present study was comparable with the one reported in the Institute of Rheumatology, Rheumatoid Arthritis (IORRA) database for the RA patients treated with TAC, which is 7.0 mg/day [32].

In this study, 21 serious respiratory, thoracic and mediastinal disorders were reported and 15 of these were interstitial pneumonia (IP). Regarding the outcome of 15 patients (16 cases); 4 cases died, 4 cases improved, 3 cases resolved, 3 cases are unknown, 2 cases did not improve. Corticosteroid was administered in 13 patients and the daily dose of corticosteroid in 3 patients when IP occurred was higher than the mean daily dose (6.8 mg/day at baseline, 6.1 mg/day at week 24). The case report forms of 13 patients said "worsening of IP" and of these, comorbidity of IP was reported in 12 patients. It has been reported that TAC-associated IP depicts various imaging patterns on thoracic computed tomography [33]. TAC-associated IP is sometimes life-threatening and should be included in differential diagnoses in RA patients who develop respiratory symptoms during treatment with TAC.

Toxicity or tolerability issues for MTX such as liver dysfunction, cytopenia, or interstitial pneumonia have been reported [34–37]. It may be useful to evaluate the effectiveness of TAC in patients who cannot tolerate further increase of MTX dose. It has been recently demonstrated that the addition of TAC to MTX for the treatment of active Japanese RA patients who failed with MTX monotherapy was effective [38, 39].

Limitations of this study include that DAS28 scores were reported in only 680 patients, and that not all RA patients who were treated with TAC were registered during the registry period.

In conclusion, this study provides evidence that TAC is well tolerated in Japanese patients with active RA. In addition, given that several risk factors were identified, screening of these risk factors prior to the treatment with TAC and careful monitoring for ADRs are necessary to obtain better benefit-risk balance of treatment with TAC.

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ORIGINAL ARTICLE
Preventive Medicine

Assessing the Cardiovascular Risk Between Celecoxib and Nonselective Nonsteroidal Antiinflammatory Drugs in Patients With Rheumatoid Arthritis and Osteoarthritis

– A 3-Year Nationwide Comparative Observational Study in Japan (ACCEPT) –

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Background: A prospective, 3-year comparative observational study compared the risk of cardiovascular events in patients with osteoarthritis or rheumatoid arthritis prescribed celecoxib or a nonsteroidal antiinflammatory drug (NSAID).

Methods and Results: Patients prescribed celecoxib (n=5,470) or NSAIDs (n=5,059) between November 1, 2007, and July 31, 2008 in 1,084 hospitals and clinics in Japan were eligible for safety analysis. Mean (standard deviation) observation for the celecoxib group was 716 (420) days and 692 (426) days for the NSAID group (P=0.004). Composite I (adjudicated cardiovascular adverse events of myocardial infarction, angina pectoris, heart failure, cerebral infarction, cerebral hemorrhage) number of events (percentage) and rate/1,000 person years was 66 (1.2%) and 6.2 (10,745 person years), respectively, for the celecoxib and 65 (1.3%) and 6.8 (9,601 person years) for the NSAID (P=0.58) groups. Composite II (all cardiovascular events) number of events (percentage) and rate/1,000 person years was 79 (1.4%) and 7.4, respectively, for the celecoxib and 84 (1.7%) and 8.8 for the NSAID (P=0.26) group. Adjusted Cox hazards ratio (95% confidence interval) was 0.89 (0.63–1.27; P=0.52) for Composite I, 0.87 (0.63–1.19; P=0.39) for Composite II and 1.03 (0.75–1.41; P=0.87) for death from all causes.

Conclusions: After adjustment for confounding variables, celecoxib was not associated with an increase of cardiovascular risk in comparison with nonselective NSAID in Japanese patients with rheumatoid arthritis or osteoarthritis in an observational setting. (*Circ J* 2014; **78:** 194–205)

Key Words: Cardiovascular risk; Celecoxib; Nonsteroidal antiinflammatory drug (NSAID); Osteoarthritis; Rheumatoid arthritis

Osteoarthritis (OA) and rheumatoid arthritis (RA) are chronic painful conditions that affect an individual's quality of life. Clinical guidelines recommend the use of nonsteroidal antiinflammatory drugs (NSAIDs) for the relief of pain and inflammation.[1–5] The cyclooxygenase-2 (COX 2) selective NSAID, celecoxib, has proven efficacy in relieving pain and inflammation and improving physical function in patients with OA or RA.[6–12]

NSAID use is associated with a risk of adverse events, including cardiovascular risk.[13–15] The risk of cardiovascular adverse events following celecoxib treatment has been reported in randomized controlled trials,[16–18] a meta-analysis,[19] systematic reviews,[20] and observational studies.[14] In particular, a meta-analysis reported no significant increases in nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death when patients treated with celecoxib 200–800 mg daily were compared

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with patients treated with nonselective NSAIDs (nsNSAIDs: diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen) or placebo.[19] However, a systematic review of population-based controlled observational studies reported an elevated cardiovascular risk overall at both low (≤200 mg daily) and high doses (>200 mg daily) of celecoxib.[14]

In 2007, celecoxib was first approved for clinical use for RA and OA.[21] The aim of this 3-year observational study was to examine the onset of cardiovascular adverse events in patients from Japan with RA or OA and compare cardiovascular adverse events among patients treated with celecoxib and nsNSAIDs.

Methods

This study was a prospective, nonblinded, non-randomized, 3-year comparative observational study to assess the occurrence of cardiovascular adverse events in patients with OA or RA prescribed either celecoxib (daily dose 200 mg for OA and 200–400 mg for RA) or comparator NSAID (allocation ratio 1:1) under a post-marketing setting in Japan. A total of 1,084 hospitals and general practice clinics were selected nationwide and included in this observational study. The investigators included orthopedic or rheumatologic physicians with experience of prescribing NSAIDs. Patients were included if they were prescribed celecoxib or NSAID between November 1, 2007, and July 31, 2008, and were enrolled in the study within 10 days of starting treatment. All patients were registered centrally using the Pharmaceuticals Post-Marketing Investigations Data Collection System (Fujitsu, Tokyo, Japan). As this was an observational study, there were no prespecified inclusion and exclusion criteria, other than in accordance with package insert.

Informed consent was not required because this non-interventional observational study did not impose a risk for patients.[22] The study protocol was reviewed and filed by the domestic regulatory agency (PMDA: Pharmaceuticals and Medical Devices Agency, Japan) and approved by institutional review boards at individual study sites, but not at all sites. The study and data collection were conducted by Astellas Pharma Inc in accordance with the Pharmaceutical Affair Act, Good Post-Marketing Study Practice in Japan and the Helsinki Declaration. All authors were advisory board members of the study and participated in the interpretation of the data and preparation of the manuscript. Astellas Pharma Inc takes responsibility for the accuracy and completeness of the data and analyses.

Study Design

This was a prospective, observational study with 4 predefined observation periods: visit 1, start day of treatment to 6 months; visit 2, 6 months to 1 year; visit 3, 1 year to 1.5 years; and visit 4, 1.5 years to 3 years. Demographics, baseline characteristics (diagnosis, sex, out-/inpatient status, age, height, weight, body mass index, preexisting cardiovascular and other diseases [diabetes mellitus, hypertension, lipid disorder], hepatic impairment, renal impairment, habitual behaviors), and pre-study medication (NSAIDs, low-dose aspirin, antithrombotic drugs) data were collected. Celecoxib and NSAID treatment information (start date [index date]), concomitant medication, survival, and onset of cardiovascular adverse events were collected at each observation period. Initial overall improvement (up to 12 weeks) was also recorded for the celecoxib group.

Observational data were collected for all patients throughout the study period, irrespective of switching to other NSAIDs or discontinuation of treatment.

Outcome Measures

Cardiovascular adverse events (regardless of causality) of myocardial infarction, angina pectoris, heart failure, cerebral infarction, cerebral (or subarachnoid) hemorrhage (Composite I), all other cardiovascular events including arrhythmia, atrial fibrillation, aorta dissociation, pulmonary embolism, peripheral embolism, and peripheral arterial disease (Composite II), and all causes of death were monitored throughout the observational period and follow-up visits. Cardiovascular events and/or death were primarily diagnosed by a physician. Details of the diagnosis and paper-based clinical descriptions, clinical records, and laboratory tests that were obtained from the clinical sites were provided to the event adjudication committee. All adverse events were coded according to criteria from the Medical Dictionary for Regulatory Activities (MedDRA), version 14.1.

