Increased Unrecognized Coronary Heart Disease and Sudden Deaths in Rheumatoid Arthritis

A Population-Based Cohort Study

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Objective. To examine the risk of clinical coronary heart disease (CHD) in patients with rheumatoid arthritis (RA) compared with age- and sex-matched non-RA subjects, and to determine whether RA is a risk factor for CHD after accounting for traditional CHD risk factors.

Methods. We assembled a population-based incidence cohort of 603 Rochester, Minnesota residents ages ≥18 years who first fulfilled the American College of Rheumatology (ACR) 1987 criteria for RA between January 1, 1955 and January 1, 1995, and 603 age- and sex-matched non-RA subjects. All subjects were followed up through their complete inpatient and outpatient medical records, beginning at age 18 years until death, migration, or January 1, 2001. Data were collected on CHD events and traditional CHD risk factors (diabetes mellitus, hypertension, dyslipidemia, body mass index, smoking) using established diagnostic criteria. CHD events included hospitalized myocardial infarction (MI), unrecognized MI, coronary revascularization procedures, angina pectoris, and sudden CHD deaths. Conditional logistic regression and Cox regression models were used to estimate the risk of CHD associated with RA, both prior to and following RA diagnosis, after adjusting for CHD risk factors.

Results. During the 2-year period immediately prior to fulfillment of the ACR criteria, RA patients were significantly more likely to have been hospitalized for acute MI (odds ratio [OR] 3.17, 95% confidence interval [95% CI] 1.16–8.68) or to have experienced unrecognized MIs (OR 5.86, 95% CI 1.29–26.64), and less likely to have a history of angina pectoris (OR 0.58, 95% CI 0.34–0.99) compared with non-RA subjects. After the RA incidence date, RA patients were twice as likely to experience unrecognized MIs (hazard ratio [HR] 2.13, 95% CI 1.13–4.03) and sudden deaths (HR 1.94, 95% CI 1.06–3.55) and less likely to undergo coronary artery bypass grafting (HR 0.36, 95% CI 0.16–0.80) compared with non-RA subjects. Adjustment for the CHD risk factors did not substantially change the risk estimates.

Conclusion. Patients with RA have a significantly higher risk of CHD when compared with non-RA subjects. RA patients are less likely to report symptoms of angina and more likely to experience unrecognized MI and sudden cardiac death. The risk of CHD in RA patients precedes the ACR criteria–based diagnosis of RA, and the risk cannot be explained by an increased incidence of traditional CHD risk factors in RA patients.

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease affecting ~1% of the adult general population (1). Recent evidence supporting an inflammatory basis for atherosclerosis (2,3) has led many investigators to study the relationship between systemic inflammatory conditions such as RA and the risk of coronary heart disease (CHD) (4–14). Patients with RA

appear to have a higher risk of CHD morbidity and mortality, but the magnitude of the CHD risk, the clinical presentation, and the outcome of CHD in RA still remain controversial. The aim of the present study was to examine the risk of clinical CHD events in a population-based incidence cohort of RA subjects compared with age- and sex-matched non-RA subjects, and to determine whether RA is a risk factor for CHD after accounting for traditional CHD risk factors.

PATIENTS AND METHODS

Data resources. This study was designed as a retrospective longitudinal cohort study using the data resources of the Rochester Epidemiology Project (REP), a diagnostic indexing and medical records linkage system. The potential of the REP for population-based studies has been described in detail previously (15,16). Population-based epidemiologic research in this community is enhanced because of its relative geographic isolation from other urban centers and because nearly all medical care is delivered to local residents by a small number of providers. Furthermore, data from all providers are contained in a single comprehensive medical records linkage system. Medical diagnoses and other key information are abstracted and entered into computerized indices to facilitate case identification. This unique population-based data resource ensures virtually complete ascertainment and followup of all clinically diagnosed cases in a geographically defined community.

Study population. The study population comprised an incidence cohort of patients with RA and a non-RA comparison cohort. A population-based incidence cohort of Rochester, Minnesota residents ages ≥18 years who fulfilled the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) 1987 criteria for RA (17) between January 1, 1955 and January 1, 1995 was assembled, as previously described (18,19). The RA incidence date was defined as the first date of fulfillment of 4 of the 7 ACR diagnostic criteria. For each subject with RA, an individual without RA from the same underlying population was randomly selected, after matching for the birth year (±3 years), sex, and length of medical history. These matched subjects comprised the non-RA comparison cohort. Subjects in the non-RA cohort were assigned an index date corresponding to the RA incidence date of the matched RA subjects.

