Disease Duration and Severity Impacts on Long-term Cardiovascular Events in Japanese Patients with Rheumatoid Arthritis

Long-term CV events in Japanese RA patients

Key words: Cardiovascular disease, Risk factors, Inflammation

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Abstract

Background: Rheumatoid arthritis (RA) increases mortality and morbidity of cardiovascular disease (CVD). However, the relationship between RA and the risk of CVD in the Japanese population remains unclear.

Methods and Results: This study comprised 571 RA patients who admitted to Juntendo University Hospital from January 1990 to December 2000. The cardiovascular events (CVEs) were defined as cardiac death, acute coronary syndrome (ACS), symptomatic stroke, and congestive heart failure. During mean follow-up of 11.7 ± 5.8 years, 7.5% of patients died from all causes and 11.0% developed CVEs. Morbidity of stroke and ACS was 3.6 and 2.5 per 1000 person-years, respectively. Mean disease duration of RA at enrolment was significantly longer in patients with CVEs than in those without CVEs (15.0 ± 12.7 vs. 10.8 ± 9.7 years, $P = 0.01$). Physical disabilities due to RA were severer in patients with CVEs compared with those without CVEs. Patients with a long disease duration with RA showed significantly higher event rates ($P = 0.033$). Cox proportional hazards analysis identified longer RA duration as an independent risk factor for CVD (HR 1.64, 95% CI 1.15–2.40, $P = 0.007$).

Conclusion: Japanese RA patients showed a relative high incidence of CVD, despite the fact that they had few coronary risk factors. The disease duration of RA was an independent risk factor for CVEs. **(219 words)**

Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects approximately 0.3% of the Japanese population.[1] RA leads to progressive joint deformity, long-term physical disability, and an increased mortality risk from multiple comorbidities. In the Western population, several studies have demonstrated that cardiovascular disease (CVD) is related to the prognosis of RA patients, although they had few traditional coronary risk factors.[2-7] CVD mortality in RA patients was found to be increased by as much as 50% compared with that in non-RA patients.[8, 9] Another study reported that RA patients were 60–70% more likely to die and 30–60% more likely to suffer a vascular event compared with osteoarthritis patients and those with no arthritis.[10] RA has recently been reported to be the cardiovascular risk equivalent of diabetes in European countries.[7, 11]

However, the relationship of RA with long-term outcomes, including cardiovascular events (CVEs), in the Japanese population remains unclear. To elucidate the impacts on RA on CVEs, we assessed the long-term prognosis in Japanese RA patients.

Methods

Study population

This was a retrospective study investigating the long-term outcomes of RA patients. We collected the medical records of 606 consecutive patients admitted to Juntendo University Hospital from January 1990 to December 2000 who had been diagnosed with RA. The reasons for hospitalization varied, with the most prevalent (37.3%) being the thorough examination of collagen diseases including RA, followed by complications by orthopedic

diseases (23.5%). We evaluated patient data including age, sex, present illness, past history, history of smoking, blood pressure (BP), body mass index (BMI), laboratory data, medications, and duration and severity of RA at enrolment. To determine the severity of RA, we used the Steinbrocker classification, which depicts the level of physical functional status in RA. We excluded patients who had a history of malignancy, or those who were diagnosed with juvenile idiopathic arthritis or adult Still's disease. Pregnant women were also excluded.

Finally, 571 patients were enrolled in this study. For each patient, in-hospital data of fasting blood samples were collected for C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), total cholesterol (TC), triglycerides (TG), creatinine, and fasting glucose levels. Furthermore, estimated glomerular filtration rate (eGFR) was calculated using serum creatinine levels, age, and gender. This study was approved by the institutional review board of Juntendo University Hospital.

