Cardiovascular admissions and mortality in an inception cohort of patients with rheumatoid arthritis with an onset in the 1980's and 1990's.

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Abstract

Background: Rheumatoid arthritis (RA) patients have increased cardiovascular disease (CVD) mortality. However, studies have suggested RA survival may have improved over recent decades. Excess CVD mortality may be due to an increased prevalence of CVD or to an increased case fatality in RA patients.

Objectives: To examine whether RA patients with disease onset in the 1980s-1990s have increased mortality rates and to compare cardiovascular admission rates in RA patients with those of the general population.

Methods: An inception cohort of 1010 RA patients attending Stockport rheumatology clinics between 1981 and 1996 was followed up to 31st December 2002 via the Office for National Statistics (ONS). Standardised mortality ratios (SMR) were calculated for all cause and cause specific mortality using the population of Stockport as the reference. CVD admission rates were ascertained for a subgroup of these patients, using national hospital episode statistics, and standardised CVD admission rates (SAR) and SMRs were calculated for this subgroup.

Results: 470 (48%) patients died during a median follow-up period of 11.4 years. All cause mortality was increased in men: (SMR 1.45 (95% 1.22, 1.71)); and women: (SMR1.84; (95% CI 1,64, 2.05)), as was CVD mortality, men: (SMR 1.36 (95% CI 1.04, 1.75); and women: (SMR 1.93 (95%CI 1.65, 2.26)). No difference in CVD admission rates was observed in men: (SAR 1.20 (95% CI 0.89, 1.58); or women: (SAR 1.10 (95% CI 0.88, 1.36)) despite excess CVD mortality in this subgroup.

Conclusion: RA patients still experience reduced life expectancy and excess CVD mortality. Despite this, standardised admission rates for CVD were not raised. This suggests either that CVD in RA has a higher case fatality than the general population or that it is frequently unrecognised in RA patients prior to the fatal event.

INTRODUCTION

The majority of mortality studies in patients with RA published since 1950 have shown an increased mortality from cardiovascular disease (CVD) (1). There is now intense interest in verifying and quantifying this excess CVD risk and understanding the underlying mechanisms.

Most previous mortality studies examined cohorts of patients with established RA (2-4). This may cause selection bias towards more severe progressive disease and left censorship. The study of inception cohorts of RA patients is less likely to reveal decreased survival rates because of the potential to include patients with milder disease (5). Several recently reported mortality studies, (6-11), have followed patients from early in their RA disease process. Four of these studies (7-9) failed to identify any increased mortality rates in RA patients with disease onset during the 1980s-90s. One study showed that mortality rates from acute myocardial infarction declined in patients with RA onset in more recent decades (11). Possible explanations for the relative improvement in RA patient survival include the earlier introduction of disease modifying therapy (8;9), or a change in the natural history of RA (7) with the disease becoming less severe over recent years (12). It is possible that excess mortality in these RA cohorts may be identified with continued long-term follow-up(13).

However, excess mortality from CVD was observed in a primary care based cohort of patients with early seropositive inflammatory arthritis (10). Data from the Mayo clinic also suggest that the excess mortality associated with RA did not fall during the 1980s-90s (14). A study of RA patients identified from the Swedish Hospital discharge register reported that, although mortality rates fell towards the end of the last century, mortality from coronary heart disease remained particularly high in RA patients (15).Thus it is difficult to know whether the survival prospects of RA patients have changed in recent years. Long term follow up of RA inception cohorts is required.

One possible explanation for the excess CVD mortality in RA is an increased prevalence of comorbid CVD. Studies in the US have shown that RA patients have higher rates of CVD events than in the general population (16;17) and describe CVD comorbidity more frequently in RA than OA patients (18). However, there have also been reports that RA patients are more likely to experience silent ischaemic heart disease and sudden cardiac death than the general population (19). An alternative explanation for the increased CVD mortality in RA could be that these patients have an increased case fatality rate from CVD events.

Aims

1) To examine whether RA patients with disease onset in the 1980s-1990s, identified in a hospital clinic setting, have increased mortality compared to the local general population.
2) To compare cardiovascular admission rates in RA patients with those of the general population.