Followup and ascertainment of CHD events. The entire inpatient and outpatient medical records of each study subject were reviewed longitudinally by 1 of 4 trained nurse abstractors, beginning with the subjects' records at age 18 years (or date of migration to Olmsted County for those who first became residents after age 18 years) and continuing until the subject's death, migration from Olmsted County, or January 1, 2001. The nurse abstractors were blinded to the study hypothesis. Data were collected on all CHD events throughout the followup period.

Published guidelines were used for classification of CHD events (20). CHD events included 1) hospitalized myocardial infarction (MI), 2) unrecognized MI, 3) coronary revascularization procedures, 4) angina pectoris, and 5) out-of-hospital sudden deaths. Hospitalized MIs were defined according to standard epidemiologic criteria (21,22) and classified as definite, probable, suspect, or no MI based on the presence of cardiac pain, biomarker values, and the Minnesota coding of the electrocardiogram (ECG) (23,24). Unrecognized MI was defined as the presence of characteristic ECG findings in a nonacute setting, or a recorded physician diagnosis of a characteristic ECG finding in a patient with no documented history of previous MI. The date of the first documentation of a characteristic ECG finding was considered the incidence date. Coronary revascularization procedures included percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass grafting (CABG). Angina pectoris was defined as cardiac pain in a patient in whom no other cause for the pain could be identified. Sudden death was defined as out-of-hospital deaths that occurred in emergency departments (including patients dead on arrival), private homes, public places, and nursing homes, and that were recorded as International Classification of Diseases, Ninth Revision, Clinical Modification codes 410–414 as the underlying cause of death on the death certificates. These criteria have been previously validated and published (25). At the end of the study (January 1, 2001), followup for vital status was complete for 90% of the study population.

CHD risk factors. Traditional CHD risk factors were ascertained throughout the followup period and were defined according to established criteria. Dyslipidemia was defined according to the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) guidelines (26,27), and was considered present if the level of low-density lipoprotein cholesterol was ≥160 mg/dl, total cholesterol was ≥240 mg/dl, high-density lipoprotein cholesterol was <40 mg/dl, and triglycerides was ≥150 mg/dl, or if there was a clearly documented history of dyslipidemia or treatment with lipid-lowering therapy. Diabetes mellitus was defined according to the 1998 World Health Organization diagnostic criteria (28), and was considered present if there were at least 2 measurements of fasting plasma glucose ≥126 mg/dl, or a 2-hour plasma glucose ≥200 mg/dl following a glucose load, or there was a clearly documented history of diabetes mellitus or treatment with hypoglycemic agents. Hypertension was defined according to the diagnostic criteria of the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure (29,30), and subjects were considered to have hypertension if 2 or more ambulatory blood pressure readings were ≥140 mm Hg systolic and/or 90 mm Hg diastolic, or if they had a physician's diagnosis of hypertension, or had received treatment with antihypertensive agents. Body mass index (BMI) was categorized as high (≥30 kg/m^2) or low (<20 kg/m^2) in accordance with the guidelines on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults (31). Cigarette smoking status at baseline was categorized as current, former, or never smoker. Finally, family history of CHD (subjects' first-degree relatives with CHD according to the specifications described above) was assessed only at baseline.

Statistical analysis. The following categories of CHD events were considered individually, both prior to and following the incidence/index date (hereafter referred to as the index

date): 1) definite and probable hospitalized MI, 2) unrecognized MI, 3) coronary revascularization procedures, 4) angina pectoris, and 5) sudden deaths. Statistical analyses of the CHD events were performed in 2 phases.

In the first phase, we examined the risk of CHD prior to the index date. The association between the prevalence of CHD and RA disease status and the CHD risk factors was examined using conditional logistic regression. Adjusted odds ratios (ORs) were calculated to determine the associations between the presence of CHD and RA status after adjusting for age, sex, and the CHD risk factors. Results were reported as ORs with 95% confidence intervals (95% CIs). Two-sided P values of less than 0.05 were considered to indicate statistical significance.

The second phase of the statistical analyses involved comparison of the incidence of CHD events following the index date. Similar to the analyses of CHD events prior to the index date, each CHD event was considered individually. Subjects with a history of CHD events prior to the index date were excluded (see footnotes in Table 3). The earliest recorded date of each CHD event was considered the event date. Additional analyses were performed using a composite CHD end point that included all CHD events. The event date for this analysis was the date of occurrence of the first CHD event.

