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The Risk of Congestive Heart Failure in Rheumatoid Arthritis

A Population-Based Study Over 46 Years

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Objective. **It is hypothesized that the systemic inflammation associated with rheumatoid arthritis (RA) promotes an increased risk of cardiovascular (CV) morbidity and mortality. We examined the risk and determinants of congestive heart failure (CHF) in patients with RA.**

Methods. **We assembled a population-based, retrospective incidence cohort from among all individuals living in Rochester, Minnesota, in whom RA (defined according to the American College of Rheumatology 1987 criteria) was first diagnosed between 1955 and 1995, and an age- and sex-matched non-RA cohort. After excluding patients in whom CHF occurred before the RA index date, all subjects were followed up until either death, incident CHF (defined according to the Framingham Heart Study criteria), migration from the county, or until January 1, 2001. Detailed information from the complete medical records (including all inpatient and outpatient care provided by all local providers) regarding RA, ischemic heart disease, and traditional CV risk factors was collected. Cox models were used to estimate the effect of RA on the development of CHF, adjusting for CV risk factors and/or ischemic heart disease.**

Results. **The study population included 575 patients with RA and 583 subjects without RA. The CHF incidence rates were 1.99 and 1.16 cases per 100 person-years in patients with RA and in non-RA subjects, respectively (rate ratio 1.7, 95% confidence interval [95% CI] 1.3–2.1). After 30 years of followup, the cumulative incidence of CHF was 34.0% in patients with RA and 25.2% in non-RA subjects ($P < 0.001$). RA conferred a significant excess risk of CHF (hazard ratio [HR] 1.87, 95% CI 1.47–2.39) after adjusting for demographics, ischemic heart disease, and CV risk factors. The risk was higher among patients with RA who were rheumatoid factor (RF) positive (HR 2.59, 95% CI 1.95–3.43) than among those who were RF negative (HR 1.28, 95% CI 0.93–1.78).**

Conclusion. **Compared with persons without RA, patients with RA have twice the risk of developing CHF. This excess risk is not explained by traditional CV risk factors and/or clinical ischemic heart disease.**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory and progressive disease characterized by persistent inflammatory synovitis, joint destruction, and increased mortality (1,2). Cardiovascular (CV) mortality has been identified as the underlying cause of a substantial proportion of deaths among patients with RA (3), with a standardized mortality ratio that ranges from 1.3 to 2.4 in most studies (4–6). Recent reports have also described an increased risk of myocardial infarction (MI) in patients with RA (4,7,8).

Congestive heart failure (CHF) is an important contributory cause of CV-associated death. The prevalence of CHF ranges from 2.4% to 5.5% in the general population older than 65 years of age (9,10), and the presence of CHF confers a 4–18-fold increased risk of dying of CV-related causes (11,12). In the general population, inflammatory cytokines have been associated with both the development and the prognosis of

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CHF (13,14). Ventricular dysfunction has been observed in echocardiographic assessments of patients with RA (15–17), and few studies have indicated an increased frequency and risk of CHF in RA prevalence cohorts (18,19), raising the question of whether the risk of developing CHF is increased in patients with RA independently of CV risk factors and ischemic heart disease.

We examined the hypotheses that the incidence of CHF is increased in patients with RA compared with age- and sex-matched non-RA subjects, and that RA is an independent risk factor for the development of CHF, after accounting for traditional CV risk factors and clinical ischemic heart disease.

PATIENTS AND METHODS

Subjects and design. We conducted a longitudinal, retrospective, population-based cohort study of patients with RA and age- and sex-matched individuals without RA. We used the medical records linkage system of the Rochester Epidemiology Project to access the entire inpatient and outpatient medical records from all health care providers in Olmsted County. These providers include the Mayo Clinic and its affiliated hospitals, the Olmsted Medical Center and its affiliated community hospital, local nursing homes, and the few private practitioners. The potential of this data resource for use in population-based research has been previously described (20,21). This study was approved by the Mayo Foundation Institutional Review Board.

We studied a previously described (1,22) inception cohort of residents of Rochester, Minnesota, who were ≥18 years of age in whom RA was first diagnosed between January 1, 1955 and January 1, 1995. A cohort of 603 patients with RA, all of whom met a minimum of 4 of the 7 American College of Rheumatology (ACR; formerly the American Rheumatism Association) 1987 criteria for RA (23), was identified, and the first date at which the ACR criteria were fulfilled was considered the RA incidence date (baseline). For each patient with RA, an individual without RA who was matched for birth year (±3 years), sex, and length of medical history was randomly selected from the same underlying population for inclusion in the non-RA cohort. Each subject in the non-RA cohort was assigned an index date corresponding to the RA incidence date (baseline) of the matched RA patient.