Definition of RA

A confirmed diagnosis of RA was based on the diagnostic criteria advocated by the American College of Rheumatology in 1987.[12]

Definition of risk factors

Covariates were selected on the basis of their potential relationship with either arthritis or CVD incidents. BMI was defined as weight in kilograms divided by height in meters squared. Hypertension (HT) was defined as taking anti-hypertensive drugs or having been diagnosed with HT in the past. Diabetes mellitus (DM) was defined as taking medications

(insulin or oral hypoglycemic drugs) or having been diagnosed with DM in the past. Smoking status was determined by patient self-report. In addition, use of acetylsalicylic acid (ASA), a non-steroidal anti-inflammatory drug (NSAID), statins, immunosuppressants (i.e., methotrexate and mizoribine), or other disease-modifying antirheumatic drugs (DMARDs: i.e., gold salts, D-penicillamine actarit, and lobenzarit) were determined by evaluating all medications taken during the period of hospitalization. This study population had not received newly developed biological medicines (i.e., TNF-alpha inhibitors and interleukin-6 receptor-inhibiting monoclonal antibodies).

Definition of incidence of CVEs

CVEs were defined as cardiac death, acute coronary syndrome (ACS), symptomatic stroke, and congestive heart failure (CHF) requiring hospitalization. ACS was identified among patients with acute myocardial infarction (AMI) or unstable angina (UAP). AMI was diagnosed based on the presence of typical chest pain with ST-segment elevation on electrocardiogram and increased serum creatine kinase levels. UAP was diagnosed according to Braunwald's clinical classification (Class I, II, and III). [13] Patients with UAP showed characteristic chest pain symptoms associated with transient ischemic ST-segment shifts and normal serum creatine kinase levels. All ACS patients underwent coronary angiography which demonstrated significant stenosis in at least one major coronary artery.[14] Stroke was defined according to World Health Organization (WHO) criteria as a focal neurological disorder with rapid onset persisting for at least 24 h or until death, which includes ischemic stroke and hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage),

and excluding transient ischemic attacks (defined as focal neurological symptoms lasting less than 24h), subdural hemorrhage, epidural hemorrhage, poisoning, and symptoms caused by trauma. Stroke diagnoses were verified by a neurologist.[15] Morbidity and mortality surveillance was conducted by monitoring hospital records from Juntendo University Hospital. The medical records of all deaths and selected morbidity outcomes including CVD were evaluated. The follow-up duration was calculated as the time between baseline examination and the endpoint, i.e., fatal or non-fatal CVE or death or last date of visit, whichever came first.

Statistical analyses

Continuous variables are expressed as mean ± standard deviation (SD) and were compared using the Student's *t*-test. Categorical data were tabulated as frequencies and percentages, and compared using the chi-square test or Fisher's exact test. The Kaplan–Meier estimation with a log-rank test was used for unadjusted analysis. We calculated the hazard ratio (HR) with 95% confidence intervals (CI) for each endpoint of each subgroup relative to the reference category, using the multivariate Cox proportional hazards model with adjustments for age, gender, BMI, BP, TC, creatinine, glucose levels, Steinbrocker classification, and duration of RA. Logistic regression analysis was adjusted for multiple potential confounders (age, gender, mean BP, BMI, CRP, TC, creatinine, glucose levels, and medical treatment). A P-value < 0.05 was considered significant. All data were analyzed using JMP software (SAS Institute, Cary, NC, USA).

Results

Baseline characteristics and coronary risk factors

Baseline characteristics of patients are shown in Table 1. The prevalence of classical coronary risk factors was relatively low in the study population. Most of patients were females, non-obese, and had normal BP. In addition, most of patients had normal levels of TC, TG, fasting glucose, and eGFR. However, the levels of several inflammatory markers were high, indicating the presence of inflammation from RA. As for medication, 397 patients had steroids, 38 had ASA, 35 had statins, 92 had immunosuppressants and 267 had other DMARDs.

Analysis for mortality and CVEs

The mean follow-up period was 11.7 ± 5.8 years. During this period, 43 patients (7.5%) died from all causes and 63 patients (11.0%) developed CVEs (Table 2). Morbidity of stroke was 3.6 per 1000 person-years and that of ACS was 2.5 per 1000 person-years.