The cumulative incidence of CHD was estimated using the product-limit life table methods, with the analysis taking into account the competing risk of death (32). The cumulative incidence estimates, adjusted for the competing risk of death, provided an estimate of the proportion of subjects who experienced the CHD event at a specific time point, in the RA and non-RA cohorts. The probabilities of CHD events in the RA and non-RA cohorts were compared using the methods described by Gray (33).

Observed and expected rates of hospitalized MI were compared using the log-rank test. The expected number of hospitalized MIs was based on the sex and age of the study subjects and on the hospitalized MI incidence rates from Olmsted County (34).

Cox regression models were used to estimate the risk of CHD in the RA and non-RA cohorts. Separate models were created for each CHD event. Age was used as the time scale for these models and the analyses were stratified by sex. The anchors for age in the time scale were, for entry, the subjects' age at the index date and, for the end point, their age at the first incident CHD event, death, or last followup. The data on subjects who died of non-CHD causes prior to any fatal or nonfatal CHD event, and the data on those who were still alive at last followup were censored. Hazard ratios (HRs) for the incidence of CHD events or sudden deaths were computed, first, univariately (age- and sex-adjusted), and then, after additional adjustment for the CHD risk factors. All traditional CHD risk factors were included in the model. Risk factors assessed throughout followup were modeled as time-dependent covariates (except for smoking). All time-dependent covariates were dichotomous.

Because cholesterol screening was not performed routinely during the early years of our study period, it is likely that lipid values were not missing at random. Propensity scoring was used to correct for potential biases associated with missing lipid values. Logistic regression models were used to determine predictors of the absence of lipid values, considering all risk

factors, as well as time trends (35). Separate models were developed for the periods before and after 1980, when cholesterol screening became more prevalent. The reciprocal of the predicted probabilities from these models was then used as a case weight in Cox models that assessed the importance of dyslipidemia as a predictor of CHD events. Propensity scoring analysis showed that dyslipidemia was not a significant predictor (HR 1.30, 95% CI 0.89–1.90), and this factor was therefore excluded from the multivariable model in order to avoid removal of subjects with missing values.

RESULTS

Characteristics of the cohort. The RA incidence cohort and the non-RA comparison cohort each consisted of 603 matched individuals (Table 1). The mean age was 58 years and 73% were female in both cohorts. RA subjects were significantly more likely to be former or current cigarette smokers. All other baseline characteristics were similar in both cohorts (Table 1). The mean followup time was 14.7 years for RA subjects and 16.8 years for non-RA subjects, corresponding to 8,672 and 10,054 person-years, respectively. During this followup period, RA subjects were significantly more likely to have low BMI ($P < 0.001$) and significantly less likely to have dyslipidemia ($P < 0.001$), when compared with non-RA subjects (Table 1).

Hospitalized MI. The prevalence of each of the CHD events prior to the index date is shown in Table 2. Definite and probable hospitalized MIs were >3 times more prevalent in RA subjects than in non-RA subjects (OR 3.40, 95% CI 1.25–9.22). Multivariable modeling with adjustment for age, sex, smoking status, BMI, and the presence or absence of diabetes mellitus and hypertension did not substantially change the prevalence estimates (Table 2).

We also examined the timing of the hospitalized MIs prior to the index date. During the 2-year period immediately prior to fulfillment of the ACR diagnostic criteria for RA, RA subjects experienced 8 hospitalized MIs, whereas the non-RA subjects experienced none ($P < 0.001$). Before this 2-year period, RA subjects experienced 9 hospitalized MIs and non-RA subjects experienced 5 ($P = 0.13$).

After excluding subjects with a history of hospitalized MI prior to the index date, we identified 40 incident hospitalized MIs among RA subjects and 46 incident hospitalized MIs among non-RA subjects (Table 3). The numbers of hospitalized MIs in the RA and non-RA cohorts were similar to what would be expected based on the age and sex-specific MI incidence rates in Olmsted County (34). Based on the expected rates and

Table 1. Characteristics of the rheumatoid arthritis (RA) and the non-RA cohorts (Rochester, Minnesota, 1955–1995)*

Characteristic	Baseline, no. (%)		After baseline, no. (rate/100 person-years)	
	RA cohort (n = 603)	Non-RA cohort (n = 603)	RA cohort	Non-RA cohort
Age, mean ± SD years	58.0 ± 15.2	58.2 ± 15.2	NA	NA
Female	441 (73)	441 (73)	NA	NA
Length of followup, mean ± SD years	NA	NA	14.7 ± 9.7	16.8 ± 10.2
CHD risk factors				
Family history of CHD	287 (48)	284 (47)	–	–
Cigarette smoking				
Never smoker	255 (45)†	329 (56)	–	–
Former smoker	148 (26)†	118 (20)	–	–
Current smoker	170 (30)†	144 (24)	–	–
Hypertension	312 (52)	298 (49)	179 (3.67)	214 (3.57)
Dyslipidemia	163 (49)	169 (52)	158 (2.71)†	228 (3.64)
Diabetes mellitus	44 (7)	41 (7)	66 (0.79)	98 (1.02)
Body mass index				
≥30 kg/m^2	71 (13)	68 (13)	35 (0.47)	54 (0.63)
<20 kg/m^2	73 (13)	65 (12)	83 (1.17)†	52 (0.64)

