Declines in Mortality From Acute Myocardial Infarction in Successive Incidence and Birth Cohorts of Patients With Rheumatoid Arthritis

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Background—Patients with rheumatoid arthritis are at high risk for acute myocardial infarction (AMI). The treatment of rheumatoid arthritis has become more intensive over the past 2 decades, resulting in tighter control of inflammation and lower levels of disability. The impact of this on atherosclerotic cardiovascular diseases is not known.

Methods and Results—Death rates from AMI in a cohort of 3862 patients with rheumatoid arthritis followed up from 1980 to 1997 were studied. Time trends in AMI mortality among successive incidence and birth cohorts were examined by use of multivariable Poisson regression models and by comparing standardized mortality ratios. The mean age was 56 years in this predominantly female cohort (76%), and median disease duration was 6.5 years. During the period of observation, the use of methotrexate increased substantially, whereas that of prednisone was relatively stable. Over the 22 209 person-years of observation, there were 157 deaths as a result of AMI, with a death rate of 7.06 per 1000 person-years. Mortality rates were higher in older age groups and in men. After adjustment for age, sex, race, and disease duration, the risk of AMI declined in successive incidence years (relative risk, 0.94; 95% CI, 0.92 to 0.96). Patients with rheumatoid arthritis incident after 1990 did not have excess AMI mortality compared with general population. Declines in mortality trends were observed in successive birth cohorts as well.

Conclusions—Mortality as a result of AMI among patients with rheumatoid arthritis has declined over time. (Circulation. 2004;110:1774-1779.)

Key Words: myocardial infarction rheumatoid arthritis mortality risk trend

At one time, rheumatoid arthritis was considered a benign disease, and the mainstays of treatment were nonsteroidal antiinflammatory drugs and corticosteroids.1 Research in the 1970s and 1980s showed that rheumatoid arthritis is not a benign disease and that morbidity and mortality from this disease were high.2 Over the past 20 to 25 years, there has been a marked shift in the treatment approach to rheumatoid arthritis toward the widespread adoption of early, complete, and sustained control of inflammation as the therapeutic goal.3 This intensive strategy, likened to tight control of blood sugar in diabetics, has resulted in increased use of disease-modifying antirheumatic drugs in this period.4 Several studies have documented a substantial excess mortality in patients with rheumatoid arthritis from AMI and other cardiovascular diseases.5 It is possible that systemic inflammation in rheumatoid arthritis may lead to an acceleration of atherogenesis.5 If this thesis is accurate, the dramatic increases in the use of disease-modifying drugs and declines in functional disability that have been recorded in the past 20 years3 can be expected to have resulted in lower cumulative inflammatory damage in individual patients with rheumatoid arthritis and consequently a lower incidence of atherosclerosis and lower mortality as a result of AMI.

Although some studies have suggested a decline in overall mortality,6 trends in AMI mortality have not been well studied, perhaps because such studies require long-term observations of patients with confirmed diagnoses who have been followed up by use of consistent methodology. The data collected by the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS) since 1980 fulfill these requirements. Our hypotheses for this study were that AMI mortality has declined among patients with rheumatoid arthritis and that the magnitude of this mortality decline would be greater than that observed in the general population during this period.7

Methods

Study Subjects
We used prospective observational data from the ARAMIS cohort for this analysis. History and methodological details of this long-running study have been described elsewhere.8,9 This cohort study is based at Stanford University, with data collection locations in North America. Non-US data collection locations and US locations that are

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1774
not actively enrolling/following up patients were excluded from our analysis. We included data from 3862 patients meeting the American College of Rheumatology criteria for rheumatoid arthritis followed up from 1980 through 1997. 10,11 The ARAMIS study has the approval of the appropriate institutional review boards.

Follow-Up and Data Collection
After informed consent, patients completed a full Health Assessment Questionnaire (HAQ) at the time of their entry into the cohort and every 6 months thereafter. This questionnaire includes a disability instrument that computes a disability index (HAQ-DI) with values from zero to 3, 3 being the worst disability. A sample copy of the questionnaire can be viewed at http://aramis.stanford.edu. Cardiac risk factor data were missing for many patients, because they were not collected systematically. For each individual, the observation started at the date of completing the first questionnaire and was censored at the date of the outcome or cutoff date of the study (December 31, 1997), whichever was earlier.

Outcome Assessment
Death caused by AMI (International Classification of Diseases, Ninth Revision, was the outcome of interest. Patient death reports were sometimes obtained by questionnaires returned from the deceased patient’s family. In those instances, after consent, death certificates were obtained for further scrutiny by a physician to verify the causes of death. The National Death Index 15 was searched for deaths among the rest.

