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Original article

Cardiovascular disease in rheumatoid arthritis: Single-center hospital-based cohort study in France

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1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease related to dysimmunity. The prevalence of RA among adults ranges from 0.3 to 0.6% [1]. Excess mortality with a 5- to 10-year reduction in life expectancy has been reported in patients with RA [2–7]. Risk factors for mortality include severe disease (most notably marked functional impairment), positive tests for rheumatoid factors, male gender, and presence of co-morbidities [3,5,8,9]. Cardiovascular events have been shown to contribute about 50% of the excess mortality seen in RA [3,8]. The relative risk (RR) of myocardial infarction compared to individuals without RA has ranged from 1.4 to 3.9 [2–5,7,10–15]. Although the mechanisms underlying the increased risk of cardiovascular disease in patients with RA remain unclear, available data incriminate not only conventional cardiovascular risk factors, but also RA-specific

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factors such as systemic inflammation [16–20]. In addition, T cells, which contribute to the pathogenesis of RA, may be critically involved in acute coronary syndromes and in plaque instability [21].

The objectives of this study were to evaluate the risk of cardiovascular events in a cohort of patients with RA recruited at a hospital in France, to identify risk factors for cardiovascular disease associated with RA, and to measure the severity of the cardiovascular events in these patients with RA.

2. Methods

We identified consecutive patients with RA admitted to the rheumatology A (Rheumatology A) department of the Cochin Teaching Hospital, Paris, France, from January 1, 1998 to March 31, 1999. The patients were identified from the hospital database, which lists the main diagnosis and co-morbid conditions determined at discharge by a senior physician in each patient. We reviewed the medical charts of the patients thus identified and selected the patients who met American College of Rheumatology criteria for RA [22] and who had no history of cardiovascular disease (myocardial ischemia, ventricular or supraventricular rhythm disorders, congestive heart failure, transient ischemic attack, stroke, or symptomatic occlusive arterial disease of the lower limbs).

For each selected patient we recorded the following: age, gender, year of the diagnosis of RA, results of the ELISA for rheumatoid factors, history of rheumatoid vasculitis, history of joint replacement surgery, and medications taken for at least 1 month (methotrexate, prednisone, infliximab, etanercept, and adalimumab). We also looked for a history of osteoporotic fractures or osteoporosis treatment, which were associated with peripheral vascular disease in a recent study [23]. We recorded cardiovascular risk factors (treated hypertension, body weight, height, treated hypercholesterolemia, smoking within the last 3 years, and type 1 or type 2 diabetes mellitus).

In October 2004, each patient was mailed a questionnaire and a prepaid return envelope. The questionnaire was designed to determine whether myocardial infarction or stroke had occurred since the index hospital stay. Patients who failed to return the completed questionnaire were interviewed over the phone. When we were unable to contact the patient by phone, we called the referring family practitioner or rheumatologist to ask about cardiovascular events and vital status of the patient; if the patient had died, we asked for the date and cause of death. When efforts to contact the physician failed, we classified the patient as lost to follow-up at the date of the last discharge summary or outpatient clinic notes (Fig. 1).

In patients with cardiovascular events, discharge summaries and medical charts were reviewed. Major cardiovascular events were defined as myocardial infarction, stroke, and cardiovascular death (due to myocardial infarction, stroke, congestive heart failure, or sudden death). A cardiologist (CM) and a neurologist (ET) validated the diagnoses of cardiovascular and neurological events. Myocardial infarction was diagnosed in patients with at least two of the following:

