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No Increased Occurrence of Ischemic Heart Disease Prior to the Onset of Rheumatoid Arthritis

Results From Two Swedish Population-Based Rheumatoid Arthritis Cohorts

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Objective. **To investigate the relative importance of shared etiologies for rheumatoid arthritis (RA) and ischemic heart disease (IHD) in terms of the well-known increased risk of IHD in patients with RA, by assessing the occurrence of IHD up until the time of the onset of the first symptoms of RA.**

Methods. **We assessed the prevalence of a history of IHD, myocardial infarction (MI), and angina pectoris before the onset of RA symptoms in 2 large population-based case–control studies. Patients with newly diagnosed RA according to the criteria of the American College of Rheumatology were included as cases. We used data from the Swedish Early Arthritis Register study and the Swedish Epidemiologic Investigation of Rheumatoid Arthritis case–control study and from general population controls. Information on IHD, MI, and angina pectoris was obtained from the nationwide Hospital Discharge Register and from self reports. We calculated odds ratios (ORs) and 95% confidence intervals (95% CIs) to compare the prevalence of a history of IHD/MI/angina pectoris among patients with RA with that among population controls.**

Results. **We could not detect any increased occurrence of IHD, MI, or angina pectoris before the onset of symptoms of RA, regardless of whether data on IHD were obtained from the Hospital Discharge Register or were self reported. As detected in the Hospital Discharge Register, the OR for IHD overall was 1.0 (95% CI 0.9–1.1), the OR for MI was 1.0 (95% CI 0.9–1.1), and the OR for angina pectoris was 1.0 (95% CI 0.9–1.2).**

Conclusion. **Shared risk factors or susceptibilities for RA and IHD are likely to contribute less than RA-related factors to the increased occurrence of IHD in patients with manifest RA. Nonetheless, the existence of shared factors associated with longer latency until the occurrence of IHD cannot be excluded.**

Patients with rheumatoid arthritis (RA) are at increased risk of premature death, mainly due to an increased risk of ischemic heart disease (IHD) (1–3). This increased risk cannot be fully attributed to traditional risk factors for IHD such as smoking, hypertension, diabetes mellitus, and hyperlipidemia (4–6). These observations point to the presence and importance of other risk factors for IHD in patients with RA but do not define what risk factors these are or whether the risk that cannot be attributed to traditional risk factors could be a consequence of RA. Thus, although a cause-and-effect association between the inflammatory burden

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imposed by RA and the occurrence of IHD has been suggested (7,8), findings such as shared genetic risk factors for RA and IHD (9) and an independent link between the HLA–DRB1 shared epitope (SE) and IHD risk in RA (10,11) suggest that the increased risk of IHD in RA might also reflect shared etiologies of RA and IHD. A correct attribution for the increased RA-related risk of IHD not only is etiologically important but also has important clinical implications. Whereas IHD risks due to a cause-and-effect association between RA and IHD might be reduced by aggressive treatment of RA, IHD risks related to shared risk factors would not be decreased.

One way to assess the relative importance of a cause-and-effect association versus shared etiology for IHD and RA is to assess the timing of IHD in relation to the onset of RA. An increase in IHD risks exclusively after the onset of RA would support a cause-and-effect association between RA disease and the occurrence of IHD. In contrast, an increased occurrence of IHD before the onset of RA would indicate an impact of shared risk factors or etiologies.

Some support for an increased occurrence and an altered spectrum of IHD before the onset of RA comes from a Mayo Clinic study (12). In that study, 603 patients with RA diagnosed between 1955 and 1995 and 603 control subjects were investigated with respect to the occurrence of IHD, and a higher-than-expected occurrence of hospitalized myocardial infarction (MI) and unrecognized MI prior to the diagnosis of RA was reported. However, the occurrence of IHD was assessed up until the time of fulfillment of the American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA (13), without any restrictions on the duration of RA symptoms before fulfillment of the ACR criteria. As a consequence, and as concluded by the authors, the increased occurrence of IHD before the development of RA might have been attributable to ongoing inflammatory activity predating the time point at which the ACR criteria were fulfilled, thus precluding the distinction between a shared etiology and a cause-and-effect association.

