CONCISE REPORT

Increased incidence of and impaired prognosis after acute myocardial infarction among patients with seropositive rheumatoid arthritis

Anna Södergren, Birgitta Stegmayr, Vivan Lundberg, Marie-Louise Öhman, Solveig Wållberg-Jonsson

Ann Rheum Dis 2007;66:263–266. doi: 10.1136/ard.2006.052456

Objective: To examine the incidence and outcome of acute myocardial infarction (AMI) in patients with rheumatoid arthritis compared with the general population, and to examine whether care and treatment of an AMI differs between patients and controls.

Methods: The Multinational Monitoring of Trends and Determinants of Cardiovascular Disease register for northern Sweden was used to compare those incidences of AMI in a cohort of patients with rheumatoid arthritis with that in the general population. 35 patients with rheumatoid arthritis who had also experienced an AMI were identified. For each patient with rheumatoid arthritis, three controls with a history of AMI but without rheumatoid arthritis were randomly selected from the same register, and matched for age, sex and year of the AMI for evaluation of case fatality and potential differences in treatment of AMI.

Results: The standardised incidence ratio for AMI was 2.9 in patients with rheumatoid arthritis compared with the general population ($p < 0.05$). During the first 10 years after an AMI, patients with rheumatoid arthritis had a higher overall case fatality compared with controls (hazard ratio (HR) 1.67, 95% confidence interval (CI) 1.02 to 2.71). Survival time was decreased in the rheumatoid arthritis group compared with controls despite the same care and treatment.

Conclusion: Both the incidence of and case fatality after an AMI were higher among patients with rheumatoid arthritis than among the general population. The results emphasise the necessity of optimising the preventive, diagnostic and caring strategies for AMI in rheumatoid arthritis.

Mortality^{1–3} and morbidity^{1,4,5} due to cardiovascular disease (CVD) is increased among patients with rheumatoid arthritis. Traditionally accepted cardiovascular risk factors cannot fully explain this observation^{1,3,4,6–8}; however, the inflammatory reaction is considered important in both patients with rheumatoid arthritis^{6–8} and the general population.⁹ Furthermore it is not known whether the increased mortality due to CVD among patients with rheumatoid arthritis is due to a higher incidence of CVD events or due to a higher case fatality.

Population-based data on CVD events are collected continuously in northern Sweden within the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) project.¹⁰ This offers an opportunity to undertake prognosis studies after a CVD event in various patient categories.

The aims of the present study were, firstly, to examine the incidence and outcome of acute myocardial infarction (AMI) in

patients with rheumatoid arthritis compared with the general population, and, secondly, whether care and treatment of an AMI differs between patients and controls.

PATIENTS AND METHODS

The patient cohort comprised all individuals ($n = 640$; 435 females, 205 males) registered with seropositive rheumatoid arthritis¹¹ at the Department of Rheumatology, University Hospital, Umeå, Sweden, in 1979, with a reference population of 250 000.^{1,7}

The northern Sweden MONICA register has been recording all cases of AMI in Västerbotten and Norrbotten since 1985.¹⁰ The protocol requires the inclusion of all incident AMIs and recording of variables reflecting risk factors, care and treatment during the AMI and at discharge from hospital. Thus, recording of an AMI, together with all other designated variables, was undertaken in exactly the same way for all individuals, with or without rheumatoid arthritis. In the MONICA project, diagnosis of an AMI is based on symptoms, electrocardiogram (ECG) and levels of cardiac enzymes due to strict criteria.¹⁰

Only patients from Västerbotten were included in the present study, resulting in a total of 5368 validated AMI events between 1985 and 2003. From the rheumatoid arthritis cohort, 35 patients with an incident AMI were identified within the MONICA project. For each patient with rheumatoid arthritis with AMI, three age-matched and sex-matched controls with AMI but without rheumatoid arthritis were randomly selected from the MONICA register. The patients and controls were matched for year of AMI event (≤ 3 years difference) to minimise time-related treatment effects. Table 1 gives the demographic data.