In addition, we examined differences in characteristics between patients with and without CVEs (CVE and non-CVE group). As shown in Table 3, patients with CVEs were significantly older, more likely to be males, and more likely to have HT, DM, and a past history of CVD. Thus, there were more ASA users in the CVE group at baseline. There were no significant differences in steroid use or the mean dose of steroids converted to the equivalent dose of prednisolone (8.4 ± 6.1 vs. 8.1 ± 7.5 mg/dl), between patients with and

without CVEs. According to laboratory data, patients with CVEs had significantly lower levels of eGFR than those without CVEs. TG levels were significantly higher in patients with CVEs than those without CVEs. TC, glucose levels, and levels of inflammatory markers did not differ between the two groups.

Focusing on RA, the mean disease duration of RA at enrollment was significantly longer in the CVE group. Moreover, Steinbrocker functional classification was relatively worse in the CVE group. We compared patients with mild physical disability (mild RA group, defined as Steinbrocker classification 1 or 2) and those with severe physical disability (severe RA group, defined as class 3 or 4). The CVE group tended to consist of patients with severe RA. We divided the study patients into tertiles based on disease duration of RA at enrolment. Mean durations of RA in each group (the Short, Moderate and Long groups) were 1.4 ± 1.5, 9.2 ± 2.6, and 22.6 ± 8.2 years, respectively. In our study population, significantly higher event rates occurred in patients who had a longer RA duration compared with patients in the first tertile of RA duration.(Figure 1A). Furthermore, severe physical disability due to RA was associated with an increase in CVE comorbidity, but this was not significant (Figure 1B). Cox proportional hazards analysis identified longer RA duration at enrollment as an independent risk factor for CVEs (HR 1.64, 95% CI 1.15–2.40, $P = 0.007$) (Table 4) after adjustment for age, gender, mean BP, BMI, CRP, TC, and creatinine and glucose levels. In addition, longer RA duration at enrollment was still an independent risk factor for CVE after adjustment for usages of steroids, ASA, statins, immunosuprressants and other DMARDs (HR 1.04, 95% CI 1.01–1.07, $P = 0.02$).

Discussion

To the best of our knowledge, this study is the first to evaluate long-term CVEs in Japanese patients with RA. Japanese RA patients have a potential risk for CVD, despite the fact that they have few traditional cardiovascular risk factors. In addition, both RA duration and physical disability were associated with future CVEs. In particular, a longer RA duration was determined to be an independent risk factor for the development of CVDs.

In the Hisayama study, the morbidity of ischemic stroke was 2.6 and 3.6 per 1000 person-years in females and males, respectively, and the morbidity of myocardial infarction was 0.9 and 1.5 per 1000 person-years in females and males, respectively.[16] In the Japan Lipid Intervention Trial (J-LIT), myocardial infarction morbidity of the primary prevention cohort was 0.87 per 1000 person-years (with AP, 1.51 per 1000 person-years) and that of the secondary prevention cohort was 4.24 per 1000 person-years.[17, 18] In our study population, stroke morbidity was 3.6 per 1000 person-years and ACS morbidity was 2.5 per 1000 person-years, although RA patients had few traditional coronary risk factors. According to the Japanese Atherosclerosis Society (JAS) Guidelines for Prevention of Atherosclerosis Cardiovascular Disease 2012, the 10-year risk of CHD death of Japanese subjects who have equivalent risk factors shown in this RA population is less than 0.5%.[19] NIPPON DATA 80 also demonstrated that stroke morbidity was 0.3 per 1000 person-years and CHD morbidity was 0.1 per 1000 person-years in both Japanese men and women who had equivalent risk factors.[20] Because the definition of CVEs in these studies differ from ours, it is difficult to compare results directly; however, CVE morbidity in our patients appeared to be higher, at least, than that of the healthy Japanese population.