* Except where indicated otherwise, values are the number (%). NA = not applicable; CHD = coronary heart disease.
† $P < 0.05$ versus non-RA cohort.

the age, sex, and clinical characteristics of the RA cohort, the expected number of hospitalized MIs in the RA cohort was 33.5, compared with the 40 observed events ($P = 0.26$ by 1-sample log rank test). Similarly, 41 hospitalized MIs were expected and 46 were observed in the non-RA cohort ($P = 0.44$).

We then examined the risk of incident hospitalized MI among RA and non-RA subjects using Cox regression models (Table 3). After adjustment for age and sex, the risk of incident hospitalized MI was not significantly different in the RA and non-RA cohorts (HR 1.06, 95% CI 0.69–1.62). The risk estimate remained essentially unchanged after additional adjustments for smoking, BMI, diabetes mellitus, and hypertension (Table 3).

Unrecognized MI. Prior to the index date, unrecognized MIs were >5 times more prevalent in RA subjects than in non-RA subjects (OR 5.50, 95% CI 1.22–24.81), and adjustment for the prevalence of CHD risk factors had no effect on the risk estimate (Table 2). The significantly higher risk of unrecognized MI among RA subjects persisted during followup. After excluding subjects with a history of hospitalized or unrecognized MI, the estimated cumulative incidence of unrecognized MI at 30 years of followup, adjusted for the competing risk of death, was 6.0% and 3.7% in the RA and the non-RA cohorts, respectively ($P = 0.050$) (Figure 1). Age- and sex-adjusted Cox regression analysis (Table 3) demonstrated that, compared with age- and sex-matched subjects without RA, RA subjects were more than twice as likely to experience an unrecognized MI (HR 2.20, 95% CI 1.18–4.18) during the course of their disease. The rate of ECGs was similar in both cohorts (data not shown).

Table 2. Prevalence of coronary heart disease in rheumatoid arthritis (RA) and non-RA subjects at index date (Rochester, Minnesota, 1955–1995)

Characteristic	Observed, no. (%)		Odds ratio (95% confidence interval)	
	RA cohort (n = 603)	Non-RA cohort (n = 603)	Age- and sex-adjusted*	Multivariable-adjusted*
Hospitalized myocardial infarction	17 (2.8)	5 (0.8)	3.40 (1.25–9.22)†	3.17 (1.16–8.68)†
Unrecognized myocardial infarction	11 (1.8)	2 (0.3)	5.50 (1.22–24.81)†	5.86 (1.29–26.64)†
Angina pectoris	27 (4.5)	43 (7.1)	0.59 (0.35–0.99)†	0.58 (0.34–0.99)†
Revascularization procedures	6 (1.0)	6 (1.0)	1.00 (0.29–3.45)	1.04 (0.30–3.60)

* Conditional logistic regression analyses were used for both the age- and sex-adjusted and the multivariable-adjusted odds ratio estimates. Multivariable-adjusted logistic regression models included age, sex, smoking status, body mass index, and the presence or absence of diabetes mellitus and hypertension.
† $P < 0.05$ between cohorts.

Table 3. Risk of coronary heart disease (CHD) in rheumatoid arthritis (RA) and non-RA subjects following the index date (Rochester, Minnesota, 1955–1995)

Outcome	No. (rate/10,000 person-years)		Hazard ratio (95% confidence interval)	
	RA cohort	Non-RA cohort	Age- and sex-adjusted	Multivariable-adjusted*
Hospitalized MI†	40 (46)	46 (46)	1.06 (0.69–1.62)	1.09 (0.71–1.68)
Unrecognized MI‡	27 (31)	15 (15)	2.20 (1.18–4.18)§	2.13 (1.13–4.03)§
Angina pectoris¶	44 (51)	65 (67)	0.76 (0.52–1.12)	0.76 (0.52–1.13)
Revascularization procedures#	28 (32)	35 (35)	0.94 (0.57–1.54)	0.94 (0.56–1.56)
PTCA	22 (25)	15 (15)	1.77 (0.92–3.41)	1.79 (0.90–3.54)
CABG	8 (9)	26 (26)	0.35 (0.16–0.78)§	0.36 (0.16–0.80)§
Sudden death	31 (35)	18 (18)	2.36 (1.30–4.27)§	1.94 (1.06–3.55)§
All CHD combined	109 (130)	107 (112)	1.19 (0.91–1.56)	1.14 (0.87–1.51)