To assess the relative contributions of a causal association and shared etiologies to the increased risk of IHD in patients with RA, and to circumvent confounding of *pre*-RA occurrence by true *post*-RA risks, we used 2 large cohorts of patients in whom RA was diagnosed shortly after the onset of RA symptoms (median latency 6 months) and 2 general population control cohorts. In these cohorts, we set out to confirm an increased risk of IHD after a diagnosis of RA and to investigate the relative risk and phenotype of IHD up until the onset of RA symptoms. Because there have been indications of marked etiologic heterogeneity in different RA subsets (14), we moreover assessed the occurrence of IHD prior to the onset of RA symptoms in subsets of patients with RA defined by the presence or absence of rheumatoid factor (RF) or anti–citrullinated protein antibodies (ACPAs), and with consideration of the major genetic RA risk variant, the SE, for which an independent link with cardiovascular disease risk in RA has been reported (10,11).

SUBJECTS AND METHODS

Design and setting. In Sweden, rheumatologists provide care for patients with RA. All residents have equal access to publicly funded health care, including inpatient care. Using the unique 10-digit national registration number issued to all Swedish residents, data from national and virtually complete registries on, for example, demographics and inpatient care, can be linked together, allowing for both unbiased identification of control subjects and assessment of morbidity (15).

In both RA patient cohorts, the date of symptom onset and the date of RA diagnosis were defined. All control subjects were assigned the same date of symptom onset and date of RA diagnosis as the matching RA patients. The Institutional Review Board of the Karolinska Institute approved the study.

The national Early Arthritis Register (EAR) study. The EAR study, which has been ongoing since the mid 1990s, includes patients throughout Sweden with newly diagnosed RA (latency between symptom onset and RA diagnosis <18 months) fulfilling the 1987 ACR criteria for RA (13). At the time of inclusion in the register, information on age, sex, RA subtype (based on RF status), date of RA symptom onset, date of RA diagnosis, and the national registration number, is recorded. For this study, we used 8,454 patients in whom RA was diagnosed between 1995 and January 2008 and in whom the median latency between symptom onset and a diagnosis of RA was 6.3 months.

Using the Swedish national population register, we identified 5 general population control subjects for each patient with RA, matched for sex, year of birth, county of residence, and marital status. Control subjects had to be alive and living in Sweden on December 31 of the year before the diagnosis of RA in the corresponding patient. A total of 42,267 control subjects were identified.

To compare the rates of IHD after a diagnosis of RA and the occurrence of IHD, acute MI, angina pectoris, and percutaneous transluminal coronary angioplasty (PTCA) before the onset of RA symptoms, we linked patients with RA and their controls to the nationwide Swedish Hospital Discharge Register from 1964 through 2006 (the International Classification of Diseases [ICD] codes used are available from the corresponding author). This register contains nearly complete information on discharges from inpatient care, countywide since 1964 and nationwide since 1987, including information on hospital and department, dates of admission and discharge, primary and secondary discharge diagnoses for each

admission as assigned by the discharging clinician coded according to ICD-7–10 (16,17), and surgical interventions coded according to Swedish classifications for surgical procedures (18). Patients who had been admitted with IHD, as either a primary or secondary diagnosis, were considered to have had IHD. Records of PTCA (with or without the placement of a stent) were used in the analysis.

The Epidemiologic Investigation of Rheumatoid Arthritis (EIRA) case–control study of incident RA. The EIRA study is a population-based case–control study performed in the middle and southern parts of Sweden, which includes patients between the ages of 18 years and 70 years with newly diagnosed RA according to the 1987 ACR criteria. In these patients, RA was diagnosed by rheumatologists at public and private clinics within the study area.

