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ORIGINAL ARTICLE

Does Rheumatoid Arthritis Equal Diabetes Mellitus as an Independent Risk Factor for Cardiovascular Disease? A Prospective Study

MIKE J. L. PETERS,[1] VOKKO P. VAN HALM,[2] ALEXANDRE E. VOSKUYL,[1] YVO M. SMULDERS,[3] MAARTEN BOERS,[2] WILLEM F. LEMS,[2] MARJOLEIN VISSER,[1] COEN D. A. STEHOUWER,[4] JACQUELINE M. DEKKER,[1] GIEL NIJPELS,[1] ROB HEINE,[1] BEN A. C. DIJKMANS,[2] AND MICHAEL T. NURMOHAMED[2]

Objective. **Rheumatoid arthritis (RA) is associated with an increased risk of cardiovascular disease (CVD), but longitudinal observations are limited and the precise magnitude is unknown. We prospectively assessed the incidence of CVD in patients with RA compared with patients with type 2 diabetes mellitus (DM) and the general population.**

Methods. **The 3-year incidence rate of CVD was determined in a prospective cohort (the Cardiovascular Research and Rheumatoid Arthritis Study) of 353 outpatients with RA, and was compared with that in 1,852 population-based cohort study participants (155 had type 2 DM). We investigated fatal and nonfatal CVD (according to International Classification of Diseases, Ninth Revision criteria) and used Cox proportional hazards models to assess the incidence of CVD in RA, type 2 DM, and the general population.**

Results. **The 3-year incidence of CVD was 9.0% in patients with RA and 4.3% in the general population, corresponding with an incidence rate of 3.30 per 100 patient-years (95% confidence interval [95% CI] 2.08–4.25) and 1.51 per 100 person-years (95% CI 1.18–1.84), respectively. Compared with the general population, the age- and sex-adjusted hazard ratio (HR) for RA was 1.94 (95% CI 1.24–3.05, $P = 0.004$). Neither exclusion of patients with prior CVD at baseline nor adjustment for cardiovascular risk factors significantly influenced this. Compared with the nondiabetic population, nondiabetic patients with RA and those with type 2 DM had comparable HRs, 2.16 (95% CI 1.28–3.63, $P = 0.004$) and 2.04 (95% CI 1.12–3.67, $P = 0.019$), respectively.**

Conclusion. **The risk of CVD in RA was significantly elevated compared with the general population, and comparable with the magnitude of risk in type 2 DM.**

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic inflammatory disease of unknown etiology affecting ~1% of the general population (1). RA increases the risk of mortality, predominantly due to an excess of cardiovascular deaths (2–4). Several investigations have demonstrated an increased incidence of cardiovascular disease (CVD) morbidity as well (5–7). In the majority of these studies, however, the investigators used register-based data, which may be inaccurate or incomplete, often lacking additional information about cardiovascular risk factors or RA disease activity. So far, only 1 prospective study, with a limited number of events and a short followup period, has investigated incident CVD and related risk factors (8). This study reported an increased incidence of CVD, which was only partly explained by traditional cardiovascular risk factors.

In a cross-sectional study, we recently found that the

[1]Mike J. L. Peters, MD, Alexandre E. Voskuyl, MD, PhD, Marjolein Visser, PhD, Jacqueline M. Dekker, PhD, Giel Nijpels, MD, PhD, Rob Heine, MD, PhD, FRCP: VU Medical Center, Amsterdam, The Netherlands; [2]Vokko P. van Halm, MD, PhD, Maarten Boers, MD, PhD, Willem F. Lems, MD, PhD, Ben A. C. Dijkmans, MD, PhD, Michael T. Nurmohamed, MD, PhD: VU Medical Center and Jan van Breemen Institute, Amsterdam, The Netherlands; [3]Yvo M. Smulders, MD, PhD: Institute for Cardiovascular Research, VU Medical Center, Amsterdam, The Netherlands; [4]Coen D. A. Stehouwer, MD, PhD: Institute for Cardiovascular Research, VU Medical Center, Amsterdam, and University Hospital Maastricht, Maastricht, The Netherlands.

Dr. Heine is employed by and has stock ownership or options in Eli Lilly.

Address correspondence to Michael T. Nurmohamed, MD, PhD, VU Medical Center, Departments of Internal Medicine and Rheumatology, PO Box 7057, 1007 MB, Amsterdam, The Netherlands. E-mail: mt.nurmohamed@vumc.nl.