* Multivariable Cox regression models were adjusted for age, sex, smoking status, body mass index, and the presence or absence of diabetes mellitus and hypertension.
† Subjects with a history of hospitalized myocardial infarction (MI) excluded.
‡ Subjects with a history of hospitalized MI and unrecognized MI excluded.
§ $P < 0.05$ between cohorts.
¶ Subjects with a history of hospitalized MI, unrecognized MI, and angina pectoris excluded.
# Subjects with a history of revascularization procedures excluded. PTCA = percutaneous transluminal coronary angioplasty; CABG = coronary artery bypass grafting.

Angina pectoris. RA subjects were half as likely as the non-RA subjects (OR 0.59, 95% CI 0.35–0.99) to have a history of angina pectoris prior to the index date (Table 2). The same pattern was observed following the index date, after exclusion of subjects with a history of hospitalized MI, unrecognized MI, or angina pectoris prior to the index date ($P = 0.025$) (Figure 1). During the course of their disease, RA subjects were ~25% less likely to report angina symptoms (HR 0.76, 95% CI 0.52–1.12) than the non-RA subjects, but the difference did not reach statistical significance (Table 3).

Revascularization procedures. Both the RA and the non-RA subjects had undergone similar numbers of coronary revascularization procedures prior to the index date (Table 2). During followup, we identified 28 PTCA and CABG procedures in the RA cohort, and 35 of these procedures in the non-RA cohort (Table 3). RA subjects were significantly less likely to undergo CABG (HR 0.35, 95% CI 0.16–0.78) compared with non-RA subjects. Analysis of time trends revealed that, as expected, use of CABG has increased significantly over time ($P = 0.0014$). Although this increase was somewhat (but not significantly) slower among RA subjects compared with non-RA subjects ($P = 0.11$), CABG rates in both groups were almost identical by 1995.

Sudden death. We identified 31 and 18 sudden deaths in the RA and non-RA cohorts, respectively. The estimated cumulative incidence of sudden death at 30 years of followup, adjusted for the competing risk of
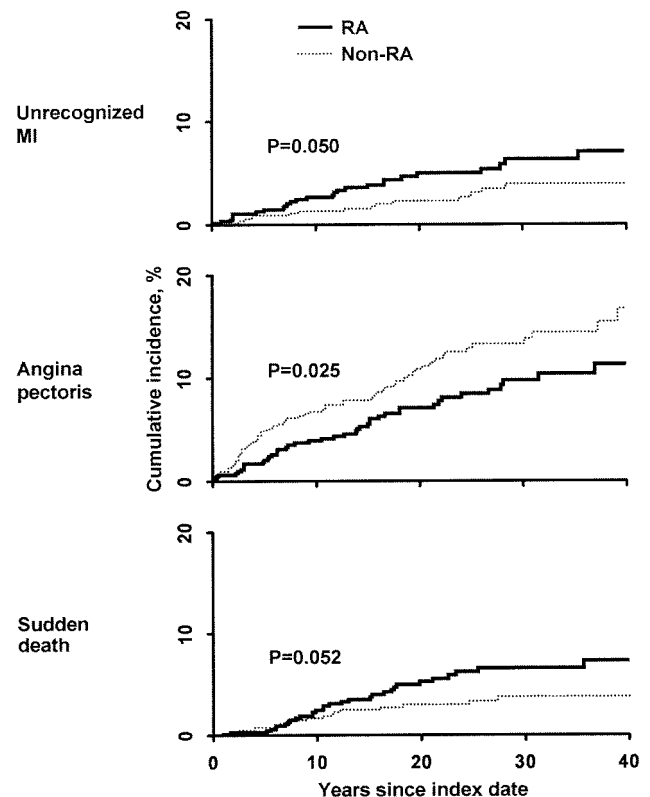
Figure 1. Cumulative incidence of unrecognized myocardial infarction (MI), angina pectoris, and sudden deaths in the rheumatoid arthritis (RA) and non-RA cohorts according to length of time since index date, adjusted for the competing risk of death.

death by other causes, was 6.7% in the RA cohort and 3.8% in the non-RA cohort ($P = 0.052$) (Figure 1). Cox regression analysis demonstrated that the RA subjects were more than twice (HR 2.36, 95% CI 1.30–4.27) as likely to experience sudden deaths (Table 3) compared with the non-RA subjects. The doubling of the risk of sudden death persisted after supplemental adjustments for the history of hospitalized or unrecognized MI and revascularization procedures (data not shown).

