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High Incidence of Cardiovascular Events in a Rheumatoid Arthritis Cohort Not Explained by Traditional Cardiac Risk Factors

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Objective. **To compare the incidence of cardiovascular (CV) events in persons with rheumatoid arthritis (RA) with that in people from the general population, adjusting for traditional CV risk factors.**

Methods. **Two hundred thirty-six consecutive patients with RA were assessed for the 1-year occurrence of 1) CV-related hospitalizations, including myocardial infarction, stroke or other arterial occlusive events, or arterial revascularization procedures, or 2) CV deaths. Both outcomes were ascertained by medical records or death certificates. For comparison, we used CV events that occurred during an 8-year period among participants in an epidemiologic study of atherosclerosis and CV disease who were ages 25–65 years at study entry. We calculated the age- and sex-stratified incidence rate ratio (IRR) of CV events between the 2 cohorts and used Poisson regression to adjust for age, sex, smoking status, diabetes mellitus, hypercholesterolemia, systolic blood pressure, and body mass index.**

Results. **Of the 236 RA patients, 234 were observed for 252 patient-years, during which 15 CV events occurred. Of these, 7 incident events occurred during the 204 patient-years contributed by patients ages 25–65 years, for an incidence of 3.43 per 100 patient-years. In the comparison cohort, 4,635 community-dwelling persons were followed up for 33,881 person-years, during which 200 new events occurred, for an incidence of 0.59 per 100 person-years. The age- and sex-adjusted IRR of incident CV events associated with RA was 3.96 (95% confidence interval [95% CI] 1.86–8.43). After adjusting for CV risk factors using Poisson regression, the IRR decreased slightly, to 3.17 (95% CI 1.33–6.36).**

Conclusion. **The increased incidence of CV events in RA patients is independent of traditional CV risk factors. This suggests that additional mechanisms are responsible for CV disease in RA. Physicians who provide care to individuals with RA should be aware of their increased risk of CV events and implement appropriate diagnostic and therapeutic measures.**

Patients with rheumatoid arthritis (RA) have a shortened lifespan (1–10). As in the general population, the most frequent cause of death in RA is cardiovascular (CV) disease. Moreover, CV mortality in persons with RA occurs in excess of what would be expected in people without RA (1,11–15). Disease severity has been associated with CV mortality in RA (8,16), but it is not clear if this association is attributable to a higher-than-normal frequency of CV events or a higher-than-normal case fatality rate when CV events occur. An increased prevalence of atherosclerosis in RA may be suspected for several reasons: atherogenic side effects of some antirheumatic medications (17), the effects of chronic systemic inflammation on the vascular endothelium (18), or shared mechanisms between RA and atherosclerosis (19). The CV risk factor profile of RA patients has not been studied thoroughly. Previous studies of CV disease in RA have focused on fatal CV events. To our knowl-

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edge, this is the first study of CV risk in RA that focuses on both fatal and nonfatal events. Our objectives were 1) to determine the incidence of CV events in a cohort of patients with RA compared with that in a population-based cohort of persons without RA, and 2) to assess the role of traditional CV risk factors in the CV events that occur in RA.

PATIENTS AND METHODS

RA cohort. *Patients.* The patients in this study have been described in other publications (20–23). Briefly, between January 1996 and December 1996, consecutive patients who presented for a scheduled appointment with a rheumatologist at 1 of 3 participating clinical centers (2 public, 1 private) and met the American College of Rheumatology (formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA (24) were invited to participate in a longitudinal study of the disablement process in RA. They represent all RA patients seen during that year at these 3 facilities. The study is known as ÓRALE (acronym for Outcome of Rheumatoid Arthritis Longitudinal Evaluation, which matches a Mexican American colloquialism for "Let's go!").

Study procedures. The study was approved by the committee that reviews research on human subjects at our institution, and all subjects provided written informed consent. Participants underwent a comprehensive clinical and psychosocial evaluation by a bilingual rheumatologist. Demographic variables (age, sex, and ethnic background) were ascertained by self-report. We used a modified version of the question employed in the 1990 US Census to ascertain a Hispanic ethnic background (23).

