Cardiovascular Morbidity and Mortality in Women Diagnosed With Rheumatoid Arthritis

Daniel H. Solomon, MD, MPH; Elizabeth W. Karlson, MD; Eric B. Rimm, ScD; Carolyn C. Cannuscio, ScD; Lisa A. Mandl, MD, MPH; JoAnn E. Manson, MD, DrPH; Meir J. Stampfer, MD, DrPH; Gary C. Curhan, MD, ScD

Background—Rheumatoid arthritis may be associated with an increased risk of cardiovascular disease. We compared the incidence rates of myocardial infarction and stroke in subjects with and without rheumatoid arthritis.

Methods and Results—A prospective cohort study was conducted among the 114 342 women participating in the Nurses' Health Study who were free of cardiovascular disease and rheumatoid arthritis at baseline in 1976. All self-reported cases of rheumatoid arthritis were confirmed by medical record review. Fatal and nonfatal myocardial infarctions and strokes were similarly confirmed. Multivariate pooled logistic regression was used to adjust for potential cardiovascular risk factors. Five hundred twenty-seven incident cases of rheumatoid arthritis and 3622 myocardial infarctions and strokes were confirmed during 2.4 million person-years of follow-up. The adjusted relative risk of myocardial infarction in women with rheumatoid arthritis compared with those without was 2.0 (95% confidence interval [CI], 1.23 to 3.29). For stroke, the adjusted relative risk was 1.48 (95% CI, 0.70 to 3.12). Women who had rheumatoid arthritis for at least 10 years had a risk for myocardial infarction of 3.10 (95% CI, 1.64 to 5.87).

Conclusion—In this large prospective cohort of women, participants with rheumatoid arthritis had a significantly increased risk of myocardial infarction but not stroke compared with those without rheumatoid arthritis. If these data are confirmed, aggressive coronary heart disease prevention strategies should be tested for persons with rheumatoid arthritis. **(*Circulation*. 2003;107:1303-1307.)**

Key Words: cardiovascular diseases ■ myocardial infarction ■ stroke ■ epidemiology

Rheumatoid arthritis (RA) is the most common systemic autoimmune disease and affects ≈2.1 million Americans, 1.5 million of whom are women.[1] Several studies have documented increased morbidity and mortality among people with RA.[2–4] A recent study found that persons with RA in Saskatoon had a median survival 17 years shorter than expected for the Canadian population.[5] Several tertiary care–based and community-based studies have found that rates of cardiovascular disease are increased for patients with RA, possibly explaining the reduced life span.[3,5–9] However, these studies overrepresented referral populations, many did not confirm cardiovascular end points, several compared patients from different cohorts, and few adequately adjusted for known cardiovascular risk factors.

The relation between RA and cardiovascular disease has become a particular focus of attention because of the increased recognition of the inflammatory underpinnings of atherosclerosis.[10] It has long been known that T-cells play a critical role in the pathogenesis of RA[11]; more recent data also suggest that T-cell abnormalities may play an important role in acute coronary syndromes and atherosclerotic plaque instability.[12,13] In addition, several different investigators have found that cytokines, C-reactive protein, and other inflammatory markers, known to be elevated in RA, are also elevated before and at the time of ischemic injuries.[14–16] In addition, one treatment for RA, methotrexate, known to downregulate T-cell activity, has been associated with reduced cardiovascular mortality in patients with RA.[17]

We examined the rates of myocardial infarction and stroke in persons with RA participating in a large prospective cohort study of women.

Methods

Study Population

The Nurses' Health Study is a prospective cohort study comprised of 121 700 women who were between the ages of 30 to 55 years when

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From the Division of Pharmacoepidemiology and Pharmacoeconomics (D.H.S.), Division of Rheumatology, Immunology, and Allergy (D.H.S., E.W.K., L.A.M.), and Division of Preventive Medicine, Channing Laboratory (J.E.M., M.J.S., G.C.C.); Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Mass; Department of Epidemiology (E.B.R., M.J.S., G.C.C.), Harvard School of Public Health, Boston , Mass; and Merck Research Laboratories (C.C.C.), West Point, Pa.