METHODS

Setting

Stockport is a large urban area, south of Manchester, UK with a population of nearly 285,000.

Stockport RA register
This inception cohort of 1,010 RA patients was identified from a register of all newly diagnosed RA patients, based on consultant rheumatologist's opinion, attending Stockport rheumatology out-patient clinics between 1981 and 1996. Patients were designated seropositive if, at the time of diagnosis, they had either an IgM rheumatoid factor (RF) titre of 1:40 or above, or rheumatoid nodules. Many of these patients were subsequently discharged from regular rheumatology follow up. Thus, unlike many previously described hospital based cohorts (2;20-24), the Stockport RA cohort is composed of patients with a broad spectrum of RA disease severity and is not restricted to those under long-term rheumatology follow-up.

MORTALITY STUDY

Patients and methods
Identification data including NHS numbers, names, dates of birth and last known address were sent to the Office for National Statistics (ONS) for flagging and notification of deaths using the National Health Service Central Register (NHSCR) (25). ONS were able to match 979 (97%) of the 1,010 patients and provided death drafts for all patients who died prior to 31st December 2002. The causes of death were coded according to WHO rules using ICD-9 until the 1st Jan 2001 when ICD-10 coding was introduced.

The Stockport district population was used as the reference group for calculating Standardised Mortality Ratios (SMRs). ONS provided mortality rates for all causes, cardiovascular causes, respiratory causes and neoplasia, for men and women separately in 10-year age bands, for the years 1982-2001. Population death rates for the year 2002 were not available at the time of analysis and cohort mortality rates in this year were compared with those in 2001. All cause and cause specific SMRs were calculated using indirect standardisation using STATA-7. Cox regression was used to examine whether RF status predicted mortality in the RA cohort adjusting for age and gender. The Cox model's proportional hazards assumptions were tested graphically using the stphplot command in STATA-7.

CARDIOVASCULAR ADMISSIONS STUDY

Patients and methods
Patients in the Stockport RA cohort who were Stockport Health Authority (HA) residents between 1994-2002 were identified by matching on NHS numbers, dates of birth and names. Dates of entering and leaving the HA register were recorded. Stockport Public Health Department provided Hospital Episode Statistics (HES) (26) for all NHS hospital admission episodes, coded with primary diagnoses of CVD, (ICD-9 codes 390-459 & ICD-10 codes I00-I99), IHD (ICD-9 codes 410-414 & ICD-10 codes I20-I25) and MI (ICD-9 codes 410, 412 & ICD-10 codes I21-I22), for Stockport Health HA residents between years 1994-2002. Population rates of CVD, IHD and MI admissions were calculated for each year using the Stockport HA population estimates (taken in October 1999 as the mid-point of the study period) as the denominator.

In total 515 of the Stockport RA cohort were identified as being residents in Stockport HA between 1994-2002. The incidence of CVD, primary diagnosis, admissions in the prevalent Stockport RA cohort was compared to the rate of CVD primary diagnosis admissions in the general Stockport population to calculate a standardised cardiovascular admission rate (SAR)

for the RA cohort. SARs for the diagnoses of CVD, IHD and MI for years 1994-2002 were calculated using STATA-7. The start of follow up was 1st April 1994, or the date of entry to the HA. The end of the follow-up period was the date of death, the date of leaving the HA or the end of the study period 31st March 2002. Each patient admitted with CVD was censored on the date of admission and a new period of follow-up was started. Patients with multiple admissions contributed several periods of person years of follow-up.

SMRs for this prevalent RA subgroup were calculated for all cause, CVD, IHD and MI mortality using the Stockport population mortality rates for these years.

RESULTS

Mortality study

Date of birth, gender, year of diagnosis and rheumatoid factor status at diagnosis were recorded for 1008 of the 1010 patients. There were 729 (72%) women and median age at diagnosis was 60.4 years [IQR 50.4, 69.6] (Table 1).

An attempt was made to validate the consultant diagnosis of RA. The medical records of 20 patients, selected randomly from the Stockport RA register, were reviewed and 18 patients met ACR classification criteria for RA. There was insufficient clinical information recorded to classify 2 patients.