Statistical Methods
We used the Nelson-Aalen estimator to plot the overall risk of death as well as risk by strata of covariate of interest, progressing with time after onset of rheumatoid arthritis. 13 Log-rank tests were performed to test for differences in mortality risk. Mortality rates were calculated by dividing the number of events by person-years of observation. 14 Calendar year of symptom onset (incidence cohort) and calendar year of birth (birth cohort) were independent of calendar year of entering the study and were used as the time scales for testing trends.

The Mantel-Haenszel method was used to examine age/sex-adjusted trends. 15 In this method, odds ratios were calculated for each individual stratum of age and sex, and a pooled odds relative risk (Mantel-Haenszel relative risk) was calculated by a weighted average of each stratum.

We used Poisson multiple regression models that allow multivariable adjusted analyses adjusting for the effects of age, sex, disease duration, and other factors. These regressions are especially suited to analyze longitudinal, person-year data with mortality outcomes and calculate the relative risk of death of each succeeding time period compared with the earliest period. We fitted regressions with calendar year as a continuous variable after stratifying it into 3 groups: incidence before 1970, during 1970 to 1979, and on or after 1980.

Variance estimations for regression coefficients were obtained from the Huber-White sandwich estimator in place of the traditional calculation. 16 This method takes into account clustering of patients within database centers and calculates a conservative (wider) confidence interval (CI). Student’s t test and Pearson’s χ² tests were performed to assess differences in means and proportions.

To adjust for the effect of declining secular trends in AMI mortality rates in the general population, 7 we analyzed trends in standardized mortality ratios (SMRs). Calendar-year–specific general population rates of AMI mortality were applied to our cohort, obtaining the expected number of deaths. SMR is the unitless metric that is the ratio between the observed number of deaths in the cohort and the expected number of related deaths. The general population thus has an SMR of 1.00, and any SMR above this signifies an increased mortality risk in the population in question. The general population AMI mortality data were obtained from the National Center for Health Statistics (URL, http://www.cdc.gov/nchs/).

In addition to the above, we performed parallel analyses on our data using the year of birth as the variable of interest (birth cohort). In addition to being used as a continuous variable, the calendar year of birth was also stratified into 3 groups: before 1925, 1925 to 1938, and after 1938. These cutoffs were selected so as to ensure reasonably equal person-years of observation between the strata. Two-way interactions between calendar year variables, age, and disease duration (multiplicative effect modification) were tested for. Finally, extensive sensitivity analyses for undue influence by strata of disease duration and data collection center were also performed.

Results
Baseline Characteristics
At the time of first observation in the study (baseline), the mean age (SD) was 56 years (14 years), and disease duration was 9.7 years (9.7 years). Median disease duration was 6.5 years (interquartile range, 2 to 14 years). Thirty-two percent of patients were over the age 65 years. Approximately three fourths of the subjects were women (76%). Whites constituted 89% of the cohort. The mean number of years of education was 11.2 (4.9). At baseline, 26% (n = 1022) of the subjects were on methotrexate, and 63% (n = 2450) reported use of prednisone. None of the patients in this study cohort were exposed to biological agents. The median year of disease onset was 1981, with 25% of the subjects having rheumatoid arthritis onset in 1991 or later.

Outcomes
During the follow-up period of 22,209 person-years, 157 patients died of AMI. The crude mortality rate (95% CI) was 7.07 (6.05 to 8.27) per 1000 person-years. Table 1 shows the age- and sex-specific mortality rates. Substantial increases in death rates with age were noted among both men and women. Figure 1 shows the steady increase in risk of death from AMI after onset of rheumatoid arthritis. When calendar year–specific general population rates were applied to our cohort, 99 deaths from AMI were expected in the 22,209 person-years of observation, as opposed to the 208 that occurred. This represented an excess mortality among patients with rheumatoid arthritis with an SMR of 1.59 (1.36 to 1.86).

Incidence Cohort Analyses
We studied 3 incidence cohorts (<1970, 1970 to 1979, >1979). In these incidence cohorts, the numbers of AMI deaths were 46, 71, and 40, respectively (Table 2). Death rates declined during this period in both men and women. This represented an age/sex-adjusted Mantel-Haenszel relative risk of 0.73 (95% CI, 0.65 to 0.90).

Hazard curves for incidence cohorts showed an interesting pattern (Figure 2). In the first few years after diagnosis, mortality risk was similar in all 3 cohorts. At 5 years after diagnosis, patients with rheumatoid arthritis diagnosed in earlier periods started experiencing a higher risk of fatal AMI. At 15 years and later, the risk of AMI death remained substantially lower in the latest incidence cohort. The hazard curves were statistically significant by log-rank test.

