

## Increased incidence of stroke and impaired prognosis after stroke among patients with seropositive rheumatoid arthritis

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## ABSTRACT

**Objective.** To examine the incidence of, and outcome after, a stroke in patients with rheumatoid arthritis (RA) compared with the general population.

**Methods.** The northern Sweden MONICA register was used to compare the incidence of stroke in a cohort of RA patients with the general population. Forty RA patients who had also suffered a stroke were identified. For each patient with RA, three controls with a history of stroke but without RA were randomly collected from the same register, and matched for age and sex.

**Results.** The standardised incidence ratio (SIR) for stroke was 2.7 in RA patients compared with the general population ( $p < 0.05$ ). During the follow-up, RA patients had a higher overall case fatality (CF) following stroke compared with controls (hazard ratio (HR) = 1.70,  $p < 0.05$ ).

**Conclusion.** Both the incidence of a stroke, and the subsequent CF, were higher among RA patients compared with the general population. The results emphasize the necessity of optimising the prevention of stroke and follow-up care after a stroke in RA.

## Introduction

Death due to cardiovascular disease (CVD) is more common amongst patients with rheumatoid arthritis (RA) than in the general population (1-3). Recent studies also suggest an increased CVD morbidity in patients with RA (3-8). The reasons for these findings are not fully understood, however, the systemic inflammation along with genetic factors and traditional CVD risk factors appear to be important (5, 9-11). We, and others, have also shown that the prognosis following a myocardial infarction is deteriorated among RA patients compared with controls (6, 12). The corresponding results regarding morbidity and mortality in stroke are contradictory (2-4, 7-8, 13) and, there is, to our knowledge, only a single study of the prognosis after stroke in patients with RA (12).

The primary aim of this study was to examine the incidence of stroke in patients with RA compared to the general population. We also evaluated the outcome after stroke in RA patients compared with matched controls.

## Material and methods

Population-based data on all stroke events (ischaemic and haemorrhagic) are collected continuously in northern Sweden within the World Health Organization Multinational Monitoring of Trends and Determinants of Cardiovascular Disease (MONICA) project since 1985 (14). The MONICA protocol requires the inclusion of all incident strokes and recording of variables reflecting risk factors, care and treatment of the stroke. Thus, recording of a stroke, together with all other designated variables, is undertaken in exactly the same way for all individuals, with or without RA. Only patients from the Västerbotten County in the MONICA register were considered for incorporation into the present study, resulting in a total of 10927 validated stroke events between 1985 and 2003.

The initial patient cohort (2) comprised all individuals ( $n = 640$ ; 435 female, 205 male) with seropositive RA in 1979 at the Department of Rheumatology, University Hospital, Umeå, Sweden, with a reference population of 250,000. From the RA cohort, in all 40 patients with an incident stroke were identified within the MONICA register during this 18-year period. For each RA patient with stroke, three controls with stroke but without RA were randomly assembled from the MONICA register. The controls were matched for age, sex and year of onset ( $\pm 4$  years for age and onset year). Demographics and traditional CVD risk factors are shown in Table I.

The standardised incidence ratio (SIR) for a stroke, *i.e.* the ratio of the observed incidence of stroke in the RA cohort to that expected according to the crude stroke incidence of the whole MONICA register, based on age-, sex-, and year-adjusted rates in the general population of Västerbotten, was calculated by means of the Poisson distribution. To estimate the outcome following a stroke, the survival time after the event was identified for all patients with RA and stroke and their corresponding controls. Variables associated with the risk of stroke, *i.e.* previous strokes or acute myocardial infarctions (AMIs) and diabetes mellitus (DM) were also

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identified. There were too many values missing to allow any further statistical analysis regarding smoking habits. Unfortunately data on hyperlipidaemia and hypertension were not routinely recorded in the MONICA register until 1995. Only data related to the first stroke occurring during the study period was used. Survivorship functions were estimated by the Product limit (Kaplan-Meier) estimator, followed by the log-rank, Breslow and Tarone-Ware tests. Simple and multiple Cox proportional hazards regression models were used to identify covariates for survival. Likelihood ratio tests, together with clinical assumptions, determined which covariates were included in the multiple regression models. *P*-values <0.05 were considered as significant. All calculations were made with SPSS 15.0 (SPSS Inc, Chicago, US).