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Correspondence to Daniel H. Solomon, MD, MPH, Divisions of Pharmacoepidemiology and Rheumatology, Immunology, and Allergy, Brigham and Women's Hospital, 221 Longwood Ave, Suite 341, Boston MA 02115. E-mail dhsolomon@partners.org

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they completed the baseline questionnaire in 1976. These women have been sent questionnaires every 2 years to update information concerning medical, lifestyle, and other health-related information.[18] The biennial mailed questionnaires ask participants about recent illness, including RA, and dates of diagnosis, dietary habits, weight, cigarette smoking, menopausal status, physical activity, blood pressure, and use of prescription and over-the-counter medications as well as dietary supplements. Women who reported RA, cardiovascular disease, and cancer (other than non-melanoma skin cancer) at baseline were excluded from this analysis. After exclusions, 114 342 women were included in these analyses. The Partners HealthCare System Institutional Review Board approved this study.

Assessment of Rheumatoid Arthritis

We conducted follow-up on the 7786 women reporting RA on any of the biennial questionnaires from 1978 to 1996. We attempted to contact each of these participants to confirm their RA diagnosis. Respondents were asked to complete a connective tissue disease screening questionnaire.[19] Based on their responses, medical records were obtained on 2170 participants who had symptoms suggestive of RA and gave permission for us to review their charts. Two rheumatologists trained in chart abstraction independently reviewed the medical records using the 1987 American College of Rheumatology diagnostic criteria for RA.[20] These criteria were assessed in a cumulative fashion, examining all available medical records. As has been used in prior epidemiologic studies, patients with 4 of the 7 diagnostic criteria were considered to have definite RA.[9,17]

Cardiovascular End Points

End points for these analyses were myocardial infarction and stroke. Both fatal and nonfatal events were included. All self-reported end points from the biennial questionnaires were verified by medical record review using validated criteria.[21,22] Sudden death was classified as a fatal myocardial infarction. A composite end point of either myocardial infarction or stroke was also constructed. Mortality follow-up for the entire cohort is completed using death certificates and the National Death Index. Follow-up for the deaths was >98% complete.[23]

Other Covariates

Known or suspected risk factors for cardiovascular disease were included as potential confounders. These consisted of age, hypertension, diabetes, reported hypercholesterolemia, parental history of myocardial infarction before age 60 years, cigarette smoking, alcohol consumption, use of exogenous hormone replacement therapy, aspirin use, physical activity, body mass index, folate and omega-3-fatty acid intakes, and vitamin E supplement use. Finally, exposure to oral corticosteroids and nonsteroidal antiinflammatory drugs (NSAIDs) was examined because of possible associations with RA and the end points of interest. Information on the use of oral corticosteroids was only available since 1994 and NSAIDs since 1990. Information on the use of disease-modifying antirheumatic drugs, such as methotrexate or hydroxychloroquine, was not collected in the medical record review or biennial questionnaires.

Statistical Analysis

Because only participants diagnosed with RA after the initial questionnaire in 1976 were included in these analyses, we could not compare potential confounders at baseline. Instead, we compared data from the 1990 questionnaire, as a representative time point, for participants who were previously diagnosed with RA with all other women. χ^2 tests were performed for categorical variables and Student's t test for continuous data. The primary analyses examined the age-specific incidence rates of the cardiovascular end points. We first calculated the duration of follow-up as the interval between the return of the 1976 questionnaire and the first diagnosis of myocardial infarction, stroke, death, or May 31, 1996, whichever came first. To reduce the potential confounding of treatments for cardiovascular disease, all women who reported coronary revascularization or angina were censored at that date. However, these were not included as end points. Relative risks were computed for the individual and combined cardiovascular end points of interest by comparing the incidence rates in people with RA to the rates in people without RA. We used pooled logistic regression to adjust for multiple potential confounders.[24] These included age in 5-year categories, hypertension, diabetes, high cholesterol level, parental history of myocardial infarction before age 60 years, body mass index, cigarette use, physical activity, alcohol use, aspirin use, menopausal status, hormone replacement therapy use, oral glucocorticoid use, nonsteroidal antiinflammatory drug use, folate intake, omega-3 fatty acid intake, and vitamin E supplement intake. All of these exposures are updated every 2 years, except dietary factors, which were first assessed in 1980 and then updated approximately every 4 years. Person-years of follow-up were allocated according to exposure status at the start of each follow-up period.