Adjudication of cardiovascular adverse events was conducted by a blinded adjudication committee, consisting of 3 medical experts not involved in the study. The committee categorized each event as cardiovascular-related or not. If the event was considered to be cardiovascular-related, it was further categorized as either a Composite I or other adverse event. The following events were excluded from the outcome analysis: hypertension, tachycardia, Wolff-Parkinson-White syndrome, traumatic cerebral hemorrhage or cerebral contusion, transient ischemic attack, postoperative (within 14 days) deep vein thrombosis, and infectious pump failure. The committee further categorized the liability of each event using a grading scale from A to E: (A) cardiovascular-related event confirmed by available data; (B) lack of data but confirmed by clinical practice and procedure, especially if the available data documented emergency rescue or surgery; (C) site physicians' diagnosis; (D) site physicians suspected event as cardiovascular-related without available data, but based on their clinical confidence; and (E) noncardiovascular-related event confirmed by available data. Fatal cases of reported cardiovascular events were considered upper-graded liability compared with nonfatal cases. Categorized A, B, and C events were provided for statistical analysis.

Statistical Analysis

The incidence of cardiovascular adverse events, including the new onset of stroke and ischemic heart disease in the cohort study of residents of Hisayama, Japan, was roughly estimated at 6.9/1,000 person years.[23] Although there were no epidemiological data available to show the emergence of cardiovascular diseases specifically in patients with OA or RA nor head-to-head comparative studies assessing cardiovascular events, it was determined that approximately 100 events might occur in both treatment groups if up to 5,000 patients were enrolled in each group and followed for up to 3 years after the start of observation. Therefore, the specified target number of 10,000 patients empirically allowed the comparison of the onset of cardiovascular adverse events between the celecoxib and nsNSAID groups. The study was not designed to be confirmatory (hypothesis testing) or to determine noninferiority of celecoxib compared with nsNSAIDs. As the study was observational, it was not necessary to calculate total patient numbers/observations to determine predefined significance levels (for noninferiority), statistical power, or drop-out rates.

The statistical comparisons between the celecoxib and nsNSAID groups were conducted by log-rank test for cumulative event rates, calculated using the Kaplan-Meier method, and by χ^2 test for hazard ratio (HR), calculated using the Cox proportional hazard models. Time-dependent Cox proportional hazard models were used to analyze risk of cardiovascular events or

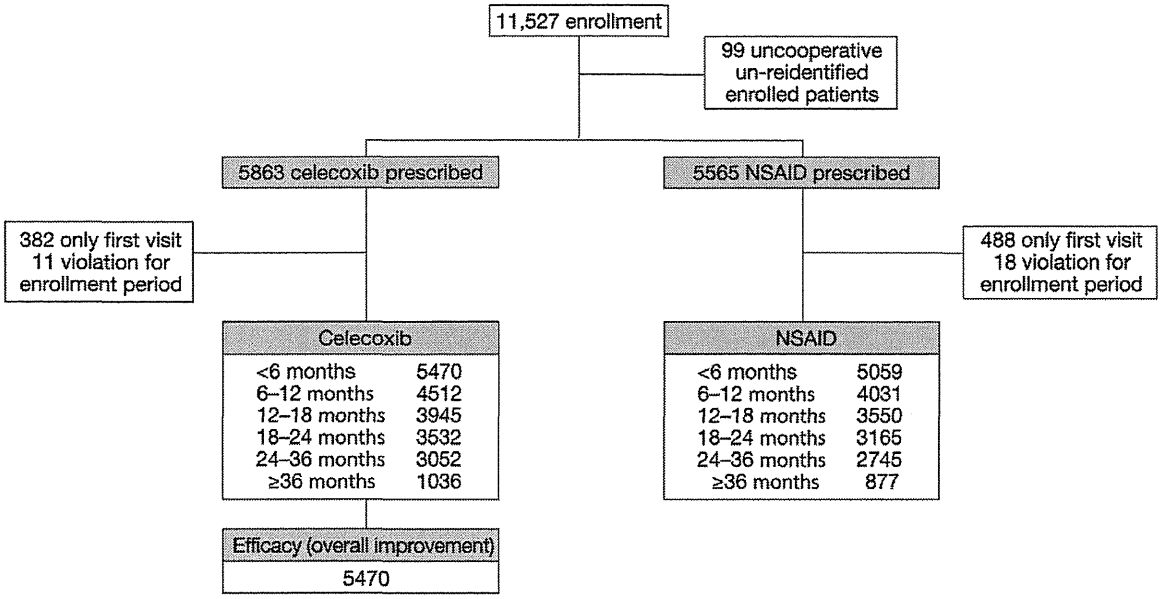

Figure 1. Patient disposition. NSAID, nonsteroidal antiinflammatory drug.

death in the 2 groups. HRs, calculated by the SAS PHREG procedure (SAS Institute Inc), were adjusted by potential confounding variables (diagnosis, sex, age, preexisting cardiovascular or other disease, and concomitant medications). Diagnosis was automatically included as a confounding variable. Other variables (continuous and categorical) with an unadjusted odds ratio of 2-fold or more determined by the univariate logistic regression model were also selected as confounding variables.

Using this model, the unadjusted odds ratio, 95% confidence interval [CI] and P value (Wald χ^2 test) of all emergent cardiovascular events (Composite II) (objective/response variable) for each explanatory variable (eg, sex, age, etc) were calculated in each group (celecoxib or NSAID). Further details are available in **Table S1**. New-onset events were included in the analysis if they occurred after the index date. Recurrence of the same event after the index date was not included in the analysis. The standardized incidence rates (rate/1,000 person years), time-to-first event analysis of Kaplan-Meier and Cox proportional hazards regression were analyzed for both Composite I and Composite II adjudicated cardiovascular adverse events (regardless of causality).

Patients with RA or OA could have multiple treatments with the same or different drugs during the clinical course. Patients in the primary study population were observed up to the end of the study period or to their first event, regardless of drug shift (last observation). The secondary study population included patients who switched drugs during the study period; these patients were censored on the date of drug shift (censored if shifted). In the NSAID group, intrashift among NSAIDs was not regarded as shifted in this analysis. Subgroup analysis by patient background was also conducted for this study population.

Statistical analysis was conducted using SAS, version 9.2. A P-value of <0.05 was considered significant and the 95% CI was 2-sided. Statistical analysis was conducted by Bell Medical Solutions Inc (Tokyo, Japan).

Results

Patients' Characteristics

In total, 11,527 patients with OA/RA from 1,084 clinical sites were enrolled in this comparative observational study between November 2007 and July 2008 (**Figure 1**); 5,470 patients with OA/RA were prescribed celecoxib and 5,059 patients were prescribed an NSAID and were eligible for safety analysis.

A diagnosis of OA applied to 4,277 (78.2%) patients in the celecoxib group and 4,287 (84.7%) patients in the NSAID group (P<0.001) (**Table 1**). The mean age was 68.5 years in the celecoxib group and 68.2 years in the NSAID group (P=0.24). The mean body mass index was 23.8 kg/m^2 and 24.0 kg/m^2 in the celecoxib and NSAID groups, respectively (P=0.01). A total of 4,248 (77.7%) patients in the celecoxib group and 3,769 (74.5%) patients in the NSAID group were female (P<0.001) and 7.3% and 7.4% of the patients in the celecoxib and NSAID groups, respectively, had preexisting cardiovascular disease (P=0.85). The mean observation duration was 716 days for the celecoxib group and 692 days for the NSAID group (P=0.004). Concomitant medication with anti-RA drugs was used by 17.6% of patients in the celecoxib group and by 11.9% in the NSAID group (P<0.001); 13.2% and 9.0% of patients in the celecoxib and NSAID groups, respectively, were using steroids (P<0.001). A total of 87.7% of the patients received a daily mean dose of celecoxib ≤200 mg. The initial overall improvement rate (marked and moderate) for celecoxib was 55.0% for RA (12 weeks) and 64.9% for OA (4 weeks).