To estimate the outcome, the survival time after an AMI was identified. Variables associated with the AMI—that is, time between onset of symptoms and medical intervention, ECG findings, admittance to the intensive care unit (ICU), duration of hospitalisation, cardioprotective drugs (ie, β antagonists, nitroglycerine, antiplatelet drugs, diuretics, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors) during and after hospitalisation, and previous AMIs, hypertension or diabetes mellitus—were also identified. Information regarding lipid levels was unavailable, while that on smoking was incomplete. Only data related to the first AMI occurring during the study period were used.

The standardised incidence ratio (SIR) for an AMI—that is, the ratio of the observed incidence of AMI in the rheumatoid

Abbreviations: AMI, acute myocardial infarction; CVD, cardiovascular disease; ECG, electrocardiogram; ICU, intensive care unit; MONICA, Multinational Monitoring of Trends and Determinants of Cardiovascular Disease; SIR, standardised incidence ratio

Table 1 Demographic data, traditional cardiovascular risk factors and pharmacological treatment

Variable	RA (n=35)	Controls (n=105)
Females*	17 (48.6)	51 (48.6)
Age at AMI (years)†	61 (58, 63)	62 (59, 64)
Year of AMI†	1990 (1986, 1996)	1990 (1989, 1996)
Diabetes mellitus*	6 (20.7)	16 (20.3)
Antihypertensive treatment*	10 (40.0)	55 (58.5)
AMI before 1985*	8 (22.9)	12 (11.9)
Corticosteroids ≥ 1 year*	21 (60)	—
DMARDs ≥ 6 months*	31 (89)	—

AMI, acute myocardial infarction; DMARDs, disease-modifying anti-rheumatic drugs; RA, rheumatoid arthritis.

*Number of individuals (percentage of individuals for whom data were available).

†Median (Q1, Q3).

arthritis cohort to that expected according to the crude AMI incidence of the whole MONICA register, based on age-adjusted, sex-adjusted and year-adjusted rates in the general population of Västerbotten—was calculated by means of the Poisson distribution.

Survivorship functions were estimated by the product limit (Kaplan–Meier) estimator, followed by the log-rank test, for all patients with rheumatoid arthritis and AMI. Survivorship functions were also estimated for the group of patients with rheumatoid arthritis and controls who had not experienced an AMI before 1985.

Simple and multiple stratified (ie, with and without rheumatoid arthritis) Cox proportional hazards regression models were used to identify covariates for survival. Likelihood ratio tests, together with clinical assumptions, determined which covariates were included. *p* Values <0.05 were considered as significant.

RESULTS

In the rheumatoid arthritis cohort, SIR for AMI was 2.9 (95% confidence interval (CI) 1.9 to 4.1), being 3.2 (95% CI 1.7 to 5.4) for women and 2.67 (95% CI 1.6 to 4.3) for men.

Overall, patients with rheumatoid arthritis had a higher risk of dying after an AMI than controls during the whole follow-up period (HR 1.7, 95% CI 1.1 to 2.7, fig 1A). During the first 10 years, the case fatality was significantly increased in patients with rheumatoid arthritis (HR 1.67, 95% CI (1.02 to 2.71); however, there were no significant differences in survival after 24 h (HR 1.26, *p* = 0.58), 28 days (HR 1.43, *p* = 0.27) or 5 years (HR 1.56, *p* = 0.11). When patients without a previous AMI were considered, survival for the study period remained significantly decreased compared with controls (fig 1A). Consequently, all patients with rheumatoid arthritis and controls were included in all subsequent calculations.

In simple Cox regression analyses, stratified for rheumatoid arthritis, previous antihypertensive treatment, ICU care, duration of hospitalisation, previous AMI and treatment with β antagonists or anti-platelet drugs during/after hospitalisation showed a statistically significant relationship with case fatality after the first AMI (table 2).