In the main analyses, only definite cases of RA contributed to exposed person-time, which began at the date that the RA diagnosis was confirmed in the medical record. We examined the sensitivity of these analyses to the definition of RA in secondary analyses, in which participants who fulfilled at least 3 of 7 criteria were considered to have possible RA. In addition, we conducted a 2-year lag analysis that excluded the first 2 years after the RA diagnosis. Both of these variations in the definition of RA produced results quantitatively similar to the main analyses and are not presented. Finally, we assessed whether specific characteristics of RA (duration, presence of rheumatoid factor, rheumatoid nodules, or erosions on plain radiographs) were associated with any of the cardiovascular end points. Separate fully adjusted pooled logistic models were constructed with 2 indicator variables for RA; one represented participants with RA who did not have the specific characteristic and the other represented participants with RA and the specific characteristic. All analyses were conducted using SAS Statistical Software (SAS 6.12).

Results

In this study involving 114 342 women and representing 2.4 million years of follow-up, we confirmed an incident diagnosis of RA in 527 women, and there were 2296 myocardial infarctions and 1326 strokes. We compared the distribution of potential cardiovascular risk factors reported by participants with RA and those without in 1990 (Table 1). The mean age of participants with RA was slightly higher than the age of those without. The frequency of hypertension, diabetes, and high cholesterol was comparable between women with RA and those without. Compared with women without RA, women with RA were more likely to have a parental history of myocardial infarction before age 60 years. Body mass index was slightly less and physical activity levels were significantly lower for participants with RA than those without. Present or past cigarette use was significantly more frequent and grams of alcohol used were significantly less in women with RA compared with those without. Women with RA were more likely to report no aspirin use than their counterparts. Current or past hormone replacement therapy use was more common in women with RA than women without. As expected, a much larger percentage of women with RA than those without reported ever using NSAIDs. Glucocorticoid data were not available until 1994. In this year, 30.2% of participants with RA compared with 1.5% reported using glucocorticoids ($P<0.001$). Daily ingestion of folate and omega-3 fatty acids were higher in participants with RA than those without; however, vitamin E supplement intakes were similar.

We calculated the age- and multivariate-adjusted relative risk of cardiovascular disease end points for participants with

TABLE 1. Characteristics of Participants in the Nurses' Health Study With and Without Rheumatoid Arthritis in 1990

	Rheumatoid Arthritis	No Rheumatoid Arthritis	*P*
Age, mean±SD, y	58.0±6.7	56.4±7.2	<0.001
Hypertension, %	33.7	29.5	0.067
Diabetes, %	4.7	4.9	0.91
High cholesterol level, %	34.6	33.3	0.56
Parental history of myocardial infarction before age 60, %	41.8	35.9	0.013
BMI, mean±SD, kg/m^2	25.3±4.9	25.8±4.9	0.081
Physical activity, mean±SD, METs per week	13.9±18.5	15.5±21.5	0.011
Cigarette use,* %	...	...	<0.001
Current	17.0	19.6	...
Past	49.1	37.4	...
Never	33.8	43.1	...
Alcohol use, g per day, mean±SD	3.3±6.6	5.1±9.5	<0.001
Aspirin use, days per month, %	...	...	<0.001
None	58.5	46.8	...
1 to 14	16.3	36.2	...
15 to 30	25.2	17.0	...
Hormone replacement therapy use, %	...	...	<0.001
Current	32.6	27.3	...
Past	22.1	15.4	...
Never	32.4	29.8	...
Premenopausal	12.9	27.5	...
NSAID use, % ever	66.6	22.0	<0.001
Folate, μg per day, mean±SD	460±242	431±225	0.022
Omega-3 fatty acids, mg per day, mean±SD	225±299	165±236	<0.001
Vitamin E supplements, mg per day, mean±SD	71±160	70±171	0.96