For each patient with RA, 1 control subject was randomly selected from the national population register and individually matched to the patient by sex, age, and residential area. If a control subject declined to participate, was not traceable, or reported having RA, a new control subject was selected according to the same algorithm. Of the patients with RA who were identified and invited, 95% participated. The corresponding participation proportion among control subjects was 82%. When the EIRA study was initiated, patients with unspecified arthritis were included, and control subjects were matched to each of those patients. These patients have been excluded from the study, but their controls are still included and used in the analyses. For more details on the EIRA study design, see previously published articles (19,20). Between May 1996 and December 2007, a total of 2,025 patients with RA and 2,760 population controls were included in the EIRA study. Because the patients with RA in the EIRA study are typically also entered in the EAR cohort, 17% of the included RA patients in the EAR cohort overlapped with the RA patients in the EIRA study. The median latency between the onset of RA symptoms and the diagnosis of RA was 6.8 months.

To detect incident IHD *after* a diagnosis of RA, we used the same method as that used in the EAR cohort. To detect IHD *before* the index date in patients with RA and control subjects in the EIRA study, we used 2 methods. According to the first method, and similar to the EAR cohort and its control cohort described above, patients with RA and control subjects in the EIRA study were linked to the Hospital Discharge Register. According to the second method, upon inclusion in the EIRA study, patients with RA and control subjects completed an extensive questionnaire covering a wide range of questions, including preexisting cardiovascular morbidity. Questionnaire items pertaining to IHD before the onset of RA specifically asked "Do you have, or have you had any cardiovascular disease which has been treated by a physician?" (yes/no), and "If yes, of what kind, and when?" The answer to this question was recorded verbatim and coded by the study secretariat according to the ICD-10. Using the EIRA questionnaire, smoking status, hypertension, and diabetes mellitus as well as body mass index (BMI) at study inclusion were assessed. BMI was categorized according to the World Health Organization classification (21). Smoking status was categorized as "ever smoker" or "never smoker."

Serum (available from 99.9% of subjects in the EIRA cohort) was obtained and tested for the presence of RF and ACPAs. RA patients with ACPA levels >25 units/ml were considered ACPA positive. RF status was determined according to the method used at each participating clinic. The presence of ACPAs was analyzed with the Immunoscan RA Mark 2 ELISA (Euro-Diagnostica, Arnhem, The Netherlands), as described elsewhere (22,23).

Information about SE alleles was available for 1,983 patients (98%) and 1,243 control subjects (45%). The genotyping procedures have been described previously (22,24,25). Individuals with 1 or 2 SE alleles were classified as being SE positive, and individuals without any SE allele were classified as being SE negative.

Statistical analysis. *IHD after RA diagnosis.* To estimate the relative risks (RRs) and 95% confidence intervals (95% CIs) for IHD following the diagnosis of RA, we used Cox proportional hazard models. All individuals were followed up from the time of the diagnosis of RA until the end of the study period (December 31, 2006), the date of death, the date of emigration, or the date of the first event, whichever occurred first. Patients who had experienced an IHD before the diagnosis of RA were excluded. In the EAR study, we stratified by the matching risk sets and adjusted for hypertension and diabetes mellitus as detected in the Hospital Discharge Register. In the EIRA study, we additionally adjusted for known and possible cardiovascular risk factors, including smoking, BMI, diabetes mellitus, and hypertension, all as self reported in the EIRA questionnaire.

IHD before index date. To compare the occurrence of IHD prior to the onset of RA symptoms, we calculated odds ratios (ORs) and 95% CIs using conditional logistic regression models, taking the matched design of the study into account. In the EAR study, we adjusted for hypertension and diabetes mellitus and stratified the analyses by age, sex, time of IHD occurrence (fewer or more than 5 years before the index date), as well as RF status among the patients. In the EIRA study, we estimated the corresponding ORs using conditional regression models as well as unconditional logistic regression (adjusted for the matching factors). Because the ORs obtained from the 2 different models were in close agreement, the more precise results from the unconditional logistic regression models are presented below. Besides the matching factors, we adjusted for known and possible confounders, including smoking, BMI, diabetes mellitus, and hypertension, all as self reported in the EIRA questionnaire. To assess possible effect modification, we stratified the analyses by age, sex, RF, ACPAs, the presence of SE alleles, and the time of IHD occurrence (fewer or more than 5 years before the index date).