All patients and controls had a definite AMI according to the MONICA criteria,¹⁰ but on arrival to hospital the patients with rheumatoid arthritis had typical ECG signs less often than controls—that is, 6 (17.1%) patients with rheumatoid arthritis versus 36 (34.3%) controls. The proportion of individuals admitted to an ICU was 69.7% for rheumatoid arthritis and 71.9% for controls. Numerically, fewer patients with rheumatoid arthritis received treatment with cardioprotective drugs

Figure 1 Estimated survival (A) after onset of an acute myocardial infarction (AMI) (B) given admittance to an intensive care unit, hospitalisation for 6 days (median value) and treatment with β antagonists and antiplatelet drugs during or after hospitalisation. *All patients taken into account. †Only patients without AMI before 1985 taken into account. Md, median survival time.

during and after hospitalisation although the differences did not reach statistical significance (data not shown).

In an estimated multiple stratified Cox regression analysis, patients not treated with β antagonists or anti-platelet drugs during/after hospitalisation, not admitted to an ICU, and having a shorter hospitalisation, had a higher overall case fatality (table 2). Inclusion of previous AMI, hypertension or diabetes mellitus had no effect on this model.

Figure 1B shows the prognosis after an AMI for patients with rheumatoid arthritis and controls, given they had received the same care and treatment.

Table 2 Estimated hazard ratio and p values for simple and multiple stratified Cox regression analyses

Variable	Simple			Multiple		
	HR	95% CI	p Value	HR	95% CI	p Value
Antihypertensive treatment	1.8/+	1.1 to 3.1	<0.05			
Diabetes mellitus	0.95/+	NS				
Previous AMI	1.88	1.05 to 3.30	<0.05			
ICU	3.05/–	1.76 to 5.31	<0.001	2.94/–	1.62 to 5.35	<0.001*
Duration of hospitalisation	0.93/day	0.88 to 0.98	<0.01	0.95/day	0.91 to 0.99	<0.05*
β antagonists†	5.03/–	3.10 to 8.15	<0.001	3.45/–	1.88 to 6.32	<0.001*
Anti-platelet drugs†	3.83/–	2.34 to 6.25	<0.001	2.78/–	1.53 to 5.05	<0.001*

AMI, acute myocardial infarction; ICU, intensive care unit.

Case fatality after the first AMI during the study period was the response variable in all analyses.

*Adjusted for the other variables in the model.

†Treatment during hospitalisation and/or at discharge.

DISCUSSION

Patients with rheumatoid arthritis showed a more than twofold greater incidence of AMI than expected. This is consistent with recent reports.^{4,5} After 10 years, as well as throughout the whole follow-up period after an AMI, patients with rheumatoid arthritis had a higher case fatality than controls, with a HR of about 1.5. The overall mortality among patients with rheumatoid arthritis is approximately 1.5 times that of the general population in community-based studies.^{1,2} This may be explained by the fact that CVD is the major cause of death among patients with rheumatoid arthritis.^{1,3} In a recent abstract, case fatality after AMI in rheumatoid arthritis approached that of diabetes mellitus.¹²

Compared with controls, survival after an AMI was poorer in patients with rheumatoid arthritis despite the same care and treatment (fig 1B), indicating that factors related to rheumatoid arthritis per se are important for survival. Several studies indicate that most traditional cardiovascular risk factors are not particularly prominent in rheumatoid arthritis.^{1,3,4,6–8} The inflammatory reaction has predictive importance for cardiovascular morbidity in rheumatoid arthritis.^{6–8} An improved survival, overall and after CVD, after disease modifying anti-rheumatic treatment has also been reported.⁷ Furthermore, a positive effect of reduced inflammation after modern anti-rheumatic treatment is implicated by the time-related decline of AMI mortality in rheumatoid arthritis.¹³ Unfortunately, variables reflecting disease activity were not recorded in the MONICA survey and could not be evaluated in the present study.

