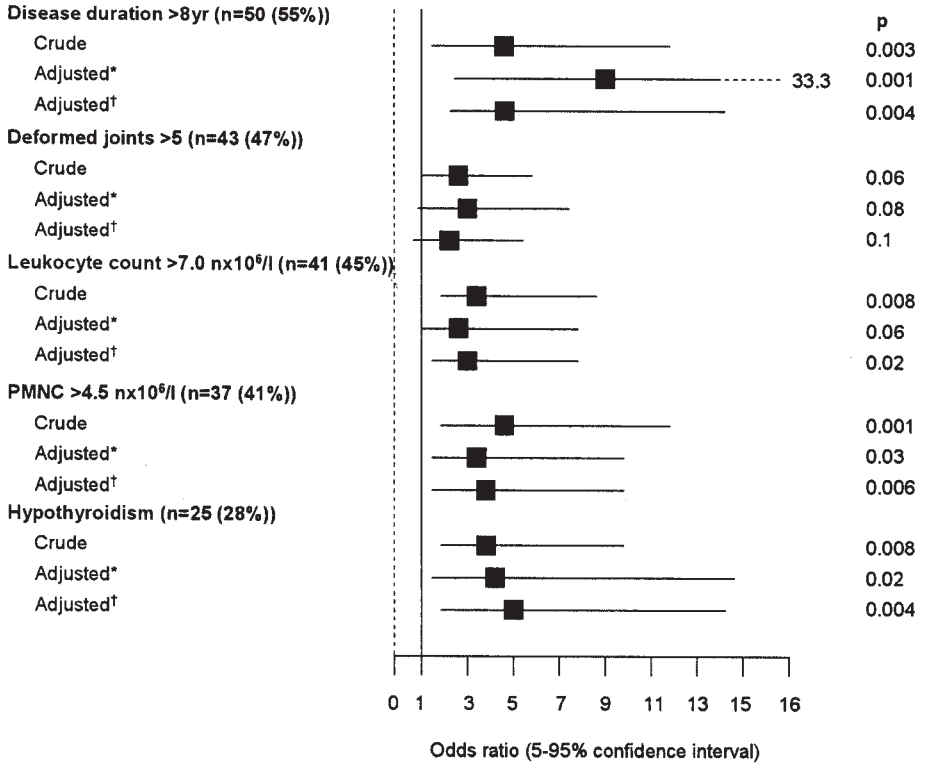

Figure 1. Associations of nontraditional CV risk factors with plaque. *Adjusted for number of traditional CV risk factors (age > 55 yrs, ever-smoking, and hypertension); †adjusted for log-transformed 10-year risk for a coronary event using the Framingham score. PMNC: polymorphonuclear cell count.

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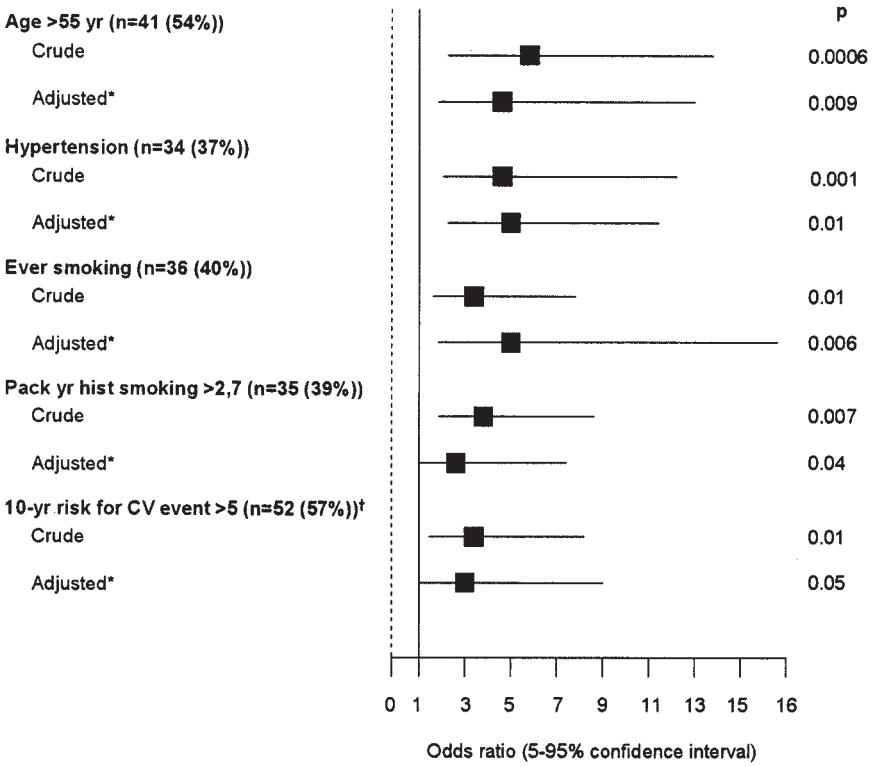

Figure 2. Associations of traditional CV risk factors with plaque. *Adjusted for number of nontraditional CV risk factors (disease duration > 8 yrs, PMN cell count > 4.5 n × 10^6/l, and hypothyroidism); †calculated using the Framingham score.