The 979 (97 %) patients matched by ONS were used in the initial mortality analysis. The median follow up period was 11.4 years [IQR 7.5, 15.4]. By 31st December 2002, 470 patients (48%) had died. The median age at death was 74.9 years [IQR 68.8, 81.0]. Women died at an older age (76.0 [IQR 70.2, 81.4]) than men (72.2 [IQR 66.1, 78.9]), and patients who were RF negative died at an older age (79.6 [IQR 71.7, 84.8]) than RF positive (74.3, [68.0, 79.9]) patients.

Table 1 -Descriptive data & mortality data for the RA cohort

	Females n=729		Males n=281		Total n=1010	
	Med	IQR	med	IQR	Med	IQR
†Age at presentation	60.4	49.8, 69.9	60.3	51.7, 68.3	60.4	50.4, 69.6
†Age (RF-ve)	62.5	49.9, 71.9	63.8	55.1, 72.9	63.1	51.6, 72.5
†Age (RF+ve)	59.8	49.8, 69.3	59.6	50.3, 67.0	59.7	49.9, 68.8
	n	%	n	%	n	%
RF +ve at time of diagnosis	542	74.3	229	81.8	772	76.4
RF –ve at time of diagnosis	187	25.7	52	18.2	238	23.6
‡Cause of Death	Females n=711		Males n=268		Total n=979	
	n	%	n	%	n	%
Cardiovascular	158	22.2	62	23.1	220	22.5
Respiratory	51	7.2	26	9.7	77	7.9
Neoplastic	52	7.3	36	13.4	88	9.0
Other mortality	67	9.4	18	6.7	85	8.7
Total mortality	328	46.1	142	53.0	470	48.0

†Date of birth not known for 2 patients in the cohort

‡Mortality data not available for 31 patients

Cause of death

Cardiovascular disease was the most frequent cause of death (Table 1), responsible for 48% of female and 44% of male deaths. Ischaemic heart disease (IHD) was recorded as the main cause of death in 125 (26%) cases and the main cause of death was ascribed to acute myocardial infarction (MI) in 72 (15%) cases (Table 2).

Rheumatoid arthritis was identified as the underlying cause in only 36 (7.6%) deaths and was recorded anywhere on the death certificates of 44 (9%) patients.

Table 2: Cardiovascular causes of death grouped by ICD9 /ICD 10 coding

Cardiovascular main causes of death	ICD-9 codes	ICD-10 codes	Female n	Male n	All RA n
Chronic rheumatic heart disease	393-398	I05-I09	2	0	2
Hypertensive disease	401-405	I10-I15	4	0	4
Acute MI	410	I21, I22	46	26	72
Acute/sub-acute IHD	411	I24	1	0	1
Chronic IHD	414	I25	36	16	52
Ischaemic heart disease (Total)	410-414	I20-I25	83	62	125
Pulmonary circulation	415-417	I26-I28	6	3	9
Other forms of heart disease	420-429	I30-I52	17	5	22
Cerebrovascular disease	430-438	I60-I69	40	8	48
Disease of arteries, arterioles and capillaries	440-448	I70-I79	4	4	8
Diseases of veins and lymphatics & other diseases of the circulatory system	451-459	I80-I89	2	0	2
Other unspecified circulatory disorders		I95-I99	0	0	0
Total number of CVD deaths	390-459	I00-I99	158	62	220

Standardised mortality ratios

Both male and female RA patients had higher than expected mortality rates (Table 3) Mortality rates from all CVD causes in women were approximately twice that expected (SMR 1.93 (95%CI 1.65, 2.26) with a more modest increase being observed in male RA patients (SMR 1.36 (95%CI 1.04, 1.75). The SMRs for IHD were raised in both men and women and female RA patients had higher mortality rates from MI. In female RA patients 77 (51%) of the 149 excess deaths were due to CVD and 40 (27%) of the excess deaths were from IHD. Cardiovascular deaths were responsible for 38% of the 44 male excess deaths and 13 of the male excess deaths (29%) were from IHD. Mortality from respiratory causes was increased in both male and female RA patients and 36 respiratory deaths were coded as being due to pneumonia, 7 deaths due to interstitial lung disease, 1 death from asthma and the remaining respiratory deaths were from chronic obstructive airways disease. The number of deaths from neoplasia was not significantly different from that seen in the general population.