CV risk factor ascertainment. The following recognized cardiac risk factors were ascertained among members of the ÓRALE cohort. Each patient's 1) age and 2) sex were determined. 3) Cigarette smoking was assessed with a questionnaire about past and present smoking, number of cigarettes smoked per day, and smoking duration. In the present analysis, subjects were considered smokers if they were current smokers by self-report (25). 4) Diabetes mellitus was classified as present if subjects had a fasting plasma glucose level of ≥7 mmoles/liter (126 mg/dl) or were taking antidiabetic medications at the time of the assessment (26). In this analysis, diabetes was classified as present or absent. 5) Obesity was measured by the body mass index (BMI), which is calculated as weight in kilograms divided by the square of the height in meters. Here, we used the BMI as a continuous variable. 6) Hypertension was measured by the blood pressure at the time of the 1996 evaluation. We evaluated the role of the systolic, diastolic, and mean blood pressures, each as continuous variables. 7) Hypercholesterolemia was considered present if subjects had ever had a fasting plasma cholesterol value ≥5.0 mmoles/liter (200 mg/dl). Because we did not have information on a fasting cholesterol level for all patients, we also considered patients to have hypercholesterolemia if they were taking lipid-lowering drugs at the time of the evaluation or if it had ever been diagnosed and recorded as such in medical records by a physician. Hypercholesterolemia was thus used as a categorical variable in this analysis.

Followup. ÓRALE participants enrolled during 1996 were recontacted during 1997 and asked to return for a followup evaluation, during which they were asked to describe any hospitalizations that had occurred since the initial visit. Death certificates were obtained for all patients who had died before the followup evaluation.

CV events. From the list of self-reported hospitalizations that occurred since the initial visit, we reviewed the medical records of those that indicated a possible CV event. We considered as a CV event 1) any hospitalization due to myocardial infarction (MI), stroke or other arterial occlusive events, or arterial revascularization procedures, or 2) death due to CV causes. Death was attributed to a CV cause if the death certificate mentioned a CV condition as the immediate or first underlying cause of death. We considered events to be incident if they occurred in persons who had no previous CV events and counted only 1 event among persons who had more than 1.

Non-RA cohort. We compared the incidence of CV events in the ÓRALE cohort with that in the San Antonio Heart Study (SAHS) cohort. Details of the design, sampling, recruitment, and field procedures of SAHS have been reported previously (27–29). Briefly, from October 1979 through November 1982, and later from October 1984 through October 1988, households were randomly sampled, stratified by low-, middle-, and high-income San Antonio neighborhoods and by ethnic background. All men and nonpregnant women between the ages of 25 and 65 years in the sampled households were eligible for the study, and a total of 5,158 community-dwelling people were enrolled.

CV risk factor ascertainment. Age, sex, BMI, blood pressure, and cigarette smoking were ascertained by methods equivalent to those employed in the ÓRALE cohort. Diabetes mellitus was defined, according to the 1997 criteria of the American Diabetes Association, as a fasting plasma glucose level of ≥7.0 mmoles/liter (126 mg/dl) or a 2-hour glucose level of ≥11.1 mmoles/liter (200 mg/dl) (26). Subjects reporting a history of diabetes and receiving insulin or oral antidiabetic drugs were also considered to have diabetes mellitus (30). Hypercholesterolemia was defined as a fasting plasma cholesterol level of ≥5 mmoles/liter (200 mg/dl) at baseline.

Followup. A 7–8-year followup to determine the incidence of type 2 diabetes mellitus and CV disease began in October 1987 and was completed in the fall of 1996. Details of the followup survey have been published elsewhere (30). Vital status of participants was determined, and those who were alive were interviewed. CV outcomes were defined on the basis of a positive response to the following questions: "Have you ever been told by a doctor that you had a heart attack?"; "Have you ever been told by a doctor that you had a stroke?"; "Have you ever had surgery on your heart?" Death certificates were obtained for all participants who had died. The listed cause of death was classified by a certified nosologist (Medical Coding and Consultation Services, Rolesville, NC). International Classification of Diseases, Ninth Revision, Clinical Modification codes 390–459 were used for CV disease, and these diseases were considered causative if there was any mention of them in the death certificates.