A non-statistically significant difference was seen for treatment with cardioprotective drugs, with somewhat lower numbers for the rheumatoid arthritis group. It is plausible that doctors hesitate to prescribe further pharmaceutical treatment to patients with rheumatoid arthritis already prescribed disease modifying anti-rheumatic drugs or non-steroidal anti-inflammatory drugs.³ A British study reported that patients with rheumatoid arthritis and an AMI were less likely to receive thrombolytic treatment.¹⁴ Furthermore, as pain is common in rheumatoid arthritis, the chest pain may be regarded differently. If then the ECG is atypical, an AMI may be inadvertently overlooked. In other studies, patients with rheumatoid arthritis more often presented with atypical AMI manifestations⁸ and were more likely to experience a silent AMI and sudden death^{8,15} compared with individuals without rheumatoid arthritis. These results resemble those for patients with diabetes mellitus in whom clinically silent CVD is relatively common.¹⁶

A strength of this study is that, in 1979, our clinic was the only reference centre for patients with rheumatoid arthritis in Västerbotten County.⁷ Consequently, our cohort would be very close to the prevalent seropositive adult population with

rheumatoid arthritis in the county at that time. Furthermore, albeit analysing recorded data retrospectively, the MONICA register of northern Sweden¹⁰ identifies all patients with suspect AMI according to the World Health Organization criteria. This gave a unique opportunity to compare the incidences of, and the outcome after, AMIs for patients with rheumatoid arthritis and controls in a community-based manner.

The main limitation of this study is that the number of patients with rheumatoid arthritis undergoing an AMI is small; consequently, there may be insufficient data to reach statistical significance when comparing patients with rheumatoid arthritis and controls. Within the incidence study, the rheumatoid arthritis cohort was identified in 1979, whereas the registration of AMIs did not start until 1985. Theoretically, premature deaths among the patients with rheumatoid arthritis may have shifted the rheumatoid arthritis cohort towards a relatively milder disease state before registration began. This would, however, only have diluted the increased incidence of AMI actually shown.

Our study indicates that the increased mortality in patients with rheumatoid arthritis is due to a higher incidence of, as well as a higher case fatality after, AMIs. The results emphasise the necessity of optimising the preventive, diagnostic and caring strategies for AMI in rheumatoid arthritis, and elucidate the importance of factors related to the rheumatoid arthritis disease itself, such as inflammatory activity, for survival after an AMI.

ACKNOWLEDGEMENTS

We thank Elsy Westerberg and Salmir Nasic at the MONICA office for excellent work with the collection and compilation of patient data. We also thank Gun-Britt Johansson at the Department for Rheumatology for excellent help with collection of patient data.

Authors' affiliations

A Södergren, S Wällberg-Jonsson, Department of Public Health and Clinical Medicine, Rheumatology, University Hospital, Umeå, Sweden

B Stegmayr, Department of Public Health and Clinical Medicine, Medicine, University Hospital, Umeå, Sweden

V Lundberg, Department of Medicine, Kalix Hospital, Kalix, Sweden

M-L Öhman, Department of Statistics, University of Umeå, Umeå, Sweden

Funding: This work was supported by grants from the Swedish Research Council (K 2003-74XD-14705-01A and 345-2003-2461), the Swedish Rheumatism Association, the Swedish Heart-Lung Foundation, King Gustaf V 80th Anniversary, and King Gustaf V and Queen Viktoria Foundations, as well as the Swedish Society of Medicine.

Competing interests: None.

Ethical approval: The study was approved by the local ethics committee of Umeå University, Umeå, Sweden.