Table-3 Standardised Mortality Ratios (SMRs) for Stockport RA cohort

Cause of death	Females n=711 Number of deaths				Males n=268 Number of deaths			
	Observed	Expected	SMR	95% CI	Observed	Expected	SMR	95% CI
All cause	328	178.59	1.84	1.64, 2.05	142	97.78	1.45	1.22, 1.71
CVD	158	81.56	1.93	1.65, 2.26	62	45.48	1.36	1.04, 1.75
IHD	83	42.52	1.95	1.55, 2.41	42	28.67	1.46	1.05, 1.98
MI	47	26.00	1.77	1.30, 2.36	26	18.89	1.38	0.90, 2.02
Respiratory	51	23.45	2.18	1.61, 2.86	26	14.52	1.79	1.17, 2.62
Neoplasms	52	46.93	1.11	0.82, 1.45	36	26.76	1.35	0.94, 1.86

Men and women with seropositive RA had increased all cause, CVD, IHD and MI mortality compared to the general population (Table 4). Sero-positive women had twice the expected cardiovascular, IHD and MI mortality. Respiratory mortality rates were significantly increased in seropositive patients. Female seronegative patients had a modest increase in all cause and CVD mortality. Male seronegative patients had no increase in all cause or cause specific mortality. However, the number of patients in this subgroup was small.

Table-4: SMRs for patients stratified by rheumatoid factor status at time of diagnosis

Cause of Death	Female patients								Male patients							
	Seropositive n=528				Seronegative n=183				Seropositive n=528				Seronegative n=183			
	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All cause	250	123.00	2.03	1.79, 2.29	78	55.48	1.41	1.11, 1.75	118	69.04	1.71	1.41, 2.05	24	28.73	0.83	0.53, 1.24
CVD	117	55.74	2.10	1.73, 2.51	41	25.82	1.59	1.14, 2.15	51	32.01	1.59	1.19, 2.09	11	13.48	0.81	0.41, 1.46
IHD	64	29.40	2.18	1.67, 2.78	19	13.13	1.44	0.87, 2.26	34	20.46	1.66	1.15, 2.32	8	8.21	0.97	0.41, 1.91
MI	37	18.53	2.00	1.41, 2.75	10	7.98	1.25	0.60, 2.30	22	13.67	1.61	1.01, 2.44	4	5.21	0.77	0.21, 1.96
Respiratory	39	15.67	2.49	1.77, 3.40	12	7.78	1.54	0.79, 2.69	23	9.79	2.34	1.49, 3.52	3	4.72	0.64	0.13, 1.86
Neoplasms	39	33.7	1.16	0.82, 1.58	13	13.24	0.98	0.52, 1.68	28	19.34	1.45	0.96, 2.09	8	7.42	1.08	0.46, 2.12

Predictors of mortality
Rheumatoid factor, univariately, did not predict all cause mortality within the RA cohort. However, RF positive patients were younger at presentation and at death. When adjusted for age at disease onset and gender, RF was a modest predictor of all cause mortality, (Hazard ratio (HR) $_{adj}$ 1.55 (95% CI 1.25, 1.94)), CVD mortality (HR $_{adj}$ 1.37 (95% CI 1.00, 1.88)) and respiratory mortality (HR $_{adj}$ 1.85 (1.04, 3.29). The proportional hazards assumption remained true for all of these models.

Cardiovascular admissions

Patient characteristics
The characteristics of the 515 RA patients who were Stockport residents between 1994-2002 are shown in table 5. The median disease duration was 5.8 years from the time of rheumatologist diagnosis of RA. The median age at diagnosis was 56.2 years (IQR 41.7, 65.5).