The study was approved by the regional ethics committee of Umeå University, Umeå, Sweden.

## Results

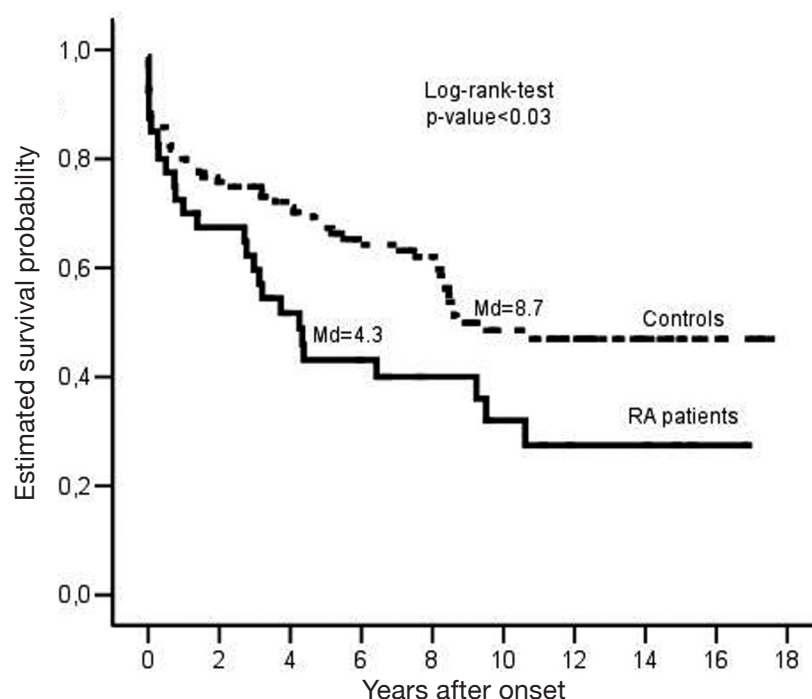
In the whole RA cohort, SIR for stroke was 2.70 (95%CI (1.85, 3.80)) being 2.05 (95%CI (1.23, 3.20)) for women and 4.76 (95%CI (2.60, 7.98)) for men. Figure 1 shows the estimated survivorship functions during the follow-up after a stroke for patients with RA and matched controls (*p*-values <0.05 for all three tests). During the whole follow-up period following the event (HR=1.70, 95%CI (1.06, 2.71)) as well as during the first 10 years (HR=1.65, 95%CI (1.03, 2.66)), and the first 5 years (HR=1.93, 95%CI (1.14, 3.26)) the case fatality (CF) was significantly increased in RA patients compared with matched controls. When only patients without a previous stroke were considered, the CF for the study period still remained significantly increased for RA patients compared with matched controls (HR=1.69, 95%CI (1.06, 2.70)). Consequently, all RA patients and controls were included in all subsequent calculations. The significantly increased CF for RA patients remained in multiple Cox regression analyses after adjusting for year of event (HR=1.7, 95%CI (1.1, 2.7)), type of stroke, *i.e.* ischaemic or haemorrhagic (HR=1.7,

**Table I.** Demographic data and traditional cardiovascular risk factors for patients with RA and stroke and controls with stroke but without RA. Data given as number of individuals (percent) or mean value  $\pm$  SD.

Variable	RA (n=40)	Controls (n=120)
Females	25 (63%)	75 (63%)
Age at stroke	65.2 $\pm$ 7.9	65.2 $\pm$ 7.9
Stroke/MI prior to 1985	10 (25%)	25 (21%)
Diabetes mellitus	6 (15%)	17 (14%)
Number of deaths	26 (65%)	55 (46%)
Age at onset of RA	42.8 $\pm$ 10.1	---
Disease duration*	22.6 $\pm$ 8.7	---

MI: myocardial infarction.

\*from onset of RA until the time of stroke.



**Fig. 1.** Estimated survival after onset of stroke in 40 patients with RA and 120 controls. Md: Median survival time

**Table II.** Estimated hazard ratio (HR) and *p*-values for simple and multiple Cox regression analyses of 40 patients with RA and 120 controls, with case fatality after stroke as response variable in all analyses.