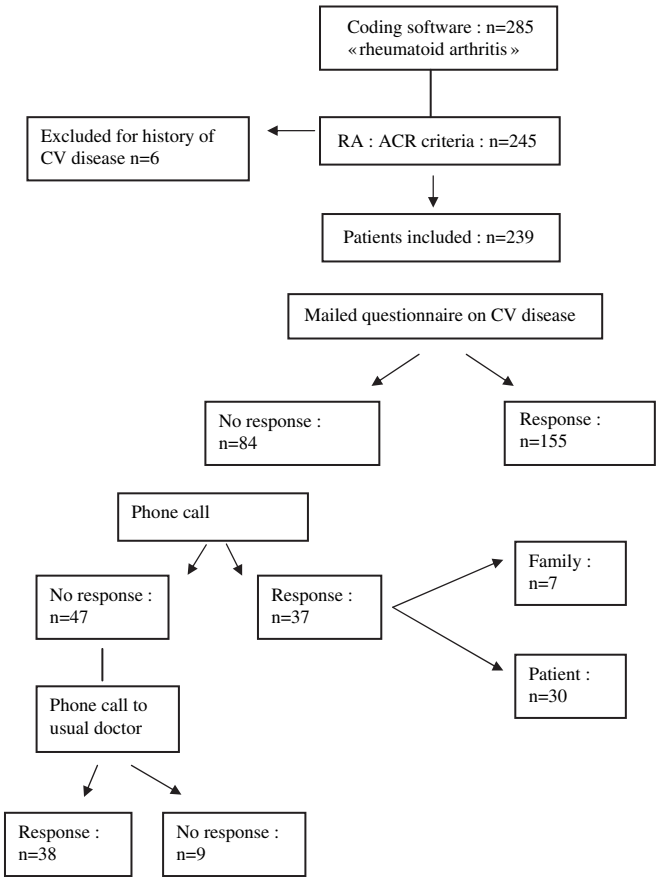

Fig. 1. Patient flow chart and cardiovascular data collection.

(1) typical chest pain or pain in a typical radiation for at least 20 min; (2) creatinine kinase (CK), CK-MB, or troponin elevation to at least twice the normal value for the laboratory, in the absence of alternative explanations; and (3) development of Q waves (40 ms) in at least two adjacent leads or development of a dominant R wave in V1 ($R \geq 1$ mm, $R/S > 1$). The following data were abstracted from the cardiology ward discharge summary: date of the myocardial infarction, treatment used (repermeabilization or pharmacotherapy only), and early and late complications. Ischemic stroke was diagnosed in patients with sudden development of a neurological deficit that persisted 24 h or longer and was associated with concordant imaging study abnormalities. Neither hemorrhagic stroke nor transient ischemic attacks were taken into account. In each patient, only the first cardiovascular event was considered.

3. Statistics

Categorical variables were compared using the chi-square test, or Fisher's exact test where appropriate. Student's *t*-tests were used for comparing continuous variables. Kaplan–Meier curves analysis was performed to determine the absolute risk of each event. Potential risk factors for myocardial infarction and stroke were evaluated by constructing a Cox model that adjusted for the following factors: age; gender; hypercholesterolemia; arterial hypertension; diabetes mellitus; osteoporosis;

Table 1
Characteristics of the 239 study patients

	Overall population ($n = 239$)	Patients without CV events ($n = 222$)	Patients with CV events ($n = 17$)	RR	95%CI	*P*-value
Age (years)	56.3 ± 15.7	55.3 ± 15.8	68.7 ± 6.2	2.2	1.4–3.3	<0.0001
Sex (% F)	82	83.8	41	3.2	1.2–8.4	0.02
Disease duration (years)	11.6 ± 8.8	11.4 ± 8.8	14 ± 7.8	–	–	0.14
Rheumatoid factors, *n* (%)	185/225 (82)	171/208 (82)	14/17(82)	1.01	0.3–3.8	0.89
Hypertension, *n* (%)	80/238 (34)	68/221 (31)	12/17 (71)	5.4	1.9–15.3	0.002
Treated hypercholesterolemia, *n* (%)	25/238 (10)	20/221 (9)	5/17 (29)	3.7	1.3–10.6	0.01
Diabetes, *n* (%)	18/238 (8)	15/221 (7)	3/17 (18)	2.5	0.7–8.8	0.15
Smoking, *n* (%)	33/219 (15)	31/202 (15)	2/17 (12)	0.7	0.2–3.0	0.61
Body mass index, mean ± SD	25.3 ± 5.4	25.3 ± 5.5	24.7 ± 4.8	–	–	0.70
Vasculitis, *n* (%)	17/235 (7)	15/218 (7)	2/17 (12)	2.5	0.6–11.1	0.22
Osteoporosis, *n* (%)	81/155 (52)	69/140 (49)	12/15 (80)	4.0	1.1–14.3	0.03
Arthroplasty, *n* (%)	81/226 (36)	74/209 (35)	7/17 (41)	1.5	0.6–3.9	0.43
Glucocorticoids, *n* (%)	211/239 (88)	195/222 (88)	16/17 (94)	1.8	0.2–13.7	0.56
Methotrexate, *n* (%)	201/237 (85)	185/220 (84)	16/17 (94)	2.4	0.3–18.3	0.4
TNF antagonists, *n* (%)	43/237 (18)	42/220 (19)	1/17 (6)	0.3	0.03–1.9	0.18