Variables were assessed at the 1990 questionnaire for participants who had previously been diagnosed with rheumatoid arthritis (n=407) and those without rheumatoid arthritis (n=113 935). Physical activity was not assessed on the 1990 questionnaire, and thus we used information from 1988. Folate and omega-3 fatty acid levels include dietary sources and supplements. METs indicates metabolic equivalent units.

*Some columns do not equal 100% because of rounding.

RA (see Table 2). The age-adjusted risk of myocardial infarction was >2-fold higher for patients with RA than those without (relative risk [RR], 2.07; 95% CI, 1.28 to 3.34). After adjusting for potential confounders, the relative risk of myocardial infarction for patients with RA was nearly identical (RR, 2.00; 95% CI, 1.23 to 3.29). The multivariable relative risk for nonfatal myocardial infarction (RR, 2.17; 95% CI, 1.22 to 3.87) and fatal myocardial infarction (RR 1.82; 95% CI, 0.75 to 4.41) were both elevated for participants with RA. Neither the age-adjusted relative risk of stroke (RR, 1.47; 95% CI, 0.70 to 3.08) nor the multivariable adjusted relative risk of stroke (RR, 1.48; 95% CI, 0.70 to 3.12) were significantly elevated for women with RA compared with those without.

Compared with women without RA, those with RA for at least 10 years had an adjusted relative risk of myocardial infarction of 3.10 (95% CI, 1.64 to 5.87) and those with RA for <10 years had an adjusted relative risk of 1.16 (95% CI, 0.52 to 2.59). The relative risks associated with other aspects of RA were as follows: presence of a positive rheumatoid factor (RR, 2.20; 95% CI, 1.20 to 4.04), rheumatoid nodules (RR, 1.54; 95% CI, 0.38 to 6.22), and erosive changes on hand or foot radiographs (RR, 2.00; 95% CI, 0.82 to 4.85). Although none of these adjusted relative risks appear different than that for patients with RA in general, small numbers of patients with these factors limit our ability to make firm conclusions.

Discussion

In this prospective cohort study involving 114 342 women, we found that women with RA had a >2-fold higher risk of myocardial infarction but a similar risk of stroke compared with women without RA. This association remained after adjusting for known and potential cardiovascular risk factors. The relative risk of myocardial infarction that we observed in women with RA is similar to what has been reported in other epidemiologic studies.[7–9] However, the adjusted relative risk of stroke was not significantly elevated for women with RA. Although prior work has come to similar conclusions, unlike this study, none has simultaneously enrolled a community-

TABLE 2. Age-Adjusted and Multivariable Relative Risks for Cardiovascular End Points According to Presence of Rheumatoid Arthritis in Nurses' Health Study, 1977 to 1996

Cardiovascular End Point	Rheumatoid Arthritis	No Rheumatoid Arthritis	*P*
Person-years of follow-up	6259	2 381 418	...
Myocardial infarction			
Incidence/100 000 person-years	272	96	...
No. of cases	17	2279	...
Age-adjusted relative risk* (95% CI)	2.07 (1.28 to 3.34)	1.0	0.002
Multivariable relative risk† (95% CI)	2.00 (1.23 to 3.29)	1.0	0.005
Stroke			
Incidence/100 000 person-years	112	55	...
No. of cases	7	1319	...
Age-adjusted relative risk (95% CI)	1.47 (0.70 to 3.08)	1.0	0.31
Multivariable relative risk (95% CI)	1.48 (0.70 to 3.12)	1.0	0.31

*Relative risk compared with participants without rheumatoid arthritis. Adjusted for age in 5-year categories.

