

Contribution of Congestive Heart Failure and Ischemic Heart Disease to Excess Mortality in Rheumatoid Arthritis

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Objective. Although mortality among patients with rheumatoid arthritis (RA) is higher than in the general population, the relative contribution of comorbid diseases to this mortality difference is not known. This study was undertaken to evaluate the contribution of congestive heart failure (CHF) and ischemic heart disease (IHD), including myocardial infarction, to the excess mortality in patients with RA, compared with that in individuals without RA.

Methods. We assembled a population-based inception cohort of individuals living in Rochester, Minnesota, in whom RA (defined according to the criteria of the American College of Rheumatology [formerly, the American Rheumatism Association]) first developed between 1955 and 1995, and an age- and sex-matched non-RA cohort. All subjects were followed up until either death, migration from the county, or until 2001. Detailed information from the complete medical records was collected. Statistical analyses included the person-

years method, cumulative incidence, and Cox regression modeling. Attributable risk analysis techniques were used to estimate the number of RA deaths that would be prevented if the incidence of CHF was the same in patients with RA and non-RA subjects.

Results. The study population included 603 patients with RA and 603 subjects without RA. During followup, there was an excess of 123 deaths among patients with RA (345 RA deaths occurred, although only 222 such deaths were expected). The mortality rates among patients with RA and non-RA subjects were 39.0 and 29.2 per 1,000 person-years, respectively. There was a significantly higher cumulative incidence of CHF (but not IHD) in patients with RA compared with non-RA subjects (37.1% versus 27.7% at 30 years of followup, respectively; $P < 0.001$). The risk of death associated with either CHF or IHD was not significantly different between patients with RA and non-RA subjects. If the risk of developing CHF was the same in patients with RA and individuals without RA, the overall mortality rate difference between RA and non-RA hypothetically would be reduced from 9.8 to 8.0 excess deaths per 1,000 person-years; that is, 16 (13%) of the 123 excess deaths could be prevented.

Conclusion. CHF, rather than IHD, appears to be an important contributor to the excess overall mortality among patients with RA. CHF contributes to this excess mortality primarily through the increased incidence of CHF in RA, rather than increased mortality associated with CHF in patients with RA compared with non-RA subjects. Eliminating the excess risk of CHF in patients with RA could significantly improve their survival.

Survival among patients with rheumatoid arthritis (RA) is poorer than that in the general population. Patients with RA have also been shown to experience an

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increased mortality risk from multiple comorbidities, including cardiovascular (1,2), renal (1,3), infectious (3,4), gastrointestinal (5,6), and malignant diseases (7,8). As discussed by Pincus, Callahan, et al (9,10), deaths caused directly by RA are rare, and thus most excess mortality in patients with RA must result from other comorbidities. However, the relative contribution of comorbid conditions to the observed excess mortality among patients with RA is unknown. The most important cardiovascular diseases that contribute to cardiovascular mortality (the major cause of death in both the RA and non-RA populations) are ischemic heart disease (IHD) and congestive heart failure (CHF). Importantly, these diseases not only significantly increase the mortality risk but also are interrelated (e.g., CHF is more likely to occur after a myocardial infarction [MI], and MI is more likely to occur after CHF).

Comorbid conditions can increase overall mortality in RA if the prevalence of fatal comorbid conditions is increased among patients with RA compared with persons without RA, if increased mortality is associated with comorbid conditions (even if the prevalence of such conditions is not increased), or if comorbid conditions are both more prevalent and more fatal. An improved understanding of the relationship between comorbid conditions (in particular, fatal comorbidities such as IHD and CHF) and mortality is an essential first step toward improving the survival of patients with RA.