Data collection. The complete (inpatient and outpatient) medical record for each study participant was reviewed longitudinally by 4 trained registered nurse abstractors, starting when the subject was 18 years of age (or on the date of migration to Olmsted County for those who first became residents after age 18 years) and continuing until either death, incident CHF (see below), migration from Olmsted County, or January 1, 2001 (end of followup for the study). The nurse abstractors were blinded to the study hypothesis. Supervision and consultation were provided on a weekly basis by the authors, who had expertise in rheumatology (SEG), cardiology (VLR), epidemiology (SJJ, SEG, and HMK), and data management/analysis (CSC and KVB).

Table 1. Framingham Heart Study criteria for the diagnosis of congestive heart failure*

Major criteria
Paroxysmal nocturnal dyspnea or orthopnea
Neck vein distention
Rales
Cardiomegaly
Acute pulmonary edema
S3 gallop
Increased venous pressure ≥16 cm of water
Circulation time ≥25 seconds
Hepatojugular reflux
Minor criteria
Ankle edema
Night cough
Dyspnea upon exertion
Hepatomegaly
Pleural effusion
Vital capacity decreased by one-third from the maximum
Tachycardia rate ≥120 beats/minute
Major or minor criteria
Weight loss ≥4.5 kg in 5 days in response to treatment

* Congestive heart failure is present if 2 major criteria or 1 major and 2 minor criteria are met. Adapted with permission of the American College of Cardiology Foundation, © 1993 (ref. 24).

CHF was defined according to the Framingham Heart Study criteria (24). These validated criteria (25) require the simultaneous presence of at least 2 major criteria or 1 major criterion and 2 minor criteria (Table 1).

Risk factors were ascertained longitudinally throughout the followup period (i.e., including the results for each risk factor over the entire followup period) and were defined as follows. Dyslipidemia was present if the total cholesterol level was ≥240 mg/dl, the low-density lipoprotein cholesterol level was ≥160 mg/dl, the high-density lipoprotein cholesterol level was <40 mg/dl, or the triglyceride level was ≥150 mg/dl, according to the diagnostic criteria of the National Cholesterol Education Program Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (26), or if the patient had a clearly documented history of dyslipidemia or treatment with specific lipid-lowering therapy. Diabetes mellitus was present if at least 2 measurements of fasting plasma glucose were ≥126 mg/dl or the 2-hour plasma glucose level was ≥200 mg/dl, according to the 1998 World Health Organization diagnostic criteria (27), or if the patient had a clearly documented history of diabetes or treatment with hypoglycemic agents. Hypertension was present if the subject had 2 or more ambulatory blood pressure readings of ≥140 mm Hg systolic and/or 90 mm Hg diastolic, according to the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure diagnostic criteria (28), or a physician's diagnosis of hypertension or treatment with antihypertensive agents. A subject's body mass index (BMI) was categorized as high (≥30 kg/m^2), based on the Expert Panel on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults clinical guidelines (29), and as low (<20 kg/m^2), as classified both at both baseline and at the date of first entry into the high BMI or low BMI category during followup. Finally, alcohol abuse was considered to be present if a physician's diagnosis of alcoholism was recorded.

Personal history of ischemic heart disease was defined both at baseline and throughout followup as the presence of one or more of the following: MI, silent MI, revascularization procedures, and a clinical diagnosis of angina pectoris. MI was defined using standardized epidemiologic criteria (30), relying on cardiac pain, biomarker levels, and Minnesota coding (31) of the electrocardiogram (EKG). These criteria have been used in Rochester Epidemiology Project studies to ascertain MI over more than 2 decades and have been shown to have excellent reliability (32). Silent MI was considered to be present at the date of the first documentation of a characteristic EKG or a recorded physician's diagnosis in a patient with no documented history of MI.

Cigarette smoking status (categorized as current, former, and never) and family history of ischemic heart disease (i.e., first-degree relatives with ischemic heart disease, as specified above) were assessed only at baseline. Patients with RA were classified as being rheumatoid factor (RF) positive if they ever had an IgM-RF titer ≥1:40.