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prevalence of CVD in RA was increased to a degree that was comparable with that in type 2 diabetes mellitus (DM) (9). Overall, cardiovascular risk management seems essential for patients with RA. For risk estimation, we rely on risk scores such as the Framingham score (often used in the US) and the Systemic Coronary Risk Evaluation (SCORE) model (often used in Europe) (10,11). Both models use traditional cardiovascular risk factors to estimate 10-year CVD risk and aid clinicians in targeting high-risk patients. Accurate CVD risk assessment in RA, however, is complex because the role of traditional risk factors contributing to the increased CVD risk is unclear.

In the present study, we have reported prospective data on the incidence of CVD in a cohort of Dutch patients with RA, compared with a cohort of patients with type 2 DM and a sample from the general population. In addition, we evaluated the Framingham score and its association with incident CVD for the patients with RA. Finally, we have addressed CVD risk factors specific to patients with RA.

PATIENTS AND METHODS

The Cardiovascular Research and Rheumatoid Arthritis (CARRÉ) study. The CARRÉ study is a cohort study investigating CVD and its risk factors in patients with RA who have been followed prospectively. In 2000, a random sample of patients with RA registered at the Jan van Breemen Institute in Amsterdam, The Netherlands, was drawn. Eligible patients fulfilled the 1987 American College of Rheumatology (formerly the American Rheumatism Association) classification criteria, were diagnosed between 1989 and 2001, and were between 50 and 75 years of age (12). Patients were enrolled between 2001 and 2002, and were seen for a second visit between 2004 and 2005. A total of 353 patients with RA participated. Of these, 18 nonwhite patients with RA were excluded from further analyses, leaving 335 patients with RA.

The Hoorn study. The Hoorn study is a Dutch cohort study of glucose metabolism and other cardiovascular risk factors that began in 1989. The cohort and its baseline measurements have been described in detail previously (13). Briefly, a random selection of 3,553 men and women 50–75 years old was taken from the population register. A total of 2,540 (71.5%) agreed to participate, and after the exclusion of 56 nonwhite participants, the Hoorn Study population comprised 2,484 men and women.

The local ethics committees approved both study protocols and all participants gave their written informed consent for the studies.

Baseline measurements. Blood pressure (BP), body mass index (BMI), and waist:hip ratio were assessed as described elsewhere (9). Measurements in both studies were done according to identical protocols. For each patient, fasting blood samples were collected for glucose and lipid levels as described previously (9). BP, lipid measures, and glucose measures, regardless of the use of antihypertensives, statins, or glucose-lowering agents, were presented. Patients were classified as nonsmokers, former smokers, or current smokers. The Framingham algorithm includes baseline cardiovascular risk factors (i.e., sex, age, low-density lipoprotein cholesterol, high-density lipoprotein [HDL] cholesterol, BP, DM, and smoking) to calculate the Framingham 10-year CVD score (10).

RA-related baseline measurements. Patients with RA attended the outpatient clinic at the Jan van Breemen Institute, where a research physician completed a questionnaire recording demographic data, medical history, and use of medication. Additionally, a physical examination was performed that included the Disease Activity Score in 28 joints (DAS28) (14). Fasting blood samples were drawn for inflammatory variables (i.e., erythrocyte sedimentation rate [ESR] and C-reactive protein [CRP] levels) and IgM rheumatoid factor (IgM-RF) antibodies as described previously (15). Functional (disability) status was assessed with the Health Assessment Questionnaire (16), and the presence or absence of erosions on the radiographs of the hands and feet was recorded (yes/no).

DM. Participants with glucose levels <6.1 mmoles/liter and not treated with glucose-lowering agents were classified as having normal fasting glucose, and those with a fasting glucose level ≥ 7.0 mmoles/liter or treated with glucose-lowering agents were classified as having type 2 DM (17). Three groups were created based on these criteria, i.e., nondiabetic RA: RA patients with normal fasting glucose levels (263 participants [84.3%]); nondiabetic population: participants from the general population having a normal fasting glucose level (1,492 participants [80.6%]); and type 2 DM: participants from the general population with a fasting glucose level ≥ 7.0 mmoles/liter or already being treated with glucose-lowering agents (155 participants [8.4%]). Of all patients with DM, 73 (47%) of 155 had known DM (11 diet-only treated, 47 taking oral glucose-lowering drugs, and 15 taking insulin). The median DM duration for these patients was 6 years (interquartile range 2–10 years). The remaining 82 patients (53%) had newly diagnosed DM based on a fasting glucose level ≥ 7.0 mmoles/liter at baseline. The mean $\pm$ SD glycosylated hemoglobin level of all DM patients was $7.2 \pm 1.7\%$. Patients with RA having an impaired fasting glucose level or type 2 DM (49 patients [15.7%]) and participants from the general population having impaired fasting glucose (205 participants [11.1%]) with fasting glucose levels ≥ 6.1 mmoles/liter and <7.0 mmoles/liter were excluded in the comparison of CVD incidence in nondiabetic patients with RA and in those with type 2 DM relative to the nondiabetic population (Figure 1).