For each 10-year increase in age.
The relative risks and *P* values shown in the table were obtained in the univariate analyses.
CV: cardiovascular; RR: relative risk; 95%CI: 95% confidence interval.

vasculitis; and use of methotrexate, TNF antagonists, and glucocorticoids. SPSS 11.0 software (SPSS, Chicago, Illinois) was used to perform the statistical tests.

4. Results

Of the 285 patients listed in the hospital database as having RA, 245 (84.5%) met ACR criteria for RA. A history of cardiovascular disease was noted in 6 (2.5%) patients. Thus, 239 (239/285, 82.4%) patients were included in the study. Fig. 1 shows the patient flow chart. Mean age was 56.3 ± 15.7 years, 82% of patients were women, and mean disease duration was 11.6 ± 8.8 years. Table 1 lists the main patient characteristics. Mean follow-up was 5.4 ± 1.8 years. Nine patients either declined to participate in the study or could not be contacted; their characteristics were not significantly different from those of the 230 other patients (data not shown).

4.1. Risk of cardiovascular events

During the follow-up period, 10 patients experienced myocardial infarction (0.8%/year) and 3 patients experienced ischemic stroke (0.2%/year); the combined risk of myocardial infarction or stroke was 0.9%/year. In addition, 9 patients died from cardiovascular causes, including 5 with myocardial infarction or stroke. Thus, 17 patients experienced major cardiovascular events (1.3%/year). Table 2 reports the absolute risks of major cardiovascular events as estimated from Kaplan–Meier curves. Cumulative risks over time are shown in Fig. 2.

Table 2
Absolute risks of cardiovascular events as estimated using Kaplan–Meier curves

Follow-up (year)	Absolute risk (%)	95% Confidence interval
1	0.4	0.1–3.0
2	0.9	0.2–3.5
3	3.2	2.5–6.6
4	4.6	3.2–8.4
5	5.6	3.2–9.7

4.2. Risk factors for cardiovascular events

The results of the univariate analysis are reported in Table 1. The multivariate Cox model identified four factors independently associated with cardiovascular events: older age (RR for 10 additional years, 2.5; 95% confidence interval [95%CI], 1.4–4.2), male gender (RR, 5.1; 95%CI, 1.8–14.7),

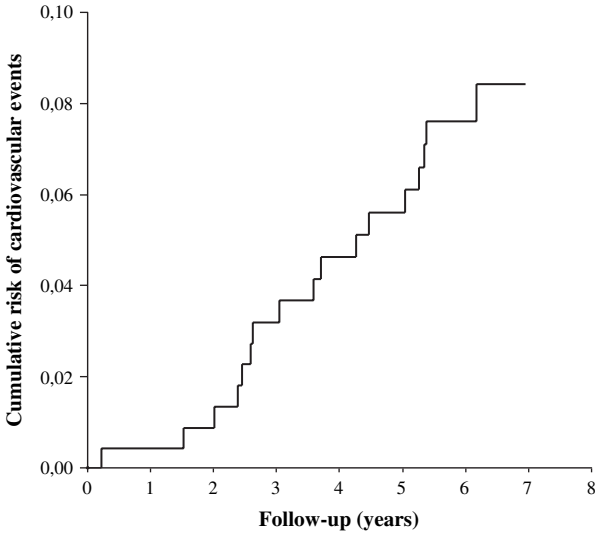

Fig. 2. Kaplan–Meier curve of the cumulative risk of cardiovascular events.

