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How Much of the Increased Incidence of Heart Failure in Rheumatoid Arthritis Is Attributable to Traditional Cardiovascular Risk Factors and Ischemic Heart Disease?

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Objective. **To compare the proportion of the risk for the development of heart failure (HF) that is attributable to traditional cardiovascular (CV) risk factors, ischemic heart disease (IHD), and alcohol abuse between subjects with and subjects without rheumatoid arthritis (RA).**

Methods. **A population-based inception cohort of RA patients was assembled along with a similar cohort of subjects without RA. All individuals were followed up through their complete medical records, until HF incidence, death, migration, or January 1, 2001. The attributable risk of HF was estimated as the difference between the observed cumulative incidence of HF in each cohort (estimated from multivariable Cox models and adjusted for the competing risk of death) and the predicted cumulative incidence of HF in the absence of risk factors, with results expressed as a percentage of the observed cumulative incidence.**

Results. **A total of 575 RA subjects and 583 non-RA subjects (mean age 57 years, 73% women) without HF at incidence/index date had a mean followup of 15.1 and 17.0 years, respectively. During that period, 165 RA and 115 non-RA subjects had a first episode of HF, with a cumulative incidence of 36.3% and 20.4%, respectively, at age 80 years. Among non-RA subjects, 77% of the HF at age 80 years was attributable to CV risk factors, IHD, and alcohol abuse combined, whereas among RA subjects, only 54% of the HF at age 80 years was attributable to these factors ($P < 0.01$).**

Conclusion. **The excess risk of HF among RA patients is not explained by an increased frequency or effect of CV risk factors and IHD.**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease of unknown etiology, affecting ~1% of the adult general population (1,2). Patients with RA have twice the risk of heart failure (HF) when compared with individuals of the same age and sex without RA (3). The mechanism behind this increased risk is unknown. The etiology of HF can be multifactorial, with several clinical risk factors coexisting and interacting to produce this clinical syndrome (4,5). Ischemic heart disease (IHD) and hypertension have long been recognized as major risk factors for HF in the general population (6–9). Therefore, elimination of traditional cardiovascular (CV) risk factors and IHD is a recognized approach to prevent HF (9).

However, we previously reported that the increased risk of HF in subjects with RA appears to be independent of the presence or effect of IHD and CV risk factors (3). Consequently, IHD and CV risk factors may play a different role with respect to the development and prevention of HF in RA subjects, compared with non-RA subjects. The aim of the present study was to compare the proportion of the risk for the development of HF that is attributable to traditional CV risk factors, IHD, and alcohol abuse between subjects with and subjects without RA.

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PATIENTS AND METHODS

A population-based inception cohort of RA patients and a non-RA comparison cohort (n = 603 in each) were assembled, as previously described (3). The study design was a retrospective, longitudinal cohort study of RA subjects and a comparison cohort of subjects without RA. Baseline was established as the RA incidence date in RA subjects, or the index date for non-RA subjects (hereafter referred to as the index date for both groups). For the purposes of this analysis, subjects with HF prior to the index date were removed from each cohort (28 RA subjects and 20 non-RA subjects). Methods of data collection and definitions of the variables analyzed have been described previously (3).

Descriptive statistics (expressed as the mean and SD) were used to summarize the age at index date and the length of followup. Characteristics, such as CV risk factors, IHD, and alcohol abuse, were summarized as ever/never during followup. The cumulative incidence of each characteristic at 30 years of followup, including those present at the index date, with censoring at the time of diagnosis of HF and adjustment for the competing risk of death, was estimated for each cohort (10), and differences in the cumulative incidence between cohorts were examined using the methods described by Gray (11).

The influence of traditional CV risk factors, IHD, and alcohol abuse on the development of HF was estimated separately for each cohort from multivariable Cox proportional hazards models. In these analyses, current smokers were compared with the combined group of former and never smokers. Dichotomous time-dependent covariates were incorporated to account for risk factors that developed after the index date. During followup, a patient's status was changed from unexposed to exposed, at the time of diagnosis of a particular risk factor. Age was used as the time scale for all Cox models; that is, the baseline risk of HF was assumed to be a function of age rather than time since index date. All models were adjusted for sex. Cox model results were used to estimate the cumulative incidence of HF, with adjustment for the risk factors, in the RA and non-RA cohorts separately.

Very few subjects had missing values for the risk factors of interest, with the exception of dyslipidemia. Missing values were assumed to be negative responses (e.g., those with missing smoking status were considered to be never/former smokers), since only minimal differences in effect size were noted when comparing these analyses with analyses in which subjects with missing values were excluded. This allowed the use of all study subjects in the multivariable models.