We also examined the risk of any CHD event by considering the date of the earliest CHD event as the CHD incidence date (Table 3). We did not observe a statistically significant difference between the RA and non-RA cohorts (HR 1.19, 95% CI 0.91–1.56). We repeated all of the analyses presented in Tables 2 and 3 by considering the incidence date to be the fulfillment of the first ACR criterion, rather than 4 of the 7 criteria. These sensitivity analyses yielded results virtually identical to those obtained above. Finally, we examined the risk of CHD according to calendar year, and no significant time trends were found ($P = 0.21$).

DISCUSSION

In this retrospective cohort study, patients with RA had a significantly higher risk of both hospitalized and unrecognized MI prior to the incidence of RA, suggesting that the risk of CHD associated with RA precedes the ACR criteria–based diagnosis of RA. Patients with RA were also less likely to have symptoms of angina, were less likely to receive CABG, and had a significantly higher risk of sudden deaths. Together, these findings indicate that the presentation of CHD differs markedly in RA subjects compared with that in persons without the disease.

A higher risk of CHD in RA was reported previously in controlled studies (9–14), including one from our group. These studies are summarized in Table 4. Despite the differences in methods and CHD end points, all of these controlled studies reported a ≥40% higher risk of CHD associated with RA. However, these previous studies included mainly RA prevalence cohorts, with limited duration of followup, and relied heavily on self-reports to ascertain CHD events. Furthermore, the CHD events were limited to hospitalized MIs and sudden deaths and did not consider the complete spectrum of CHD events (20). The present study extends the findings of previous studies by demonstrating the complete spectrum of CHD events and reveals the striking shift in clinical presentation of CHD in RA.

The first major finding of this study is the dem-

onstration of a higher risk of both hospitalized and unrecognized MI prior to the clinical onset of RA. This finding is consistent with the absence of any association between cardiovascular mortality and RA disease duration in this cohort (36). Furthermore, recent studies demonstrated the presence of systemic inflammatory activity and serologic abnormalities several years prior to the onset of RA symptoms (37). Therefore, our findings are in accordance with the presence of a preclinical phase of RA, during which the risk of CHD appears to be elevated. Investigation of the risk of CHD prior to RA incidence was feasible, due to our unique ability to accurately ascertain and confirm incident CHD events using established reproducible criteria over an average period of 27 years prior to and 15 years following the RA incidence/index date in population-based cohorts. Previous studies included prevalent RA cohorts with limited or no followup data prior to study entry (Table 4), and therefore, it was not possible to accurately distinguish the timing of CHD events. This was further complicated by reliance on self-reports or physician diagnoses to ascertain CHD events, as well as lack of validation in most studies. In addition, analysis of combined end points, as was the case in previous studies, does not distinguish between the various CHD events. Thus, it is possible that excess CHD-related deaths in previous studies were driven, in large part, by an excess risk of sudden cardiac deaths.

The CHD event rates (i.e., hospitalized MI and sudden death) in our study are within the range of values reported in various CHD surveillance studies, including one in our community (34,38,39), but are substantially higher than those reported among the participants of the Nurses' Health Study (11). This may be due, in part, to censoring of subjects at the time of revascularization and angina in that study, and due, in part, to inclusion of a healthier cohort of health-conscious nurses with a more favorable CHD risk profile and lower CHD rates (40).

The second major finding of our study is the demonstration of a higher risk of unrecognized MIs and sudden deaths and a lower likelihood of angina symptoms in RA patients. These consistent findings demonstrate that CHD manifests differently in RA. Access to the original ECGs performed for screening or other clinical purposes in the routine clinical setting allowed us to reexamine ECG findings, using current diagnostic criteria, consistently throughout the long followup. The rates of coronary angiograms and ECGs were similar in both cohorts, both prior to and following the index date, excluding the possibility of differential ascertainment of unrecognized MIs in the 2 cohorts. Thus, if the likeli-

Table 4. List of controlled studies examining the risk of coronary heart disease (CHD) in rheumatoid arthritis (RA)*