We sought to describe the excess mortality in a population-based incidence cohort of patients with RA and a matched non-RA comparison cohort that was identified from the same underlying population. We then evaluated the contribution of IHD, including MI, and CHF to this excess mortality by 1) comparing the cumulative incidence of IHD and CHF in patients with RA compared with non-RA subjects, and 2) examining the mortality associated with IHD and CHF in patients with RA compared with non-RA subjects. Finally, we estimated the number of RA deaths that hypothetically would be prevented if patients with RA had the same risk of CHF as individuals without RA.

PATIENTS AND METHODS

Subjects and design. We conducted a longitudinal, retrospective, population-based study using the medical records linkage system of the Rochester Epidemiology Project (11,12). This system allows ready access to the complete (inpatient and outpatient) records from all health care providers for Olmsted County, including 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 source for use in population-based research has been previously described (11,12). This system ensures virtually complete information on clinical comorbidities and vital status for all subjects. This study was approved by the Mayo Foundation Institutional Review Board and the Olmsted Medical Center Institutional Review Board.

Using this data resource, we assembled a population-based incidence cohort of all cases of RA first diagnosed between January 1, 1955 and January 1, 1995 among Rochester, Minnesota, residents ≥ 18 years of age, as previously described (13,14). All cases fulfilled the 1987 American College of Rheumatology (ACR; formerly, the American Rheumatism Association) criteria for RA (15). The incidence date was defined as the first date of fulfillment of at least 4 of the 7 diagnostic criteria. For each patient with RA, a subject without RA, matched for birth year (± 3 years), sex, and previous length of medical history, was randomly selected from among residents of Rochester, Minnesota. Matching for previous length of medical history or date of first medical contact ensured that patients with RA and corresponding non-RA subjects had the same opportunity for clinical detection and reporting of risk factors, outcomes, and comorbidities. Each subject in the non-RA comparison cohort was assigned an index date corresponding to the RA incidence date.

Data collection. The complete medical records (inpatient and outpatient care from all local health care providers) for each study participant were 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, 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 provided guidance and had expertise in rheumatology (SEG), cardiology (VLR), epidemiology (SJJ, SEG, and HM-K), and data management/analysis (CSC and KVB).

CHF was defined according to the Framingham Heart Study criteria (16). IHD was defined as being present at the earliest date of the occurrence of a hospitalized MI, silent MI, angina, or revascularization procedure. The definition of hospitalized MI (17,18) included MIs classified as definite or probable, based on the presence of cardiac pain, biomarker values, and the Minnesota electrocardiography coding system (19,20). Silent MI was defined as the presence of a characteristic electrocardiogram result in a nonacute setting, or a recorded physician's diagnosis of a characteristic electrocardiogram result in patients without any documentation of previous MI. The date of first documentation was considered the silent MI incidence date. Angina pectoris was defined as documentation in the medical record by a physician of cardiac pain in a patient in whom no other causes for pain could be identified. Coronary revascularization procedures included percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. The frequency and rate of occurrence of each individual IHD condition in these cohorts are described elsewhere (21).

Statistical analysis. Descriptive statistics such as means, medians, and proportions were used to summarize the

data. The frequency of IHD, hospitalized MI, and CHF in the RA and non-RA cohorts at the RA incidence/index date was compared using chi-square tests. Person-year methods were used to estimate event rates during followup. An F test was used to compare event rates for the RA and non-RA cohorts (22).

The distribution of survival times was estimated using the Kaplan-Meier method (23). "Expected" mortality was based on the death experience in the non-RA cohort, which was sex- and age-matched with the RA cohort at the RA incidence date. Observed and expected mortality were compared using the log rank test (24). The expected number of deaths in subjects without RA was estimated by applying age- and sex- specific non-RA mortality rates to the age- and sex-specific person-years of followup observed in the RA cohort. Excess mortality was computed as the difference between observed and expected mortality.

To estimate the survival of subjects with and those without CHF in both cohorts, subjects were censored from the "no CHF" group at the time of a CHF diagnosis and were then added to the CHF group at that time point. Therefore, subjects in whom CHF developed after the RA incidence/index date would contribute to the estimates of both survival without CHF and survival with CHF during nonoverlapping time intervals.