Multivariable Poisson regressions with calendar year of incidence of rheumatoid arthritis as a continuous variable indicated a statistically significant relative risk of 0.92 (95% CI, 0.90 to 0.95). Table 3 gives the age, sex, race, and disease...
duration adjusted relative risks of death from AMI in the 3 periods. These indicate that compared with those who had rheumatoid arthritis onset before 1970, the risk of AMI declined by 33% in those who had the disease in the period 1970 to 1979 and by 67% in those who had the disease in and after 1980. These declines were independent of the trends in the general population, as evinced by declining SMRs. The SMR was 1.60 (1.20 to 2.14) in the 1970 group and 1.83 (1.45 to 2.30) in the 1980 to 1990 group. In the cohort of rheumatoid arthritis incident after 1980, the SMR was 1.3, with a CI including unity, suggesting a risk not statistically different from the general population.

**Birth Cohort Analyses**

Parallel analyses performed with calendar year of birth as the variable of interest showed a substantial decline in AMI death rates in later years. Among those born before 1924, the rate was 15.6 per 1000 (13.0 to 18.8); among those born between 1925 and 1938, it was 5.2 per 1000 (3.9 to 7.1); and among those born later than 1938, the rate was 0.4 (0.2 to 1.30). The Mantel-Haenszel age- and sex-adjusted relative risk was 0.91 (0.89 to 0.94).

In multivariable Poisson regressions adjusted for age, race, sex, and disease duration, the decline in risk of fatal AMI was statistically significant, with a relative risk of 0.9 (0.87 to 0.93).

Extensive sensitivity analyses and tests for interaction between databank centers and other covariates confirmed that the observed declines are robust. To test whether the declines in mortality were influenced by disease duration, stratified multivariable Poisson regressions were performed for all the tertiles of disease duration. A declining trend was seen for all the strata (Table 4). Finally, separate multivariable analyses were performed for each of the strata of the HAQ-DI (0 to 1, 1 to 1.9, 2.0 to 3.0). These showed a statistically significant decline in AMI risk for all levels of HAQ-DI.

**Trends in Medication Use**

The proportion of patients entering the study on methotrexate (considered a surrogate for aggressive disease-modifying

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**TABLE 1. Age- and Sex-Specific Mortality Rates From Acute Myocardial Infarction**

<table>
<thead>
<tr>
<th>Sex</th>
<th>Age, y</th>
<th>No. of Deaths</th>
<th>Person-Years of Observation</th>
<th>Rate/1000 Person-Years</th>
<th>95% Confidence Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;40</td>
<td>1</td>
<td>4.562</td>
<td>0.22</td>
<td>0.03 - 1.56</td>
</tr>
<tr>
<td>Women</td>
<td>40–49</td>
<td>6</td>
<td>5.547</td>
<td>1.08</td>
<td>0.49 - 2.41</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>27</td>
<td>7.611</td>
<td>3.55</td>
<td>2.43 - 5.17</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>44</td>
<td>7.373</td>
<td>5.97</td>
<td>4.44 - 8.02</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>45</td>
<td>3.489</td>
<td>13.00</td>
<td>9.63 - 17.00</td>
</tr>
<tr>
<td>Men</td>
<td>&lt;40</td>
<td>1</td>
<td>0.785</td>
<td>1.27</td>
<td>0.18 - 9.05</td>
</tr>
<tr>
<td></td>
<td>40–49</td>
<td>3</td>
<td>1.361</td>
<td>2.20</td>
<td>0.71 - 6.84</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>21</td>
<td>2.282</td>
<td>9.20</td>
<td>6.00 - 14.00</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>30</td>
<td>2.377</td>
<td>13.00</td>
<td>8.82 - 18.00</td>
</tr>
<tr>
<td></td>
<td>≥70</td>
<td>27</td>
<td>1.282</td>
<td>21.00</td>
<td>14.00 - 31.00</td>
</tr>
</tbody>
</table>

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**Figure 1.** Increasing risk of fatal AMI after onset of rheumatoid arthritis (157 deaths in 22,209 person-years).
treatment) substantially increased in successive incidence cohorts (11%, 25%, and 37%, trend-test $P<0.05$). The use of prednisone, however, remained steady during this period (65%, 65%, and 61%, $P=0.81$).