Authors, year (ref.)	Study design	Data source	RA definition	Population-based	Incidence cohort	MI definition	Risk estimate
Gabriel et al, 1999 (9)	Cohort	Rochester Epidemiology Project	ACR 1987 criteria (n = 450)	Yes	No	Physician diagnosis, validation with medical records (n = 111)	1.35†
Del Rincon et al, 2001 (10)	Cohort (external control group) with 1 year followup	ORALE cohort‡	ACR 1987 criteria (n = 236)	No	No	Hospitalized MI (n = 7) + revascularization + stroke	3.96
Solomon et al, 2003 (11)	Cohort with >10 years followup	NHS§	Self-reports verified for ACR 1987 criteria (n = 527)	No	No	Self-reports of MI verified by medical record review, MI + sudden death (n = 2,296)	2.00
Wolfe et al, 2003 (12)	Cross-sectional survey	Participants of NDB¶	Rheumatologist diagnosis (n = 9,093)	No	No	Self-reports + 50% medical record validation	2.14
Watson et al, 2003 (13)	Cohort with 4.5 years followup	GPRD#	Physician diagnosis, no validation (n = 11,633)	No	No	Physician diagnosis, no validation	1.60
Fischer et al, 2004 (14)	Case–control (MI)	GPRD#	Physician diagnosis, no validation (n = 770)	No	No	Physician diagnosis, partial validation (n = 8,688)	1.47

* MI = myocardial infarction; ACR = American College of Rheumatology.
† Not adjusted for CHD risk factors. All other estimates are adjusted for baseline CHD risk factors.
‡ The Outcome of Rheumatoid Arthritis Longitudinal Evaluation (ORALE) cohort includes consecutive RA patients ascertained in 1996 through 3 rheumatology clinics in Texas.
§ The Nurses' Health Study (NHS) began in 1976 when >100,000 female registered nurses completed a questionnaire about their medical history, cardiac risk factors, menopausal status, and lifestyle factors. The cohort was followed up every 2 years with mailed questionnaires that update exposure information and inquired about newly diagnosed medical illnesses, as well as height, weight, smoking habits, and family history.
¶ The National Databank for Rheumatic Diseases (NDB) is a chronic rheumatic disease data bank and includes RA patients seen at the Wichita Arthritis Center (5%) as well as participants in a national incidence cohort of RA (6%), subjects recruited from several community rheumatologists for the leflunamide surveillance program (27%), and subjects contributed by practices of several US community rheumatologists (62%).
# The General Practice Research Database (GPRD) is an electronically available research database in the United Kingdom, encompassing >3 million residents. The medical information is recorded electronically by participating general practitioners and provided electronically to researchers after removal of patient identifiers.

hood of recognizing an MI is lower among RA subjects than among non-RA subjects, then in comparison with a prospective design with regular ECG assessments, our study would result in an underestimation of the true risk of unrecognized MI in RA.

Unrecognized MIs constitute up to 30% of the MIs in the community and were previously described in other diseases, such as diabetes mellitus and end-stage renal disease (41). Several pathophysiologic mechanisms have been implicated (41,42), including individual differences in pain perception and generalized hyposensitivity to myocardial ischemia (41), and more recently, the balance between proinflammatory and antiinflammatory cytokines (43,44). According to the inflammation-based hypothesis, there is higher production of antiinflammatory cytokines with lower expression of CD11b/CD18 adhesion molecules on phagocytes among patients with asymptomatic ischemia (43). It is possible that the actual experience of angina itself is equally frequent in the RA and the non-RA subjects, but the RA patients may be less likely to consult a physician for this symptom, or they may be more inclined to rationalize their chest pain and think that it may be related to their arthritis. It is equally possible that their physicians do not label the problem as being of cardiac origin. Further investigation of these possible mechanisms is warranted in RA patients because the long-term prognosis after an unrecognized MI may be worse than that after a recognized MI (41,42). Because these infarctions are accompanied by minimal or no symptoms, they escape detection until ultimately resulting in sudden deaths, as was observed in our study.

Our findings also indicate that RA subjects were almost 70% less likely to undergo CABG than the non-RA subjects. This is not surprising, because a main impetus for undergoing revascularization procedures is pain, and in the absence of angina pectoris, subjects would be less likely to receive these procedures.

An interesting observation in our study was the higher incidence of hospitalized MIs during the 2 years preceding RA diagnosis. This may be due to Berkson's bias (45,46), i.e., people who are seen in medical settings are more likely to have other diseases identified. Alternatively, an inflammatory activation or trigger that contributes to the acute MI event may, at the same time, cause a flare of RA symptoms that leads to diagnosis of RA. Further elucidation of this hypothesis may provide new insights into the inflammatory mechanisms of both CHD and RA. Moreover, the higher risk of acute hospitalized MI immediately prior to RA diagnosis in conjunction with the higher risk of sudden deaths raises

the possibility that some individuals who would have become RA subjects (i.e., fulfilled the diagnostic criteria for RA) may have died before RA was diagnosed. This suggests that the risk of CHD prior to RA could have been underestimated and emphasizes the importance of studying incidence cohorts, rather than referral cohorts, when examining outcomes such as MI, which may be fatal at first presentation.