A longer RA duration at enrolment was significantly associated with CVEs in our study population. Long RA duration correlated with the risk of CVD, including coronary artery calcification and carotid artery intima–media thickness.[21, 22] The presence of inflammation may potentially explain the increased CVD morbidity in RA patients. Several inflammatory markers linked to CVD, including CRP, fibrinogen, and soluble intercellular adhesion molecule-1, are elevated in patients with RA.[1, 3] These inflammatory cytokines, along with prothrombotic and adhesion molecules, may mediate a predisposition to vascular damage in RA. In an inflammatory state, endothelial cell activation, vascular dysfunction, and subsequent atherosclerosis can develop.[23-26] Moreover, methotrexate, a potent immunosuppressant, has been shown to improve the prognosis of RA patients by reducing CVD mortality.[27] Tumor necrosis factor-α inhibitors may alter the CVD risk of RA patients by increasing HDL-C and adiponectin, improving insulin resistance, and reducing CRP.[28-30] Another explanation is an adverse effect of medical treatment. Particularly, long-term use of steroids may induce atherosclerosis,[31] although steroid treatment did not differ between the CVE and non-CVE group in our study.

The progression of physical disability was also related to the incidence of CVE. Improvement in functional status with higher physical activity may be associated with a decline in AMI mortality in RA patients.[32] The advanced damage of joints in RA has led to the notion that RA patients should rest because exercise may enhance joint damage. However, several studies have provided substantial evidence to reveal that exercise inhibits disease progression and improves both wellbeing and functional ability of RA patients.[33] Physical

activity is closely linked to inflammation, which is an independent risk factor for CVEs.[34-37] Thus, maintaining physical activity in RA patients may be important to prevent the occurrence of future CVEs.

Study limitations

Our study was retrospective, based only on medical records from the Juntendo University Hospital. It is possible that some events may have been lost. Therefore, we may have underestimated the real incidence of CVE. Even if this is taken into consideration, our study showed a relative high incidence of CVEs in Japanese RA patients. In addition, this study has no suitable controls to evaluate the incidence rate of CVE in the Japanese RA population. To establish a definite relationship between RA and CVD, a cohort study should be conducted in Japan, as in the Western countries. Furthermore, since we enrolled patients admitted to our hospital from 1990 to 2000, this study population had not received newly developed biological medicines (i.e., tumor necrosis factor-α inhibitors and interleukin-6 receptor-inhibiting monoclonal antibodies), which have anti-inflammatory effects. Therefore, further prospective studies are warranted to elucidate the effects of these biological medicines on the development of CVD in Japanese RA patients.

Conclusions

Japanese RA patients showed a potential risk for CVD, although they had few coronary risk factors. In addition, a long RA duration and physical disability were found to be risk

factors for future CVEs. Therefore, we should regard RA as a condition associated with a higher risk for CVD and start early to control disease activity in order to lower the risk.

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Disclosure

None.

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Figure legends

Figure 1A

Significantly higher event rates were seen in rheumatoid arthritis (RA) patients with a longer disease duration (log-rank test: $P = 0.048$).

Figure 1B

Patients with severe physical disability due to RA tended to show higher event rates than those with mild physical disability (log-rank test: $P = 0.10$).

Table 1. Baseline characteristics of patients with and without a history of cardiovascular events (CVEs)

	n = 571
Age (years)	58 ± 13
Male (%)	95 (16.6)
BMI (kg/m^2)	21.2 ± 4.1
Current smoker (%)	91 (15.9)
DM (%)	56 (9.8)
Hypertension (%)	93 (16.3)
Systolic BP (mmHg)	126 ± 20
Diastolic BP (mmHg)	72 ± 13
Past history of CHD	37 (6.5%)
Duration of RA (years)	11.3 ± 10.2
Steinbrocker classification	2.2 ± 0.8
Total cholesterol (mg/dl)	183 ± 45
Triglyceride (mg/dl)	114 ± 53
Glucose (mg/dl)	96 ± 28
Creatinine (mg/dl)	0.75 ± 0.78
eGFR (ml/mi/1.73 m^2)	104 ± 45
CRP (mg/dl)	2.9 ± 3.4
ESR (mm/h)	52.3 ± 40.7
Rheumatoid factor (U/ml)	265 ± 808
Medications	
Steroids (%)	397 (70.3)
ASA (%)	38 (6.7)
Statins (%)	35 (6.6)
Immunosuppressants (%)	92 (16.1)