Followup and incident CVD. All participants were followed up for the occurrence of fatal and nonfatal CVD. The mean followup duration was calculated as the time between baseline examination and the end point fatal or nonfatal cardiovascular event or death, or date of visit, whichever came first (mean $\pm$ SD 2.7 ± 0.7 years). For non-RA subjects, the mean followup duration was calculated as the time between the baseline examination and the

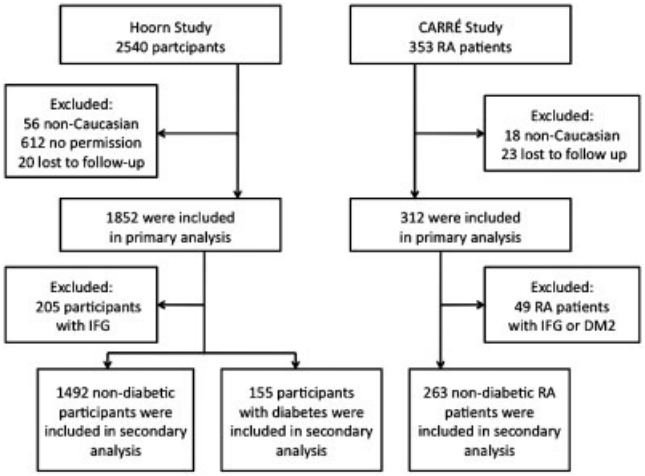

Figure 1. Study design. CARRÉ = Cardiovascular Research and Rheumatoid Arthritis; IFG = impaired fasting glucose; DM2 = type 2 diabetes mellitus; RA = rheumatoid arthritis.

end point fatal or nonfatal cardiovascular event or death, or the general cessation date of January 1, 1994, whichever came first (mean ± SD 2.9 ± 0.7 years). Participants with prevalent CVD were included, and if they developed a cardiovascular event during followup, the followup time until this event was used.

Information about fatal and nonfatal incident and prevalent CVD was extracted from the medical records of general practitioners and local hospitals, and was adjudicated on the basis of standardized criteria by an independent trained person according to the International Classification of Diseases, Ninth Revision codes 410.0–410.9, 8038, and 8036 for coronary disease, 435.9 and 436 for cerebral arterial disease, and 798 (sudden death, cause unknown) because, generally, sudden death is from cardiovascular origin (17,18).

Statistical analyses. The baseline characteristics of the patients with RA were compared with those of the non-RA subjects by parametric or nonparametric tests, as appropriate. Likewise, baseline characteristics of patients with RA with incident CVD during followup were compared with those of RA patients without incident CVD.

Incidence rates for fatal and nonfatal cardiovascular events were calculated per 100 person-years. To compare the risk of cardiovascular events in the RA population with that of the general population, hazard ratios (HRs) and 95% confidence intervals (95% CIs) were calculated by Cox proportional hazards models. These primary analyses were performed with all participants, including those with prevalent CVD at baseline, and then again after the exclusion of individuals who had prevalent CVD at baseline. These analyses are presented separately from one another in the text and in the tables.

Three models were analyzed: the first was adjusted for age and sex, the second was adjusted for multiple potential confounders (age, sex, systolic BP, diastolic BP, antihypertensive use, total cholesterol, HDL cholesterol, statin use, smoking, BMI, DM, and aspirin use), and the third was adjusted for Framingham score and cardioprotective treatment. In addition, secondary analyses were performed comparing cardiovascular events in nondiabetic patients with RA and cardiovascular events in patients with type 2 DM relative to the nondiabetic population. These secondary analyses were similar to the primary analyses except for the adjustment of DM. Analyses were carried out using SPSS software, version 14.0 (SPSS, Chicago, IL), and *P* values less than 0.05 were considered statistically significant. No correction for multiple testing was performed.