Statistical analysis. To estimate the incidence rates of CHF, person-years of observation for each cohort were stratified by age and sex. CHF rate ratios were obtained with 95% confidence intervals (95% CIs), estimated using an F approximation (33). The cumulative incidence of CHF was estimated using the product-limit life-table method, accounting for the competing risk of death (34).

Cox regression models were used to estimate the association of risk factors with the incidence of CHF, using age as a time scale and stratification by sex. Individuals who died prior to the development of CHF were censored. Subjects are included in the analysis starting at the age of their index date and ending at the age of CHF, death, or last followup. Factors assessed throughout followup were modeled as dichotomous time-dependent covariates. A subject's status changed from unexposed to exposed at the time of the diagnosis of a particular risk factor during followup.

Variables for which values were missing (smoking, family history of ischemic heart disease, and dyslipidemia) were examined in multiple ways. Considering missing values as negative responses did not change the covariate effect for smoking and family history of ischemic heart disease, so this approach was used in multivariate modeling. Because cholesterol screening was not performed routinely during the early years of our study period, lipid values probably were not randomly missed. 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 reciprocals of the predicted probabilities from these models were then used as case weights in Cox models that assessed the importance of dyslipidemia as a predictor of CHF. Dyslipidemia was not a significant predictor of CHF after propensity scoring analysis and, therefore, was excluded from the multivariate model in order to avoid removal of subjects with missing values.

After all significant risk factors were entered into a multivariate model, covariates identifying the cohorts of interest (non-RA, RA, RF-negative RA, RF-positive RA) were added to the model. All two-way interactions among significant main effects were examined. All tests were 2-sided, and P values less than 0.05 were considered significant.

RESULTS

From 1955 through 1994, 603 patients who fulfilled criteria for RA were age- and sex-matched to 603 non-RA subjects. A total of 48 subjects (28 patients with RA and 20 non-RA subjects) ($P = 0.24$ by chi-square test) fulfilled the Framingham criteria for a CHF episode before the index date (baseline) and were excluded from this study. The final study population thus comprised 575 patients with RA and 583 non-RA subjects.

The baseline characteristics of the RA and the non-RA cohorts are shown in Table 2. In both cohorts, 73% were women, and the mean age at baseline was 57 years. Compared with subjects without RA, those with RA were more frequently current or former smokers at the index date ($P < 0.01$). All other characteristics of the 2 groups were similar. The median lag time between the first recorded RA criteria and the date of fulfillment of the ACR diagnostic criteria was 3 months (interquartile range 0–53.4 months). Patients with RA were further classified as rheumatoid factor (RF) positive (n = 374 [65%]) or RF negative (n = 201 [35%]).

The median followup time was 11.8 years for patients with RA and 14.5 years for non-RA subjects, corresponding to 8,107 and 9,521 person-years, respec-

Table 2. Baseline characteristics in the RA and non-RA cohorts*

Characteristic (no. in RA group/ no. in non-RA group)	Cohort	
	RA	Non-RA
Age, mean ± SD years (575/583)	57.1 ± 14.9	57.5 ± 15.0
Women (575/583)	418 (73)	427 (73)
Family history of IHD (575/583)	276 (48)	277 (48)
Personal history of IHD (575/583)	49 (9)	52 (9)
Never smoker (547/572)	247 (45)	319 (56)†
Former smoker (547/572)	135 (25)	115 (20)†
Current smoker (547/572)	165 (30)	138 (24)†
Hypertension (575/583)	287 (50)	285 (49)
Dyslipidemia (306/313)	149 (49)	162 (52)
BMI ≥30 kg/m^2 (535/521)	69 (13)	66 (13)
BMI ≤20 kg/m^2 (535/527)	66 (12)	66 (12)
Diabetes mellitus (575/583)	41 (7)	37 (6)
Alcohol abuse (575/554)	12 (2)	18 (3)

* Except where indicated otherwise, values are the number (%). RA = rheumatoid arthritis; IHD = ischemic heart disease; BMI = body mass index.
† $P \leq 0.05$ versus RA cohort.