A unique application of statistical methods was used to estimate attributable risk in this longitudinal setting. Attributable risk (or etiologic fraction) is the proportion of disease in a population that could be prevented by elimination of an exposure, or risk factor. Attributable risk is commonly calculated as

$$AR = [P(D) - P(D|\bar{F})]/P(D),$$

where AR is the attributable risk, P(D) is the probability of disease (i.e., HF), and $P(D|\bar{F})$ is the conditional probability of disease among individuals without the risk factor. In actuality, attributable risk is a function of time, since it depends on the prevalence of the risk factor, which changes over time, but this is often ignored. In this study we explicitly estimated attributable risk as a function of age. The cumulative incidence of HF, adjusted for the competing risk of death, was used to estimate the probability of HF at age t, and these estimates were obtained from Cox models to allow for adjustment for multiple risk factors. The conditional probability of HF at age t for those without a risk factor was estimated from the same Cox models, but with a target cohort that matched the observed cohort except that it lacked the risk factor of interest. Bootstrap sampling and 2-sample *t*-tests were used to compare mean estimates of attributable risk between cohorts. *P* values less than 0.05 were considered to be statistically significant.

RESULTS

The study population comprised 575 subjects with RA (incident cases) and 583 non-RA subjects. RA subjects were followed up for 8,107 person-years (mean 15.1 years) and non-RA subjects were followed up for 9,521 person-years (mean 17.0 years). The mean age of RA subjects was 57.1 years and the mean age of non-RA subjects was 57.5 years (Table 1). Seventy-three percent of each cohort were women. The number of patients in each cohort who had CV risk factors, IHD, or alcohol abuse at any time during followup is presented in Table 1, along with the cumulative incidence of each risk factor at 30 years after the index date. The cumulative incidence of a body mass index (BMI) <20 kg/m^2 was higher

Table 1. Characteristics and cumulative incidence of cardiovascular risk factors, ischemic heart disease (IHD), and alcohol abuse in 575 subjects with incident rheumatoid arthritis (RA) and 583 non-RA subjects*

	RA (n = 575)	Non-RA (n = 583)
Characteristic		
Age, mean ± SD years	57.1 ± 14.9	57.5 ± 15.0
Female	418 (72.7)	427 (73.2)
Length of followup, mean ± SD years	15.1 ± 9.7	17.0 ± 10.2
Deaths	357	306
Family history of IHD	276 (48.0)	277 (47.5)
Cigarette smoker	165 (28.7)	138 (23.7)
Incident feature at followup†		
IHD	164 (37.9)	157 (36.8)
Hypertension	460 (86.5)	493 (92.1)
Dyslipidemia	291 (59.8)	381 (74.9)‡
BMI $\geq$30 kg/m^2	128 (24.8)	138 (28.7)
BMI $<$20 kg/m^2	175 (36.8)	149 (28.3)‡
Diabetes mellitus	98 (23.5)	125 (29.6)
Alcohol abuse	36 (9.0)	26 (5.2)

* Except where indicated otherwise, values are the no. (%).
† Values are the observed no. ever during followup (% cumulative incidence at 30 years after index, including those with the condition at index date, adjusted for the competing risk of death). BMI = body mass index.
‡ $P < 0.05$ versus RA subjects.

Table 2. Multivariable risk of heart failure associated with the risk factors of interest in 575 RA subjects and 583 non-RA subjects*

Risk factor	RA, HR (95% CI)	Non-RA, HR (95% CI)
Male sex	1.04 (0.72–1.51)	1.44 (0.93–2.22)
Family history of IHD	0.97 (0.70–1.35)	0.92 (0.63–1.36)
IHD	3.25 (2.35–4.51)†	4.94 (3.30–7.38)†
Cigarette smoker	1.23 (0.94–2.73)	1.64 (1.04–2.59)†
Hypertension	1.60 (0.94–2.73)	2.99 (1.18–7.53)†
Dyslipidemia	0.92 (0.66–1.27)	0.90 (0.61–1.34)
BMI $\geq$30 kg/m^2	1.52 (1.05–2.20)†	1.01 (0.62–1.64)
BMI $<$20 kg/m^2	1.59 (1.12–2.25)†	1.17 (0.73–1.88)
Diabetes mellitus	1.46 (0.99–2.16)	1.62 (1.01–2.59)†
Alcohol abuse	1.72 (0.88–3.36)	0.68 (0.27–1.73)

* The hazard ratio (HR) and 95% confidence interval (95% CI) were computed from the estimated coefficients (and standard errors) in multivariable Cox regression models. See Table 1 for other definitions.
† $P < 0.05$.

in RA subjects (36.8%) compared with non-RA subjects (28.3%). RA subjects were significantly more likely to have a BMI $<$20 kg/m^2 and were less likely to have dyslipidemia, compared with non-RA subjects.