Correspondence to: A Södergren, Department of Rheumatology, University Hospital, 901 85 Umeå, Sweden; anna.sodergren@medicin.umu.se

Accepted 10 July 2006

Published Online First 19 July 2006

REFERENCES

- 1 **Wällberg-Jonsson S**, Öhman M-L, Rantapää Dahlqvist S. Cardiovascular morbidity and mortality in patients with seropositive rheumatoid arthritis in northern Sweden. *J Rheumatol* 1997;**24**:445–51.
- 2 **Wolfe F**, Mitchell DM, Sibley JT, Fries JF, Bloch DA, Williams CA, et al. The mortality of rheumatoid arthritis. *Arthritis Rheum* 1994;**37**:481–94.
- 3 **Boers M**, Dijkmans B, Gabriel S, Maradit-Kremers H, O'Dell J, Pincus T. Making an impact on mortality in rheumatoid arthritis: targeting cardiovascular comorbidity. *Arthritis Rheum* 2004;**50**:1734–9.
- 4 **del Rincón I**, Williams K, Stern MP, Freeman GL, Escalante A. High incidence of cardiovascular event in a rheumatoid arthritis cohort not explained by traditional cardiac risk factors. *Arthritis Rheum* 2001;**12**:2737–45.
- 5 **Turesson C**, Jarenros A, Jacobson L. Increased incidence of cardiovascular disease in patients with rheumatoid arthritis: results from a community based study. *Ann Rheum Dis* 2004;**63**:952–5.
- 6 **Maradit-Kremers H**, Nicola PJ, Crowson CS, Ballman KV, Gabriel SE. Cardiovascular death in rheumatoid arthritis. *Arthritis Rheum* 2005;**52**:722–32.
- 7 **Wällberg-Jonsson S**, Johansson H, Öhman ML, Rantapää-Dahlqvist S. Extent of inflammation predicts cardiovascular disease and overall mortality in seropositive rheumatoid arthritis. A retrospective cohort study from disease onset. *J Rheumatol* 1999;**12**:2562–71.
- 8 **Douglas KM**, Pace AV, Trehan GJ, Saratzis A, Nightingale P, Erb N, et al. Excess recurrent cardiac events in rheumatoid arthritis patients with acute coronary syndrome. *Ann Rheum Dis* 2006;**65**:348–53.
- 9 **Ridker PM**. High-sensitivity C-reactive protein. Potential adjunct for global risk assessment in the primary prevention of cardiovascular disease. *Circulation* 2001;**103**:1813–18.
- 10 **Stegmayr B**, Lundberg V, Asplund K. The events registration and survey procedures in the Northern Sweden MONICA project. *Scand J Public Health* 2003;**31**(Suppl 61):9–17.
- 11 **Ropes MW**, Bennet GA, Cobb S. Diagnostic criteria for rheumatoid arthritis. *Ann Rheum Dis* 1959;**18**:49–53.
- 12 **Singh G**, Mithai A, Mendelsohn A, Tridafilopoulos G. Acute myocardial infarctions in rheumatoid arthritis and diabetes: a tale of two diseases and a call for action [abstract]. *Ann Rheum Dis* 2004;**63**(Suppl):OP0037.
- 13 **Krishnan E**, Lingala VB, Singh G. Declines in mortality from acute myocardial infarction in successive incidence and birth cohorts of patients with rheumatoid arthritis. *Circulation* 2004, **110**:1774–9.
- 14 **Goodson NJ**, Lynch MP, Hardy K. A comparison of treatment and early outcome of acute myocardial infarction in rheumatoid arthritis patients and a non-rheumatic control group [abstract]. XIV European League Against Rheumatism Congress, 1999, Glasgow, UK. *Ann Rheum Dis* 1999;(Suppl):61.
- 15 **Maradit-Kremers H**, Crowson CS, Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased unrecognized coronary heart disease in rheumatoid arthritis: a population-based cohort study. *Arthritis Rheum* 2005;**52**:402–11.
- 16 **Almeda FQ**, Kason TT, Nathan S, Kavinsky CJ. Silent myocardial ischemia: concepts and controversies. *Am J Med* 2004;**116**:112–18.