Table 3
Characteristics of myocardial infarction (10 patients)

Age at inclusion (years, mean ± SD)	68. ± 7.1
Female-to-male ratio	6/4
Hypercholesterolemia (*n*)	3
Diabetes (*n*)	2
Osteoporosis (*n*)	8
Hypertension (*n*)	6
Age at MI diagnosis (years, mean ± SD)	74.4 ± 19.4
Type of MI (*n*)	
ST elevation	7
No ST elevation	2
Myocardial ischemia	1
Early complications (*n*)[a]	4
Late complications (*n*)[b]	5
Residual symptomatic CHF (*n*)	4
Revascularization procedure (*n*)	1
Percutaneous transluminal coronary angioplasty (with or without stent implantation) (*n*)	5
Cardiovascular death (*n*)[c]	4

MI: myocardial infarction; CHF: congestive heart failure.
[a] Death, cardiogenic shock, pericarditis, left ventricular aneurysm.
[b] Death, rhythm disturbances, congestive heart failure, acute pulmonary edema, recurrence.
[c] Causes of death after myocardial infarction: residual congestive heart failure ($n = 2$) and acute pulmonary edema ($n = 2$).

Table 4
Causes of death (30 patients)

Cardiovascular	
Total	9
Myocardial infarction	4
Other[a]	5
Cancer	6
Infections	4
Other[b]	4
Unknown	7

[a] Sudden death, acute pulmonary edema, congestive heart failure ($n = 2$), dilated cardiomyopathy.
[b] Trauma, depression, acute renal failure complicating fibrosis, vasculitis.

hypercholesterolemia (RR, 6.0; 95%CI, 1.8–20.7), and hypertension (RR, 4.3; 95%CI, 1.4–13.2). Osteoporosis was not entered into the model, as data were unavailable for 84 patients. In another Cox model that included osteoporosis, this factor was associated with a RR of 9.1 (95%CI, 1.2–67.1).

4.3. Characteristics of the cardiovascular events

Of the 10 cases of myocardial infarction (Table 3), 5 led to symptomatic congestive heart failure and 4 others were followed by cardiovascular death after a mean of 1.6 ± 1.1 years. At the end of the study period, 30 patients had died (2%/year) including 9 from cardiovascular causes (0.7%/year). Cause of death was available for 23 patients (Table 4).

5. Discussion

In this historical cohort of patients admitted in France for RA, annual risks over a mean follow-up of 5.4 ± 1.8 years were 0.8%, 0.2%, and 1.3% for myocardial infarction, stroke, and major cardiovascular events, respectively. In addition, nearly 40% of deaths were related to cardiovascular disease, in keeping with earlier data [3–8]. We are not aware of previous studies of the risk of cardiovascular events in RA patients having a low overall risk of cardiovascular disease. Compared to other geographic areas such as North America and Northern Europe (UK, and Scandinavian countries), France has a low risk of cardiovascular disease. RA was associated with a significantly increased risk of myocardial infarction compared to controls in studies done in North America and Northern Europe [2–5,7,10–15]. In a prospective study from Sweden [14], RRs were 1.8 for myocardial infarction (95%CI, 1.2–2.4) and 1.5 for stroke (95%CI, 0.7–1.9); annual risks for these two events were 1.2% and 0.4%, respectively, in agreement with our findings. Higher rates of cardiovascular events were noted in other studies. In hospital-based cohorts, incidence rates were 1.6/100 patient-years [3] and 5.2/100 patient-years [11]. Table 5 reports data from studies of the cardiovascular risk associated with RA. The discrepancies across studies may be ascribable to differences in disease severity (e.g., different disease durations or hospital-based vs. community-based recruitment), in the prevalence of cardiovascular events, or in the methods used to detect cardiovascular events. Nevertheless, these studies consistently showed an about 50% increase in the risk of cardiovascular events in patients with RA. We did not include a control group. However, in the general population in France having the same age and gender distribution as our study population, the annual risk of myocardial infarction is 0.1–0.5% [24] and the annual risk of stroke is 0.07% [25]. Our results are the first to be obtained in France. They suggest that the excess risk associated with RA may be present consistently, in all populations. Several studies investigated measurements of atheroma (e.g., arterial stiffness or carotid plaque) instead of clinical events. Both conventional cardiovascular risk factors and inflammatory rheumatoid manifestations were significantly associated with atheroma of the carotid arteries [19,26]. In our population, we found no increase in cardiovascular mortality in patients with recent-onset RA. Conceivably, early aggressive management of the disease may influence the cardiovascular risk [27–29].