A total of 165 RA subjects and 115 non-RA subjects had a validated diagnosis of incident HF (1.99 and 1.16 HF cases per 100 person-years, respectively) during followup ($P < 0.001$). Table 2 shows the multivariable risk of HF associated with CV risk factors, IHD, and alcohol abuse for the RA and non-RA cohorts. IHD was significantly associated with the risk of HF among both RA and non-RA subjects. In RA subjects, low BMI ($<$20 kg/m^2) and obesity (BMI $\geq$30 kg/m^2) were significantly associated with the risk of HF, and diabetes showed a borderline association with HF risk ($P = 0.05$). Among the non-RA subjects, smoking, hypertension, and diabetes were significantly associated with the risk of HF. When the risk factors were assessed individually, the effect of IHD on the risk of HF was significantly smaller in RA subjects compared with non-RA subjects ($P = 0.02$ for interaction) (results not shown). Similarly, the effect of male sex was smaller in RA subjects than in non-RA subjects ($P = 0.05$ for interaction). However, in the multivariable models, the effect of these risk factors on the development of HF did not differ significantly between the RA and non-RA cohorts (Table 2).

Figure 1 displays the observed cumulative incidence of HF as a function of age among the RA subjects and the non-RA subjects, along with the predicted cumulative incidence of HF in the absence of CV risk factors, IHD, and alcohol abuse for each cohort. The cumulative incidence of HF rose steadily with age in both cohorts (Figure 1, curves A and B). The observed cumulative incidence of HF at age 80 years was 36.3% in the RA subjects, whereas it was only 20.4% in non-RA subjects ($P < 0.001$). Curves C and D in Figure 1 represent the predicted cumulative incidence of HF for each cohort, in the absence of exposures to traditional CV risk factors, IHD, and alcohol abuse. For example, among the RA subjects, the predicted cumulative incidence of HF in the absence of CV risk factors, IHD, and alcohol abuse was 16.5% at age 80 years, whereas it was only 4.8% at age 80 years among the non-RA subjects. The difference between the observed cumulative incidence of HF and the predicted cumulative incidence of HF in the absence of CV risk factors, IHD, and alcohol abuse (i.e., the risk difference) was similar in both cohorts, indicating that these factors have similar absolute impact in both cohorts. The predicted cumulative incidence of HF in RA subjects remained higher than in non-RA subjects, even after eliminating the effect of CV risk factors, IHD, and alcohol abuse.

The attributable risk of HF in each cohort was estimated as the difference between the observed cumulative incidence of HF and the predicted cumulative incidence of HF in the absence of the risk factors, expressed as a percentage of the observed cumulative incidence. Among non-RA subjects, the risk of HF attributable to the combination of all CV risk factors, IHD, and alcohol abuse rose from 65% at age 53 years

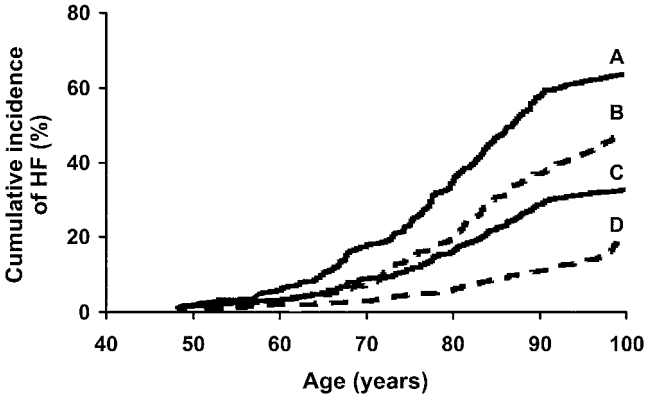

Figure 1. Cumulative incidence of heart failure (HF) as a function of age among 575 subjects with rheumatoid arthritis (RA) and 583 non-RA subjects, along with estimated cumulative incidence of HF in the absence of cardiovascular (CV) risk factors, ischemic heart disease (IHD), and alcohol abuse for each cohort. Curves A and B correspond to the observed cumulative incidence of HF in the RA and non-RA cohorts, respectively. Curve C displays the predicted cumulative incidence of HF in the RA cohort if all CV risk factors, IHD, and alcohol abuse were eliminated. Curve D displays the predicted cumulative incidence of HF for the non-RA cohort if all CV risk factors, IHD, and alcohol abuse were eliminated.