Results were largely similar regardless of whether analyses were based on events listed as a primary diagnosis only or on events listed as either primary or secondary diagnoses in the Hospital Discharge Register (the latter are presented).

RESULTS

The characteristics of the patients with RA in the EAR cohort and the corresponding control subjects are shown in Table 1. The characteristics of the patients with RA in the EIRA study and the corresponding control subjects are shown in Table 2.

Table 1. Baseline characteristics of the Early Arthritis Register study participants*

Characteristic	RA patients (n = 8,454)	Population controls (n = 42,267)
Age at onset of RA, mean ± SD years	57.1 ± 15.3	57.1 ± 15.3
Female sex	5,831 (69.0)	29,155 (69.0)
Male sex	2,623 (31.0)	13,112 (31.0)
Age distribution, years		
14–49	2,378 (28.1)	11,887 (28.1)
50–59	2,088 (24.7)	10,440 (24.7)
60–69	2,019 (23.9)	10,095 (23.9)
70–94	1,969 (23.3)	9,845 (23.3)
Rheumatoid factor positive	5,499 (65.0)	NA
Hypertension†	460 (5.4)	2,322 (5.5)
Diabetes mellitus†	242 (2.9)	1,211 (2.9)

* Except where indicated otherwise, values are the number (%). All control subjects were assigned the same age at onset of rheumatoid arthritis (RA) as the matching RA patients. The rheumatoid factor status was not specified in 395 patients. NA = not assessed.
† As detected in the Hospital Discharge Register.

Relative risk for IHD following the diagnosis of RA. In the EAR cohort, 343 patients with RA (4.6% of the 7,388 RA patients who did not have a history of IHD at the time of the RA diagnosis) and 1,163 control subjects (3.2% of the 36,658 control subjects who did not have a history of IHD at the time RA was diagnosed in the corresponding patient with RA) experienced a first IHD event during followup, corresponding to an adjusted RR of 1.4 (95% CI 1.3–1.6). In the EIRA study, 55 patients with RA (2.8% of the 1,965 patients with RA who did not have a history of IHD at the time of the diagnosis of RA) and 51 control subjects (1.9% of the 2,680 control subjects who did not have a history of IHD at the time RA was diagnosed in the corresponding patient) experienced an IHD event, corresponding to an adjusted RR of 1.5 (95% CI 0.9–2.3).

Relative risk for IHD before the onset of RA symptoms. In the EAR study, 490 (5.8%) of the 8,454 patients with RA and 2,397 (5.7%) of the 42,267 population-based control subjects had been discharged from the hospital with a diagnosis of IHD before the onset of RA symptoms, resulting in an adjusted OR of 1.0 (95% CI 0.9–1.1). Two hundred thirty-three patients with RA (2.8%) and 1,198 control subjects (2.9%) had a history of having been hospitalized with a diagnosis of MI before the onset of RA symptoms (adjusted OR for MI 1.0 [95% CI 0.9–1.1]), and 373 patients with RA (4.4%) and 1,811 control subjects (4.3%) had been diagnosed with angina pectoris (adjusted OR 1.0 [95% CI 0.9–1.2]). The lack of differences in the occurrence of IHD, MI, or angina pectoris between patients with RA and control subjects was not modified by age, sex (data not shown), or RF status among the patients (Table 3). There were no differences when assessing the overall occurrence of IHD fewer than or more than 5 years before the index date (data not shown). The crude OR for RA associated with a PTCA before the onset of symptoms was 1.2 (95% CI 0.8–1.6), based on 42 events among RA patients and 178 events among control subjects.