Statistical analysis. We compared the characteristics of both cohorts using Student's *t*-test or chi-square, as appropriate. For all comparisons of the rate of CV events, we used

Table 1. Baseline characteristics of subjects compared in ÓRALE and SAHS*

Individual characteristics	ÓRALE cohort (n = 236)	SAHS cohort (n = 4,635)	*P*
Age in years, median (range)	56 (22–80)	43.3 (25–65)	≤0.0001
Women	147 (62.3)	2,667 (58)	0.15
Ethnic background			
NonHispanic whites	49 (21)	1,668 (36)	≤0.0001
NonHispanic blacks	11 (5)	0	–
Asians	5 (2)	0	–
Hispanics	171 (72)	2,967 (64)	0.01
Diabetes mellitus	38 (16.1)	442 (9.5)	≤0.0001
Age <55	9/109 (8.3)	240/3,672 (6.7)	0.5
Age ≥55	29/127 (22.8)	202/963 (20.1)	0.7
Systolic blood pressure, mean ± SD mm Hg†	128.5 ± 17.9	116.4 ± 15.4	≤0.0001
Hypercholesterolemia	54 (22.9)‡	2,258 (48.7)§	≤0.0001
Age <55 years	24/109 (22)	1,626/3,672 (44)	≤0.0001
Age ≥55 years	30/127 (24)	632/963 (66)	≤0.0001
Cigarette smoking	57 (24.2)	1,276 (27.5)	0.25
Age <55 years	29/109 (27)	1,015/3,672 (28)	0.8
Age ≥55 years	28/127 (22)	261/963 (27)	0.2
Body mass index, mean ± SD kg/m^2†	29.8 ± 7.4	27.4 ± 5.6	≤0.0001
Years with RA, median (range)	10 (0.2–52)	NA	
Rheumatoid factor positive	201 (85)	NA	
ESR, mm/hour median (range)	37 (2–115)	NA	
Tender joints, median (range)	18 (0–48)	NA	
Swollen joints, median (range)	3 (0–25)	NA	
Deformed joints, median (range)	6 (0–38)	NA	
Subcutaneous nodules	117 (49.5)	NA	
Taking methotrexate	150 (64)	NA	
Taking glucocorticoids	119 (50.4)	NA	

* Except where indicated otherwise, values are the number (%). ÓRALE = Outcome of Rheumatoid Arthritis Longitudinal Evaluation; RA = rheumatoid arthritis; NA = not applicable; ESR = erythrocyte sedimentation rate.
† Values shown are age-adjusted to the San Antonio Heart Study (SAHS).
‡ Fasting plasma cholesterol ≥200 mg/dl from a review of clinical records of laboratory tests or from a physician's diagnosis, or receiving lipid-lowering drugs.
§ Fasting plasma cholesterol ≥200 mg/dl.

data only from subjects who were between age 25 and 65 years at baseline, because this was a criterion for entry into the SAHS. We provide the rate of all CV events that occurred during the observation period and of events that occurred in persons without a previous history of CV disease. For participants with multiple events, we counted only the first that occurred during the observation period. We calculated the age- and sex-adjusted incidence rate ratio (IRR) of CV events using 2 age strata for each sex: ages 25–54 and 55–65. We selected these age ranges to ensure that there was at least 1 CV event per stratum in both cohorts. The age- and sex-stratified IRR of CV events was pooled and weighted according to the Mantel-Haenszel method (31).

The number of events that occurred in the ÓRALE cohort was not sufficient to form strata according to age, sex, and the CV risk factors ascertained. Therefore, we used Poisson regression to model the incidence rate of CV events in the RA cohort relative to the population-based cohort, adjusting for CV risk factors. In the Poisson model, the dependent variable was the occurrence of a CV event, and the independent variables were age, sex, smoking status, diabetes mellitus, hypercholesterolemia, systolic blood pressure, and BMI (32). Age, systolic blood pressure, and BMI were used as continuous variables in the model. However, in order to facilitate interpretation of the risk coefficients, we report the results in 10-year increments for age, 15-mm/Hg increments for blood pressure, and 5-kg/m^2 increments for BMI. The exposure variable required for Poisson regression was provided by the period at risk of each study participant, defined as the interval between baseline and followup observations. The IRR and 95% confidence interval (95% CI) were calculated. Because participants in the SAHS were recruited over a 9-year period, we used logistic regression to look for a trend in the incidence of CV events according to year of recruitment, adjusting for age and sex. All analyses were conducted using SAS software (SAS Institute, Cary, NC).