Incidence of Adjudicated Cardiovascular Events

In the primary population (last observation), the number of cardiovascular Composite I (adjudicated) events and the standardized rate/1,000 person years was 66 (1.2%) and 6.2 in the celecoxib group and 65 (1.3%) and 6.8 in the NSAID group, respectively (**Table 2**). The HR (95% CI) was 0.89 (0.63–1.27) (P=0.52) when adjusted for confounding factors. The adjusted

Table 1. Characteristics of Patients With Arthritis in the 2 Treatment Groups

	Celecoxib	NSAID	P value
No. of pts.	5,470	5,059	
Diagnosis			
RA	1,193 (21.8)	772 (15.3)	<0.001
OA	4,277 (78.2)	4,287 (84.7)	
Sex			
Female	4,248 (77.7)	3,769 (74.5)	<0.001
Out/inpatient			
Out	5,377 (98.3)	5,006 (99.0)	0.004
Age (years)			
<65	1,767 (32.3)	1,692 (33.4)	0.21
≥65	3,703 (67.7)	3,367 (66.6)	
≥75	1,888 (34.5)	1,690 (33.4)	0.23
Mean±SD	68.5±12.0	68.2±11.8	0.24
(Min, max)	(18, 97)	(15, 96)	
Height (cm)			
Mean±SD	153.6±8.4	154.3±8.6	0.003
Weight (kg)			
Mean±SD	56.2±11.0	57.4±11.4	<0.001
Body mass index (kg/m²)			
Mean±SD	23.8±3.9	24.0±4.0	0.01
Preexisting cardiovascular disease			
Yes	402 (7.3)	372 (7.4)	0.85
MI	20 (0.4)	15 (0.3)	0.56
AP	159 (2.9)	151 (3.0)	0.73
HF	68 (1.2)	39 (0.8)	0.02
Cel	109 (2.0)	114 (2.3)	0.31
CH	1 (0.0)	2 (0.0)	0.51
Other	124 (2.3)	102 (2.0)	0.43
Other preexisting disease			
Yes	2,178 (39.8)	1,986 (39.3)	0.93
DM	450 (8.2)	394 (7.8)	0.52
Hypertension	1,734 (31.7)	1,565 (30.9)	0.67
Lipid disorder	799 (14.6)	742 (14.7)	0.73
Hepatic impairment			
Yes	145 (2.7)	135 (2.7)	0.57
Renal impairment			
Yes	121 (2.2)	114 (2.3)	0.54
Habitual behaviors			
Current smoker	345 (6.3)	337 (6.7)	0.18
Alcohol consumption	596 (10.9)	559 (11.0)	0.40
Exercise	530 (9.7)	412 (8.1)	0.02
Observation day			
Mean±SD	716.4±419.6	692.4±426.1	0.004
(Min, max)	(1, 1,370)	(2, 1,355)	
Median	924.0	862.0	
Prescription day			
Mean±SD	434.5±428.6	391.9±416.0	<0.001
(Min, max)	(1, 1,370)	(1, 1,348)	
Median	244.0	186.0	
Prescription shift			
Yes	1,006 (18.4)	974 (19.3)	0.26
Prescription at start			
Celecoxib	5,470 (100)		
Loxoprofen		1,742 (34.4)	
Etodolac		1,144 (22.6)	

(Table 1 continued the next page.)

	Celecoxib	NSAID	P value
Meloxicam		849 (16.8)	
Lornoxicam		372 (7.4)	
Diclofenac		352 (7.0)	
Zaltoprofen		293 (5.8)	
Other		307 (6.1)	
Pre-study medication			
NSAID			
Yes	1,656 (30.3)	1,109 (21.9)	<0.001
Low-dose aspirin			
Yes	221 (4.0)	196 (3.9)	0.73
Antithrombotic drugs			
Yes	171 (3.1)	170 (3.4)	0.45
Concomitant medication			
Low-dose aspirin			
Yes	243 (4.4)	228 (4.5)	0.87
Antithrombotic drugs			
Yes	243 (4.4)	219 (4.3)	0.78
Heart failure therapeutics			
Yes	82 (1.5)	54 (1.1)	0.05
Antianginal therapeutics			
Yes	137 (2.5)	110 (2.2)	0.26
Antiarrhythmic therapeutics			
Yes	68 (1.2)	60 (1.2)	0.79
Antirheumatic drugs			
Yes	960 (17.6)	604 (11.9)	<0.001
Steroids			
Yes	722 (13.2)	453 (9.0)	<0.001
Celecoxib daily mean dose (mg)*			
≤200	4,799 (87.7)		
>200	598 (10.9)		
Celecoxib overall improvement, marked and moderate (%)			
RA	55.0		
OA	64.9		

Values are n (%) unless otherwise specified. *As-needed prescription cases were not included.
AP, angina pectoris; CH, cerebral hemorrhage; CeI, cerebral infarction; DM, diabetes mellitus; HF, heart failure; OA, osteoarthritis; MI, myocardial infarction; NSAID, nonsteroidal antiinflammatory drug; RA, rheumatoid arthritis.

Table 2. Incidence of Cardiovascular Events (Adjudicated) Among Patients With Arthritis in the 2 Treatment Groups: Last Observation

	Celecoxib (n=5,470; 10,745 person years)			NSAID (n=5,059, 9,601 person years)			Celecoxib vs. NSAID P value (log-rank)	Crude HR (95% CI) P value (χ^2)	Adjusted HR* (95% CI) P value (χ^2)
	n (%)	/1,000 person years	KM est (%)	n (%)	/1,000 person years	KM est (%)			
CV composite I (1–5)	66† (1.2)	6.2	1.65	65‡ (1.3)	6.8	1.86	0.58	0.91 (0.64–1.28) 0.57	0.89 (0.63–1.27) 0.52
(1) Myocardial infarction	9 (0.2)	0.8	0.24	4 (0.1)	0.4	0.12	0.23	2.02 (0.62–6.55) 0.24	1.59 (0.47–5.42) 0.46
(2) Angina pectoris	6 (0.1)	0.6	0.12	16 (0.3)	1.7	0.45	0.02	0.33 (0.13–0.85) 0.02	0.32 (0.11–0.91) 0.03
(3) Heart failure	17 (0.3)	1.6	0.45	18 (0.4)	1.9	0.51	0.62	0.85 (0.44–1.64) 0.62	0.72 (0.35–1.48) 0.38
(4) Cerebral infarction	28 (0.5)	2.6	0.72	21 (0.4)	2.2	0.62	0.55	1.19 (0.68–2.10) 0.55	1.27 (0.71–2.28) 0.42
(5) Cerebral hemorrhage (inclusive of subarachnoid)	8 (0.1)	0.7	0.20	11 (0.2)	1.1	0.29	0.35	0.65 (0.26–1.62) 0.36	0.64 (0.25–1.62) 0.34
Composite II (all CV events)	79 (1.4)	7.4	1.93	84 (1.7)	8.8	2.44	0.26	0.84 (0.62–1.14) 0.26	0.87 (0.63–1.19) 0.39
Death from all causes	93 (1.7)	8.7	2.44	71 (1.4)	7.4	2.05	0.33	1.16 (0.86–1.59) 0.33	1.03 (0.75–1.41) 0.87

*Adjusted for diagnosis (RA/OA), sex, age, preexisting CV disease, hypertension, lipid disorder, diabetes mellitus, hepatic impairment, renal impairment, habitual smoking, pre-study medication (low-dose aspirin, antithrombotic drugs), and concomitant medication (low-dose aspirin, antithrombotic drugs, heart failure therapeutics, antianginal therapeutics, antiarrhythmic drugs, antirheumatic drugs, and steroids). †One patient experienced both myocardial infarction and heart failure and 1 patient experienced both angina pectoris and cerebral infarction. ‡One patient experienced angina pectoris, cerebral infarction, and cerebral hemorrhage (inclusive of subarachnoid) and 3 patients experienced heart failure and cerebral infarction.
CV, cardiovascular; HR, hazard ratio; KM est (%), Kaplan-Meier time-to-first event curve estimation at 34 months (1,039 days): number left for celecoxib 2,445 and NSAID 2,137. Other abbreviations as in Table 1.