In the EIRA study, smoking and diabetes mellitus were more prevalent among patients with RA than among control subjects (26), as were SE alleles (27). In contrast, there was no difference in the self-reported occurrence of hypertension ($P = 0.40$). When hospitalization data were used to define IHD before the onset of RA, 48 patients with RA (2.4%) and 60 control subjects (2.2%) were found to have a history of any IHD, corresponding to a crude OR of 1.1 (95% CI 0.7–1.6) (Table 4). Adjusting for BMI, smoking, hypertension,

Table 2. Baseline characteristics of the Epidemiological Investigation of Rheumatoid Arthritis study participants*

Characteristic	RA patients (n = 2,025)	Population controls (n = 2,760)
Age at onset of RA, mean ± SD years	51 ± 12.6	50 ± 12.9
Female sex	1,437 (71.0)	1,909 (69.0)
Male sex	588 (29.0)	851 (31.0)
Age distribution, years		
18–49	748 (36.9)	1,097 (39.8)
50–59	662 (32.7)	887 (32.1)
60–70	615 (30.4)	776 (28.1)
Antibody status		
RF positive	1,338 (66.3)	NA
ACPA positive	1,144 (62.1)	NA
Presence of 1 or 2 HLA–DRB1 SE alleles	1,462 (73.7)	632 (50.8)
Ever smoker	1,370 (69.4)	1,404 (62.5)
BMI, kg/m^2		
<24	1,063 (53.9)	1,203 (54.3)
25–29	653 (33.1)	744 (33.4)
≥30	256 (13.0)	274 (12.3)
Diabetes mellitus†	85 (4.4)	66 (3.0)
Hypertension†	182 (9.0)	230 (8.3)

* Except where indicated otherwise, values are the number (%). Control subjects were assigned the same date of rheumatoid arthritis (RA) onset as the matching RA patients. The anti–citrullinated protein antibody (ACPA) status was missing for 183 patients with RA, the rheumatoid factor (RF) status was missing for 10 patients, the smoking status was missing for 50 patients and 514 control subjects, the body mass index (BMI) values were missing for 53 patients and 533 control subjects, and the shared epitope (SE) status was missing for 42 patients and 1,517 control subjects. NA = not assessed.
† Self reported.

Table 3. Ischemic heart disease (IHD) before the onset of rheumatoid arthritis (RA) among participants in the Early Arthritis Register study, according to RF status*

RF status	No. of events		Crude OR (95% CI)†	Adjusted OR (95% CI)‡
	Cases	Controls		
IHD, total				
All subjects	490	2,397	1.0 (0.9–1.1)	1.0 (0.9–1.1)
RF positive	299	1,418	1.1 (0.9–1.2)	1.1 (1.0–1.2)
RF negative	169	872	1.0 (0.8–1.2)	0.9 (0.8–1.1)
Myocardial infarction				
All subjects	236	1,198	1.0 (0.9–1.1)	1.0 (0.9–1.1)
RF positive	145	692	1.1 (0.9–1.3)	1.1 (0.9–1.3)
RF negative	82	444	0.9 (0.7–1.2)	0.9 (0.7–1.1)
Angina pectoris				
All subjects	373	1,811	1.0 (0.9–1.2)	1.0 (0.9–1.2)
RF positive	229	174	1.1 (0.9–1.2)	1.1 (0.9–1.3)
RF negative	127	699	0.9 (0.8–1.2)	0.9 (0.7–1.1)

* The rheumatoid factor (RF) status was not specified in 395 cases. OR = odds ratio; 95% CI = 95% confidence interval.
† Conditional regression taking the matched design into consideration.
‡ Conditional logistic regression with adjustments for hypertension and diabetes mellitus.

and diabetes mellitus yielded similar results (Table 4). Stratifying patients with RA according to RF and ACPA status yielded some elevated point estimates with low precision (Table 4). According to self reports, 2.6% of the patients with RA (n = 52) and 2.1% of the control subjects (n = 57) had a history of any IHD event before

Table 4. Ischemic heart disease (IHD) before rheumatoid arthritis (RA) onset in the EIRA study*