Other DMARDs (%)	267 (46.8)

CHD = coronary heart disease; BMI = body mass index; DM = diabetes mellitus; BP = blood pressure; eGFR = estimated glomerular filtration rate; RA = rheumatoid arthritis; CRP = C-reactive protein**;** ESR = erythrocyte sedimentation rate; ASA = acetylsalicylic acid; DMARDs = Disease-modifying antirheumatic drugs.
Class indicates the Steinbrocker classification, which shows the level of physical functional status in RA.

Table 2. Summary of cardiovascular events (CVEs) and deaths

	N
All cause death (%)	43 (7.5)
Cardiovascular death (%)	8 (1.4)
Coronary heart diseases	3
Stroke	0
Cardiac sudden death	2
Congestive heart failure	3
Cancer (%)	8 (1.4)
Infection disease (%)	14 (2.5)
Gastrointestinal disease (%)	2 (0.4)
Respiratory disease (%)	11 (1.9)
Non-fatal cardiovascular events (%)	55 (9.6)
Acute coronary syndrome (%)	17 (3.9)
Symptomatic stroke (%)	24 (4.2)
Admission of heart failure (%)	14 (2.4)

Table 3. Comparison of characteristics of patients with or without cardiovascular events (CVEs)

	CVE (+) (n = 63)	CVE (−) (n = 508)	*P*
Age (years)	61 ± 9	58 ± 13	0.009
Male (%)	20 (31.7)	75 (14.7)	0.002
BMI (kg/m^2)	21.5 ± 4.6	21.1 ± 4.0	NS
Current smoker (%)	13 (20.6)	78 (15.3)	NS
Past history of CHD (%)	10 (15.9)	27 (5.3)	0.033
DM (%)	11 (17.5)	45 (8.9)	0.041
Hypertension (%)	24 (38.0)	69 (13.6)	<0.001
Systolic BP (mmHg)	131 ± 22	125 ± 20	0.044
Diastolic BP (mmHg)	74 ± 16	71 ± 12	NS
Duration of RA (years)	15.0 ± 12.7	10.8 ± 9.7	0.013
Steinbrocker classification	2.3 ± 0.8	2.2 ± 0.8	NS
Steinbrocker Class 3 or 4	20 (31.7)	111 (21.9)	0.082
TC (mg/dl)	186 ± 47	182 ± 45	NS
Triglyceride (mg/dl)	133 ± 66	112 ± 51	0.031
Glucose (mg/dl)	99 ± 32	95 ± 28	NS
Creatinine (mg/dl)	1.01 ± 1.12	0.72 ± 0.73	0.057
eGFR (ml/mi/1.73 m^2)	68.9 ± 29.7	84.6 ±31.2	<0.001
CRP (mg/dl)	2.62 ± 3.06	2.98 ± 3.48	NS
ESR (mm/h)	51.1 ± 33.9	52.5 ± 41.5	NS
Rheumatoid factor (U/ml)	202 ± 371	272 ± 847	NS
Medications			
Steroids (%)	41 (65.0)	360 (70.9)	NS
ASA (%)	10 (15.9)	28 (5.5)	0.005

Statins (%)	6 (9.5)	29 (5.7)	NS
Immunosuppressants (%)	9 (14.3)	83 (16.3)	NS
Other DMARDs (%)	23 (36.5)	244 (48.0)	NS