Table 3. Incidence of Cardiovascular Events (Adjudicated) Among Patients With Arthritis in the 2 Treatment Groups: Censored if Shifted

	Celecoxib (n=5,470; 9,360 person years)			NSAID (n=5,059, 8,917 person years)			Celecoxib vs. NSAID P value (log-rank)	Crude HR (95% CI) P value (X^2)	Adjusted HR* (95% CI) P value (X^2)
	n (%)	/1,000 person years	KM est (%)	n (%)	/1,000 person years	KM est (%)			
CV composite I (1–5)	54† (1.2)	5.8	1.51	61‡ (1.2)	6.9	1.87	0.34	0.84 (0.58–1.21) 0.34	0.82 (0.57–1.20) 0.31
(1) Myocardial infarction	7 (0.2)	0.8	0.19	4 (0.1)	0.4	0.13	0.41	1.66 (0.49–5.68) 0.42	1.41 (0.39–5.04) 0.60
(2) Angina pectoris	4 (0.1)	0.4	0.11	16 (0.3)	1.8	0.49	0.005	0.23 (0.08–0.70) 0.009	0.27 (0.08–0.94) 0.04
(3) Heart failure	14 (0.3)	1.5	0.40	17 (0.4)	1.9	0.50	0.50	0.78 (0.39–1.59) 0.50	0.80 (0.37–1.74) 0.57
(4) Cerebral infarction	24 (0.4)	2.6	0.70	19 (0.4)	2.1	0.58	0.56	1.19 (0.65–2.18) 0.56	1.32 (0.71–2.48) 0.38
(5) Cerebral hemorrhage (inclusive of subarachnoid)	6 (0.1)	0.6	0.16	10 (0.2)	1.1	0.31	0.27	0.57 (0.21–1.56) 0.28	0.53 (0.19–1.48) 0.22
Composite II (all CV events)	64 (1.4)	6.9	1.79	78 (1.5)	8.8	2.42	0.13	0.78 (0.59–1.08) 0.13	0.81 (0.58–1.14) 0.24
Death from all causes	83 (1.5)	8.9	2.54	71 (1.4)	8.0	2.23	0.51	1.11 (0.81–1.53) 0.52	0.95 (0.69–1.32) 0.76

*Adjusted for diagnosis (RA/OA), sex, age, preexisting CV disease, hypertension, lipid disorder, diabetes mellitus, hepatic impairment, renal impairment, habitual smoking, pre-study medication (low-dose aspirin, antithrombotic drugs), and concomitant medication (low-dose aspirin, antithrombotic drugs, heart failure therapeutics, antianginal therapeutics, antiarrhythmic drugs, antirheumatic drugs, and steroids). †One patient experienced both angina pectoris and cerebral infarction. ‡One patient experienced angina pectoris, cerebral infarction, and cerebral hemorrhage (inclusive of subarachnoid) and 3 patients experienced heart failure and cerebral infarction.
Abbreviations as in Tables 1,2.

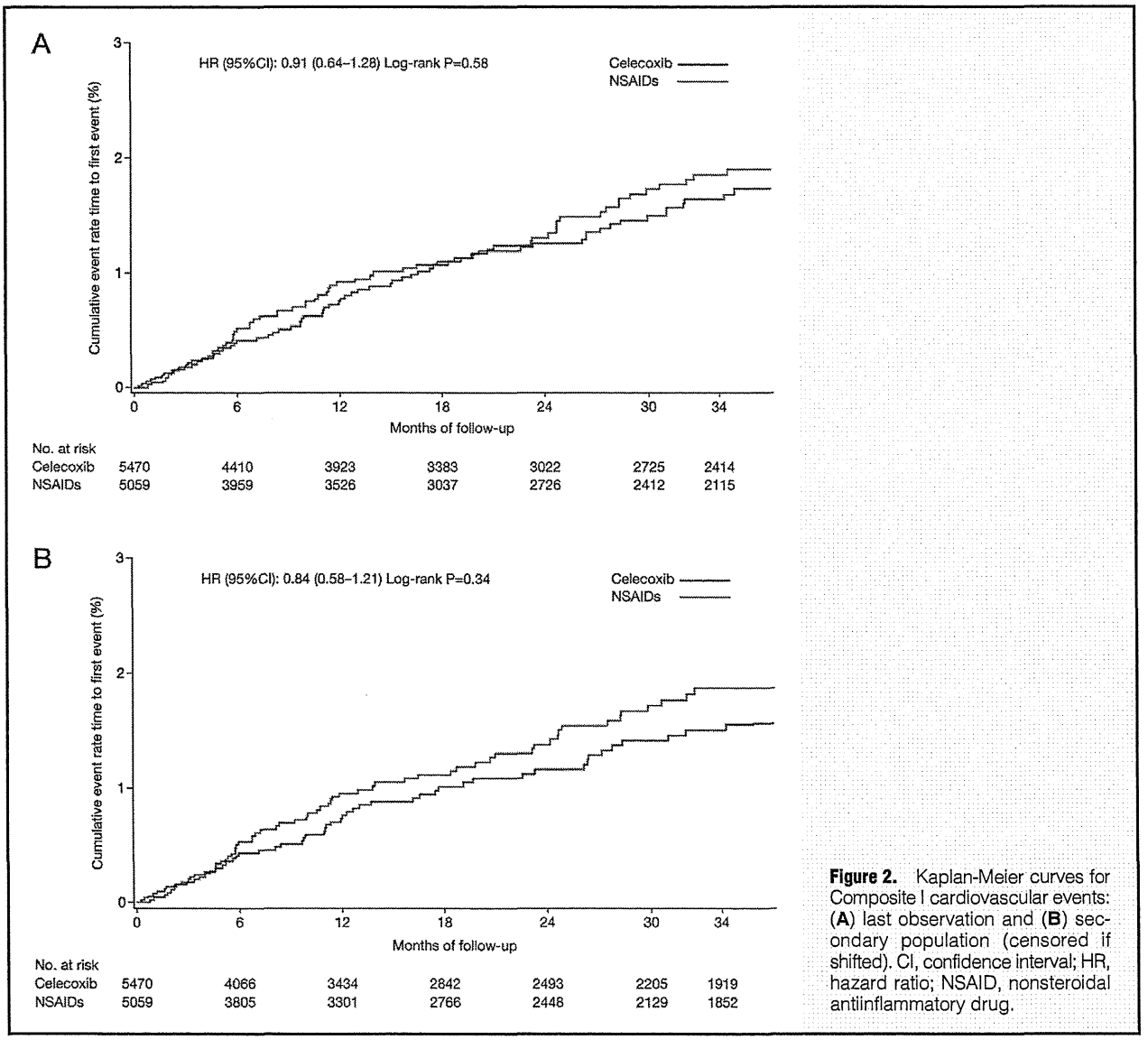

Figure 2. Kaplan-Meier curves for Composite I cardiovascular events: (**A**) last observation and (**B**) secondary population (censored if shifted). CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.