The cumulative incidence of IHD and that of CHF at 30 years were estimated by adding the prevalence of these conditions at baseline to their cumulative incidence after 30 years of followup, with adjustments made for the competing risk of death (25). Differences in cumulative incidence between the RA and non-RA cohorts were assessed using the methods described by Gray (26).

Cox regression models, using age as the time scale and stratified by sex, were used to compare the impact of IHD and CHF (as time-dependent variables) on mortality among patients with RA and non-RA subjects (27). Two-way interactions between these conditions and cohort (RA versus non-RA) were examined to determine whether the impact of the conditions differed by cohort. *P* values less than 0.05 were considered significant.

Finally, we used attributable risk analysis techniques to estimate the number of RA deaths that would be prevented if the cumulative incidence of IHD or CHF were the same in patients with RA and non-RA subjects. In typical attributable risk analyses, the impact of eliminating an exposure from the population is estimated. In this analysis, we instead examined the impact of reducing the cumulative incidence of IHD and/or CHF in the RA cohort to the observed incidence of these conditions in the non-RA cohort. To do this, a series of simulated RA cohorts were randomly created, in which a subset of CHF events was assumed to be prevented so that the cumulative incidence of CHF in the simulated RA cohort was equivalent to the cumulative incidence of CHF observed in the non-RA cohort. The attributable risk (or etiologic fraction) was then estimated by comparing the mortality in the actual RA cohort with the estimated mortality in the simulated RA cohorts (on average). A Cox model was used to estimate the cumulative incidence of death in the simulated RA cohorts.

Table 1. Demographic characteristics of subjects, and prevalence of congestive heart failure and ischemic heart disease at the RA incidence/index date*

Characteristic	RA	Non-RA
Age, mean \pm SD years	58.0 \pm 15.2	58.2 \pm 15.2
Female sex	441 (73)	441 (73)
Congestive heart failure	28 (4.6)	20 (3.3)
Ischemic heart disease	66 (11.0)	69 (11.4)
Hospitalized myocardial infarction	17 (2.8)†	5 (0.8)
Congestive heart failure + ischemic heart disease	18 (3.0)	18 (3.0)

* Except where indicated otherwise, values are the number (%). RA = rheumatoid arthritis.

† *P* < 0.05 versus non-RA.

RESULTS

The study population comprised 603 patients who first fulfilled the ACR criteria for RA between 1955 and 1995. The median time interval between the first recorded RA criterion and the date of fulfillment of the ACR diagnostic criteria was 46 days (interquartile range 4 days to 1.3 years). The comparison group included 603 subjects without RA who were age- and sex- matched to patients with RA at the RA incidence date. The median followup was 12.7 years for patients with RA and 14.9 years for non-RA subjects, corresponding to 8,842 and 10,101 person-years of followup, respectively. The baseline characteristics as well as the prevalence and incidence rates of IHD and CHF in patients with RA and non-RA subjects are shown in Tables 1 and 2. In both cohorts, 73% of the subjects were women, and the mean age at baseline was 58 years. The prevalence of prior hospitalized MI at baseline and the incident rate of CHF over the followup period were significantly higher in patients with RA. In the majority of patients with RA

Table 2. Occurrence of congestive heart failure and ischemic heart disease in patients with RA and non-RA subjects during followup*

Characteristic	RA		Non-RA	
	n	Rate per 1,000 person-years (95% CI)	n	Rate per 1,000 person-years (95% CI)
Congestive heart failure	165	19.0 (16.2–22.2)†	115	11.6 (9.6–13.9)
Ischemic heart disease	136	16.4 (13.8–19.5)	118	12.6 (10.4–15.1)
Hospitalized myocardial infarction	40	4.6 (3.3–6.3)	46	4.6 (3.3–6.1)
Congestive heart failure + ischemic heart disease	98	11.2 (9.1–13.7)	81	8.1 (6.5–10.1)

* RA = rheumatoid arthritis; 95% CI = 95% confidence interval.