RESULTS

Baseline characteristics in the RA group and general population. For the present study, we excluded 612 subjects (24.1%) from the Hoorn study with missing data on morbidity (because they did not give permission to access their hospital files). These participants did not differ essentially from the rest of the cohort with respect to cardiovascular risk factors at baseline (19). Information about incident CVD was not obtained from 23 patients (6.5%) with RA and from 20 (1.1%) of the remaining persons from the general population because they stopped participating or had moved away from the area (Figure 1). Baseline characteristics of these subjects also did not significantly differ from the rest of the subjects included in both studies (data not shown).

The mean age of the patients with RA was 63 years and 65% were women (Table 1). A total of 222 (71%) of 312 patients were IgM-RF positive, and 255 (82%) had erosions on radiographs. Average RA disease duration was 7 years, and disease activity was moderate with a mean DAS28 score of nearly 4. In terms of cardiovascular risk, patients with RA were slightly older and more often women compared with the general population (Table 1). In addition, patients with RA had higher rates of prior CVD (diagnosed before inclusion), smoking, and cardioprotective drug use, i.e., antihypertensives, statins, and aspirin. Systolic BP and diastolic BP were higher but serum cholesterol levels were lower in patients with RA. Overall, the Framingham score was significantly lower in patients with RA. No significant differences were observed for body composition, i.e., waist:hip ratio and BMI.

Fatal and nonfatal cardiovascular events in the RA group and general population. During the followup period, 28 patients with RA (9.0%) and 80 persons from the general population (4.3%) had a fatal or nonfatal cardiovascular event. The mean followup period of both studies was nearly 3 years, resulting in a total followup of 848 patient-years for patients with RA and of 5,307 patient-years for the general population. These numbers translate into a CVD incidence rate of 3.30 per 100 patient-years (95% CI 2.08–4.52) for patients with RA and 1.51 per 100 person-years (95% CI 1.18–1.84) for the general population (Table 2).

Cox regression hazards analyses revealed a 2-fold increased age- and sex-adjusted (model I) HR for incident CVD in patients with RA in comparison with the general population (Table 2). Exclusion of individuals with prev-

Table 1. Baseline characteristics*

	General population (n = 1,852)	RA population (n = 312)
Demographic variables		
Age, years	62 ± 7	63 ± 8†
Women, %	53	65†
Cardiovascular risk factors		
Previous CVD, %	7	13†
Systolic BP, mm Hg	135 ± 20	142 ± 20†
Diastolic BP, mm Hg	82 ± 10	81 ± 8†
Total cholesterol, mmoles/liter	6.6 ± 1.2	5.8 ± 1.1†
HDL cholesterol, mmoles/liter	1.3 ± 0.4	1.4 ± 0.5†
LDL cholesterol, mmoles/liter	4.6 ± 1.1	3.7 ± 1.0†
Triglycerides, median (IQR) mmoles/liter	1.4 (1.0–1.9)	1.3 (1.0–1.8)†
TC/HDL ratio	5.4 ± 1.7	4.4 ± 1.6†
Smoking, %		
Never	34	21†
Former smoker	36	49†
Current smoker	30	30†
Waist:hip ratio	0.89 ± 0.09	0.89 ± 0.08
Body mass index, kg/m^2	26 ± 3	27 ± 5
Glucose status		
Normal fasting glucose levels, %	81	84
IFG levels, %	11	8
DM, %	8	7
Known/newly diagnosed DM, %	47/53	65/35
HbA_{1c} level	7.2 ± 1.7	–
DM disease duration, median (IQR) years‡	6 (2–10)	–
Framingham score, median (IQR)	14 (9–22)	13 (8–18)†
Medication, %		
Antihypertensive drugs	20	26†
Statins	2	12†
Aspirin	3	17†
RA variables		
Age at onset of RA, years		56 ± 8
RA duration, median (IQR) years		7 (4–10)
IgM-RF ≥30 IU/ml, %		71
Erosions on radiographs, %		82
DAS28 score (range 0–10)		3.9 ± 1.3
HAQ score (range 0–10), median (IQR)		0.8 (0.3–1.1)
Current methotrexate, %		59
Current sulfasalazine, %		16
Current hydroxychloroquine, %		7
Current prednisone, %		17
Current biologic agents, %		10

* Values are the mean ± SD unless otherwise indicated (continuous variables presented as means ± SDs in case of a normal distribution or as medians [interquartile ranges; IQR] in case of a non-normal distribution. Dichotomous variables presented as the percentage of total cases). RA = rheumatoid arthritis; CVD = cardiovascular disease; BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; TC = total cholesterol; IFG = impaired fasting glucose; DM = diabetes mellitus; HbA_{1c} = glycosylated hemoglobin; IgM-RF = IgM rheumatoid factor; DAS28 = Disease Activity Score in 28 joints; HAQ = Health Assessment Questionnaire.
† Significantly different from the general population.
‡ Among those with a prior diagnosis of DM.

alent CVD at baseline (model I) did not significantly change the HR estimates (Table 2). Adjusting for cardiovascular risk factors (i.e., total cholesterol, HDL cholesterol, statins, systolic BP, diastolic BP, antihypertensive agents, smoking, BMI, DM, and aspirin; model II) had no significant influence on either HR (Table 2). When adjusted for the Framingham score and cardioprotective treatment (model III), the HR decreased slightly (Table 2).