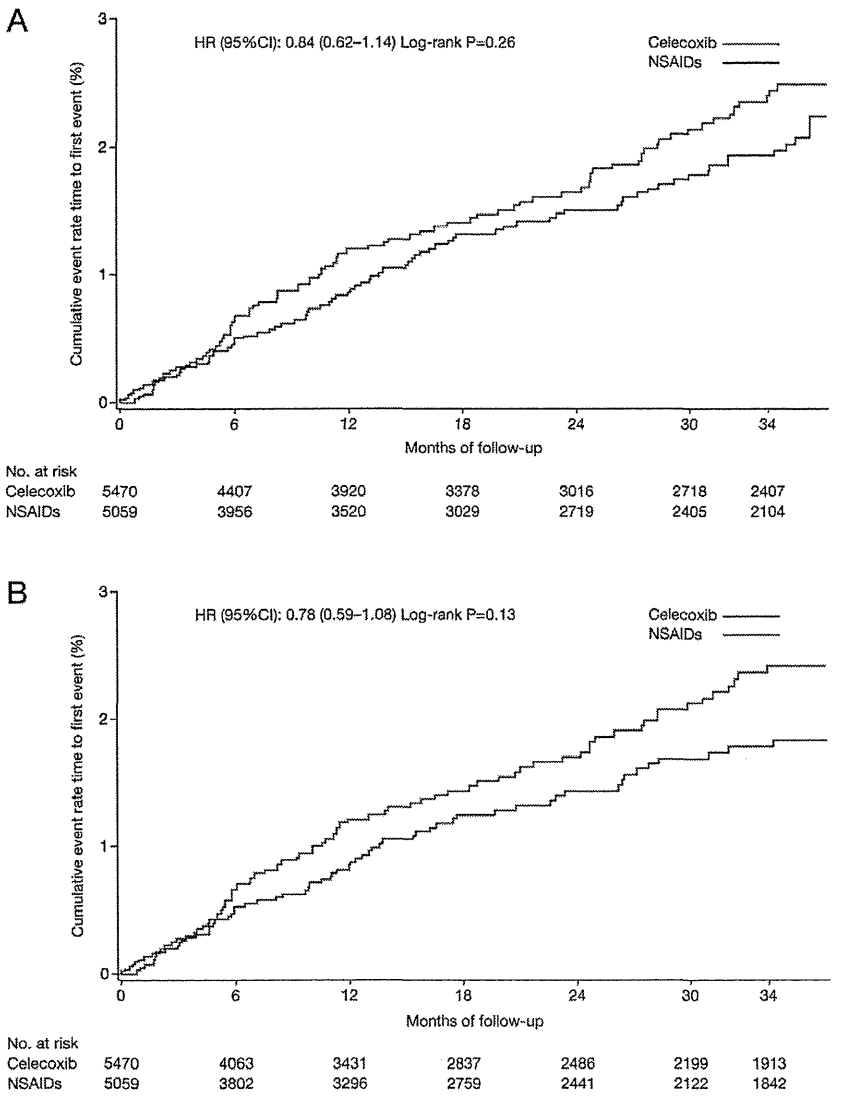

Figure 3. Kaplan-Meier curves for Composite II cardiovascular events: (**A**) last observation and (**B**) secondary population (censored if shifted). CI, confidence interval; HR, hazard ratio; NSAID, nonsteroidal antiinflammatory drug.

HRs of individual cardiovascular events were 1.59 (0.47–5.42, P=0.46) for myocardial infarction, 0.32 (0.11–0.91, P=0.03) for angina pectoris, 0.72 (0.35–1.48, P=0.38) for heart failure, 1.27 (0.71–2.28, P=0.42) for cerebral infarction, and 0.64 (0.25–1.62, P=0.34) for cerebral (or subarachnoid) hemorrhage. The most frequently observed cardiovascular Composite I events, in both the celecoxib and NSAID groups, were cerebral infarction and heart failure. The incidence of angina pectoris was more frequent in the NSAID group (P=0.02).

The number of cardiovascular Composite II events (all cardiovascular events) and the standardized rate/1,000 person years was, respectively, 79 (1.4%) and 7.4 in the celecoxib group and 84 (1.7%) and 8.8 in the NSAID group (**Table 2**). The adjusted HR was 0.87 (0.63–1.19; P=0.39).

In the secondary population (censored if shifted), the number of cardiovascular Composite I (adjudicated) events and the standardized rate/1,000 person years was, respectively, 54 (1.2%) and 5.8 in the celecoxib group and 61 (1.2%) and 6.9 in the NSAID group (**Table 3**). The adjusted HR (95% CI) was 0.82 (0.57–1.20) (P=0.31). The adjusted HRs of individual cardiovascular events were 1.41 (0.39–5.04, P=0.60) for myocardial infarction, 0.27 (0.08–0.94, P=0.04) for angina pectoris, 0.80 (0.37–1.74, P=0.57) for heart failure, 1.32 (0.71–2.48, P=0.38) for cerebral infarction, and 0.53 (0.19–1.48, P=0.22) for cerebral (or subarachnoid) hemorrhage.

The number of cardiovascular Composite II events and the standardized rate/1,000 person years was, respectively, 64 (1.4%) and 6.9 in the celecoxib group and 78 (1.5%) and 8.8 in the NSAID group (**Table 3**). The adjusted HR was 0.81 (0.58–1.14; P=0.24).

The Kaplan-Meier cumulative event rate estimation for Composite I cardiovascular events at 34 months (number of patients remaining: 2,414 celecoxib and 2,115 NSAID) was 1.65% and 1.86% in the celecoxib and NSAID groups, respectively (log-rank P=0.58) (**Table 2, Figure 2A**).

In the secondary population (censored if shifted), the Kaplan-Meier cumulative event rate estimation for Composite I cardiovascular events at 34 months (number of patients remaining: 1,919 celecoxib and 1,852 NSAID) was 1.51% and 1.87% in the celecoxib and NSAID groups, respectively (log-rank

Table 4. Subgroup Analysis by Patient Background for Composite I Cardiovascular Events (Adjudicated) -Censored If Shifted Among Patients With Arthritis in the 2 Treatment Groups

Treatment Factor	Celecoxib (9,360 person years)				NSAID (8,917 person years)				Crude			Adjusted*		
	No. of pts.	n	%	KM (%)	No. of pts.	n	%	KM (%)	HR	95% CI	P (χ^2)	HR	95% CI	P (χ^2)
Overall	5,470	54	1.0	1.51	5,059	61	1.2	1.87	0.84	(0.58–1.21)	0.34	0.82	(0.57–1.20)	0.31
RA	1,193	11	0.9	1.18	772	12	1.6	2.16	0.60	(0.26–1.35)	0.21	0.83	(0.33–2.07)	0.68
OA	4,277	43	1.0	1.65	4,287	49	1.1	1.81	0.92	(0.61–1.39)	0.69	0.86	(0.57–1.31)	0.48
Sex														
Male	1,222	19	1.6	2.53	1,290	25	1.9	3.44	0.82	(0.45–1.49)	0.52	0.72	(0.36–1.44)	0.35
Female	4,248	35	0.8	1.24	3,769	36	1.0	1.39	0.88	(0.55–1.40)	0.58	0.78	(0.48–1.25)	0.30
Age (years)														
<65	1,767	4	0.2	0.39	1,692	8	0.5	0.95	0.47	(0.14–1.55)	0.21	0.50	(0.09–2.90)	0.44
65–74	1,815	11	0.6	0.92	1,677	15	0.9	1.34	0.71	(0.32–1.54)	0.38	0.75	(0.33–1.74)	0.51
≥75	1,888	39	2.1	3.00	1,690	38	2.2	3.14	0.97	(0.62–1.51)	0.88	0.88	(0.55–1.40)	0.59
BMI (kg/m²)														
<25	1,793	13	0.7	0.92	1,529	21	1.4	1.96	0.53	(0.27–1.06)	0.07	0.49	(0.24–1.02)	0.06
25–29	785	10	1.3	2.21	693	9	1.3	1.90	1.03	(0.42–2.53)	0.95	0.99	(0.35–2.80)	0.98
≥30	171	2	1.2	1.98	185	2	1.1	1.20	1.15	(0.16–8.17)	0.89	n/a	n/a	n/a
Preexisting CVD														
Yes	402	22	5.5	7.80	372	18	4.8	6.41	1.20	(0.65–2.24)	0.56	1.25	(0.65–2.40)	0.51
No	4,775	32	0.7	1.01	4,358	41	0.9	1.46	0.73	(0.46–1.15)	0.18	0.66	(0.40–1.08)	0.10
Preexisting hypertension														
Yes	1,734	29	1.7	2.40	1,565	36	2.3	3.12	0.75	(0.46–1.22)	0.24	0.70	(0.42–1.15)	0.16
No	3,443	25	0.7	1.05	3,165	23	0.7	1.26	0.96	(0.55–1.66)	0.87	0.82	(0.45–1.50)	0.52
Preexisting lipid disorder														
Yes	799	17	2.1	3.01	742	10	1.3	1.92	1.64	(0.75–3.57)	0.22	1.52	(0.64–3.63)	0.34
No	4,378	37	0.8	1.21	3,988	49	1.2	1.86	0.68	(0.45–1.04)	0.08	0.65	(0.42–1.01)	0.05
Preexisting DM														
Yes	450	10	2.2	3.74	394	9	2.3	3.62	1.09	(0.44–2.67)	0.86	1.07	(0.38–3.02)	0.90
No	4,727	44	0.9	1.32	4,336	50	1.2	1.71	0.80	(0.53–1.19)	0.27	0.72	(0.48–1.09)	0.12
Preexisting hepatic impairment														
Yes	145	4	2.8	2.72	135	2	1.5	0.87	1.96	(0.36–10.69)	0.44	n/a	n/a	n/a
No	3,349	43	1.3	1.83	2,910	45	1.5	2.17	0.84	(0.55–1.28)	0.41	0.79	(0.51–1.21)	0.27
Preexisting renal impairment														
Yes	121	2	1.7	2.72	114	7	6.1	7.76	0.29	(0.06–1.42)	0.13	n/a	n/a	n/a
No	3,361	44	1.3	1.83	2,917	40	1.4	1.88	0.97	(0.63–1.48)	0.88	0.92	(0.59–1.42)	0.69
Habitual behavior smoking														
Yes	345	7	2.0	3.13	337	8	2.4	3.47	0.85	(0.31–2.34)	0.75	1.00	(0.29–3.51)	1.00
No	3,242	40	1.2	1.71	2,900	38	1.3	1.87	0.92	(0.60–1.42)	0.71	0.93	(0.60–1.45)	0.75
Habitual behavior alcohol consumption														
Yes	596	9	1.5	2.05	559	13	2.3	3.73	0.63	(0.27–1.47)	0.28	0.72	(0.26–1.97)	0.52
No	2,994	38	1.3	1.78	2,686	33	1.2	1.58	1.09	(0.69–1.73)	0.72	0.96	(0.59–1.54)	0.85
Habitual behavior exercise														
Yes	530	8	1.5	2.36	412	5	1.2	1.54	1.30	(0.43–3.98)	0.65	1.15	(0.22–5.90)	0.87
No	3,045	37	1.2	1.69	2,806	39	1.4	2.09	0.83	(0.54–1.28)	0.39	0.90	(0.57–1.40)	0.63
Pre-study NSAID medication														
Yes	1,656	24	1.4	2.05	1,109	20	1.8	2.47	0.89	(0.49–1.60)	0.69	1.34	(0.70–2.58)	0.38
No	3,252	28	0.9	1.31	3,337	38	1.1	1.77	0.75	(0.46–1.21)	0.24	0.66	(0.39–1.11)	0.11
Pre-study low-dose aspirin medication														
Yes	221	9	4.1	5.81	196	9	4.6	6.38	0.93	(0.37–2.33)	0.87	0.49	(0.16–1.58)	0.23
No	4,723	45	1.0	1.44	4,338	48	1.1	1.70	0.88	(0.58–1.32)	0.53	0.88	(0.58–1.35)	0.56
Pre-study antithrombotic drug medication														
Yes	171	10	5.8	8.37	170	10	5.9	7.87	1.01	(0.42–2.44)	0.98	1.05	(0.37–2.95)	0.92
No	4,779	44	0.9	1.38	4,371	48	1.1	1.70	0.86	(0.57–1.29)	0.45	0.91	(0.59–1.38)	0.64

