Trend in and predictors for cardiovascular mortality in patients with rheumatoid arthritis over a period of 15 years: a prospective cohort study

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Abstract

Objective

To investigate a) the cardiovascular (CV) mortality in a clinical cohort of patients with established rheumatoid arthritis (RA) in comparison with the general population over 15 years, b) the trend in this CV mortality during the study period, and c) for a broad range of predictors, which baseline variables predict CV mortality.

Methods

In 1997, a sample of 1222 patients was randomly selected from the register of a rheumatology outpatient clinic in Amsterdam. Their CV mortality between 1997 and 2012 was obtained from Statistics Netherlands. The standardised mortality ratio (SMR) for CV mortality was calculated. A linear poisson regression analysis was performed to investigate if there was a trend in SMR over time. A Cox regression analysis was performed to determine which baseline variables predicted CV mortality.

Results

Mean age of the population at baseline was 60.4 (SD 15.4) years and 72.6% of the patients were women. Estimated SMR (95% confidence interval) for CV mortality was 1.24 (1.05, 1.43). The SMR decreased with 3% annually (p=0.16). Higher age, higher erythrocyte sedimentation rate, having CV comorbidity and diabetes mellitus (DM) were predictors for CV mortality.

Conclusion

CV mortality among patients with RA in the past 15 years was still higher than in the general population. CV mortality decrease was not statistically significant. As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are advocated.

Key words

rheumatoid arthritis, mortality, cardiovascular, cohort study, longitudinal studies, comorbidity

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Introduction

Patients with rheumatoid arthritis (RA) have a higher mortality risk compared with the general population (1). This higher mortality risk is mainly attributable to cardiovascular (CV) diseases (2-7). The CV mortality risk seems to be about 50% higher than in the general population (8). The higher CV mortality risk in RA is caused both by traditional CV risk factors (such as smoking, hypertension and dyslipidaemia), which occur more frequent in patients with RA, and the underlying chronic inflammatory process (9, 10, 11). A population-based study in individuals from Northern Spain performed in the past decade disclosed that chronic inflammation, expressed by the mean CRP and ESR over an extended follow-up, was associated with increased cardiovascular mortality in patients with RA (12). Inflammation plays an important role in atherosclerosis and amplifies some traditional CV risk factors such as dyslipidaemia, obesity and insulin resistance (13-16). Besides traditional CV risk factors and chronic inflammation, a genetic component may also explain the increased rate of cardiovascular disease observed in patients with RA (12, 17).

Time trends in CV mortality have been studied less. Studies investigated trends in all-cause mortality (18-20). However, only one meta-analysis investigated the trend in CV mortality between 1945–1995 and found no change in CV mortality rate (21). Nevertheless, recent years have witnessed the introduction of tight disease control and of more intensive treatment consisting of high dose treatment with disease-modifying anti-rheumatic drugs (DMARDs) from the 1990s onwards and the introduction of biologicals after 2000 (22, 23). Moreover, the increased CV risk in patients with RA is nowadays widely acknowledged and thus the need for CV risk management (24, 25). These improvements in medical care may have resulted in lower CV mortality.

Demographic as well as clinical and functional variables predict CV mortality. Age, gender and socioeconomic status (SES) predict CV mortality both in the general population and in patients with RA (9). Likewise, disease activity markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) level and Disease Activity Score in 28 joints (DAS28) (2, 10, 26), disease duration (27), comorbidities (CV disease, hypertension, diabetes mellitus (DM) (9, 10)) and physical functioning predict CV mortality in RA (7, 26). Until now, the impact of these variables on CV mortality has been studied separately and not in combination. A EULAR task force for CV risk management noted this unmet need and advocated to study for a broad range of variables the combined contribution (demographic, as well as inflammatory, and traditional risk factors) to CV mortality in patients with RA in large prospective cohort studies (24).

The aims of this study were:

a) to investigate the CV mortality in a clinical cohort of patients with established RA in comparison with the general population over 15 years;

b) to study the trend in CV mortality in these patients during the study period;

c) to investigate a broad range of predictors, whose baseline variables predict CV mortality in patients with established RA.