CVD in nondiabetic patients with RA and patients with type 2 DM compared with the nondiabetic population. Cox regression analyses were performed comparing the incidence of CVD in nondiabetic patients with RA, patients with type 2 DM, and the nondiabetic population, with the latter group as reference category (Table 3). The age- and sex-adjusted HR of cardiovascular events was 2.16 (95% CI 1.28–3.63, $P < 0.01$) for nondiabetic patients

Table 2. Hazard ratios and 95% confidence intervals for incident CVD in patients with RA relative to the general population*

	General population	RA	*P*
All patients			
Fatal and nonfatal CV events			
Patients, no.	1,852	312	
Total followup, years	5,307	848	
Cases, no.	80	28	
Incidence per 100 patient-years	1.51	3.30	
Models			
I†	1.0	1.94 (1.24–3.04)	0.004
II‡	1.0	1.97 (1.16–3.34)	0.012
III§	1.0	1.61 (0.98–2.66)	0.056
Patients with prevalent CVD excluded¶			
Fatal and nonfatal CV events			
Patients, no.	1,723	272	
Total followup, years	4,965	729	
Cases, no.	64	19	
Incidence per 100 patient-years	1.29	2.61	
Models			
I†	1.0	1.88 (1.12–3.16)	0.017
II‡	1.0	2.05 (1.14–3.69)	0.017
III§	1.0	1.97 (1.15–3.38)	0.014

* CVD = cardiovascular disease; RA = rheumatoid arthritis; CV = cardiovascular.
† Adjusted for age and sex.
‡ Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statins, smoking, body mass index, diabetes mellitus, and aspirin.
§ Adjusted for Framingham risk score, antihypertensive agents, statins, and aspirin.
¶ CVD according to the International Classification of Diseases criteria.

with RA and 2.04 (95% CI 1.12–3.67, $P = 0.02$) for patients with type 2 DM. The cardiovascular event-free probability during the followup period and an illustration of how the CVD HR for nondiabetic patients with RA and patients

Table 3. HRs and 95% CIs for incident CVD in nondiabetic patients with RA and in patients with type 2 DM relative to nondiabetic population*

	HR	95% CI	*P*
All patients			
Model I†			
Nondiabetic population	1.00	Reference	–
Type 2 DM	2.04	1.12–3.67	0.019
Nondiabetic patients with RA	2.16	1.28–3.63	0.004
Model II‡			
Nondiabetic population	1.00	Reference	–
Type 2 DM	1.42	0.77–2.62	0.261
Nondiabetic patients with RA	1.90	1.04–3.47	0.036
Patients with prevalent CVD excluded§			
Model I†			
Nondiabetic population	1.00	Reference	–
Type 2 DM	3.05	1.64–5.68	0.001
Nondiabetic patients with RA	2.38	1.30–4.36	0.005
Model II‡			
Nondiabetic population	1.00	Reference	–
Type 2 DM	2.15	1.11–4.19	0.024
Nondiabetic patients with RA	2.31	1.19–4.48	0.010

* HRs = hazard ratios; 95% CIs = 95% confidence intervals; CVD = cardiovascular disease; RA = rheumatoid arthritis; DM = diabetes mellitus.
† Adjusted for age and sex.
‡ Adjusted for age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive agents, total cholesterol, high-density lipoprotein cholesterol, statins, body mass index, smoking, and aspirin.
§ CVD according to the International Classification of Diseases criteria.