(Table 4 continued the next page.)

Treatment Factor	Celecoxib (9,360 person years)				NSAID (8,917 person years)				Crude			Adjusted*		
	No. of pts.	n	%	KM (%)	No. of pts.	n	%	KM (%)	HR	95% CI	P (χ^2)	HR	95% CI	P (χ^2)
Concomitant medication low-dose aspirin														
Yes	243	18	7.4	10.08	228	23	10.1	13.98	0.81	(0.44–1.50)	0.51	1.08	(0.54–2.15)	0.84
No	5,227	36	0.7	1.07	4,829	38	0.8	1.17	0.89	(0.56–1.40)	0.61	0.84	(0.53–1.34)	0.46
Concomitant medication antithrombotic drug														
Yes	243	26	10.7	14.77	219	11	5.0	5.88	1.39	(0.76–2.53)	0.28	1.67	(0.86–3.20)	0.13
No	5,227	28	0.5	0.78	4,838	43	0.9	1.36	0.61	(0.38–0.99)	0.04	0.49	(0.30–0.80)	0.005
Concomitant medication heart failure therapeutics														
Yes	82	15	18.3	28.21	54	16	29.6	34.93	0.77	(0.38–1.55)	0.46	1.00	(0.45–2.20)	0.99
No	5,388	39	0.7	1.13	5,003	45	0.9	1.37	0.82	(0.53–1.26)	0.36	0.86	(0.55–1.34)	0.50
Concomitant medication antianginal therapeutics														
Yes	137	8	5.8	8.36	110	13	11.8	15.03	0.52	(0.22–1.23)	0.14	0.50	(0.17–1.47)	0.21
No	5,333	46	0.9	1.32	4,947	47	1.0	1.51	0.93	(0.62–1.39)	0.72	0.97	(0.63–1.48)	0.87
Concomitant medication antiarrhythmic drugs														
Yes	68	8	11.8	15.10	60	6	10.0	14.72	1.24	(0.43–3.58)	0.69	1.61	(0.24–10.92)	0.63
No	5,402	46	0.9	1.30	4,997	55	1.1	1.66	0.79	(0.53–1.17)	0.24	0.70	(0.47–1.04)	0.08
Concomitant medication, antirheumatic drug														
Yes	960	9	0.9	1.11	604	11	1.8	2.38	0.53	(0.22–1.28)	0.16	0.66	(0.25–1.77)	0.41
No	4,510	45	1.0	1.65	4,453	50	1.1	1.78	0.93	(0.62–1.39)	0.71	0.87	(0.58–1.31)	0.51
Concomitant medication, steroid														
Yes	722	7	1.0	1.30	453	10	2.2	3.02	0.46	(0.17–1.20)	0.11	0.89	(0.28–2.82)	0.84
No	4,748	47	1.0	1.56	4,604	51	1.1	1.73	0.92	(0.62–1.37)	0.68	0.86	(0.57–1.29)	0.46

*Adjusted for diagnosis (RA/OA), sex, age, preexisting cardiovascular disease, hypertension, lipid disorder, diabetes mellitus, hepatic impairment, renal impairment, habitual smoking, pre-study medication (low-dose aspirin, antithrombotic drugs), concomitant medication (low-dose aspirin, antithrombotic drugs, heart failure therapeutics, antianginal therapeutics, antiarrhythmic drugs, antirheumatic drugs, and steroids).
BMI, body mass index; CVD, cardiovascular disease; n/a, number of events were insufficient for statistical analysis. Other abbreviations as in Table 1.

P=0.34) (**Table 3, Figure 2B**).

The Kaplan-Meier cumulative event rate estimation for Composite II cardiovascular events at 34 months (number of patients remaining: 2,407 celecoxib and 2,104 NSAID) was 1.93% and 2.44% in the celecoxib and NSAID groups, respectively (log-rank P=0.26) (**Table 2, Figure 3A**).

In the secondary population (censored if shifted), the Kaplan-Meier estimation of the risk of Composite I events at 34 months (number of patients remaining: 1,913 celecoxib and 1,842 NSAID) was 1.79% and 2.42% in the celecoxib and NSAID groups, respectively (log-rank P=0.13) (**Table 3, Figure 3B**).

Subgroup analysis by patient background for Composite I cardiovascular events was also conducted for the secondary population (censored if shifted). Adjusted HRs in favor of celecoxib were body mass index (<25 kg/m^2) 0.49 (0.24–1.02, P=0.06), no preexisting lipid disorder 0.65 (0.42–1.01, P=0.05), no concomitant medication of antithrombotic drugs 0.49 (0.30–0.80, P=0.005) and no antiarrhythmic drugs 0.70 (0.47–1.04, P=0.08). No statistical significance in favor of NSAIDs was observed in any of the subgroup analyses (**Table 4**).

Adverse Events (Death From All Causes)

Deaths from all causes and the standardized rate/1,000 person years was, respectively, 93 (1.7%) and 8.7 in the celecoxib group and 71 (1.4%) and 7.4 in the NSAID group (P=0.33; **Table 2**). The adjusted HR (95% CI) was 1.03 (0.75–1.41) (P=0.87; **Table 2**). In the secondary population (censored if shifted), deaths from all causes and the standardized rate/1,000 person years for death from all causes was, respectively, 83 (1.5%) and 8.9 in the celecoxib group and 71 (1.4%) and 8.0 in the NSAID group (P=0.51; **Table 3**). The adjusted HR (95% CI) was 0.95 (0.69–1.32) (P=0.76; **Table 3**).

Deaths from cardiovascular events (heart failure, myocardial infarction, cerebral infarction, cerebral and subarachnoid hemorrhage) were similar in both groups (**Table S2**). Pneumonia accounted for 24 deaths in the celecoxib group (RA=14 cases) (0.4%) and 6 cases in the NSAID group (RA=1 case) (P=0.003); however, these deaths were remote from drug causality in both groups.