RESULTS

The baseline characteristics of the 236 patients in ÓRALE and those of the SAHS cohort are shown in Table 1. The RA patients were older, with a slightly higher proportion of Hispanics. There was no difference between groups in the proportion of women. The mean

Table 2. Cardiovascular events occurring in members of the ÓRALE cohort during the period at risk*

Patient	Age/sex/ethnic group	Outcome-defining event	Included in comparisons with SAHS?
1	45/M/H	Coronary artery disease and coronary bypass	Yes
2	48/F/H	Coronary artery disease and angioplasty	Yes
3	56/M/W	Unstable angina and coronary bypass	Yes
4	58/F/H	MI and angioplasty	Yes
5	60/M/H	Coronary artery disease and angioplasty	Yes
6	63/M/H	Coronary artery disease and angioplasty	Yes
7	64/M/W	MI	Yes
8	57/F/H	Popliteal artery occlusion	No†
9	59/M/W	MI and coronary bypass	No‡
10	66/M/W	MI	No
11	68/M/H	Stroke	No
12	70/M/H	MI	No
13	71/M/H	MI (fatal)	No
14	75/M/W	Stroke	No
15	76/F/H	MI (fatal)	No

* We compared events only between participants ages 25–65 years at the time of entry. H = Hispanic; W = nonHispanic white (see Table 1 for other definitions).
† Patient excluded because of a lack of comparable outcome definition in the SAHS.
‡ Patient excluded because of a previous myocardial infarction (MI) prior to the baseline evaluation.

systolic blood pressure and the BMI were higher in the RA cohort. Although diabetes mellitus was more frequent in the RA cohort, this was probably attributable to a difference in age, because the difference disappeared when we stratified by age. The probability of smoking cigarettes was equivalent in the 2 cohorts, and RA patients were significantly less likely to have hypercholesterolemia.

We obtained followup information on 234 (99%) of the ÓRALE patients. The mean length of time between the initial visit and the earliest of either 1) the followup visit, 2) CV death, or 3) the censoring date of December 31, 1997, was 1.07 years (range 2 months–1.9 years), for a total period at risk of 252 patient-years. During the period at risk, 67 of the 234 ÓRALE patients were hospitalized a total of 103 times. Of the 67 hospitalized patients, 16 attributed 19 hospitalizations to "chest pain," "heart attack," "stroke," "loss of consciousness," "shortness of breath," "open heart surgery," or "heart bypass," which we considered potentially due to a CV cause. In addition, 1 patient was hospitalized for an amputation below the knee. We reviewed the records of these 20 hospitalizations and found that 2 of the patients had strokes and 1 underwent coronary angioplasty before the initial visit for the ÓRALE study. In 1 additional patient, the suspected CV-related hospitalization was due to pneumonia rather than a CV event. We thus did not include these 4 cases in our estimates of the rate of CV events, leaving 16 CV-related hospitalizations in 13 patients. In addition to the hospitalizations, 5 deaths occurred during the observation period, 2 of which we counted as CV related, because the death certificates listed MI as the cause of death.

In total, 15 persons in the ÓRALE cohort experienced CV events during the observation period: 7 MI (2 fatal), 2 strokes, 5 coronary revascularization procedures, and 1 occlusion of the popliteal artery due to atherosclerosis, requiring amputation (Table 2). Of the 15 events, 13 were in persons who had no history of CV events. The incidence of CV events in the ÓRALE cohort was 5.9 events per 100 person-years (95% CI 3.3–9.8) for all events, and 5.2 per 100 person-years (95% CI 2.7–8.8) for new events.

In the SAHS cohort, followup information on CV events that occurred 7–8 years after the baseline assessment was available for 4,635 participants (90%). The total period at risk was 35,631 person-years. Compared with SAHS participants with followup information, those without followup information were older at baseline (44.7 $\pm$ 0.5 versus 43.3 $\pm$ 0.2 years; $P = 0.01$), had a higher BMI (28.0 $\pm$ 0.3 kg/m^2 versus 27.4 $\pm$ 0.1 kg/m^2; $P = 0.03$), a higher plasma cholesterol level (207 $\pm$ 2 mg/dl versus 202 $\pm$ 0.6 mg/dl; $P = 0.03$), and were more likely to be women (57.6% versus 52.3%; $P = 0.04$). There was no significant difference in ethnic background, baseline blood pressure, fasting blood sugar level, or history of smoking between SAHS participants with and without followup information.