Relationships between the number of traditional and nontraditional CV risk factors and plaque. Each of the independent traditional and nontraditional CV risk factors identified in this study occurred in 28% to 55% of patients and were associated with a 2 to 5-fold increased risk for plaque (except for disease duration, which was associated with an 8.8-fold increased risk for plaque in the model adjusted for the number of traditional CV risk factors, Table 2) with extensively overlapping 5% to 95% confidence intervals. We recorded a total of 111 traditional and 112 nontraditional CV risk factors in the 91 patients with RA. The mean number of traditional and nontraditional CV risk factors per patient was 1.23 (95% CI 1.02–1.41) and 1.23 (95% CI 1.05–1.41), respectively.

In Figure 3, we show the association of plaque prevalence with the number of traditional and nontraditional CV risk factors. The percentage of patients with plaque was 0, 10%, 50%, and 83% in those with 0–1, 2, 3, and 4–6 CV risk factors, respectively. The increase in the frequency of patients with plaque in association with an increased number of CV risk factors was highly significant. Two of the patients with plaque had no traditional risk factors. By contrast, all patients with plaque had at least one nontraditional risk factor.

Table 2. Associations of number of traditional and nontraditional CV risk factors with plaque.

Variable	Model 1 OR (95% CI)	p	Model 2 OR (95% CI)	p	Model 3 OR (95% CI)	p
No. traditional CV risk factors, 0–3	4.20 (2.17–8.11)	< 0.0001			4.77 (2.07–10.92)	0.0002
No. nontraditional CV risk factors, 0–3			5.38 (2.50–11.58)	< 0.0001	5.69 (2.36–13.71)	0.0002
Diagnostic accuracy of the model, %						
Sensitivity	71		68		58	
Specificity	78		80		93	
Positive predictive value	63		64		82	
Negative predictive value	84		83		81	
Cases correctly classified, %	76		76		81	

In model 1, the number of traditional risk factors was entered as the independent variable and in model 2, the number of nontraditional risk factors was entered as the independent variable. In model 3, number of both traditional and nontraditional risk factors were considered. CV: cardiovascular.

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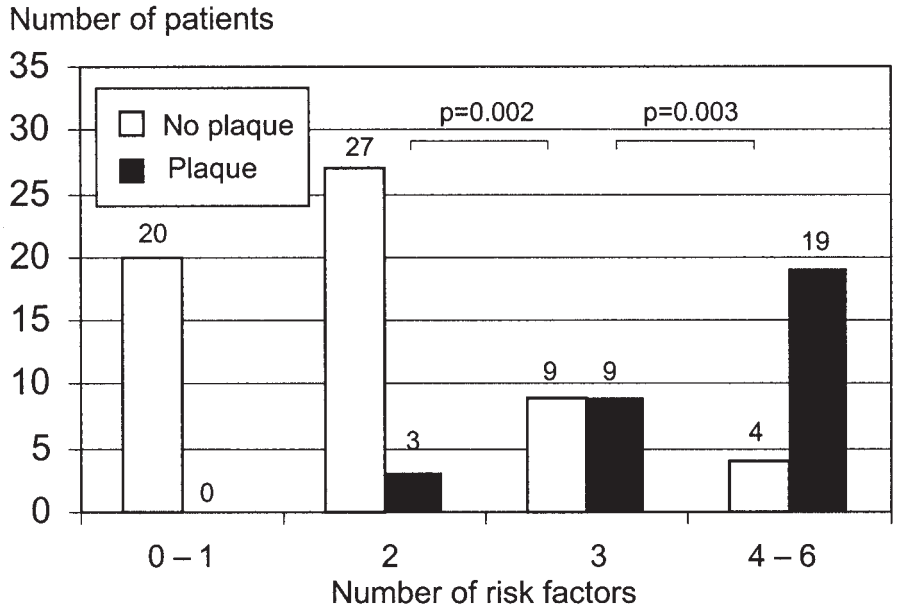

Figure 3. Numbers of patients with plaque in patients with 0 or 1, 2, 3, and 4 to 6 CV risk factors. Data were analyzed by Fisher's exact test.