Variable	Simple			Multiple		
	HR	95%CI	<i>p</i> -value	HR	95%CI	<i>p</i> -value
Type of stroke	0.88/ischaemic	0.50 – 1.55	0.66	---		
Sex, female	1.002/+	0.64 – 1.56	0.99	---		
RA	1.70/+	1.06 – 2.71	0.027	1.79/+	1.11 – 2.86	0.016
Age	1.05/year	1.02 – 1.09	0.002	1.06/year	1.03 – 1.10	0.001
Year of event	0.96/year	0.90 – 1.02	0.17	0.93/year	0.87 – 0.99	0.016
Diabetes mellitus	1.92/+	1.09 – 3.38	0.023	1.93/+	1.09 – 3.42	0.024

95%CI (1.1, 2.7)), or DM (HR=1.7, 95%CI (1.1, 2.7)). In simple Cox regression models RA, age and DM were related to the CF after stroke (Table II).

In a multiple Cox regression model, controlling for age, year of event and DM, RA still was related to the CF after stroke (Table II).

## Discussion

In the present study patients with RA had a nearly three times greater incidence of stroke than would have been anticipated based on statistics for the general population. Studies on CVD in RA are frequent (1-8), however studies on the incidence of stroke in RA are more scarce. Most recent studies have shown an increased risk of stroke in RA to about the same extent as ours (3, 8, 13), although there are some studies with contradicting results (4, 7). The difference in results might, in part, be explained by different inclusion or exclusion criteria, follow-up times, and type of cohort, sex ratios and different size of the study cohorts. In our study, all CVD events were validated in accordance with strict WHO-criteria (14), and the recording was undertaken exactly the same way in patients with RA and the general population. Another explanation might be the fact that the different populations studied have different genetic backgrounds.

Patients with RA died at approximately twice the rate of the controls following a stroke. Accumulating evidence indicates that factors related to RA *per se*, for example, inflammation, increase the risk of CVD as well as overall mortality in patients with RA (5, 9-11, 15.). We showed that RA was an independent risk factor for death after stroke even when adjusting for available traditional risk factors for CVD and death. Atherosclerosis is regarded as an inflammatory process (16) and it is speculated whether RA and atherosclerosis share pathogenetic mechanisms (5). Furthermore, it has been found that inflammation in RA may be additive to traditional CVD risk factors when developing CVD (10). New anti-rheumatic treatments, like TNF- $\alpha$  inhibitors, may therefore decrease the morbidity and mortality due to CVD in the future (17). Previous studies have demonstrated age and DM to be prognostic for the outcome after a stroke in the general population (18) and this study verified that finding in patients with RA. Moreover, a stroke can give a long-term loss of ability to move (18) and when this handicap is added to the already disabled patient with RA it might lead to a more

vulnerable patient who dies relatively soon following a stroke. Furthermore, patients with one chronic disease may be under treated for other diseases (9). Treatment and care after a stroke has improved significantly during the last decades. This was also reflected by an improved prognosis after stroke events in the more recent years compared to that after stroke events in early years during the follow up. Since the patients with RA and controls were matched for year of event in the present study our results should not have been biased by this mortality trend. It is possible that there are differences in size of stroke, treatment after the stroke and rehabilitation between RA patients and controls that might have contributed to our findings, however, those factors were not possible to evaluate.

A strength of this study is that, in 1979 our clinic was the only reference centre for rheumatological patients in Västertotten County (2). Consequently, our cohort would be very close to the prevalent seropositive adult RA population in the county at that time. Furthermore, albeit analysing recorded data retrospectively, the MONICA register of northern Sweden (14) identifies all patients with suspect stroke events according to WHO criteria. This gave a unique opportunity to compare the incidence of, and the outcome after, a stroke for RA patients and controls in a community-based manner. The main limitation of this study is that the number of RA patients undergoing a stroke is small and that the MONICA register does not include data on inflammation or antirheumatic treatment. Within the incidence study, the RA cohort was identified in 1979 whereas the registration of stroke events did not start until 1985. Theoretically, premature deaths among the RA patients may have shifted the RA cohort towards a relatively milder disease state before registration began. This would, however, only have diluted the increased incidence of stroke actually demonstrated. In conclusion, our study indicates that the increased mortality in RA patients is in part due to a higher incidence of, as well as a worse prognosis after, a stroke. These findings emphasize the

necessity of optimizing the prevention of stroke and follow-up care after a stroke in RA patients.

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