to 77% at age 80 years (Figure 2), whereas only 41% of HF at age 53 years and 54% of HF at age 80 years among RA subjects was attributable to these factors ($P < 0.01$). In other words, among the non-RA subjects, about one-fourth (23%) of the HF at age 80 years could not be attributed to the known CV risk factors, IHD, or alcohol abuse, whereas among those with RA, nearly one-half (46%) of the HF at age 80 years could not be attributed to these factors.

When IHD was removed from the analyses, the risk of HF attributable to CV risk factors and alcohol abuse was only 54% at age 53 years and 72% at age 80 years among the non-RA subjects and was 33% at age 53 years and 45% at age 80 years among the RA subjects. Although these attributable risks were smaller, the difference between the RA and non-RA cohorts persisted.

When the risk factors were examined individually, the risk of HF attributable to IHD was 11% among RA subjects and 17% among non-RA subjects at age 60 years, but this difference widened by age 80 years to 38% in the non-RA subjects compared with only 20% in the RA subjects (Figure 3), after adjustment for all other CV risk factors, IHD, and alcohol abuse. The attributable risk of HF associated with hypertension peaked at age 70 years in both groups, accounting for 56% of the risk of HF among non-RA subjects, but only 27% among RA subjects. In contrast, the attributable risk of HF associated with smoking peaked early in both groups, accounting for, at most, 21% of the risk of HF among the non-RA cohort and only 8% among the RA cohort. Finally, the attributable risk of HF associated with abnormal BMI (either ≥30 or <20 kg/m^2) was consistently higher among the RA subjects compared with the non-RA subjects (at age 60 years, 18% in RA subjects versus 3% in non-RA subjects).

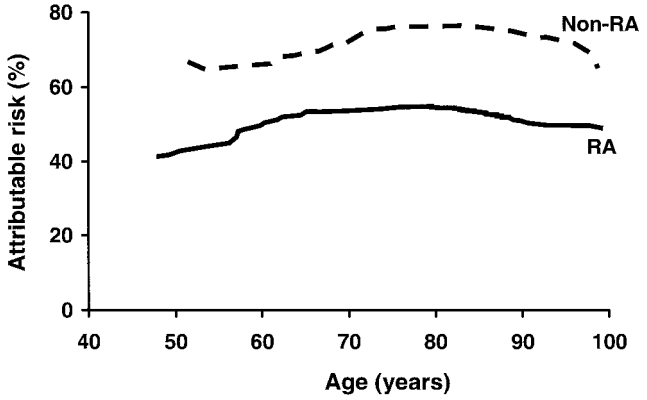

Figure 2. Risk of HF attributable to all CV risk factors, IHD, and alcohol abuse as a function of age in 575 RA subjects and 583 non-RA subjects. See Figure 1 for definitions.

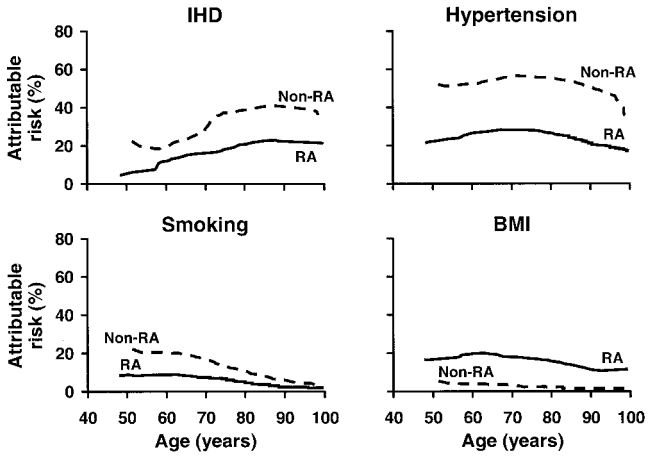

Figure 3. Risk of HF attributable to individual CV risk factors or IHD among RA and non-RA subjects. BMI = body mass index (see Figure 1 for other definitions).