The factors independently associated with cardiovascular events in our study were well-recognized cardiovascular risk factors: older age, male gender, hypertension, and hypercholesterolemia. However, we included treated hypercholesterolemia in our evaluation of cardiovascular risk factors, which may have influenced the effect of hypercholesterolemia. Our results are consistent with other studies showing a predominant effect of conventional cardiovascular risk factors (older age,

Table 5
Risk of myocardial infarction and stroke in studies of patients with rheumatoid arthritis

	Recruitment	Number of patients and number of RA cases	Follow-up	Overall mortality RR or SMR/absolute risk RA	Myocardial infarction RR or SMR/absolute risk RA	Stroke RR or SMR/absolute risk RA
Watson et al. [3]	Population-based (UK)	2.37×10^6; 11,633 RA	4.7 years (0–12)	RR = 1.6; 3.2/100 patient-years	RR = 1.6; 1.6/100 patient-years	RR = 1.4; 0.76/100 patient-years
Solomon et al. [4]	Population-based (USA)	114,342; 527 RA	2.4×10^6 person-years	–	RR = 2; 1.1/100 patient-years	RR = 1.48 (0.7–3.12); 0.3/100 patient-years
Gabriel et al. [5]	Hospital	450 RA	–	–	R = 1.35	–
Myllykangas-Luosujarvi et al. [7]	Population-based (Finland)	Death certificates 1186 RA in 1 year	–	SMR = 1.34	SMR = 1.51	–
Wolfe et al. [10]	Hospital (USA)	3501 RA (4 centers)	9–35 years	SMR = 2.26 1.3/100 patient-years	RR = 3.96	SMR = 2.45
Del Rincon et al. [11]	Hospital (USA)	4871; 236 RA	35,631 patient-years 252 patient-years with RA	SMR = 1.57	SMR = 1.54; 5.2/100 patient-years	–
Fischer et al. [12]	Population-based (England)	33,329; 208 RA	–	–	RR = 1.47	–
Maradit-Kremers et al. [13]	Hospital (USA)	603 RA	15 years	SMR = 2	RR = 3.17	–
Turesson et al. [14]	Population-based (Sweden)	207,846; 1022 RA	–	SMR = 1.60; 4.4/100 patient-years	SMR = 1.76; 1.2/100 patient-years	SMR = 1.21; 0.4/100 patient-years
Bjornadal et al. [15]	Population-based (Sweden)	61,899 RA	574,561 patient-years	SMR = 2.03	SMR = 1.79	SMR = 1.5

RR: relative risk; SMR: standardized mortality ratio.