Discussion

This prospective 3-year observational study was conducted to evaluate the effect of celecoxib on the risk of cardiovascular adverse events in a population from Japan. Celecoxib was not associated with an increased cardiovascular risk (myocardial infarction, angina pectoris, heart failure, cerebral infarction, cerebral hemorrhage, and all cardiovascular events) when compared with NSAIDs, after adjusting for confounding factors. In addition, the fact that the secondary study population (censored if shifted, sole medication of celecoxib) showed no significant differences in the 2 groups means that the data not only support

the robustness of the results from the primary study population (last observation) but also indicate that the pharmacoepidemiology of the newly commercially introduced COX 2 inhibitor, celecoxib, would not potentiate nor affect the cardiovascular risk of RA and OA patients treated with conventional NSAIDs in Japan.

This was the first large-scale (>10,000 patients) prospective observational study in Japan that included cohorts who were treated with either celecoxib or nsNSAIDs, with a defined observational starting point, to enable a comparison of the cardiovascular risk of celecoxib in patients with RA or OA. All patients were celecoxib-naïve, because this study commenced shortly after the launch of celecoxib in Japan.

Among the subjects included in this study was a relatively small proportion of coronary artery disease (myocardial infarction, angina pectoris) events and a large proportion of heart failure and cerebral infarction (or hemorrhage) in both treatment groups when compared with Western populations. Generally, coronary artery disease in Western populations is more prevalent whereas cerebral infarction is more prevalent in Japanese (or Asian) populations; higher recurrence rates of stroke in a Japanese community than in Western populations were shown in the Hisayama study.[24]

Nonfatal or fatal cardiovascular events in this study are consistent with other interventional trials and observational studies evaluating the risk of cardiovascular adverse events. The incidence of cardiovascular events, in particular myocardial infarction, was shown to be comparable among celecoxib, ibuprofen, and diclofenac treatment groups following 6 months of treatment in the Celecoxib Long-term Arthritis Safety Study (CLASS).[16] No significant increases in nonfatal myocardial infarction, nonfatal stroke, and cardiovascular death were reported when patients were treated with celecoxib (200–800 mg daily) compared with patients treated with a nsNSAID (diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen) or placebo.[19]

An association between celecoxib and an increased risk of myocardial infarction, stroke, congestive heart failure, or cardiovascular-related death was reported by the Adenoma Prevention with Celecoxib (APC) trial.[17] Furthermore, a systematic review and meta-analysis of randomized double-blind clinical trials have shown that 6 weeks' treatment with celecoxib was associated with an increased risk of myocardial infarction when compared with placebo and comparator treatment groups.[20] A recent meta-analysis found no significant increase in risk with celecoxib for cardiovascular events, cardiovascular deaths, and stroke, but low (≤200 mg daily) and high (>200 mg daily) doses were shown to be associated with an elevated overall cardiovascular risk.[14]

In the case of high cardiovascular risk for patients with prior myocardial infarction, treatment with rofecoxib, celecoxib, and nsNSAIDs is associated with an increased risk of death and rehospitalization for myocardial infarction.[25] Use of rofecoxib, celecoxib, and diclofenac also increases the risk of acute myocardial infarction in patients with a prior history and in those with no history of cardiovascular risk factors.[26] Rofecoxib is no longer available because of the concerns of increased cardiovascular risk with long-term, high-dosage use.

In this observational study that targeted patients with RA or OA and varying cardiovascular risk, no significant differences were found in the incidence of myocardial infarction or heart failure in the celecoxib and NSAID groups. The reason for the increased incidence of angina pectoris observed in the NSAID group is not clear. The chest discomfort or pain that is associated with angina pectoris could be alleviated by pain control; however, drug efficacy was not assessed in this study.

Subgroup analysis showed that male sex, age, preexisting cardiovascular disease, hypertension, lipid disorder, diabetes mellitus, habitual smoking or alcohol consumption, and prestudy medication of low-dose aspirin and antithrombotic drugs were risk factors for a cardiovascular event. Adjusted HRs in favor of celecoxib were observed with body mass index (<25 kg/m^2), preexisting lipid disorder (no), concomitant medication of antithrombotic drugs (no) and antiarrhythmic drugs (no). There was no apparent increase in cardiovascular risk in the celecoxib group compared with the NSAID group in patients with RA or OA with a higher risk of cardiovascular disease.

Because patients who are aged ≥80 years or who have hypertension, prior myocardial infarction, prior cardiovascular disease, RA, chronic renal disease, and chronic obstructive pulmonary disease are at an elevated risk for cardiovascular events when using COX 2-selective NSAIDs and nsNSAIDs,[15] it is important to assess the relevant risk factors in individual patients prior to treatment selection. A cross-trial safety analysis that investigated the relationship between celecoxib dose (400 mg daily, 200 mg twice daily and 400 mg twice daily) and cardiovascular risk, showed that the risk increased with dose.[27] The majority of patients (87.7%) in the present study were prescribed 200-mg daily dose of celecoxib. In Japan, a daily dose of 400 mg celecoxib is covered by public health insurance for the treatment of RA. Therefore, the relationship between dosage and cardiovascular risk could not be assessed in this study.

More deaths from pneumonia in the celecoxib group were observed; however, these were remote from drug causality and were not associated with drug exposure but attributable to underlying differences in patient characteristics (RA) and concomitant medications (anti-RA drugs and steroid use) in the 2 groups.

The Prospective Randomized Evaluation of Celecoxib Integrated Safety vs. Ibuprofen or Naproxen (PRECISION) trial, currently recruiting patients and in which celecoxib is being compared with naproxen and ibuprofen, is expected to answer the question of overall risk of cardiovascular adverse events in the treatment of arthritic pain.[28]

Study Limitations

This study was subject to some limitations. It was a nonblinded, nonrandomized observational study, with similar baseline demographics in the 2 treatment groups and with low frequency rates of cardiovascular events that were highly affected by well-known risk factors. To adjust for the slight differences between treatment groups when calculating HRs, proportional Cox regression by way of the prevailing statistical procedure (SAS, PHREG procedure) for adjustment of confounding variables was used. However, the differences of the pre-undefined and influential risk factors, such as the therapeutic use of medication for lipid disorder, or diabetes mellitus, as well as blood pressure, lipids and blood glucose levels, could not be assessed in this study. Moreover, therapy with angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, β-blockers and calcium-channel blockers, which have documented effects of reducing hypertension and cardiovascular events [29–32] could not be controlled for, which could represent an additional limitation. As baseline levels of preexisting hypertension, lipid disorder, or diabetes mellitus were similar between treatment groups, the precise influence of these cardiovascular risk factors is limited in this population.[33] In randomized studies, undefined or unknown factors are regarded to occur partially, but

it is impossible to adjust for undefined or unknown cardiovascular risk factors in observational studies.

The difference between a RA and OA diagnosis introduces bias to the study. COX 2-selective NSAIDs are associated with a lower incidence of gastrointestinal injury than nsNSAIDs.[34] Consequently, COX 2-selective NSAIDs would be the preferred treatment for the long-term requirements of RA, the elderly, and patients with stomach complaints. Therefore, prescription bias could not be controlled in this observational study as treatment options may have been based on the symptomatic condition and medical gastrointestinal history of the patient.[35]

Because this was not a confirmatory or noninferiority study, we can only report on the incidence of adverse cardiovascular events that occurred during the observational period following treatment. However, our findings should be a useful adjunct to previously published, randomized, placebo-controlled studies that have directly compared celecoxib with similar treatments in terms of safety.

Self-medication was not assessed in this study. Use of medications such as over-the-counter compress formulations of indomethacin (the Japanese preference in managing focal pain), oral aspirin, or ibuprofen was not accounted for. These would have been important factors to include in the adjustment of the data.

The possible extension of our results should be far from conspicuous to the previous analyses of selective and nsNSAIDs for cardiovascular risk within Western populations in the past decade, as the results are highly dependent on the difference in the involuntary nature of the emergence of cardiovascular events.

Conclusions

After adjusting for confounding variables that may influence the risk for cardiovascular adverse events, the selective COX 2 inhibitor celecoxib is not associated with an increase in cardiovascular risk compared with nonselective NSAIDs in a Japanese OA or RA population where all patients were celecoxib-naïve. These results add to the current pool of knowledge of risk factors associated with celecoxib and the data may be useful to physicians when making treatment decisions for their patients with OA or RA.