Accuracy of detecting plaque using CV risk factor assessments. Seventy-six percent of patients were correctly classified in models in which the numbers of either traditional or nontraditional CV risk factors were entered as independent variables (models 1 and 2, respectively, in Table 2). The sensitivity, specificity, and positive and negative predictive value were also similar for both models. When the numbers of traditional and nontraditional CV risk factors were entered together in the model, 81% of patients were correctly classified (model 3 in Table 2). In this model, the sensitivity was lower whereas the specificity and positive predictive value were markedly higher compared to the 2 previous models.

ROC curves for diagnosis of the presence of plaque are shown in Figure 4. The AUC for the number of traditional risk

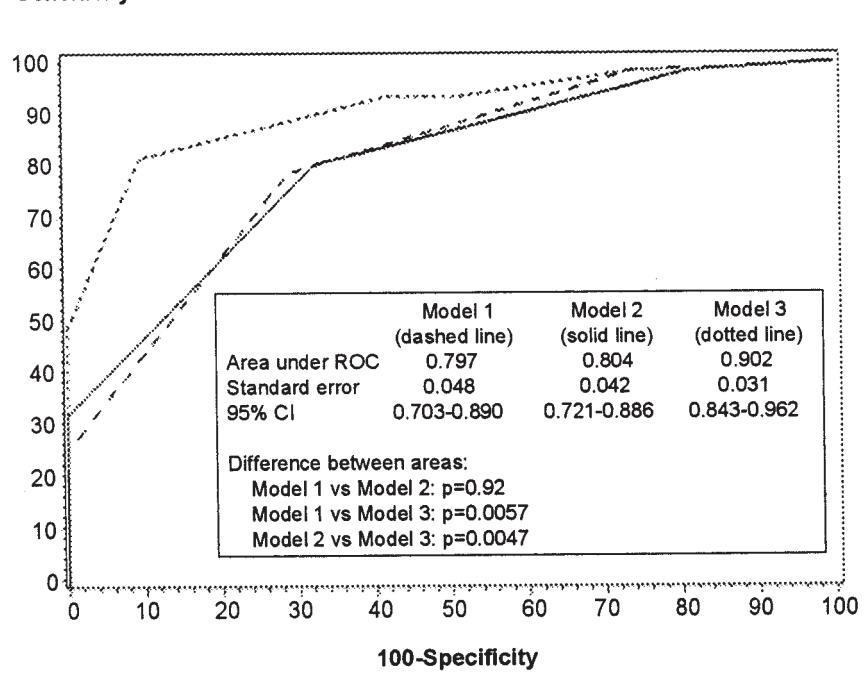

Figure 4. ROC curves for logistic regression models in which the number of traditional CV risk factors (broken line; Model 1 in Table 4), number of nontraditional CV risk factors (solid line; Model 2 in Table 4), and number of traditional and nontraditional CV risk factors (dotted line; Model 3 in Table 4) were entered as independent variables. Areas under the curves were compared as reported[41].

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factors entered as the independent variable was similar to that for the number of nontraditional risk factors entered as the independent variable. However, when traditional and nontraditional CV risk factors were considered together, the AUC was greater than that for traditional or nontraditional CV risk factors entered as separate components in the model, indicating a greater degree of accuracy in the diagnosis of carotid artery plaque. None of these findings was materially altered when each of the 6 risk factors identified in this study were entered as independent variables or when the independent variable of the number of traditional risk factors was replaced by the log 10-year risk for a CV event calculated using the Framingham score.

DISCUSSION

The main finding of our study is that, compared to the use of traditional CV risk factors only (in this investigation age > 55 yrs, hypertension, and ever-smoking; or 10-yr risk for a CV event using the Framingham score), the use of nontraditional CV risk factors associated with carotid artery plaque in RA, including a disease duration > 8 years, PMN cell count > 4.5 n × 10^6/l, and hypothyroidism, increased the accuracy of diagnosing the presence of carotid artery plaque when assessed in combination with traditional CV risk factors.

Although the relative contribution of individual traditional and nontraditional risk factors toward CV disease has to some extent been reported[11,13], there are no studies assessing whether the accuracy of diagnosing the presence of atheroma is improved by the inclusion of nontraditional CV risk factors in the overall risk assessment in RA. Our study provides clear evidence that the inclusion of nontraditional risk factors in the overall CV risk assessment in patients with RA does indeed enhance the accuracy of the diagnosis of carotid artery plaque. Importantly, there was a strong dose-response relationship between the number of these CV risk factors and the presence of plaque. Patients with no risk factor or one risk factor did not have plaque, whereas the prevalence of plaque was 10%, 50%, and 83% in those with 2, 3, and 4 to 6 risk factors, respectively.