Among SAHS cohort members, 269 cardiovascular events occurred, for an incidence rate of 0.75 events

Table 3. Age- and sex-stratified incidence rates of new cardiovascular events in the ÓRALE and SAHS cohorts*

	ÓRALE cohort			SAHS cohort				
	Events	Patient-years	Incidence (per 100 patient-years)	Events	Person-years	Incidence (per 100 person-years)	Stratum-specific IRR	95% CI
Women 25–54	1	93	1.07	36	15,440	0.23	4.61	0.11–27.39
Women 55–65	1	52	1.92	45	3,924	1.15	1.68	0.04–9.83
Men 25–54	1	25	4.01	49	11,721	0.41	9.57	0.24–55.86
Men 55–65	4	34	11.73	70	2,796	2.50	4.70	1.24–12.58
Pooled								
Crude	7	204	3.43	200	33,881	0.59	5.81	2.31–12.20
Weighted Mantel-Haenszel†							3.96	1.86–8.43

* Only events in persons ages 25–65 years who had not had cardiovascular events prior to enrollment in the cohorts are included in this comparison. Test of homogeneity: $P = 0.7$. IRR = incidence rate ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).
† See ref. 31.

per 100 person-years (95% CI 0.66–0.85). Events recorded in the SAHS included 79 heart attacks, 73 strokes, 76 heart surgeries, and 54 CV deaths. Of these, 200 occurred among persons with no history of CV events, who contributed 33,881 person-years at risk, for a new-event incidence rate of 0.59 per 100 person-years. The types of new events included 70 heart attacks, 60 strokes, 53 heart surgeries, and 31 CV deaths (only the first event occurring during the observation period was used for calculating incidence rates). Subjects in the SAHS were recruited over a 9-year period. We compared the incidence of CV events in the SAHS according to year of recruitment, using logistic regression to adjust for age and sex, and found no significant difference. Specifically, participants recruited in the latter years did not have a higher rate of CV events than did early enrollees (odds ratio 1.02 per year of recruitment, 95% CI 0.98–1.07), nor was there a difference in the probability of heart surgery between participants enrolled early or late in the SAHS.

Because the SAHS was targeted to persons ages 25–65 years, we compared incidence rates between the 2 cohorts only among subjects who were in that age range at entry. We thus excluded 46 ÓRALE cohort members, among whom 6 CV events occurred during followup, and 3 SAHS participants, among whom no CV events occurred, because they were older than age 65 at the time of the baseline evaluation. We also excluded a CV event in 1 ÓRALE cohort member who was in the 25–65 age range but had experienced a CV event prior to the study period and 1 ÓRALE participant who had a popliteal artery occlusion, because we did not have an equivalent outcome in the SAHS. Table 3 shows the number of new events in each cohort, in strata defined by age and sex. The stratum-specific IRRs were higher in the RA cohort in all 4 age and sex strata but, because of the small number of events in each stratum, reached significance only in the stratum of men ages 55–65 years. The Mantel-Haenszel pooled age- and sex-adjusted IRR was nevertheless significantly increased (almost 4 times higher) in the RA cohort, with no significant heterogeneity among strata.

Because of the possibility that differences in the incidence of CV events between the 2 cohorts could be attributable to differences in the prevalence of CV risk factors, we modeled the incidence of CV events using Poisson regression. In this multivariate model, the predictor variables were 1) cohort membership (ÓRALE = 1, SAHS = 0), 2) age, 3) sex (men = 1, women = 0), 4) diabetes mellitus (yes = 1, no = 0), 5) cigarette smoking (yes = 1, no = 0), 6) systolic blood pressure, and 7) BMI. Risk coefficients associated with each of these predictor variables are shown in Table 4. This analysis revealed

Table 4. Multivariate analysis of the incidence of new cardiovascular events in ÓRALE and SAHS participants ages 25–65 years*

Predictor variables	IRR	95% CI
Cohort membership (ÓRALE = 1, SAHS = 0)	3.17	1.33–6.36
Age (per 10 years)	2.15	1.83–2.55
Sex (men = 1, women = 0)	1.99	1.50–2.66
Diabetes mellitus (yes = 1, no = 0)	2.28	1.65–3.12
Systolic blood pressure (per 15 mm Hg)	1.18	1.03–1.33
Body mass index (per 5 kg/m^2)	1.13	0.99–1.28
Cigarette smoking (yes = 1, no = 0)	1.37	1.01–1.83
Hypercholesterolemia (yes = 1, no = 0)	1.35	1.01–1.82