The strengths of our study are several-fold. This is the first population-based study examining the risk of CHD in RA. This study extends the findings of previous studies, and addresses various limitations through the longitudinal followup of an RA incidence cohort and a non-RA cohort sampled from the same community. In contrast to previous studies, we accessed and reviewed the entire inpatient and outpatient medical records of all subjects, including review of the original ECGs, for ~27 years prior to and 15 years following the index date. We examined the complete spectrum of CHD events, including angina pectoris, revascularization procedures, and unrecognized MIs. We applied rigorous and validated diagnostic criteria to ascertain CHD events and CHD risk factors. Our CHD criteria are identical to the case definitions used in CHD surveillance studies in the United States (20,38). Furthermore, we ascertained the traditional CHD risk factors throughout followup, and used them as time-dependent variables to fully account for the risk factors that developed during followup. To our knowledge, this is the first study to demonstrate that the increased risk of CHD in RA actually precedes the ACR criteria–based diagnosis of RA, and that unrecognized MIs and sudden deaths are the major contributors to the CHD risk in these subjects.

Our results should be interpreted in light of some potential limitations. Our findings may not be generalizable to nonwhite individuals, because the Rochester population during the calendar years under investigation was >95% white. With the exception of a higher proportion of the working population employed in the health care industry, and correspondingly higher education levels, the local population is socioeconomically similar to American whites (16). Second, we were not able to examine whether the increased risk of CHD was directly due to RA itself or to a complication of RA-associated therapy, because only 57% of the RA patients in our study ever received a disease-modifying antirheumatic drug. However, the absence of any calendar-year effect on the incidence of CHD in the RA cohort ($P = 0.21$) suggests that the increased risk cannot be completely explained by RA-associated therapy. Third, selection bias is a potential problem due to losses to

followup. At the end of the study, the vital status of 10% of the study population was not known. In fact, these subjects remained under observation (and at risk for the CHD outcomes) for a mean of 13.1 years (median 10.7 years, interquartile range 5.6–19.1 years). Their followup data were censored in the analysis. There were no differences with respect to vital status followup information between the RA and the non-RA cohorts, and comparison of the baseline characteristics of subjects who remained under observation during the entire followup period (n = 1,086) and those who had either migrated or were lost to followup (n = 120) revealed that there were no baseline differences and there were no differences in availability of vital status data in the RA and the non-RA cohorts (P = 0.56). Therefore, the absence of vital status data is unlikely to affect the comparison of the CHD risk in the RA and non-RA cohorts. Fourth, this was a retrospective cohort study that relied on the clinical information recorded in the patients' medical records, and therefore, it was not possible to ascertain risk factors and CHD outcomes prospectively at regular intervals. Similarly, conditions not recorded in the medical records would have been missed. This could have been a potential problem for the ascertainment of unrecognized MIs. However, ECG rates were similar in both cohorts, suggesting that differential misclassification is unlikely. Fifth, multivariable analysis of CHD events and risk factors prior to the incidence/index date was essentially cross-sectional and did not distinguish among the risk factors that preceded the CHD event. Our ongoing analyses are focused on investigating whether RA acts as an effect modifier by interacting with the traditional CHD risk factors to increase the risk of CHD. Furthermore, the role of RA disease characteristics and medications on the clinical presentation and outcome of CHD in RA warrants further investigation.

Our findings provide compelling evidence that the increased risk of CHD precedes the ACR criteria–based diagnosis of RA and is not due to an increased incidence of traditional CHD risk factors. CHD in RA may remain unrecognized and may manifest as sudden cardiac deaths. In addition to the etiologic implications of these findings with regard to the inflammation-based etiology of atherosclerosis in RA, we believe that these findings have important implications for the detection and prevention of CHD comorbidity in RA patients. Physicians who care for RA patients should be aware of the higher risk of CHD that is already present at the time of initial diagnosis of RA and should actively monitor for subclinical CHD. A more vigilant and aggressive approach to screen for unrecognized CHD, using noninvasive methods, and to initiate treatment of CHD comorbidity may be warranted, since it could lead to reductions in the rate of CHD-related mortality in RA patients.

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