Table 3. Followup characteristics in the RA and non-RA cohorts*

Characteristic (no. in RA group/no. in non-RA group)	RA	Non-RA	Rate ratio (95% CI)
Followup, total years (575/583)	8,107	9,521	NA
Followup, median (IQR) years (575/583)	11.8 (7–20)	14.5 (8–23)	NA
Subsequent development of IHD (526/531)	116 (1.5)	106 (1.2)	1.28 (0.99–1.67)
Hypertension (288/298)	173 (3.7)	207 (3.6)	1.03 (0.84–1.26)
Diabetes mellitus (534/546)	57 (0.7)	88 (1.0)	0.77 (0.55–1.07)
Dyslipidemia (415/414)	142 (2.7)	220 (3.8)†	0.71 (0.57–0.87)
BMI ≥30 kg/m^2 (481/496)	34 (0.5)	51 (0.6)	0.78 (0.50–1.19)
BMI <20 kg/m^2 (463/474)	63 (1.0)	41 (0.5)†	1.80 (1.23–2.69)
Alcohol abuse (563/536)	24 (0.3)	8 (0.1)†	3.17 (1.54–7.64)

* Except where indicated otherwise, values are the number of events per 100 person-years. The rate ratio (95% confidence interval [95% CI]) corresponds to the ratio of person-year event rates for each risk factor among patients with rheumatoid arthritis (RA) and non-RA subjects. NA = not applicable; IQR = interquartile range; IHD = ischemic heart disease; BMI = body mass index.
† $P \leq 0.05$.

tively. Table 3 compares the incidence of the risk factors in the RA and non-RA cohorts from baseline until the end of followup. During followup, patients with RA had a 3.17-fold higher incidence of alcohol abuse (95% CI 1.54–7.64), an 1.80-fold higher incidence of low BMI (95% CI 1.23–2.69), and a 29% lower incidence of dyslipidemia (rate ratio 0.71, 95% CI 0.57–0.87) as compared with non-RA subjects.

Incidence of CHF. A total of 165 patients with RA and 115 non-RA subjects (1.99 and 1.16 CHF cases per 100 person-years, respectively) had a validated diagnosis of CHF during followup. The age- and sex-specific incidence rates of CHF in both cohorts are illustrated in Figure 1. Patients with RA experienced a significantly higher incidence of CHF compared with the non-RA subjects (rate ratio [RR] 1.7, 95% CI 1.3–2.1). This excess risk was observed across all age groups. The higher incidence of CHF was more pronounced among women (RR 1.9, 95% CI 1.4–2.5) compared with men (RR 1.3, 95% CI 0.9–2.0). We observed no evidence of a calendar-year effect on the risk of CHF in either cohort (P for interaction = 0.8).

Figure 2 shows the cumulative incidence of CHF since baseline in both cohorts, after adjusting for the competing risk of death. At 30 years of followup, the cumulative incidence of CHF in patients with RA was 34.0%, while the cumulative incidence of CHF in non-RA subjects was 25.2%. The difference in the cumulative incidence of CHF in patients with RA and non-RA subjects was apparent very early in the followup

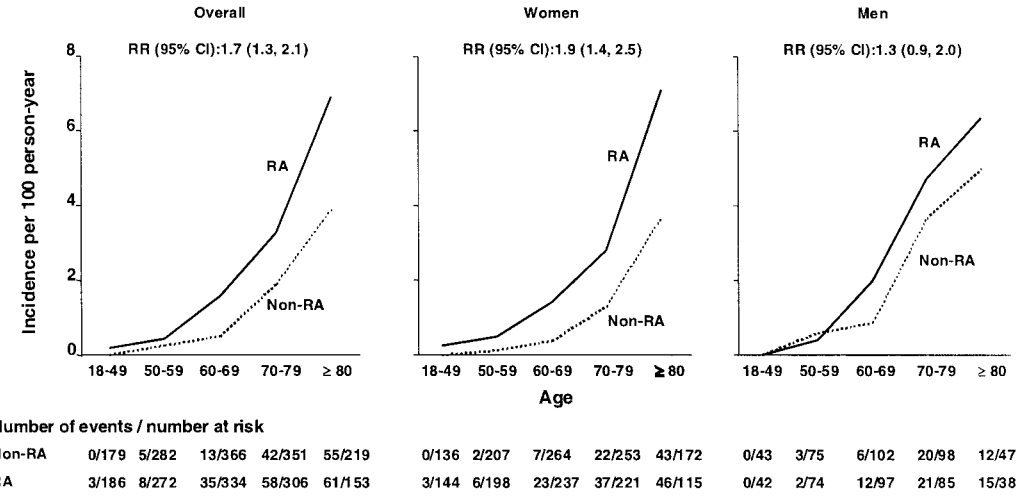

Figure 1. Comparison of the incidence of congestive heart failure, according to age and sex, among 575 patients with rheumatoid arthritis (RA) and 583 non-RA subjects. RR = rate ratio; 95% CI = 95% confidence interval.