† *P* < 0.05 versus non-RA.

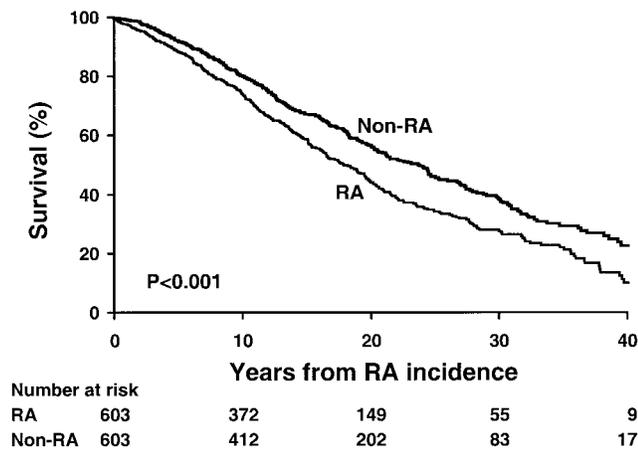


Figure 1. Comparison of survival among Rochester, Minnesota residents with rheumatoid arthritis (RA) and matched subjects without RA, beginning at the incidence/index date.

and non-RA subjects in whom CHF or IHD developed during followup, in fact both conditions developed.

The survival of patients with RA compared with that of non-RA subjects is shown in Figure 1. Overall survival was significantly worse among patients with RA compared with non-RA subjects ($P < 0.001$). During followup, a total of 345 patients with RA died, while only 222 deaths would have been expected based on the experience of non-RA subjects. This resulted in an excess of 123 deaths among patients with RA. Overall mortality rates among patients with RA and non-RA subjects were 39.0 and 29.2 per 1,000 person-years, respectively ($P < 0.001$).

Table 3 shows the cumulative incidence of IHD and that of CHF among patients with RA and non-RA subjects after 30 years of followup. These cumulative incidences were computed by considering IHD and CHF that was present either at baseline or during the followup period. The cumulative incidence of CHF was significantly greater among patients with RA compared with non-RA subjects ($P < 0.001$), with a difference of 9.4% at 30 years of followup. IHD was somewhat (2.9%) more common in patients with RA compared with non-RA subjects, but this difference did not reach statistical significance ($P = 0.39$). The cumulative incidence of hospitalized MI was similar in the 2 groups ($P = 0.58$). To determine whether significant changes in the cumulative incidence of CHF and IHD occurred in subjects who entered the study in the earlier (1955–1984) versus the more recent study period (1985–1994), we compared differences in the cumulative incidence of these conditions between these 2 cohort subsets. The

Table 3. Cumulative incidence of congestive heart failure, ischemic heart disease, and hospitalized myocardial infarction among patients with RA and non-RA subjects 30 years after the RA incidence/index date*

Comorbid condition	Cumulative incidence		<i>P</i>
	RA (n = 603)	Non-RA (n = 603)	
Congestive heart failure	37.1 (32.5–41.7)	27.7 (23.3–32.1)	<0.001
Ischemic heart disease	38.3 (33.8–42.8)	35.4 (31.0–39.9)	0.39
Hospitalized myocardial infarction	10.8 (7.9–13.7)	10.2 (7.4–12.9)	0.58

* Values are the percent (95% confidence interval). The cumulative incidence at 30 years after the rheumatoid arthritis (RA) incidence/index date (including subjects who had the condition at the incidence/index date) was adjusted for the competing risk of death.

results of all comparisons were nonsignificant (data not shown), indicating that no major changes in the cumulative incidence of CHF, IHD, or hospitalized MI occurred in either patients with RA or non-RA subjects during the study period.