Patients and methods

Study design and population

In 1997, our research group started a cohort study on health outcomes in patients with RA (28). A sample of 1222 patients was randomly selected from the register of a large rheumatology outpatient clinic in Amsterdam, which included the patients from seven allied outpatient clinics. For inclusion in the study, patients had to fulfil the following eligibility criteria:

a) being diagnosed with RA according to the American College of Rheumatology (ACR) Criteria for RA (29);

b) being 16 years of age or older;

c) having sufficient command of the Dutch language;

d) having visited a rheumatologist at least once in the previous two years.

Data were collected by means of self-administered questionnaires (30), which comprised questions about socio-demographic characteristics (age, gender, marital status, educational level, em-

ployment status and living situation), clinical characteristics (pain, comorbidity), functional characteristics (disability and quality of life), health characteristics and the utilisation of health-care services. In addition, with respect to the clinical characteristics, information on disease duration and rheumatoid factor were retrieved from the patients' medical records, and disease activity was assessed during clinical examination at baseline. All participants provided written informed consent. The study was approved by the Reade/Slotervaart Institutional Review Board.

Assessments

Cardiovascular mortality

All patients were linked to Statistics Netherlands' mortality records for the period 1997–2012 (31). The Statistics Netherlands' databank provides death/life status, death dates, and primary and secondary causes of death. We used the primary cause of death of the category 'diseases of the circulatory system' (31). The primary cause of death is defined as the underlying cause of death, which starts a sequence that finally results in death. The linkage of the patients to the mortality data was anonymous, using only date of birth, gender, and, if available, civil registration number, and was performed by staff of Statistics Netherlands (32). In order to compare patients with the general population, age and gender specific CV mortality data for the general population were provided by Statistics Netherlands (33).

Predictors

Sociodemographic, clinical and functional variables were investigated. Variables were selected which are known to be associated with CV mortality (2, 9, 10, 26) or all-cause mortality in patients with RA (7, 34, 35, 36).

Sociodemographic variables

The sociodemographic variables include age, gender and SES. SES was indicated by educational level. We divided SES into 3 categories: low SES (no education or education at the primary school level), medium SES (education at the secondary school level); and high SES (college or university level education).

Clinical variables

The clinical measures include ESR, DAS28, disease duration, rheumatoid factor, pain, CV comorbidity, hypertension and DM. Disease activity was assessed by means of the ESR and the DAS28, scoring separately swelling and tenderness of 28 joints (and without using the visual analogue scale for general health assessment). Disease duration was computed using the date of RA diagnosis, which was retrieved from the patient's medical record. Information about rheumatoid factors was abstracted from the patient's records. Pain was measured with the Visual Analogue Scale (VAS), ranging from no pain at all to pain as bad as it could be. CV comorbidity, hypertension and DM were measured with a self-report list adapted from the Health Interview Survey of Statistics Netherlands, a validated list amenable to self-reporting (37). Patients were asked to indicate whether they had had the condition in the previous 12 months. CV comorbidity included myocardial infarction, any other serious heart disorders, or stroke. Respondents indicating the presence of at least one or more conditions were classified as having CV comorbidity.

Functional variables

Physical functioning was measured with the validated Dutch version of the Health Assessment Questionnaire (HAQ) and the physical scales of the Dutch version of the RAND-36 (38). The HAQ category score was raised when aids or devices were indicated by the patient. Mental functioning was measured with the mental scales of the Dutch version of the RAND-36. A Physical Component Scale (PCS) and a Mental Component Scale (MCS) were calculated according to the manual for SF-36 health summary scales (39), using Dutch population means, standard deviations and factor score coefficients (40).

Statistical analyses

The standardised mortality ratio (SMR) was computed to compare the CV mortality in the RA cohort with the general population. The SMR is the ratio of the number of observed deaths in a study population divided by the number of expected deaths in the case where the study population would have had the same age, gender, and calendar year specific mortality rates as the general population. We calculated the SMR for CV mortality, for each year, the mean of 3 years, the mean of 5 years, and the mean of all 15 years. Ninety-five percent confidence intervals were calculated using Byar's approximation.

Linear poisson regression analysis was performed to determine if there was a trend towards an increase or decrease in the SMR over time (41). The 1997 data were excluded from the calculation of the mean SMR and the regression analysis, because the precise date of inclusion in the cohort, and thus the amount of persontime in this year was not known.