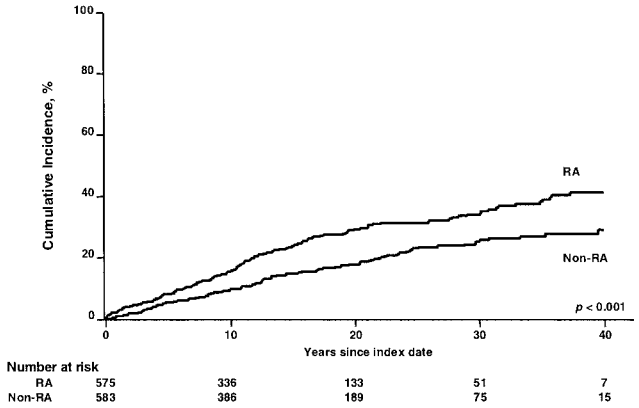

Figure 2. Comparison of the cumulative incidence of congestive heart failure in the rheumatoid arthritis (RA) cohort and the non-RA cohort, according to the number of years since the index date, adjusting for the competing risk of death.

period. The cumulative incidence in both cohorts increased steadily over time.

Effect of ischemic heart disease and risk factors on the development of CHF. In order to understand how ischemic heart disease and CV risk factors influenced the risk of CHF in patients with RA compared with non-RA subjects, univariate and multivariate models were examined, sequentially incorporating ischemic heart disease, CV risk factors, and all variables simultaneously (Table 4). In age- and sex-adjusted models, patients with RA had twice the risk for the development of CHF (hazard ratio [HR] 1.96, 95% CI 1.54–2.49)] compared with non-RA subjects. After accounting for the presence of both ischemic heart disease and CV risk factors, the increased risk of CHF in patients with RA remained essentially unchanged (HR 1.87, 95% CI 1.47–2.39).

When considering only RF-negative patients with RA, the age- and sex- adjusted risk of developing CHF was 43% higher (HR 1.43, 95% CI 1.03–1.96) compared with that in non-RA subjects. This increased risk was no longer significant after adjusting for ischemic heart disease and/or CV risk factors (adjusted HR 1.28, 95% CI 0.93–1.78). However, RF-positive patients with RA had an age- and sex-adjusted HR of developing CHF that was 2.49-fold higher than that of non-RA subjects (HR 2.49, 95% CI 1.90–3.26). Adjustments for ischemic heart disease and/or CV risk factors essentially did not change this increased risk (adjusted HR 2.59, 95% CI 1.95–3.43) (Table 4).

DISCUSSION

We followed up a population-based inception cohort of 575 patients with RA for a total of 8,107 person-years, and compared their risk of developing CHF with that among an age-, and sex-matched cohort of 583 subjects without RA who were followed up for a total of 9,521 person-years. Our results indicate that patients with RA are at increased risk of developing CHF beginning soon after the onset of RA and continuing throughout the disease course. We found that the higher risk of CHF among RF-positive patients with RA did not change after adjusting for traditional CV risk factors or clinical ischemic heart disease. These observations suggest that RA or factors associated with RA but unrelated to traditional CV risk factors, including clinical ischemic heart disease, may play a role in the increased risk of CHF in patients with RA.

We described the incidence of CHF during 46 years of followup of patients with RA and non-RA subjects, noting several interesting observations. The difference in the incidence of CHF between individuals with RA and those without RA (i.e., a higher incidence of CHF among patients with RA) appeared to be relatively constant during the followup period. This finding is consistent with the results of our previous study regarding CV mortality in RA, in which the hazard

Table 4. Risk of developing CHF among 575 patients with RA and 583 non-RA subjects*

Model	All patients with RA vs. all non-RA subjects	RF-negative patients with RA vs. non-RA subjects	RF-positive patients with RA vs. non-RA subjects
Adjusted for age and sex	1.96 (1.54–2.49)†	1.43 (1.03–1.96)†	2.49 (1.90–3.26)†
Adjusted for age, sex, and ischemic heart disease	1.95 (1.53–2.49)†	1.27 (0.92–1.76)	2.83 (2.14–3.73)†
Adjusted for age, sex, and CV risk factors	1.82 (1.43–2.32)†	1.34 (0.97–1.84)	2.29 (1.74–3.02)†
Adjusted for age, sex, CV risk factors, and ischemic heart disease	1.87 (1.47–2.39)†	1.28 (0.93–1.78)	2.59 (1.95–3.43)†