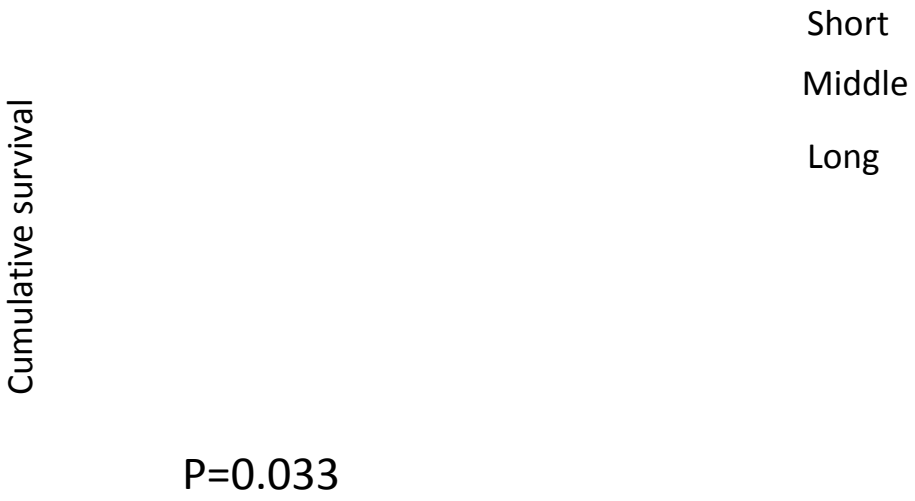
CHD = coronary heart disease; BMI = body mass index; DM = diabetes mellitus; BP = blood pressure; TC = total cholesterol; eGFR = estimated glomerular filtration rate; RA = rheumatoid arthritis; CRP = C-reactive protein**;** ESR = erythrocyte sedimentation rate; ASA = acetylsalicylic acid; DMARDs = Disease-modifying antirheumatic drugs.

Table 4. Multivariate Cox proportional hazards regression analysis for cardiovascular events (CVEs)

	HR	95% CI	*P*
Age	1.01	0.98–1.03	NS
Male	2.32	1.10–4.71	0.039
BMI	0.99	0.92–1.07	NS
Mean BP	1.02	1.00–1.04	NS
TC	1.00	0.99–1.01	NS
Creatinine	1.33	1.03–1.60	0.033
Glucose	1.00	1.00–1.01	NS
RA duration at enrollment	1.64	1.15–2.40	0.007

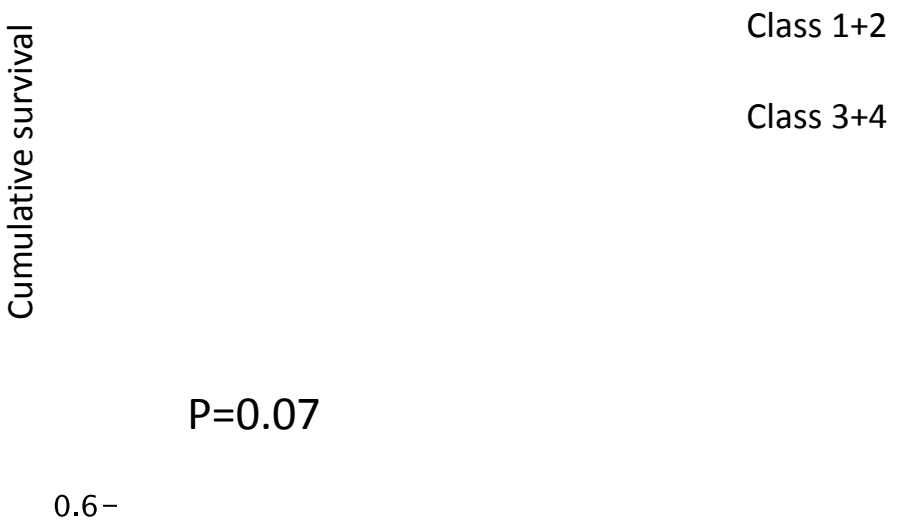
BMI = body mass index; BP = blood pressure; TC = total cholesterol; RA = rheumatoid arthritis

A



Duration of RA at enrolment (years)	Follow-up (years)				
Short (1.4±1.5)	186	177	174	173	173
Middle (9.2±2.6)	188	179	174	168	168
Long (22.6±8.2)	197	178	170	168	167

B



Severity of RA	Follow-up (years)				
Class 1+2	294	276	272	265	265
Class 3+4	131	118	113	111	111