To answer the first (CV mortality) and second research question (trend in CV mortality), the 1222 patients who were selected at baseline were linked to Statistics Netherlands. No information about CV mortality could be obtained for 14 patients and therefore, these patients were excluded. Hence, data of 1208 out of 1222 patients (99%) were used for the analyses.

To determine which baseline predictors were associated with CV mortality, we performed a Cox regression analysis. The outcome measure was CV mortality as primary cause of death (32). Patients who died from other causes of death were considered as censored. First, univariate analyses for each variable were performed. Second, variables for a multivariate analysis were selected using backward selection excluding variables with p-values >.05. All models were adjusted for age and gender. Including multiple risk factors in the model increases the risk for multicollinearity. The only variables that were highly correlated were physical functioning measured with the HAQ and measured with the SF-36. Removing one of these variables from the model did not change the results. Multiple imputation was used to handle missing baseline values. All analyses were carried out using SPSS, version 20.0.

To answer the third research question (predictors for CV mortality) data of

patients who responded to the questionnaire were used. A previous study in the same cohort investigated predictors for (non-) response through a telephone interview of the non-respondents. Patients who responded to the questionnaire reported less pain and were using more often additional health care than patients who did not respond, whereas ESR, disease duration, comorbidity and physical functioning were not different in both groups. Of the patients who were selected at baseline, 882 returned the questionnaire in 1997 and for this number of patients baseline predictor variables were available. Out of these 882 patients, 876 could be linked to the Statistics Netherlands and 6 patients were excluded from the analyses, because mortality data was not available

Results

Study population

Mean age at baseline of the 1208 patients (first and second research question) was 60.4 (SD 15.4) years and 73% of the patients were women. A total number of 172 (out of 1208) patients died due to CV disease as the primary cause of death during the study period.

Mean age at baseline of the 882 patients (third research question) was 59.3 (SD 14.8) years, 72% were women, median disease duration was 5.0 (IQR 2.0–14.0) years, the mean DAS28 score was 3.6 (SD 1.3), and the mean HAQ score was 1.14 (SD 0.80) (Table I). A total number of 117 (out of 876) patients died due to CV disease during the study period.

Cardiovascular mortality

The estimated SMR (95% confidence interval) for CV mortality was 1.24 (1.06, 1.45) over the period of 15 years, which indicates a 24% higher risk of CV mortality compared with the general Dutch population.

Trend in cardiovascular mortality

Figure 1 shows the annual SMR. Table II shows the mean SMR for CV mortality over 3 and 5 years intervals, and over the total study period. The outcome of the regression analysis showed that the SMR decreased with 3% annually, but the decrease did not reach statistical significance (p=0.16).

Table I. Baseline description of study population (n=882)

Sociodemografic variables			
Gender, no (%)	Women	634	(71.9)
	Men	248	(28.1)
Age, mean (SD)		59.3	(14.8)
Socioeconomic status, no (%)	Low	220	(24.9)
	Middle	526	(59.6)
	High	123	(13.9)
Clinical variables			
ESR (mm/h), mean (SD)		25.0	(19.8)
DAS28, mean (SD)		3.6	(1.1)
Disease duration (years), median (IQR)		5.0	(2.0-14.0)
Reumafactor, no (%)	Neg	331	(37.5)
	Pos	551	(62.5)
Pain (VAS) mean (SD)		40.6	(28.1)
Cardiovascular comorbidity, no (%)	No	833	(94.4)
	Yes	49	(5.6)
Hypertension, no (%)	No	702	(79.6)
	Yes	174	(19.7)
Diabetes mellitus, no (%)	No	833	(94.4)
	Yes	43	(4.9)
Functional variables			
Health Assessment Questionnaire, mean (SD)		1.1	(0.8)
SF-36, Physical Component Summary, mean (SD)		35.8	(10.8)
SF-36, Mental Component Summary, mean (SD)		49.2	(11.4)

SD: standard deviation; ESR: erythrocyte sedimentation rate; DAS28: disease activity score of 28 joints; VAS: visual analogue scale; SF-36: 36-item short form health survey.