* From univariate (for age and sex adjustments only) and multivariate Cox regression models. Values are the hazards ratio (95% confidence interval). Among the patients with rheumatoid arthritis (RA), 201 were rheumatoid factor (RF) negative, and 374 were RF positive. Cardiovascular (CV) risk factors that remained in the model were smoking, hypertension, and diabetes mellitus. CHF = congestive heart failure.
† $P \leq 0.05$.

for CV death did not appear to be associated with RA disease duration (3). It is in contrast to some echocardiographic studies in which an association between ventricular dysfunction and RA disease duration was observed (15–17). However, our age-matched cohort design, use of time-dependent variables, and use of age as the time scale allowed us to more comprehensively model the effect of age on risk factors and CHF over time.

The observation that the difference in the rate of CHF between patients with RA and non-RA subjects remains constant throughout followup suggests that the higher risk of CHF in patients with RA may not simply be the result of cumulative inflammatory burden or disease activity. Also, although the CHF incidence rates are lower in women without RA than in men without RA, as would be expected based on reports from the general population (36), the difference in CHF incidence rates between the sexes seems to be attenuated in patients with RA. In addition, the increased risk of CHF in the RA cohort is present at the incidence date (Figure 2), and more patients with RA were excluded from this study because of the development of CHF before the RA incidence date. These findings are consistent with recent reports showing a higher risk of MI (both silent MI and MI requiring hospitalization) at the RA incidence date (37), higher levels of C-reactive protein (38), and a higher prevalence of RF and anti–cyclic citrullinated peptide antibody positivity (39,40) years after the onset of RA symptoms. These observations suggest the hypothesis of a constitutional effect (common susceptibility for developing RA or CHF) or a shared pathogenesis relating RA and CHF.

Notably, the risk of CHF in patients with RA did not change substantially after adjusting for either clinical ischemic heart disease, CV risk factors, or both. Although the higher risk among RF-negative patients with RA compared with non-RA subjects seems to be largely explained by clinical ischemic heart disease and/or CV risk factors, this was not the case among RF-positive patients with RA. Thus, RF status appears to discriminate 2 groups of patients with RA with different CHF risk levels, possibly through different pathophysiologic mechanisms. In our previous study of CV mortality in this cohort of patients with RA, RF positivity was also associated with higher CV mortality (3). The role of RF positivity with respect to increased CHF risk in patients with RA, as well as other markers of RA disease severity, should be the subject of further research.

The role of systemic inflammation in the etiology of CHF has been addressed in recent studies. Higher levels of systemic inflammatory markers have been shown to predict the risk of CHF developing in the elderly population (41), even in the absence of MI (42,43). However, with the exception of MI (42), these studies did not account for changes in CV risk factors during followup. Our observation of an increased risk of CHF among patients with RA, even after accounting for the effect of clinical ischemic heart disease and/or CV risk factors, provides evidence in support of the hypothesis that systemic inflammation may promote the development of CHF.

However, other hypotheses should also be considered. A higher prevalence of unrecognized or subclinical ischemic heart disease and/or CV risk factors (44) could, at least partly, contribute to our findings. We extensively accounted for silent MI, the incidence of which we recently reported to be increased in patients with RA (37), angina, and revascularization. Pericardial disease, a possible complication of RA, could contribute to CHF risk (45). However, this is a rare complication of RA. In a study of 424 patients with RA from this same Olmsted County RA cohort, Turesson et al (46) reported that pericarditis was diagnosed in only 18 patients (4.3%). The cardiotoxic effect of drugs taken by patients with RA, particularly nonsteroidal antiinflammatory drugs (47,48) and, more rarely, chloroquine (49,50) or D-penicillamine (51), may also contribute to the increased risk of CHF in these patients. Nevertheless, 2 observations argue against the suggestion that an increased risk of CHF in patients with RA is fully explained by the possible cardiotoxicity of RA-related drugs. First, the higher risk of CHF in patients with RA does not increase with disease duration (Figure 2). Second, the higher risk of CHF in patients with RA did not change between 1955 and 2001, a period marked by major changes in RA therapy. Also, several studies found that RA-related therapy is associated with a decrease, or no change, in the risk for CV morality (52–57). These hypotheses should be subject to further study.