The comparison of mortality associated with IHD and CHF among patients with RA and non-RA subjects is shown in Table 4. The risk of death associated with CHF was similar among patients with RA and non-RA subjects (hazard ratios 4.86 and 4.25, respectively; P for interaction = 0.62). Likewise, the hazard ratios for death associated with IHD and with hospitalized MI among patients with RA and non-RA subjects with IHD and with hospitalized MI were very similar (P for interaction = 0.23 and 0.10, respectively) (Table 4). To determine whether mortality changed with the calendar year, we compared the risk of death after CHF and IHD in patients with RA and non-RA subjects who entered the study in an earlier period (1955–1984) with the risk in those who entered the study in a more recent period (1985–1994). The results of all comparisons were nonsignificant (data not shown).

Table 4. Mortality risk associated with congestive heart failure, ischemic heart disease, and hospitalized myocardial infarction among patients with RA and non-RA subjects*

Comorbid condition	Hazard ratio (95% CI)		<i>P</i> for interaction
	RA	Non-RA	
Congestive heart failure	4.86 (3.8–6.1)	4.25 (3.3–5.5)	0.62
Ischemic heart disease	1.84 (1.5–2.3)	1.93 (1.5–2.5)	0.23
Hospitalized myocardial infarction	2.89 (2.1–4.1)	3.85 (2.8–5.3)	0.10

* Hazard ratios were adjusted for age, sex, and calendar year. RA = rheumatoid arthritis; 95% CI = 95% confidence interval.

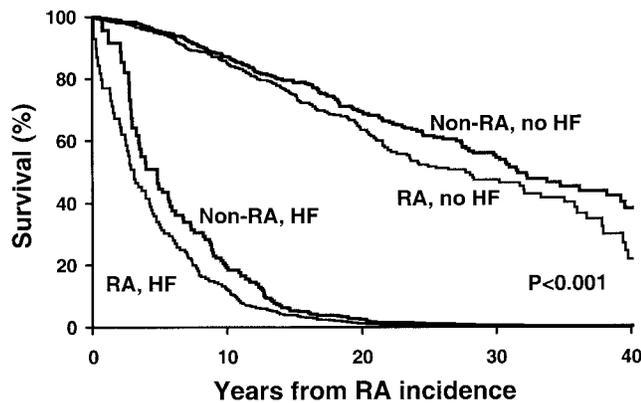


Figure 2. Comparison of survival among patients with rheumatoid arthritis (RA; $n = 603$) and subjects without RA (non-RA; $n = 603$), beginning at the incidence/index date, grouped according to heart failure (HF) status. Subjects were censored from the “no HF” group and added to the “HF” group at the time of the diagnosis of HF.

Thus, although the cumulative incidence of CHF was significantly higher among patients with RA compared with non-RA subjects, the mortality associated with CHF did not appear to be significantly different in these 2 groups. These findings are further illustrated in Figure 2, which shows that the differences in survival between RA patients with and those without CHF were very similar to the differences in survival between non-RA subjects with and those without CHF. Similarly, survival among RA patients with and those without IHD was also very comparable with survival among non-RA subjects with and those without IHD (data not shown). Together, these data suggest that CHF contributes to the increased mortality among patients with RA primarily through the increased incidence of CHF in RA, rather than increased mortality associated with CHF among patients with RA compared with non-RA subjects. Furthermore, IHD appeared to make a much smaller contribution to the excess mortality in patients with RA.