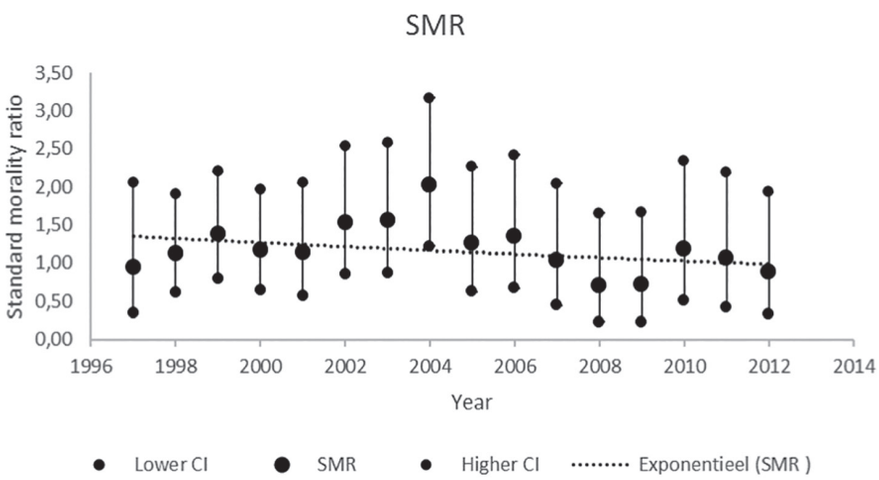

Fig. 1. Trend in cardiovascular mortality.

Predictors for cardiovascular mortality

Outcomes of the Cox regression analyses showed that higher age, higher ESR, having CV comorbidity and DM were predictors for CV mortality (Table III). Note that the hazard ratio for age and ESR is for each extra year and each extra mm/h respectively and the increased risk for comorbidity (CV and DM) is for patients having the comorbidity compared to patients not having the comorbidity.

Discussion

Results from this prospective cohort study showed that CV mortality in patients with established RA in the past 15 years was still higher than in the general Dutch population. CV mortality was determined through the primary cause of death. The primary cause of death is defined as the underlying cause of death, which started a sequence that finally resulted in death. Because RA was often indicated as the primary cause of death, the SMR for CV mortality us-

Table II. Cardiovascular mortality in RA population for different time intervals.

		95% CI	
SMR (mean three years)		Lower	Upper
1998-2000	1.23	0.69	2.03
2001-2003	1.42	0.77	2.39
2004-2006	1.57	0.85	2.64
2007-2009	0.83	0.30	1.80
2010-2012	1.05	0.42	2.15
SMR (mean five years)			
1998-2002	1.27	0.70	2.12
2003-2007	1.47	0.78	2.53
2008-2012	0.91	0.34	1.95
SMR (mean fifteen years)			
1998-2012	1.24	1.06	1.45

CI: confidence interval; SMR: standard mortality rate.

ing both primary and secondary cause of death was also computed. Nevertheless this did not change the conclusions (data not shown).

Although mortality rate seemed to decrease during the study period, this trend did not reach statistical significance. During the course of the study tight disease control, more intensive treatment and management of traditional CV risk factors have been introduced. We therefore expected to see a decrease in CV mortality rate (42). Probably not all patients were treated according to this policy from disease onset, because this was a cohort of patients with established RA, and the CV burden may already have been occurred. Thus the effect of intensive treatment on CV mortality may have been less effective than when intensive treatment started at disease onset. Moreover, also in the general population the management of traditional CV risk factors was further improved during the study period, which could explain why no decrease in CV mortality during the study period could be observed. Some recent studies also investigating SMR of cardiovascular mortality found inconsistent results. One study, following patients with RA from disease onset, did not found an increase in CV mortality (43). Another study did found an increase in CV disease despite advances in RA disease management (44). A reason for the inconsistent results could be the different types of cohort and followup time (27). Studies are required investigating cohorts from disease onset and following patients during a long follow-up period. Predictors for CV mortality were higher age, higher ESR, CV comorbidity and DM. These predictors were also reported in other studies (9, 10). In this study we use self-reported measurements of comorbidity. The questionnaire was tested for its validity in a separate study, whereby patients' self-reported data were compared with general practitioners' reported data derived from the medical record. The results of this validation study indicated that the agreement between patient self-reported and GP reported was high especially for some diseases, including cardiovascular diseases (37). This study was initially designed to study health outcomes in patients with RA. Therefore, other important potential confounders

Table III. Predictors for cardiovascular mortality.