**Discussion**

This study demonstrates for the first time that the AMI mortality risk among patients with rheumatoid arthritis has been declining over time, independently of age, sex, race, and disease duration. Similar annual declines were observed with each succeeding birth cohort. The decline in AMI risk in rheumatoid arthritis patients is greater in magnitude compared with the decline in AMI mortality rates in the US general population, suggesting possible gains resulting from improving healthcare of these patients.7 Although our estimate of elevated risk of AMI is similar to many other reports 17–29 and fits in with the reports of declining overall mortality from Europe,6,30 some US-based studies have not recorded improvements in total mortality in rheumatoid arthritis.31

The role of inflammation in AMI has been well described.32,33 Lower levels of inflammation, in turn, are known to be associated with lower risk of atherosclerosis and thereby lower incidence of AMI.34 Relatively small changes in blood pressure associated with the use of common nonsteroidal antiinflammatory drugs can have a significant effect on the cardiovascular risk profile.35 In addition, some disease-modifying antirheumatic drugs can directly improve lipid profile and reduce use of nonsteroidal antiinflammatory drugs.36 Active rheumatoid arthritis is associated with an adverse lipid profile that improves substantially with aggressive treatment.37 Effective suppression of disease activity (ie, inflammation) with a number of disease-modifying antirheumatic drugs has been observed to be associated with decreased mortality, especially from AMI.37,38 A recent empirical study suggested a substantial reduction of AMI with use of methotrexate,37 an agent whose use in our cohort has shown dramatic increases over the period of observation. We also observed increased use of methotrexate and declining risk of acute myocardial infarction. However, because of potential “confounding by indication,” one cannot attribute causality to this association.

Another possibility is that improvements in functional status in our cohort over time3 might have facilitated higher levels of physical activity and thereby decreased risk profile for AMI. However, declines in AMI mortality were found among all levels of functional disability. Increasing recognition of rheumatoid arthritis as a risk factor may have led to better medical management of high-risk patients with AMI, with the resultant mortality reduction, but a test of this hypothesis would require an analysis of case-fatality rates.

### TABLE 2. Time Trends in AMI by Year of Symptom Onset

<table>
<thead>
<tr>
<th>Calendar Year of Symptom Onset</th>
<th>No. of Deaths</th>
<th>Person-Years</th>
<th>Rate/1000 Person-Years (95% CI)</th>
<th>Mantel-Haenszel Age-/Sex-Adjusted Relative Risk (95% CI)</th>
<th>Standardized Mortality Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before 1970</td>
<td>46</td>
<td>5133</td>
<td>8.96 (6.71–11.96)</td>
<td>0.73 (0.60–0.90)</td>
<td>1.60 (1.20–2.14)</td>
</tr>
<tr>
<td>1970–1979</td>
<td>71</td>
<td>8601</td>
<td>8.26 (6.54–10.42)</td>
<td>1.83 (1.45–2.30)</td>
<td></td>
</tr>
<tr>
<td>On or after 1980</td>
<td>40</td>
<td>8475</td>
<td>4.72 (3.46–6.43)</td>
<td>1.28 (0.94–1.75)</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Comparing risk of fatal AMI after disease onset in successive incidence cohorts of rheumatoid arthritis (157 deaths in 22 209 person-years).
Several potential limitations of this study merit discussion. Risk factor data, if available to us, would have allowed analysis of complex time-variant interplay between disease activity, drugs, and risk factors. Second, our patient population was primarily from rheumatology practices, a source likely to involve individuals with more severe rheumatoid arthritis than those in the general community. The mean disease duration was 10 years, and median duration was 6.5 years. Nevertheless, we had sufficient numbers of patients in all strata of disease duration as well as functional disability to perform valid subgroup analyses.

In a longitudinal study like ours, in which consecutive patients are recruited in a rolling fashion, time trends could potentially be confounded by left censoring, leading to noninclusion of patients with aggressive disease course and early deaths. It can also be argued that the trends we observed reflect the referral pattern. We believe that these concerns do not apply here, because the mortality decline was evident in successive incidence and birth cohorts, the 2 time scales that do not necessarily correlate with time of enrollment. In addition, potential confounding effect modification by disease duration was adjusted for by multivariable modeling as well as stratified analyses.

Socioeconomic conditions can influence access to health care, an important determinant of fatality from AMI. Approximately 1 in 6 people with rheumatoid arthritis in the United States have poor or no access to medical care.

In our analyses, we have adjusted for race, a marker of socioeconomic status. Our risk estimates were adjusted for the effects of databank center, thereby minimizing the confounding effect of health disparities associated with geographical region.

In conclusion, our study provides epidemiological evidence of decreasing mortality from AMI in rheumatoid arthritis patients. Whether the observed mortality gains in our cohort of patients motivated to be a part of research are shared by all patients with rheumatoid arthritis in the United States needs to be addressed by studies based on large population-based data sets. Further research is needed to study trends in mortality from other cardiovascular causes, such as stroke and congestive heart failure.

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