Finally, we addressed the question of how much of the excess overall mortality in RA could potentially be reduced if the excess risk of CHF in RA was hypothetically eliminated. As indicated above, the overall difference in the mortality rate among patients with RA and non-RA subjects is 9.8 per 1,000 person-years (95% confidence interval [95% CI] 8.6–19.2). If, instead, we assumed that patients with RA had the same cumulative incidence of CHF as that of non-RA subjects, we estimated that the overall mortality rate in the RA cohort hypothetically would decrease by 1.8 deaths per 1,000 person-years (95% CI 1.4–2.1). This implies that

the difference in overall mortality between patients with RA and non-RA subjects would be reduced from 9.8 to 8.0 excess deaths per 1,000 person-years. Thus, if the incidence and prevalence of CHF were the same in patients with RA and in non-RA subjects, approximately 16 (13%) of the 123 excess RA deaths (approximately 1 of every 8 excess RA deaths) hypothetically could be prevented.

DISCUSSION

The contribution of a comorbid condition to excess mortality in RA is a function of the cumulative incidence of the condition and its fatality in patients with RA compared with non-RA subjects. In this analysis, we included CHF and IHD that occurred both before and after the RA incidence date. We also analyzed hospitalized MI separately as a well-defined form of IHD. Our results show that CHF (but not IHD) appears to be an important contributor to the observed excess mortality in RA. Furthermore, this excess mortality risk in patients with RA appears to be explained by the increased cumulative incidence of CHF in these patients rather than increased mortality after CHF has occurred.

We recently reported that patients with RA are at increased risk for the development of CHF (28) and IHD (21). CHF is the final stage in many heart diseases. In a previous study, we observed that patients with RA had an increased risk of CHF compared with non-RA subjects, and that this increased risk was independent of traditional cardiovascular risk factors and/or clinically overt IHD (28). We hypothesized that pathologic mechanisms unrelated to clinically overt IHD or traditional cardiovascular risk factors could be responsible for the increased risk of CHF in patients with RA compared with non-RA subjects. According to the results of the Framingham study (29) and the Cardiovascular Health Study (30), the factors that contribute most to CHF in the general population are hypertension and coronary heart disease, followed by diabetes, smoking, and other factors. Interestingly, C-reactive protein was reported to contribute 10% of the risk attributable to CHF (30).

We recently described a study in which we compared the attributable risk for CHF among patients with RA and non-RA subjects (31). In that study, we observed that the proportion of the risk of CHF attributable to traditional cardiovascular risk factors and clinically overt IHD was 23% lower among patients with RA compared with non-RA subjects. We concluded that the excess risk of CHF among patients with RA was not explained by an increased frequency, or effect, of either

cardiovascular risk factors or clinically overt IHD. In the present study, we extend our previous findings by showing that this excess risk of CHF is also an important contributor to the excess mortality in RA.

Our findings should not be interpreted as meaning that cardiovascular risk factors or clinically overt IHD are not as important to the risk of CHF or mortality in RA as they are in the general population. Rather, patients with RA seem to have not only the CHF risk associated with IHD and traditional cardiovascular risk factors that is observed in the general population, but also an additional risk apparently not associated with traditional cardiovascular risk factors or clinically overt IHD, which contributes to their excess mortality. Several possible etiologic mechanisms involved in the increased risk of CHF in patients with RA have been described. Results of recent studies suggest that in the elderly population, higher levels of systemic markers of inflammation predict the risk of CHF (32), even in the absence of MI (33,34). Other possible explanations include a higher prevalence of unrecognized or subclinical IHD and/or cardiovascular risk factors that could, at least partially, promote CHF. Pericardial and valvular disease, which are possible complications of RA (35), and the potential cardiotoxic effect of RA drugs such as nonsteroidal antiinflammatory drugs (36,37), corticosteroids, chloroquine (38,39), D-penicillamine (40), or biologic agents (especially tumor necrosis factor inhibitors) may also play a role.

The possibility that CHF may play a major role in RA mortality was first suggested by Mutru et al (41), who followed up 1,000 patients with RA and 1,000 matched non-RA subjects over a period of 10 years. Of all cardiovascular disease-related deaths, CHF was the only one that was more prevalent among patients with RA compared with non-RA subjects. However, that study, and others that relied on death certificates (42), considered only one cause of death per subject and thus did not examine the relative participation of other heart diseases and comorbidities to RA mortality. Although several groups of investigators have reported higher cardiovascular mortality in RA, they did not include or discriminate CHF as a potential contributor (2,3,5–8,43–46) or only evaluated the risk of death associated with CHF (1), not accounting for the potential contribution of CHF to excess mortality in RA due to its prevalence (47,48).