Age, hypertension, smoking, and disease duration have been shown to be strongly associated with atherosclerosis in RA[11,16,17,19,23,25], and PMN cell counts were found to predict the progression of atherosclerosis[18] and mortality in RA[43]. Seventy-four (78%) patients in this cohort formed part of our recent report on atherosclerosis in RA[13]. Using a deeper analysis, we have confirmed our previously identified independent associations of age, hypertension, PMN cell counts, and hypothyroidism with plaque. In addition, we found that smoking and disease duration were strongly predictive of atherosclerosis in this investigation. Taken together, our data support findings reported by others.

High-grade inflammation-mediated insulin resistance has been suspected to contribute to atherogenesis in RA and this was recently documented[44]. Our results further confirm an association of insulin resistance with carotid artery plaque in patients with RA. However, since insulin resistance was associated with hypertension, it was not assessed further in multivariable analysis. Also, since antihypertensive therapy reflected previously diagnosed hypertension, this variable was not entered in multivariable analysis.

With respect to the potential mechanism responsible for increased PMN cell counts in RA, corticosteroids are known to increase PMN cell counts through demargination[45]. An association of PMN cell counts with corticosteroid therapy as well as with disease activity in RA has been reported[43]. In our previous[13] and current investigations, corticosteroids were used very sparingly, and the PMN cell count was strongly associated with current disease activity and inflammation. Leukocytes were shown to be associated with atherosclerosis in non-RA subjects[46]. It was reported that in active RA, PMN cells produce excessive amounts of S100A8 and S100A9[47], 2 calcium-binding proteins that induce expression of endothelial adhesion molecules and that were shown to be involved in atherogenesis[48].

Our finding that 25 patients in this cohort had subclinical or overt hypothyroidism is in keeping with other reports in RA[40]. Hypothyroid patients with RA typically have high circulating concentrations of antithyroid peroxidase or/and antithyroglobulin antibodies[40]. Both overt and subclinical hypothyroidism is associated with CV disease in the general population. Dyslipidemia and hypertension are common complications of hypothyroidism[49]. In our study, hypothyroidism remained associated with atherosclerosis after these risk factors were controlled for. Recently, hypothyroidism has also been shown to be associated with endothelial dysfunction, vascular stiffness, hyperhomocysteinemia, and coagulation abnormalities[49,50], all of which could promote atherogenesis. However, in our study, hypothyroidism was not associated with homocysteine concentrations (data not shown) and we did not evaluate endothelial function, vascular stiffness, and coagulation profiles.

In the determination of preventive interventions for CV disease in RA, cardiovascular risk assessments based on traditional CV risk factors together with the addition of active RA[28] or a diagnosis of RA[24] as a risk factor have recently been recommended. In contrast, using a well validated and widely recommended global disease activity score, we found that currently active RA (DAS > 2.4)[37] was not associated with atherosclerosis. This apparent discrepancy warrants further study.

The strength of our study is that we comprehensively defined CV risk factors; some limitations of it include the following. Our cross-sectional design precludes drawing inferences about causality. However, our results together with data reported by others[11] indicate that the presence or absence of several nontraditional CV risk factors substantially alters CV disease extent within RA populations. Our study is also limited in that only 91 patients from a single center were studied.

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Consequently, only 6 of our patients had diabetes and thus we failed to identify an association between diabetes and the degree of atherosclerosis. We also excluded patients taking lipid-lowering agents, whereas hypercholesterolemia, as defined by the use of lipid-lowering agents or a raised serum cholesterol concentration, has been reported to be associated with atherosclerosis in RA[11]. Finally, the finding that up to 81% of patients were correctly classified in regression models for plaque (see Table 2) is undoubtedly an overestimate, since this result was obtained in the same dataset in which the associations of CV risk factors with plaque were observed.

Our study provides the first evidence to indicate that the use of nontraditional CV risk factors in RA, including a disease duration > 8 years, polymorphonuclear cell count > 4.5 n $\times 10^6$/l and hypothyroidism, in combination with traditional risk factors, increases the diagnostic accuracy of identifying subclinical atheroma. These data support the notion that a composite of traditional and nontraditional risk factors may be useful in determining CV risk in patients with RA. We believe that our findings merit external validation.

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