Exposure assessment, serologic status	No. of events		OR (95% CI)†	OR (95% CI)‡
	Cases	Controls		
IHD, total				
Self reported, any	52	57	1.2 (0.8–1.7)	0.9 (0.6–1.4)
Hospital Discharge Register				
Any	48	60	1.1 (0.7–1.6)	1.1 (0.7–1.7)
ACPA positive	23	60	0.9 (0.6–1.5)	1.0 (0.6–1.7)
ACPA negative	23	60	1.4 (0.8–2.3)	1.5 (0.9–2.6)
RF positive	31	60	1.1 (0.7–1.7)	1.1 (0.6–1.7)
RF negative	17	60	1.0 (0.6–1.8)	1.2 (0.6–2.1)
Myocardial infarction				
Self reported, any	28	24	1.6 (0.9–2.7)	1.1 (0.7–2.0)
Hospital Discharge Register				
Any	25	35	1.0 (0.6–1.6)	1.0 (0.6–1.8)
ACPA positive	16	35	1.2 (0.6–2.1)	1.2 (0.6–2.2)
ACPA negative	9	35	0.9 (0.4–2.0)	1.0 (0.5–2.3)
RF positive	18	35	1.1 (0.6–1.9)	1.1 (0.6–2.1)
RF negative	7	35	0.7 (0.3–1.7)	0.8 (0.6–1.9)
Angina pectoris				
Self reported, any	28	36	1.0 (0.6–1.6)	0.8 (0.5–1.4)
Hospital Discharge Register				
Any	36	42	1.1 (0.7–1.8)	1.2 (0.7–2.0)
ACPA positive	18	42	1.1 (0.6–1.9)	1.2 (0.6–2.1)
ACPA negative	16	42	1.3 (0.7–2.4)	1.5 (0.8–2.7)
RF positive	25	42	1.2 (0.7–2.1)	1.3 (0.7–2.2)
RF negative	11	42	1.0 (0.5–1.9)	1.0 (0.5–2.1)

* EIRA = Epidemiological Investigation of Rheumatoid Arthritis; OR = odds ratio; 95% CI = 95% confidence interval; ACPA = anti–citrullinated protein antibody; RF = rheumatoid factor.
† Unconditional logistic regression adjusted for matching variables age, sex, and residential area.
‡ Unconditional regression adjusted for matching variables and diabetes, body mass index, hypertension, and smoking.

Table 5. Ischemic heart disease (IHD), as detected in the Hospital Discharge Register, before the onset of rheumatoid arthritis (RA) in the EIRA study, according to SE status*

SE status	No. of events		Crude OR (95% CI)†	Adjusted OR (95% CI)‡
	Cases	Controls		
IHD, total				
SE positive	35	15	1.0 (0.6–1.9)	0.9 (0.5–1.8)
SE negative	13	13	1.3 (0.6–2.8)	1.3 (0.6–2.9)
Myocardial infarction				
SE positive	18	7	1.2 (0.5–2.8)	1.0 (0.4–2.5)
SE negative	7	7	1.3 (0.5–3.9)	1.4 (0.5–4.0)
Angina pectoris				
SE positive	28	12	1.1 (0.5–2.1)	1.0 (0.5–2.0)
SE negative	8	10	1.0 (0.4–2.6)	1.0 (0.4–2.7)

* EIRA = Epidemiological Investigation of Rheumatoid Arthritis; SE = shared epitope; OR = odds ratio; 95% CI = 95% confidence interval.
† Unconditional logistic regression adjusted for matching variables age, sex, and residential area.
‡ Unconditional logistic regression adjusted for matching variables and diabetes mellitus, hypertension, body mass index, and smoking.

the onset of RA symptoms. The multivariable adjusted OR was 0.9 (95% CI 0.6–1.4) (Table 4).

Analyses stratified by the RF status of the patients (Table 4) or by SE status (Table 5) did not reveal any obvious heterogeneity in the occurrence of IHD. Stratifying according to ACPA status did not alter the results from the overall analysis. No major sex- or age-specific association emerged (data not shown).