Our findings extend prior observations and address the limitations of previous studies. By describing the excess mortality among patients with RA compared with the mortality in subjects without RA, examining the

cumulative incidence of IHD and CHF in patients with RA compared with non-RA subjects (inclusively before baseline), and comparing the mortality associated with these conditions in patients with RA compared with non-RA subjects, we were able to delineate the contribution of CHF and IHD to the excess mortality observed among patients with RA in a manner that would not be possible otherwise. The strengths of our investigation include the population-based design (i.e., a large community-based incidence cohort including all ranges of RA severity, with extensive followup), the completeness of ascertainment of IHD, CHF, and mortality, the use of standardized measurements, and the use of consistent diagnostic criteria for both cardiovascular events and RA. Finally, we applied novel statistical techniques to examine the potential effect of hypothetically reducing the excess risk of CHF in patients with RA to the same level as that in non-RA subjects.

One potential concern regarding our observations is that major changes in the epidemiology of CHF, IHD, and MI may have occurred in the last several decades. Although population-based studies have indicated no or a slight decrease in the incidence of CHF (49–51) and IHD (52–55), survival in the setting of both CHF (49,50,56) and IHD (53,54,57) has improved in recent years. Further analysis comparing our results obtained before 1985 with those obtained after 1985 demonstrated no calendar-year effect, which suggests that differences in the incidence and mortality of CHF and IHD between patients with RA and non-RA subjects have not changed significantly, and that changes in the epidemiology of these heart diseases appear to have similarly affected patients with RA and those without RA. Thus, our observations are relevant to RA patients today.

It is important also to acknowledge potential study limitations. This study was retrospective and relied on medical record information accrued over a 4-decade period. Also, for a medical condition to be ascertained, it had to come to medical attention, be diagnosed by a physician, and documented in the patient's medical records. We acknowledge that medical practices may have changed over this time period. In addition, cardiovascular events that were unrecognized by patients and/or health professionals would not have been ascertained. This may underestimate the number or timing of cardiovascular events, particularly silent MI or angina. Finally, we cannot rule out the possibility of nondifferential ascertainment of cardiovascular events. It is possible, for example, that mild angina is less likely to be reported among patients with RA compared with

non-RA subjects because of the high frequency of analgesic use among patients with RA. This may result in an underestimate of the risk of angina in patients with RA compared with non-RA subjects. However, the comprehensive medical records linkage system of the Rochester Epidemiology Project (covering inpatient and outpatient care from all local providers) allowed us to access complete health care information for a median of 14.1 years of followup. Because in this geographically well-defined population almost all residents come to medical attention in any 3-year period (12), differential ascertainment bias is less likely to affect our results. Also, the study population was composed largely of white individuals, which may limit the generalizability of the results to more diverse populations. Finally, although our analyses did not demonstrate a significant difference in mortality between CHF patients with and those without RA, our study did not have adequate power to detect small, but possibly clinically important, differences in mortality between these groups.

We observed that the contribution of CHF to the observed excess mortality in RA appeared to be explained primarily by the increased cumulative incidence of CHF in RA, and that survival following CHF and IHD was similar among patients with RA and non-RA subjects. We further showed that approximately 1 of every 8 excess deaths among patients with RA could be prevented if the risk of CHF was the same in patients with RA and non-RA subjects. Further research is needed to better understand the mechanism underlying the excess risk of CHF among patients with RA, including subclinical or clinically unrecognized IHD and non-traditional cardiovascular risk factors, and to explore potential interventions to decrease or eliminate this excess risk.

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