Table 5: Demographics of the 515 RA patients monitored for CVD admissions

		All RA patients n=515		Female RA n=371		Male RA n=144	
RF positive at RA diagnosis	n (%)	388	(75.3)	275	(74.1)	113	(78.5)
Age (yrs) start of admissions study	Med [IQR]	62.9	53.8, 72.3	63.6	53.5, 72.9	61.8	54.7, 72.9
Duration of RA (yrs)	Med [IQR]	5.8	2.8, 9.8	5.8	2.8, 9.8	5.8	1.8, 8.8

The 515 patients accumulated 3173.3 person years of follow-up between 1/4/1994 and 31/3/2002. During this time 93 (18%) of the RA patients experienced 134 CVD admissions and 30% of these patients had more than one admission. These patients were admitted to Hospitals in Manchester, Stockport and East Cheshire.

Standardised admission ratios
The SAR for CVD was not raised in either males or females (Table 6). There were only a small number of admissions with IHD & MI.There were no significant increases in CVD SARs for seropositive RA patients (female seropositive patients SAR 1.10 (95% CI 0.54, 2.10); male seropositive patients SAR 1.44 (95% CI 0.95, 3.32)).

Table-6 Standardised admission rates (SAR) for cardiovascular disease

Cause of Admission	Females n=371 Number of admissions				Males n=144 Number of admissions			
	Obs	Exp	SAR	95% CI	Obs	Exp	SAR	95% CI
CVD	83	75.45	1.10	0.88, 1.36	51	42.51	1.20	0.89, 1.58
IHD	18	21.66	0.83	0.49, 1.31	10	16.84	0.59	0.28, 1.09
MI	10	7.55	1.34	0.64, 2.46	4	5.48	0.73	0.20, 1.87

Standardised mortality ratios in the admissions cohort

There were 182 deaths in this group of 515 prevalent RA patients with 100 deaths being due to CVD causes (Table 7). Cardiovascular mortality was significantly increased in both male (SMR 2.40; 95% CI 1.64, 3.39) and female (SMR 2.77; 95% CI 2.15, 3.51) patients. Women and seropositive patients had higher SMRs. Mortality from IHD was also increased in both sexes, but was more marked in women and seropositive patients. Mortality rates from MI were significantly increased in women. Approximately 15% of all deaths in this cohort were attributed to acute MI. There were more excess deaths from CVD than there were excess CVD admissions. Only 42 of the 100 patients in the RA cohort who died from CVD had any prior CVD admissions during the follow-up period.

Table-7 SMRs for all cause and CVD causes of mortality in the RA admissions group

Cause of Death	RA group	Females n=371 Number of deaths				Males n=144 Number of deaths			
		Obs	Exp	SMR	95% CI	Obs	Exp	SMR	95% CI
All Cause	All RA	129	56.45	2.29	1.90, 2.71	53	29.55	1.79	1.34, 2.34
	RF+	93	38.37	2.42	1.96, 2.97	40	19.30	2.07	1.48, 2.82
	RF-	36	18.1	1.99	1.39, 2.75	13	10.25	1.27	0.67, 2.17
CVD	All RA	68	24.50	2.77	2.15, 3.51	32	13.3	2.40	1.64, 3.39
	RF+	50	16.45	3.04	2.26, 4.00	24	8.58	2.79	1.79, 4.16
	RF-	18	8.06	2.23	1.32, 3.53	8	4.72	1.69	0.72, 3.34
IHD	All RA	36	12.48	2.89	2.02, 3.99	19	8.25	2.30	1.38, 3.60
	RF+	27	8.46	3.19	2.10, 4.65	13	5.42	2.40	1.27, 4.10
	RF-	9	4.02	2.24	1.02, 4.25	6	2.82	2.12	0.77, 4.62
MI	All RA	19	7.00	2.71	1.63, 4.24	8	4.92	1.62	0.70, 3.20
	RF+	15	4.75	3.15	1.76, 5.20	6	3.26	1.83	0.67, 4.00
	RF-	4	2.24	1.78	0.48, 4.56	2	1.65	1.20	0.13, 4.36

The median time between the first CVD event and death was 4.8 months [IQR 0.6, 21.6]. Cox regression adjusted for age and gender revealed that a cardiovascular admission was a very strong predictor of subsequent all cause mortality, (HR_{adj} 4.2 (95%CI 2.9, 5.9)) and CVD mortality (HR_{adj} 8.8 (95%CI 5.7, 13.6)).