When separate analyses were performed according to the period of time between the occurrence of IHD and the onset of RA symptoms, there were some indications in the EIRA study of an association during the last 5 years before the onset of RA symptoms, which did not attain statistical significance, whereas there was no association for IHD occurring more than 5 years before the onset of RA symptoms (Table 6).

DISCUSSION

In both of our cohorts, we were able to confirm an increased risk of IHD *after* the diagnosis of RA. In contrast, there was no evidence in either of the cohorts of an increased occurrence of IHD *before* the onset of RA symptoms nor of any altered spectrum of IHD before the occurrence of RA. Adjustments for IHD risk factors, including smoking, diabetes mellitus, hypertension, and BMI, did not alter our findings.

In a study of 603 patients with RA in Rochester, Minnesota, from 1955 to 1995 (12), patients with RA had a several-fold increased occurrence of hospitalization for MI (17 events) and of unrecognized MI (11 events) by the time they fulfilled the ACR criteria for RA, compared with population controls. There was a

Table 6. Ischemic heart disease (IHD), as detected in the Hospital Discharge Register, stratified by timing of the event in relation to rheumatoid arthritis (RA) onset in the EIRA study*

Time between IHD and onset of RA symptoms, diagnosis	No. of events		Crude OR (95% CI)†	Adjusted OR (95% CI)‡
	Cases	Controls		
More than 5 years				
IHD, total	28	43	0.9 (0.5–1.4)	1.0 (0.6–1.9)
Myocardial infarction	14	25	0.8 (0.4–1.5)	0.9 (0.4–1.8)
Angina pectoris	19	29	0.9 (0.5–1.5)	1.0 (0.5–2.0)
5 years or less				
IHD, total	20	17	1.5 (0.8–3.0)	1.2 (0.6–2.4)
Myocardial infarction	11	10	1.4 (0.6–3.4)	1.3 (0.5–3.6)
Angina pectoris	17	13	1.7 (0.8–3.6)	1.4 (0.6–3.0)

* EIRA = Epidemiological Investigation of Rheumatoid Arthritis; OR = odds ratio; 95% CI = 95% confidence interval.
† Unconditional logistic regression adjusted for matching variables and age, sex, and residential area.
‡ Unconditional logistic regression adjusted for matching variables and diabetes mellitus, hypertension, body mass index, and smoking.

tendency toward a higher relative risk during the last years before fulfillment of the ACR criteria for RA. In our study, we observed neither any altered risk nor any altered spectrum of IHD disease. Besides small numbers, one explanation for the apparent discrepancy compared with our results may be the fact that the Mayo Clinic group assessed IHD events occurring prior to fulfillment of the ACR criteria in a cohort in which the majority of the patients, at the time of fulfillment of the ACR criteria, already had clinical disease for a considerable period of time. In contrast, our study populations encompassed patients with a latency of <18 months between the first occurrence of RA symptoms and the date of the RA diagnosis (median 6.3 months) and in whom IHD events were assessed up until the first occurrence of RA symptoms rather than until RA was diagnosed. This interpretation receives some support from our observation, at least in the EIRA study, of higher, yet statistically nonsignificant, risks of IHD in the 5 years before the onset of RA symptoms.

Recently, the SE has been suggested to be an independent risk factor for IHD in patients with manifest RA (10,11). In our study, there was no difference in the occurrence of IHD before the onset of RA symptoms between SE-positive and SE-negative individuals, which would indicate that the SE per se, although a marker of IHD risk after the onset of RA (10,11), does not constitute a risk factor for IHD independently of RA disease.

We minimized the risk of recall bias by using events detected in an independent external source, the Hospital Discharge Register. This register is a high-quality nationwide register of all inpatient care in Sweden. The diagnoses of MI in this register have been validated and found to have a false-positive rate of 5% and a false-negative rate of 3% in unselected samples as well as among patients with RA, further reducing misclassification (refs. 28 and 29, and Askling J: personal communication).