†Relative risk compared with participants without rheumatoid arthritis. Adjusted for age in 5-year categories, hypertension, diabetes, high cholesterol level, parental history of myocardial infarction before age 60 years, body mass index, cigarette use, physical activity, alcohol use, aspirin use, menopausal status, hormone replacement therapy use, oral glucocorticoid use, nonsteroidal antiinflammatory drug use, folate intake, omega-3 fatty acid intake, and vitamin E supplement intake.

based cohort rather than a referral population of more severely ill patients with RA; prospectively collected information on cardiovascular risks and outcomes; included a concurrent population of women without RA; controlled for important potential confounders such as body mass index, high blood pressure, elevated cholesterol, diabetes mellitus, and tobacco use; and conducted long-term follow-up.

What factors may underlie this increased risk of myocardial infarction for persons with RA? Inflammation has been long recognized as a hallmark of RA, and several lines of evidence now suggest that atherosclerosis also has an important inflammatory component.[10] Many of the cells comprising the inflammatory infiltrate in the joint lining are likewise found in atherosclerotic plaques.[12] Several investigators have shown that inflammatory markers typically elevated in RA, such as C-reactive protein, are higher before and at the time of ischemic injuries.[14–16] Additionally, methotrexate, a potent immunosuppressive, has been found to be associated with a reduced rate of cardiovascular mortality in patients with RA.[17]

Other possible links between RA and cardiovascular disease include the reduced physical activity often associated with RA, medications taken for RA, and differential use of cardiovascular prevention for patients with RA. Even after adjusting for the lower physical activity levels reported by participants with RA in this cohort, the risk of myocardial infarction was still elevated. The medicines used to treat RA, such as glucocorticoids,[25] methotrexate,[17,26] hydroxychloroquine,[27,28] and inhibitors of cyclooxygenase,[29] may induce or protect from thrombotic events or atherogenesis. We did control for the use of corticosteroids and nonsteroidal antiinflammatory drugs in these analyses, and the risk of myocardial infarction persisted in the group with RA. Finally, the complex nature of care for RA may impede strict adherence to recommended cardiovascular disease prevention activities.[30,31] We did perform a 2-year lag analysis to examine whether any acute changes in care around the time of RA diagnosis affected cardiovascular outcomes. Although these analyses yielded very similar results, additional studies will be required to understand whether the utilization rates of lipid-lowering drugs and other coronary heart disease prevention measures differ for participants with and without RA.

The results of the study must be interpreted within the limitations of the methodology. The information we had on the use of glucocorticoids and nonsteroidal antiinflammatory drugs was somewhat limited. Questions on these exposures were only added to the biennial questionnaire in 1994 and 1990, respectively, and precise information on dosage or duration of use is not available. We did not collect information in the biennial questionnaires or chart review on use of disease-modifying antirheumatic drugs and thus have no information on the use of other medications used to treat RA. We censored participants at the time of coronary revascularization or angina on the grounds that their care would be altered, thus affecting the relationship between RA and acute myocardial infarction. Because patients with RA may undergo coronary revascularization and report angina at lower rates than persons without RA (data not shown), it is possible that this may have allowed for longer follow-up and detection of more myocardial infarctions in persons with RA. We did not have information on inflammatory markers, such as C-reactive protein, in this data set and were unable to directly examine the role of such inflammatory markers on cardiovascular disease. Finally, there were relatively few women with a positive rheumatoid factor, rheumatoid nodules, or erosive changes on radiographs, and thus these results are based on small numbers.

RA should be recognized as a marker of increased risk for myocardial infarction. It is possible that the disease process underlying RA explains only part of its relationship with myocardial infarction and that the treatments for RA or the lack of adequate cardiovascular preventive care may contribute to the associated risk. We believe it would be prudent to consider aggressive cardiac preventive measures in patients with RA to address established coronary heart disease risk factors. In addition, it would be useful to examine whether early treatment of RA with disease-modifying antirheumatic drugs may reduce the future risk of myocardial infarction.

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