A high risk of CHF in RA was suggested in previous studies. Mutru et al (58) conducted a 10-year followup study of 500 men and 500 women with RA and age- and sex-matched controls and reported cause-specific mortality. Based on a review of death certificates and autopsy reports, they concluded that heart failure was the underlying cause of death in many of the patients with RA. Our group previously described a 60% increased risk of physician-diagnosed CHF among 450 population-based prevalent cases of RA (18). Some of these patients are also included in the present study. In

a recent prevalent cohort study based on responses to a mailed survey of participants in the National Data Bank for Rheumatoid Diseases, Wolfe and Michaud (19) compared 13,171 patients with RA and 2,568 patients with osteoarthritis and reported that the prevalence of CHF was higher among patients with RA (3.9%) than among those with osteoarthritis (2.3%), after adjusting for demographic characteristics. Because of the fatal nature of CHF, prevalence studies will inevitably be subject to survival bias and will tend to underestimate the magnitude of the incidence of CHF.

This study extends the findings and addresses the limitations of previous studies. Use of a 46-year longitudinal population-based inception cohort, sampled from a well-defined community, ensured minimal volunteer and selection bias and inclusion of all ranges of RA severity. Our unique data resources allowed for the identification of an age- and sex-matched comparison group selected from the same underlying community, matched for length of available past medical history. We accessed the complete inpatient and outpatient medical record for all participants, with observations made several years before the incidence (or index) date and continuing for 40 years thereafter, using rigorous and validated criteria to identify RA cases, CV risk factors, and CV events. Time-dependent variables were used to capture risk factors that developed during the disease course. Because the risk for atherosclerotic events could be higher in patients with RA, we also separately considered personal history of clinical ischemic heart disease occurring prior to and after the RA incidence date. Taken together, these methods allowed us to elucidate the complex relationships between CV risk factors and the development of CHF among persons with RA.

Our findings must be interpreted in light of several potential study limitations. First, our study sample is composed largely of white individuals, which may limit the generalizability to more diverse populations. Second, it is not feasible to ascertain risk factors and outcomes at regular intervals in a study with a retrospective cohort design. However, the comprehensive medical record system of the Rochester Epidemiology Project allowed us to access a median of 26 years of complete medical history (covering inpatient and outpatient care from all local providers) prior to the incidence or index date, as well as a median of 15 years of followup. In this geographically well-defined population, almost all residents come to medical attention in a 3-year period; therefore, differential ascertainment bias is less likely to affect our results (21). Definitions of risk factors and outcomes were based on well-established epidemiologic and diagnostic criteria, assuring the consistent assessment of conditions across the many decades of the study. Third, the Framingham Heart Study criteria for CHF do not identify individuals with subclinical disease (i.e., compensated left ventricular systolic or diastolic dysfunction). However, in comparison with echocardiographic evaluation, the Framingham criteria would, if anything, result in an underestimation of the true incidence of CHF. The Framingham criteria were assessed in a random sample of ~500 medical records from the Rochester, Minnesota population showing an International Classification of Diseases, Ninth Revision, code of 428 (heart failure), and it was concluded that in only 2% of the cases would missing information preclude the fulfillment of the Framingham classification criteria (59). Thus, it is unlikely that a substantial proportion of CHF cases were missed in our study. Also, because these criteria primarily rely on congestive symptoms and signs, it is unlikely that RA disease characteristics confounded the identification of CHF among RA and non-RA subjects.

We observed that patients with RA have twice the risk of developing CHF compared with subjects without RA. This excess risk remained even after fully adjusting for CV risk factors and ischemic heart disease, and was higher in patients with RA who were RF positive than in those who were RF negative. Our results suggest that the observed increased risk of CHF among patients with RA is not attributable to an increased frequency or effect of either CV risk factors (i.e., hypertension, smoking, diabetes) or clinical ischemic heart disease, but rather, through independent RA or RA-disease associated factors. Physicians who care for patients with RA should be aware of the increased risk of CHF in these patients. This increased risk may be present at the earliest stages of the disease and may occur in the absence of overt CV risk factors or ischemic heart disease. Further research should address characteristics that predict the CHF incidence, severity, and survival in these patients, as well as determine the role of RA therapy.

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