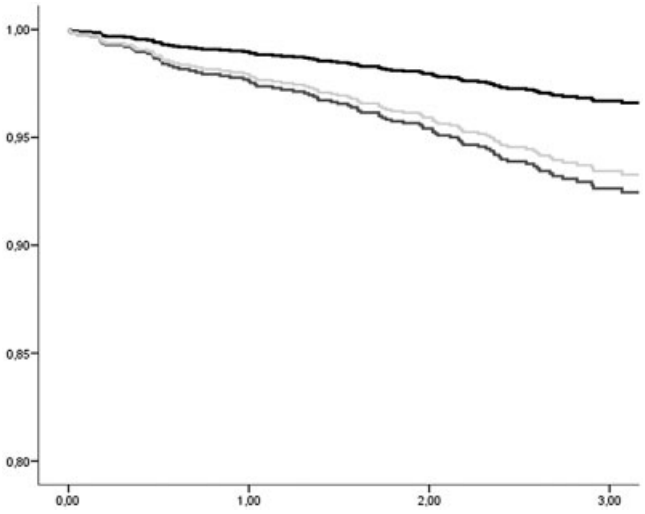

Figure 2. Cardiovascular event–free probability to 3 years among nondiabetic controls (black line), patients with type 2 diabetes mellitus (DM) (light grey line), and nondiabetic patients with rheumatoid arthritis (RA) (dark grey line). The hazard ratios for the nondiabetic controls and patients with RA as compared with nondiabetic controls were as follows: for patients with type 2 DM, 2.0 (95% confidence interval [95% CI] 1.1–3.7); for nondiabetic patients with RA, 2.2 (95% CI 1.3–3.6). Differences were estimated from age- and sex-adjusted Cox proportional hazards models.

with type 2 DM is significantly and roughly equally elevated compared with the nondiabetic population are shown in Figure 2. After adjustment for cardiovascular risk factors, the HR for nondiabetic patients with RA remained (1.90 [95% CI 1.04–3.47, $P = 0.04$]), whereas the relative HR for patients with type 2 DM diminished (1.42 [95% CI 0.77–2.62, $P = 0.26$]). Similar results were observed when analyses were done excluding the patients with prevalent CVD (Table 3).

Baseline differences in patients with RA with and without incident CVD. At baseline, several traditional cardiovascular risk factors were increased in the group of patients with RA who developed a cardiovascular event during the followup period (Table 4). As compared with RA patients without incident CVD, RA patients with incident CVD were older, more often men, had higher rates of smoking, and had a higher systolic BP. Similarly, the Framingham score was significantly higher in RA patients with incident CVD (18% versus 11%; $P = 0.001$). These results remained when RA patients with prevalent CVD were excluded.

In addition, previous CVD was present more often in patients with RA who developed a cardiovascular event during followup, and these patients more frequently used antihypertensive agents, statins, and aspirin. Disease activity variables were somewhat higher in RA patients with incident CVD, but none of these variables reached statistical significance. With regard to antirheumatic treatment, methotrexate was used significantly less often, whereas coxibs and glucocorticoids were used more frequently in patients with incident CVD. When RA patients with prevalent CVD were excluded, the reported differences remained (Table 4).

DISCUSSION

Our prospective study of 2 cohorts confirms that Dutch patients with RA have an ~2-fold higher CVD risk than the general population, and that the magnitude of this increased CVD risk is comparable with the CVD risk in patients with type 2 DM. These findings confirm our previous cross-sectional findings (9). Traditional cardiovascular risk factors, although associated with incident CVD, did not explain the excess CVD in patients with RA. Consequently, the calculated Framingham score at baseline underestimated the true cardiovascular risk in RA, indicating that primary cardiovascular prevention strategies in RA should not only be aimed at targeting traditional cardiovascular risk factors, but also at the inflammatory burden in RA. In contrast to previous epidemiologic studies, we did not find a significant difference in CVD mortality between patients with RA and controls, which might be due to a lack of statistical power.

RA and DM are associated with an adverse profile of traditional cardiovascular risk factors, but this does not seem to fully explain their increased CVD incidence (20–22). In this study, patients with RA, as compared with the general population, reported higher rates of smoking and higher systolic BP. Smoking is a strong and independent cardiovascular risk factor and increases susceptibility for the development of RA as well as its severity (23). Hypertension can be seen as a reflection of increased arterial stiffness, which has been demonstrated in patients with RA and appears to be linked to the presence of inflammation (24–26). However, no such correlation between acute-phase markers and pulse pressure was found in our study (data not shown).

Dyslipidemia, another traditional cardiovascular risk factor, occurred less often in RA. This is most probably due to the fact that the CARRÉ study was carried out approximately a decade later than the Hoorn study, in a period of time showing a nationwide trend of decreasing lipid levels, probably caused mostly by lifestyle measures and an increase in the prescription of statins (27). Altogether, traditional cardiovascular risk factors identify RA patients with a higher CVD risk, but it seems that they either do not or only to a limited extent explain the excess CVD in RA, because adjustment for cardiovascular risk factors did not lower the risk of CVD in patients with RA.