male gender, hypertension, hypercholesterolemia, smoking, and diabetes mellitus) in the occurrence of cardiovascular events in patients with RA [16,17]. In our second Cox model, treated osteoporosis or a history of osteoporotic fractures was associated with cardiovascular events. Nevertheless, this result should be interpreted with circumspection given the small number of patients in the second model. In addition, we were not able to evaluate the cumulative glucocorticoid dose, which may have acted as a confounder. Peripheral vascular disease was significantly associated with osteoporosis in a recent study [23]. Joint destruction correlated with low cortical bone mineral density, suggesting that this last feature may indicate aggressive RA [30]. Alternatively, both atheroma and osteoporosis may indicate poor general health. Severe joint destruction as evaluated based on the need for joint replacement surgery was not associated with cardiovascular events. However, a radiographic study would allow a more accurate assessment. In several studies, laboratory evidence of inflammation or a low body mass index was associated with cardiovascular events in patients with RA, independently from conventional cardiovascular risk factors [8,11,16,17,31]. In addition, systemic inflammation, which is among the hallmarks of RA, contributes to the pathophysiology of atheroma [18–20]. In the general population, high levels of acute-phase reactants such as C-reactive protein or fibrinogen are risk factors for cardiovascular events [32]. Anti-inflammatory drugs used to treat RA, most notably TNF antagonists and methotrexate, have been reported to improve endothelial function [33] and to decrease cardiovascular mortality [34,35]. We found no effect of medication use on cardiovascular risk. However, 84% of patients were treated with methotrexate, so that the group of nonusers may have been too small to allow detection of a significant difference. Methotrexate may decrease cardiovascular mortality [35]. The preponderant role for conventional cardiovascular risk factors in our study indicates that risk factor detection and management should be pursued aggressively in patients with RA.

Our data suggest greater severity of cardiovascular events in patients with RA. Thus, of the 10 patients who experienced myocardial infarction, 5 exhibited clinical manifestations of congestive heart failure and 4 died from cardiovascular cause's 1.6 ± 1.1 years on average after the event. In the general population, death and congestive heart failure occur in about 20% of patients after myocardial infarction [36]. Few studies have evaluated the severity of cardiovascular events in patients with RA. Greater severity of these events, together with an excess risk of atheroma, may contribute to the excess mortality seen in RA patients. In a case–control study of patients with myocardial infarction, 40% of patients with RA died, compared to 15% of patients without RA [37]. Conceivably, patients with RA may ascribe chest pain to their joint disease, which may delay the diagnosis and management of cardiovascular disease [13]. In keeping with this hypothesis, the number of admissions for cardiovascular disease was similar in patients with and without RA, but mortality was higher in the group with RA, indicating delayed treatment [38]. In a case–control study comparing selective coronary arteriogram from 75 patients with RA and 128 patients with similar conventional cardiovascular risk factors but no RA, the coronary artery lesions were more diffuse in the RA group [39].

In addition, the rheumatoid inflammatory process may promote multiple plaque rupture, increase the risk of re-stenosis, and exacerbate ventricular remodeling [21].

Because we used a historical cohort, we were unable to evaluate parameters such as the Health Assessment Questionnaire score or variations in inflammatory parameters during the course of the disease [8,11,16,17,20]. Prospective studies are needed to assess these factors. In addition, we were unable to assess the impact of risk factor management or RA control on the risk of cardiovascular events. Nevertheless, the excess cardiovascular mortality in our cohort is similar in magnitude to that reported in prospective studies. The severity of cardiovascular events in patients with RA, which was not assessed in earlier studies, should be evaluated further. Our data suggest that increased severity of cardiovascular events may contribute to the excess mortality seen in RA patients. Finally, we were unable to evaluate the role for glucocorticoid therapy or nonsteroidal antiinflammatory drugs, which have been suggested to influence the risk of cardiovascular events. Specific studies are needed to investigate this issue.

Our results suggest an increased risk of cardiovascular events in patients managed in France for RA. In addition, they raise the possibility that increased severity of cardiovascular events may contribute to the excess mortality seen in patients with RA. Therefore, patients with RA and a previous cardiovascular event should be considered at high risk for severe complications in the short and medium term. Conventional cardiovascular risk factors were significantly associated with clinical events in our cohort. Patients with RA should be carefully evaluated for cardiovascular risk factors, which should be treated aggressively.

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