	Univariate Model*			Multivariate Model**			Backward Model*		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Sociodemographic variables									
Gender (Women)				1.35	(0.88-2.08)	0.17	1.30	(0.87-1.95)	0.20
Age				1.10	(1.08-1.13)	0.00	1.11	(1.09-1.13)	0.00
Socioeconomic status	0.79	(0.57-1.09)	0.15	0.84	(0.60-1.17)	0.31			
Clinical variables									
ESR	1.02	(1.01-1.02)	0.00	1.02	(1.01-1.03)	0.00	1.02	(1.01-1.02)	0.00
DAS28	1.12	(0.94-1.32)	0.22	0.89	(0.72-1.11)	0.31			
Disease duration	1.11	(1.10-1.12)	0.00	1.00	(0.98-1.01)	0.61			
Rheumatoid factor	1.38	(0.94-2.02)	0.11	1.38	(0.82-1.83)	0.32			
Pain (VAS)	1.00	(1.00-1.01)	0.20	1.00	(0.99-1.01)	0.62			
Cardiovascular comorbidity	2.10	(1.25-3.52)	0.01	2.10	(1.05-3.15)	0.03	2.04	(1.21-3.43)	0.01
Hypertension	1.46	(0.99-2.16)	0.06	1.46	(0.87 3.10)	0.13			
Diabetes Mellitus	1.87	(1.04-3.36)	0.04	1.87	(0.89 2.01)	0.16	1.77	(0.97 -3.24)	0.06
Functional variables									
HAQ	1.34	(1.01-1.78)	0.05	1.34	(0.59-1.51)	0.81			
SF-36, PCS	0.98	(0.97-1.00)	0.05	0.98	(0.96-1.01)	0.31			
SF-36, MCS	0.99	(0.98-1.01)	0.52	0.99	(0.98-1.01)	0.59			

Outcome Cox regression analyses (n=882). *Adjusted for age and gender. **Adjusted for all other variables.
HR: hazard ratio; CI: confidence interval; SD: standard deviation; ESR: erythrocyte sedimentation rate; DAS28: disease activity in 28 joints; VAS: visual analogue scale; HAQ: health assessment questionnaire; SF-36: 36-item short form health survey; PCS: physical component summary; MCS: mental component summary.

like smoking, BMI and cholesterol were not investigated. In addition, we assessed variables at baseline only. For some variables, such as disease activity, annual assessments over time, allowing AUC calculations, could have contributed to predicting CV mortality. Baseline ESR turned out to be a strong predictor for CV mortality. We expect that further ESR assessments would have strengthened this relationship.

The strengths of this study were the large cohort and the use of recent mortality data. The high number of deaths made it possible to study the annual SMR for cardiovascular death and to study the trend in CV mortality. Another strength of this study was that 99% of the patients could be linked to the Statistics Netherlands' mortality records.

As CV mortality in RA is still higher than in the general population, continued attention for CV diseases in RA is important. Both tight control of disease activity and good care for comorbid conditions (CV diseases and DM) are strongly advocated. According to the EULAR recommendations for CV risk management, the CV risk estimate resulting from traditional CV risk factors should be multiplied by 1.5 when a patient with RA meets two or more of the following criteria: a disease duration of more than 10 years, RF or anti-CCP positively or the presence of severe extra-articular manifestations. The authors of these recommendations choose a conservative factor of 1.5, because most studies did not adjust for social- and economic variables, physical functioning, and stress (24). In the present study SES, physical functioning and mental functioning were included in the model. Patients with a high disease activity had increased risk of CV mortality, whereby the risk increased with 2% for each mm/h. These results can be converted in a risk score for a patient with a disease activity of ≥30 mm/h. For patients above this cut off point the risk of CV mortality is increased with 80%. Our results do not support the conservative approach (factor 1.5 instead of 1.8) from the EULAR recommendations for patients with high disease activity.

In conclusion, the CV mortality among patients with RA in the past 15 years was still higher than in the general population and did not decrease statistically significant. Both tight control of disease activity and good care for comorbid conditions are advocated.

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