The role of inflammation in the pathogenesis of CVD in RA remains unclear. Previous studies have suggested that both disease activity as well as disease duration are associated with atherosclerosis and a higher mortality rate caused by coronary artery diseases (28–32). Moreover, effective antirheumatic treatment, such as methotrexate and anti–tumor necrosis factor, actually seem to lower the cardiovascular risk in RA (33–35). However, several observational studies still indicate an increased mortality rate in RA despite more aggressive treatment in the past 20 years (36,37). In our study, inflammatory variables at baseline, i.e., DAS28 score, ESR, CRP level, and disease duration, were only slightly and nonsignificantly higher in patients with RA developing a cardiovascular event. This might be due to a Type II error, because the study was not designed

Table 4. Characteristics of patients with RA with and without incident CVD*

	All patients with RA		Without prevalent CVD	
	Non-CVD (n = 284)	CVD (n = 28)	Non-CVD (n = 253)	CVD (n = 19)
Demographic variables				
Age, years	63 ± 7	67 ± 7†	63 ± 7	67 ± 6†
Women, %	66	46†	68	40†
Cardiovascular risk factors				
Previous CVD, %	13	29†	–	–
Systolic BP, mm Hg	141 ± 19	150 ± 25†	141 ± 19	152 ± 23†
Diastolic BP, mm Hg	81 ± 8	82 ± 11	81 ± 8	82 ± 9
Total cholesterol, mmoles/liter	5.8 ± 1.1	5.4 ± 0.9	5.9 ± 1.1	5.6 ± 1.1
HDL cholesterol, mmoles/liter	1.5 ± 0.5	1.3 ± 0.5	1.5 ± 0.5	1.2 ± 0.5
LDL cholesterol, mmoles/liter	3.7 ± 1.0	3.4 ± 1.0	3.8 ± 1.0	3.7 ± 1.1
Triglycerides, median (IQR) mmoles/liter	1.3 (1.0–1.8)	1.2 (0.9–1.8)	1.3 (1.0–1.8)	1.2 (0.9–2.0)
TC/HDL ratio	4.4 ± 1.5	4.7 ± 2.3	4.4 ± 1.5	5.2 ± 2.4†
Smoking, %				
Never	22	11	24	10
Former smoker	29	52	29	50
Current smoker	49	37	47	40
Waist:hip ratio	0.89 ± 0.08	0.91 ± 0.07	0.88 ± 0.08	0.92 ± 0.08
Body mass index, kg/m^2	27 ± 5	27 ± 4	27 ± 5	27 ± 4
DM, %	6	11	6	11
Framingham score, median (IQR)	11 (7–18)	18 (13–27)†	11 (7–16)	19 (11–27)†
Medication				
Antihypertensive drugs, %	23	48†	20	40
Statins, %	11	25†	6	10
Aspirin, %	15	43†	6	30†
RA variables				
Disease duration, median (IQR) years	7 (4–10)	8 (5–10)	7 (4–10)	8 (5–10)
IgM-RF ≥30 IU/ml, %	72	70	71	68
Erosions on radiographs, %	81	85	82	84
DAS28 score (range 0–10)	3.9 ± 1.4	4.1 ± 1.3	3.8 ± 1.3	4.0 ± 1.1
ESR, median (IQR) mm/hour	16 (8–28)	22 (11–27)	17 (9–29)	22 (12–29)
CRP level, median (IQR) mg/liter	6 (3–16)	8 (3–27)	7 (3–17)	10 (3–28)
HAQ score, median (IQR) (range 0–10)	0.8 (0.3–1.1)	0.5 (0.3–1.1)	0.8 (0.3–1.1)	0.5 (0.4–1.1)
Current methotrexate, %	62	39†	62	42
Current sulfasalazine, %	15	21	15	23
Current hydroxychloroquine, %	7	7	8	4
Current prednisone, %	16	29	16	31
Current biologic agent, %	10	11	11	12
Current NSAIDs, %	59	50	59	50
Current COX-2 inhibitor, %	11	25†	12	27†

* Values are the mean ± SD unless otherwise indicated. Continuous variables are presented as means ± SDs in case of a normal distribution or as medians [IQR] in case of a non-normal distribution. Dichotomous variables are presented as the percentage of total cases. ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; NSAIDs = nonsteroidal antiinflammatory drugs; COX-2 = cyclooxygenase 2. See Table 1 for additional definitions.
† Significantly different from the non-CVD RA group.

to investigate CVD risk at different levels of inflammatory burden.