Our findings are further strengthened by the concordance of results between our 2 RA cohorts. The higher prevalence of a history of IHD in the EAR study (5.8%) compared with the EIRA study (2.8%) is largely attributable to their different age distributions: the EAR study includes all newly diagnosed cases of RA regardless of the patient's age at diagnosis, whereas the EIRA study includes only patients who were younger than age 70 years at the time of the diagnosis of RA.

Other strengths of our report include the large number of patients with newly diagnosed RA, giving us the ability to detect even small differences in the occurrence of IHD. The population-based setting, with rheumatology units reporting cases throughout Sweden and control subjects selected from the general population, increases the generalizability of our results. With participation rates of 95% among patients with RA and 82% among control subjects in the more detailed EIRA study, the impact of possible selection bias is small. Moreover, the observation of increased risks of IHD after a diagnosis of RA, the magnitude of which was well in line with previous studies, suggests that our study population was comparable with other RA cohorts in this regard (30,31), and thus that the non-increased occurrence of IHD before the onset of RA was not attributable to failure of our study design.

Although we studied 2 alternative definitions of IHD, hospitalized IHD detected via ICD coding in a nationwide register and self-reported events of IHD, we could not study the entire range of IHD morbidity. For example, we were not able to detect and study the occurrence of silent MIs before RA onset, as was done in the Rochester study (12). Furthermore, MI was diagnosed clinically by physicians, and we did not have access to individual electrocardiograms or to results from laboratory analyses for blinded diagnostic review. Although the IHD diagnoses have been shown to have high validity (29), and although we have no reason to believe that this validity would depend on the future risk of RA developing, a lack of characterization of each individual exposure is a limitation of our study. Also, we cannot formally exclude the possibility of shared factors associated with longer latency until the occurrence of IHD (and thus manifesting exclusively after a diagnosis of RA) or a shared etiology that would lead to excess fatal IHD events in a population of individuals in whom, had they remained alive, RA would have developed.

In theory, PTCAs that were performed before the occurrence of an MI prompted by IHD symptoms might have altered the distribution of clinically manifest IHD events. In the Hospital Discharge Register, surgical interventions, including PTCA procedures, are listed. In our study, 98% of all patients with RA who underwent PTCA were also registered with an IHD before the diagnosis of RA; the corresponding proportion among the control subjects was 99%. The OR for RA associated with a PTCA before a diagnosis of RA (1.2 [95% CI 0.8–1.6]) in the EAR study indicates that the null results presented above are not attributable to an increased occurrence of PTCAs in patients with RA compared with control subjects.

When the data from the EIRA study were stratified by serologic status (Table 4), age, and sex (data not

shown), we noted some point estimates indicating an increased occurrence of IHD. It is, however, not possible to draw a conclusion regarding whether these point estimates from subgroup analysis reflect a true association, because these point estimates are of low precision, with few exposed in each stratum. The large quantity of subgroup analyses performed also introduces the possibility that the somewhat elevated point estimates represent chance findings. The fact that in the larger EAR study we could not detect any point estimates corresponding to those observed in the EIRA study favors a null association overall.

To our knowledge, this is the first study of the occurrence of IHD before the onset of symptoms of RA. By studying IHD before the onset of RA symptoms, we reduced the possible impact of RA-associated inflammation having already exerted adverse effects on the risk of IHD. With no increased occurrence of IHD before the onset of RA symptoms in a population with a documented increased risk of IHD after a diagnosis of RA, our results provide support for the hypothesis that RA is an independent risk factor for IHD in RA, and that despite their existence (9,11), shared risk factors or genetic susceptibilities for RA and for cardiovascular inflammation, as in arteriosclerosis, play a minor role in this regard.

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 published. Dr. Holmqvist 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.

Study conception and design. Holmqvist, Klareskog, Nyberg, Rantapää-Dahlqvist, Alfredsson, Askling.

Acquisition of data. Holmqvist, Alfredsson, Askling.

Analysis and interpretation of data. Holmqvist, Wedrén, Jacobsson, Klareskog, Nyberg, Rantapää-Dahlqvist, Alfredsson, Askling.

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