DISCUSSION

In this study we compared the proportion of the risk of HF attributable to traditional CV risk factors, IHD, and alcohol abuse in a population-based inception cohort of subjects with RA compared with a similar cohort of subjects without RA. Our results indicate that the proportion of the risk of HF attributable to traditional CV risk factors, IHD, and alcohol abuse is much lower among RA subjects than among non-RA subjects. The amount of risk of HF attributable to all risk factors and IHD combined differed by 23% between the 2 cohorts. The risk of HF attributable to hypertension was also dramatically different between the 2 cohorts, with 56% attributable to hypertension among non-RA subjects and only 27% among RA subjects. Together these findings indicate that the excess risk of HF among RA subjects is not explained by an increased frequency or effect of either CV risk factors or IHD.

Recent studies (12), including 2 from our group (3,13), indicated that subjects with RA are at an increased risk of developing HF. HF is a complex clinical syndrome and it is the final and most severe manifestation of nearly every form of heart disease (4,5). The prognosis of HF is particularly poor, with fewer than 50% of subjects remaining alive by 5 years, and only 10% by 10 years following the initial diagnosis (14–17). Likewise, we recently found that HF is an important contributor to the excess overall mortality in RA (Crow-

son CS, et al: unpublished observations). HF contributes to this excess mortality primarily through an increased incidence of HF in RA, rather than through an increased mortality rate associated with HF in RA, compared with non-RA subjects. Therefore, prevention of HF may be an important step in efforts to improve life expectancy in RA patients. This can only be achieved through a better understanding of the etiology of HF in RA and the attributable risk of traditional CV risk factors for HF in RA versus non-RA subjects.

IHD and hypertension have long been recognized as the 2 major traditional risk factors for HF in the general population (6–9). Other common etiologies include diabetes mellitus, valvular heart disease, and nonischemic cardiomyopathies. In most cases of HF, multiple different clinical risk factors coexist and interact to produce disease (9). Attributable risk analyses combine the prevalence of each risk factor with its influence on the risk of HF, which therefore allows us to examine the potential impact of aggressive strategies to control these known risk factors for HF. Our findings indicate that, as expected, elimination of CV risk factors, IHD, and alcohol abuse in RA subjects significantly lowers their rate of HF, but the excess risk of HF in RA still persists (Figure 1). In other words, even in the unlikely event that all CV risk factors, IHD, and alcohol abuse were eliminated, RA subjects would still experience more HF than non-RA subjects.

These findings have both clinical and etiologic implications. Clinically, detection and management of CV risk factors and CV conditions in RA is important for identifying RA patient groups at particularly high risk, for whom preventive efforts might be usefully focused. Since much of the HF among RA subjects is not preceded by recognized IHD, HF may be the first manifestation of IHD in otherwise-asymptomatic RA patients. Moreover, since the excess risk of HF among RA subjects is not entirely explained by an increased frequency or effect of clinical CV risk factors or clinical IHD, other mechanisms may be involved in the etiology of HF in RA. Inflammation is emerging as a key underlying mechanism in the initiation and progression of HF (5) and it is conceivable that the uncontrolled chronic inflammatory state in RA may result in not just local damage to the joints, but also the "spillover" of cytokines into the systemic circulation may lead to adverse effects on distant tissues, including the myocardium (18,19). Other factors, particularly RA-related features, may improve the ability to identify RA subjects at an increased risk of developing HF. Further research is needed in this area.

The strengths of our study are several-fold. This is the first study examining the attributable risk of HF in RA. Through a unique application of statistical methods, we were able to examine attributable risk at various ages, rather than as just a single-point estimate. We used a validated algorithm to define HF cases and we used standardized criteria to ascertain the traditional CV risk factors, IHD, and alcohol abuse. In addition, we ascertained the risk factors throughout followup, and used them as time-dependent variables to fully account for their effect.

Our results should be interpreted in light of some potential limitations. First, 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 IHD outcomes prospectively at regular intervals. Although it is possible that different health care utilization rates could lead to bias in risk factor ascertainment, this is unlikely in the present study because of the long followup of these cohorts and the high frequency of medical care in this population (20). Similarly, conditions not recorded in the medical records, such as subclinical heart disease, would have been missed. In addition, 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 (20). Furthermore, HF is a complex disease and some of its causes are still unknown. It is possible that an unknown potential confounder exists which could modify these attributable risk estimates. Finally, the role of RA disease characteristics and medications on the attributable risk of HF in RA warrants further investigation.

In conclusion, the excess risk of HF among RA subjects is not explained by an increased frequency or effect of either CV risk factors or IHD. Despite their public health importance, the prevention and control of these factors may not have the same impact on reducing the risk of HF in RA patients as has been observed in the general population. Efforts to improve life expectancy in RA require an improved understanding of the characteristics and determinants of HF in this population.

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