The excess of CVD in DM, a well-established cardiovascular risk factor, is strongly related to DM-related factors, such as type and duration of DM, ethnicity, family history, and renal function (22). Therefore, the investigators from the SCORE risk model concluded that their model is equally sufficient for DM patients, but underlined that the estimated risk is at least twice as high in diabetic men and 4 times higher in diabetic women compared with the score given by the charts (11). This may also apply for RA, because the Framingham score also seems to underestimate the true CVD risk.

To investigate to what extent cardiovascular risk factors, i.e., Framingham risk score estimates, explain the excess cardiovascular risk in patients with RA, we introduced the Framingham risk score estimate, cardioprotective treatment, age, and sex into a single statistical model. This model revealed a remaining 1.6-fold (borderline significant: $P = 0.056$) higher risk for patients with RA relative to controls. Therefore, the increased cardiovascular risk in RA is partially explained by traditional cardiovascular risk factors, raising the possibility of introducing a multiplication factor of ~1.6 when using the Framingham score. In addition, these observations emphasize the importance of proper treatment of traditional cardiovascular risk factors.

Alternatively, thresholds for initiating antihypertensive and lipid-lowering therapy could be lowered when dealing with patients with RA. Unfortunately, this study lacks the statistical power to ascertain individual multiplication estimates for male and female patients with RA separately. Obviously, more research in larger populations is urgently needed to investigate sex differences and to gauge the prognostic importance of RA-specific variables, such as disease duration and disease activity, but also anti–cyclic citrullinated peptide or RF positivity and the presence of extraarticular manifestations.

The difficulty of such research is increased by the potentially confounding effects of antirheumatic agents, e.g., nonsteroidal antiinflammatory drugs (NSAIDs), cyclooxygenase 2 inhibitors, disease-modifying antirheumatic drugs, and glucocorticoids. Each of these may influence both disease activity and the risk of CVD (38–40). Especially, the net effects of glucocorticoids on CVD in RA are currently impossible to assess due to confounding by indication. Our study was underpowered to accurately assess drug effects. Nevertheless, our patients with RA taking methotrexate had a significantly lower risk of developing CVD, which is in line with previous findings (33). We found no difference in CVD risk for patients taking NSAIDs, but patients with RA who developed CVD were significantly more often treated with coxibs. Glucocorticoid use was higher in patients with incident CVD, but this difference was not statistically significant.

The strengths and limitations of the present study merit careful consideration. Major advantages of this study are its longitudinal study design and the additional information about both traditional cardiovascular risk factors and RA-specific variables. As a consequence we, in contrast to previous studies, were able to adequately adjust for the presence of traditional cardiovascular risk factors by introducing them as continuous variables.

However, this study also has some limitations. The Hoorn study may have included some patients with RA because we had insufficient data to exclude RA prevalence. However, the effect of this is likely to be small, if any, and would be expected to result in an underestimation of risk associations. Another limitation is that the Hoorn study was conducted about a decade before the CARRÉ study. Standards of care have been changed significantly over time, as well as the definition of DM and hypertension, and this may weaken the comparison of incidence rates of CVD for patients with RA, patients with DM, and controls. Patients with RA had a better lipid profile and more often received cardioprotective treatment. Because these differences may have confounded our overall results, we adjusted for cardioprotective treatment in our statistical analyses. Nevertheless, these baseline differences in cholesterol levels and cardioprotective treatment between the 2 cohorts complicate the interpretation of our results, particularly from the statistical models including both the Framingham risk score and cardioprotective treatment. Additionally, incident CVD has declined markedly in The Netherlands in the 1990s (41). However, these limitations are likely to result, if anything, in underestimation rather than overestimation of the differences between patients with RA, patients with DM, and controls. Finally, we did not use the European SCORE mortality risk score in this study because most (76%) of the CVD events in this cohort were nonfatal, and because it does not include DM as a risk factor. A comparison between Framingham and SCORE should be done in other cohorts.

Taken altogether, this study demonstrated an increased risk of CVD in RA that equals the risk for CVD in type 2 DM. Traditional cardiovascular risk factors contribute to a higher CVD risk in patients with RA, but they do not explain the excess CVD risk, indicating that, on the one hand, RA should be considered as an independent cardiovascular risk factor and, on the other, that preventive strategies targeting traditional risk factors as well as the inflammatory burden are needed.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Nurmohamed had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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