* The number of cardiovascular events that occurred during the observation period was used as the dependent variable in a Poisson regression model. IRR = incidence rate ratio; 95% CI = 95% confidence interval (see Table 1 for other definitions).

that the incidence of CV events in the RA cohort was more than triple that in the population-based cohort, independent of the influence of other cardiac risk factors. Because of the possibility that the increased rate of CV events in the ÓRALE cohort was explained by increased use of CV procedures, we fit a second Poisson model using only incident heart attacks or MI as the outcome, adjusting for CV risk factors. Although <1 primary MI was expected to occur during the 1-year period of observation among ÓRALE cohort members ages 25–65 years, we observed 2 such events. The IRR of primary MI associated with ÓRALE cohort membership was thus increased at 2.65, but the 95% CI did not exclude unity, at 0.64–7.19, because of the small number of events.

DISCUSSION

That people with RA would have a high rate of CV morbidity and mortality may at first seem surprising. The predilection for RA to occur in women and its frequent treatment with aspirin and other nonsteroidal antiinflammatory drugs, with their well-known antiplatelet effect, could be expected to protect RA patients from CV disease. Yet, RA is not the only chronic inflammatory disease of women that is associated with CV disease. Systemic lupus erythematosus is also characterized by a high rate of coronary artery disease (33), mediated at least in part by chronic inflammation (18). Indeed, previous studies demonstrated excess CV mortality in RA (1,11–15), a phenomenon not fully explained at present.

Perhaps because this high rate of CV mortality in RA has only recently been recognized, few studies have investigated the frequency of traditional risk factors in persons with RA, and their results were sometimes contradictory. For example, smoking, a factor strongly associated with atherosclerosis, had a protective influence on the susceptibility to RA in one study (34), while others found that smoking increased the risk of RA (35–37). The lipid profiles of patients with RA have also been investigated (38–41). One study showed that the levels of cholesterol, very low-density lipoprotein, low-density lipoprotein, and high-density lipoprotein were reduced in RA patients (38), while others indicated that levels of lipoprotein(a) were increased (39–41). Diabetes mellitus, an important cardiac risk factor, has been found to occur with a similar frequency in patients with RA and controls (42). The above studies of CV risk factors in RA thus do not conclusively demonstrate that CV risk factors are increased in persons with RA.

The number of CV events we observed in RA patients was almost 4 times higher than what would be expected in persons without RA of the same age and sex. Because these findings could be attributable to a higher frequency of CV risk factors in RA, we adjusted our comparisons for the influence of traditional risk factors. Indeed, RA patients were older than persons without RA in our study, and the age-adjusted mean systolic blood pressure and BMI were also higher in the RA group. However, not all CV risk factors were more common in RA: although RA patients as a whole had diabetes mellitus more frequently, this was likely because they were older, since the age-stratified prevalence of diabetes did not differ between the 2 groups (Table 1). Similarly, RA patients were significantly less likely to have hypercholesterolemia than were the controls.

We adjusted our comparisons for the CV risk factors we measured and for the different periods of observation between the 2 cohorts, using Poisson regression. In our models, the higher incidence of CV events in RA was independent of the influence of CV risk factors. Therefore, traditional CV risk factors are not the sole explanation for high rates of CV events in RA.

Recent evidence suggests that systemic inflammation may play a role in the development of atherosclerosis (43–49). Fatty streaks, the earliest atherosclerotic lesions, contain macrophages and T lymphocytes and are rich in inflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-1 (IL-1) and IL-2, and adhesion molecules (50). Advanced atherosclerotic lesions, representing the fibrotic phase of inflammation, are also characterized by the expression of multiple cytokines and growth factors (43). In addition to the pathologic evidence, it has been recognized for some time that the level of acute-phase reactants rises during acute MI (51), and that coronary events are often temporally related to infections (47,52,53). Acute-phase reactants also predict myocardial ischemia in patients with angina, those with multiple risk factors, and even in apparently healthy male physicians (46,54,55,57). It is also possible that RA and atherosclerosis share pathogenic mechanisms (19). In view of this evidence, accelerated atherosclerosis in RA should be expected.