DISCUSSION

These studies have demonstrated that all cause and cardiovascular mortality is still increased in RA patients in the UK with an onset of disease in the 1980s and 1990s. Mortality was higher in, but not confined to, those patients who were RF positive at baseline. It seems likely that the absence of excess mortality described in other recent studies of patients with early RA may be attributed to aggressive disease control in these patients (7-9). They were conducted in the context of early arthritis clinics where patients might experience early treatment with DMARDs. By contrast the Stockport RA cohort was managed in routine rheumatology outpatients and many were followed up in primary care.

Other studies have also observed a greater excess mortality in female than male RA patients (27;28). This gender difference may be deceptive, in that population rates of CVD are lower in women than in men. Thus if RA had the same impact in men and women with respect to CVD, one would expect higher SMRs for women given the lower number of expected cases in the denominator.

In the prevalent RA cohort CVD admission rates were not increased, despite CVD mortality rates being twice those observed in the general population. One possible explanation could be that RA patients are less likely to experience multiple CVD admissions than the general population. Of the RA patients admitted to hospital, 70% had only one CVD admission during the 8 years of follow-up. This situation might occur if RA patients were more likely to die after or during their first CVD admission. If RA patients are less likely to experience or interpret significant angina symptoms they would be less likely to present at secondary care for treatment. This may lead to increased rates of unrecognised myocardial infarction and sudden cardiac death (19). During the period of this study 34 (52%) of the RA patients, identified as having CVD admissions, died after their first CVD admission. Unfortunately, the number of first CVD admissions for the general population was not available. Therefore, it was not possible to compare the number of first CVD events in the RA cohort and the general population.

The study of respiratory outcomes was not one of the main aims of this study. However, We observed increased respiratory mortality rates in the RA patients and seropositive disease was a predictor of respiratory death after adjusting for age and gender. Possible explanations for the increased respiratory mortality include: 1) respiratory complications of RA, although only a small number of deaths were due to interstitial lung disease, or 2) the effects of cigarette smoking, which is identified as a risk factor for RA and seropositive disease (29). We were not able to examine associations between smoking and mortality in this study.

A strength of this study is that it was able to identify hospital admissions throughout the country for both the RA cohort and the local population controls.

The study has a number of limitations. Firstly, inclusion on the RA register was based on consultant diagnosis rather than application of the 1987 ACR classification criteria for RA (30). Whilst this method lends a degree of external validity, as a consultant rheumatologist made the clinical diagnosis of RA, which reflects common rheumatological practice, it may have introduced misclassification bias. It is likely that simply using a consultant diagnosis of RA will have included patients with inflammatory polyarthritis who did not meet 4 out of 7 of the ACR classification criteria. These patients might be expected to have milder disease and therefore make it more difficult to detect an association with increased CVD mortality.

Baseline data on disease severity and disability were not collected. Nor was information on smoking, social history, or comorbid conditions recorded. Opportunities to look for predictors of mortality within the cohort were therefore limited.

This study relies on death certificate data for the main cause of death and hospital episode statistics for the main cause of admission. There are several limitations that can give rise to inaccuracies in mortality (31;32) and admission data (33;34). Although it seems that the accuracy of coding for specific admission diagnoses has improved over recent years (35). However, as population mortality and admission data are subject to the same inaccuracies it is unlikely that this will have introduced significant bias. Conversely if CVD is more likely to

remain clinically silent in RA it is likely that CVD diagnoses will be recorded less frequently as the primary cause of admission in this group. This may explain the similar rates of CVD admissions observed in this study. As described by others, RA was recorded infrequently on the death certificates of these patients (36;37).

In summary, patients who have developed RA in the last two decades continue to experience excess cardiovascular mortality in the 21st century. This excess cardiovascular mortality is not reflected by an increased CVD admission rate. This may be due to high mortality during the first event or a failure to diagnose CVD before death.

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Ethics approval
Approval for the study was given by the Stockport Local Research Ethics Committee, Oak House, Stepping Hill Hospital, Stockport, SK2 7JE.

Competing interest statement
The Authors of this manuscript declare no competing interests

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