How the inflammation that occurs in RA would lead to increased atherosclerosis is not clear, but evidence points toward an indirect effect of inflammation centered on the synovium, acting at a distance on the systemic vascular endothelium. Although inflammation in RA centers in synovial tissue, inflammation mediators spill into the systemic circulation, where they can easily interact with endothelial cells. IL-1 and TNFα, 2 of the

central cytokines in RA that are found in high concentrations in the blood of RA patients (58–62), have profound effects on endothelial cells, up-regulating them to express adhesion molecules, increasing their permeability, and facilitating migration of inflammatory cells into vessel walls (63). C-reactive protein (CRP), the level of which rises in periods of RA disease activity, may also play a direct role in atherothrombosis. CRP stimulates macrophages to produce tissue factor, an important procoagulant that may be found in atherosclerotic plaques (64,65). The localization of CRP in atheromatous lesions (66) also suggests a causative link between CRP and coronary events. From the above evidence, it is clear that a wide range of inflammatory mechanisms may explain accelerated atherosclerosis in RA and that further research is needed.

In addition to the inflammatory phenomena occurring in the joints, other factors may contribute to atherosclerosis in patients with RA. Corticosteroids have a recognized atherogenic effect, mediated through their effects on plasma lipids (17). However, these agents are used in only half of all RA patients and in low dosage, usually <10 mg per day. Some studies have not even been able to demonstrate an association between CV mortality and steroid use in RA (67,68). Methotrexate is another drug used in RA that could cause atherosclerosis by inducing hyperhomocysteinemia, a novel factor recently associated with atherothrombosis (69). However, this effect is counterbalanced by the concomitant use of folic acid in methotrexate-treated RA (70). A sedentary lifestyle may also be more frequent among RA patients, secondary to the physical impairments caused by the disease.

Among the strengths of our study is its longitudinal design, with followup obtained on most members of both the ÓRALE and the SAHS cohorts. The availability of a comparison group of community-dwelling people from the general population of the same city, such as the SAHS cohort, in which CV risk factors and outcomes have been carefully ascertained, is an added strong point, because it enables inferences on the incidence of events observed in our RA patients. In addition, our analysis strategy allowed us to adjust our relative risk estimates for the competing effect of traditional cardiovascular risk factors, in effect isolating the contribution of RA itself to cardiovascular morbidity.

The main potential limitation of the present analysis is the possibility of differences in the methods used to ascertain outcomes and predictors in the 2 cohorts. In the case of predictor ascertainment, the measurement methods used in both studies were similar, with the possible exception of plasma cholesterol measurement. However, as has been the case in previous comparisons between RA patients and controls, we found that cholesterol levels in the ÓRALE patients were lower than those in the SAHS cohort (38). Thus, we believe the potential for differential ascertainment of hypercholesterolemia is small.

Determination of CV outcomes may also differ between the 2 cohorts. Patients in ÓRALE are followed up medically, and CV events in this cohort may be more likely to be recognized. We aimed to counterbalance this possibility by defining CV events more conservatively from a self-reported list of hospitalizations, confirmed by review records of those with potentially CV causes. By comparison, most SAHS outcomes are based on self-reported heart attack, heart surgery, or stroke. This could potentially lead to a higher frequency of outcomes falsely reported as CV-related compared with ÓRALE, which would be more likely to introduce bias toward the null hypothesis of no difference between the 2 cohorts.

Followup of the SAHS cohort began 7–16 years before and ended during the year in which we recruited the ÓRALE cohort. This nonconcurrency is a potential source of bias toward an increased rate of events in the ÓRALE cohort, which was followed up later than the SAHS cohort, because cardiac surgery may have become more commonplace in the interim. However, nonconcurrency could also bias toward the null hypothesis of no difference, because of the secular trend toward reduced CV mortality in the population. The lack of a significant trend in either direction in the incidence of CV events or heart surgery during the 8-year followup of the SAHS is evidence that neither of these 2 biases is operating to a significant degree in our study. Likewise, it is unlikely that the 10% of SAHS participants who were lost to followup would have had a sufficiently high rate of CV events to erase the increased rate in RA, given the small differences between respondents and those lost to followup in the SAHS.

In conclusion, we have shown that CV events occur more frequently than would be expected in RA, and that this increased incidence is not entirely explained by traditional CV risk factors. Physicians who provide medical care to patients with RA should recognize that this disease is characterized by a predisposition to atherosclerosis and CV disease and should implement appropriate prophylactic or therapeutic measures, as clinically indicated. Further research is needed to understand the mechanisms of increased atherogenesis in RA.

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