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Supplementary Files

Supplementary File 1

Table S1. Univariate logistic regression analysis of all cardiovascular events (Composite II) in 2 treatment groups of patients with arthritis

Table S2. List of fatal cases in 2 treatment groups of patients with arthritis

Please find supplementary file(s);
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Chapter 6

EFFECTS OF ADIPOKINES ON PROSTAGLANDIN E2 PRODUCTION BY RHEUMATOID SYNOVIAL FIBROBLASTS

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ABSTRACT

Eicosanoids, including prostaglandins (PGs), leukotrienes (LTs), and lipoxins (LXs), regulate a wide variety of physiological responses and pathological processes. Among them, PGE_2 is one of the key molecules, especially in relation to inflammation and immunity. Rheumatoid arthritis (RA) is characterized by extensive inflammation and proliferation of the synovium in various joints of the body. Since proinflammatory cytokines, such as tumor necrosis factor-α (TNFα) and interleukin (IL)-1β, induce PGE_2 production by synovial fibroblasts, joint inflammation in RA is at least partly mediated by overproduction of PGE_2. We previously reported

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that PGE_2 overproduction led to a vicious cycle of inflammation because PGE_2 itself promotes the increased expression of microsomal prostaglandin E synthase-1 (mPGES-1), a downstream enzyme of cyclooxygenase-2 (COX-2).

Adipose tissue has long been considered to be merely a structural component of many organs and a site for energy storage. However, recent studies have demonstrated that the major cellular component of adipose tissue, the adipocyte, has the ability to synthesize and release various physiologically active molecules, including diponectin, leptin, and resistin, as well as well-known proinflammatory cytokines like TNFα and IL-6. These molecules are called adipokines. We recently found that adiponectin stimulates PGE_2 production by increasing the expression of COX-2 and mPGES-1 in rheumatoid synovial fibroblasts.

In this review, we summarize the significance of adipokines with regard to PGE_2 and rheumatoid inflammation. We also suggest that adiponectin might have a role as a proinflammatory cytokine in rheumatoid arthritis.

PROINFLAMMATORY CYTOKINES IN RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is characterized by extensive inflammation and proliferation of the synovium in multiple joints. Since proinflammatory cytokines, such as tumor necrosis factor-α (TNFα), interleukin (IL)-1β, and IL-6, play a central role in the pathophysiologic mechanisms underlying RA, novel strategies to neutralize these cytokines by employing monoclonal antibodies or soluble receptors have recently been developed as new treatments for RA [1].

Although the pathogenesis of RA is still unknown, the intricate network of proinflammatory cytokines involved in this disease has been studied extensively. Various secreted cytokines stimulate other cells to produce various bioactive molecules, including metabolites of arachidonic acid (AA), resultingin the inflammatory and destructive processes of RA.

Cytokines and Adipokines

Adipose tissue was long considered to be just a structural component of many organs and a site for energy storage. However, some recent studies have shown that the adipocyte (the major cellular component of adipose tissue) can

synthesize and release physiologically active molecules or cytokines, including adiponectin, leptin, and resistin, as well as conventional cytokines such as IL-6 and TNFα [2]. These molecules are collectively called adipokines.

Although blockade of TNFα, IL-1β, or IL-6 is clinically beneficial, such strategies are not curative and the effect is only partial, with failure to respond being common [1]. Therefore, it seems possible that other proinflammatory cytokines may contribute to the pathophysiology of RA.

It has been suggested that adiponectin may play a central role in the regulation of insulin resistance [3]. However, adiponectin is also involved in many aspects of inflammation and immunity [4, 5]. We found that the serum levels of leptin and adiponectin were elevated in patients with RA [6]. Other studies have also shown that serum levels of resistin [7-9], leptin [9, 11-13], and adiponectin [9, 10, 13-15] are higher in RA patients than in healthy controls. These results suggest that some adipokines have a rolein the pathophysiological process of RA as doproinflammatory cytokines.

AA Cascade in RA

Phospholipase A2

Figure1 shows the AA cascade. Biosynthesis of eicosanoids, including prostaglandins (PGs), thromboxanes (TXs), leukotrienes (LTs) and lipoxins (LXs), depends on the availability of free AA [16]. When tissues are exposed to physiological and pathological stimuli, such as growth factors, hormones, or cytokines, AA is produced from membrane phospholipids by the action of phospholipase A2s (PLA2s). PLA2s show structural diversity. Among them, cytosolic phospholipase A2α (cPLA2α) has been well characterized with respect to its protein structure and properties, and it is thought to play an essential role in eicosanoid production [17, 18]. cPLA2α undergoes translocation from the cytosol to the perinuclear membrane when stimulated by intracellular Ca^{2+} at submicromolar levels [19], after which it hydrolyzes AA-containing phospholipids and supplies AA to downstream enzymes such as cyclooxygenase (COX) and lipoxygenase (LOX). These enzymes produce various eicosanoids.

COX

AA can be metabolized by three main enzymatic pathways, which are p-450 epoxygenase, COXs, and LOXs (Figure1).

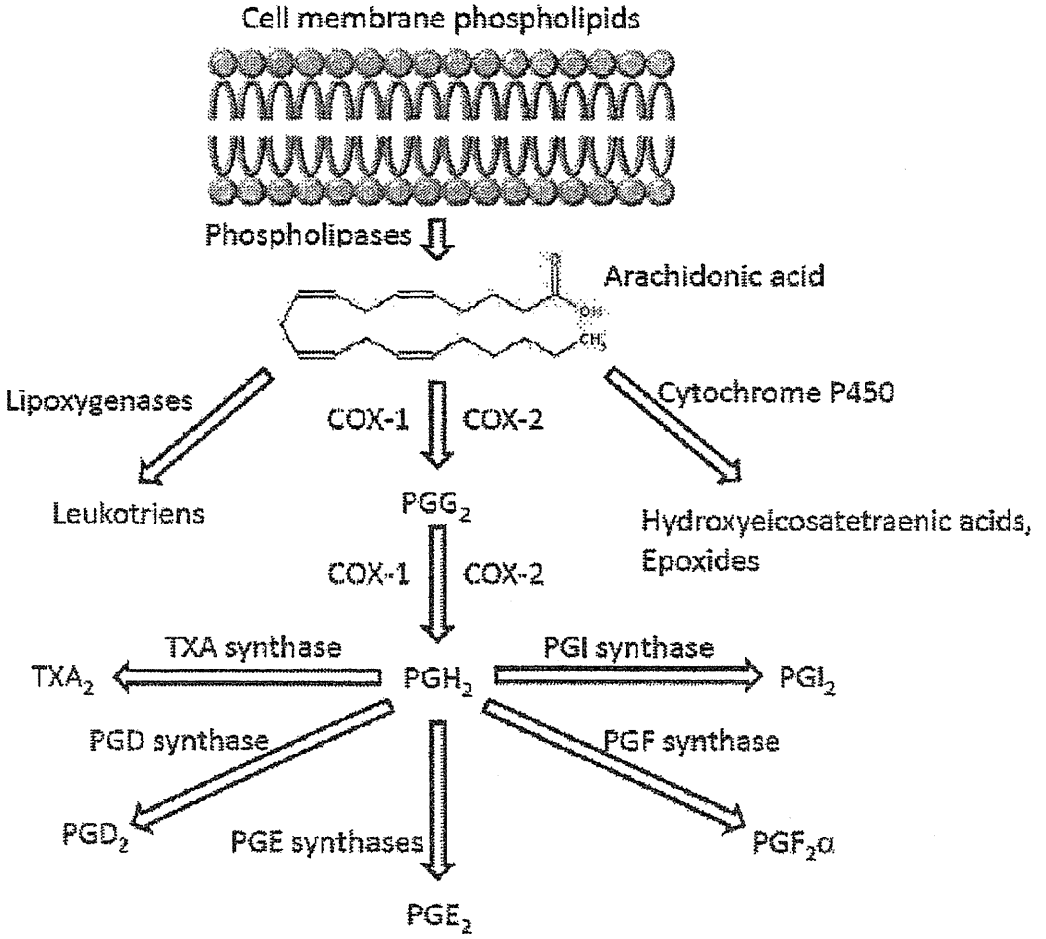

Figure1. Arachidonic acid cascade. COX, cyclooxygenase; PG, prostaglandin; TX, thromboxane.

COX has 2 isozymes, COX-1 and COX-2, which differ with respect to their basal level of expression, tissue localization, and induction during inflammation [20-22].

COX-1 is constitutively expressed by various cells and tissues, and has an important role in maintaining homeostasis. In contrast, COX-2 expression is induced in inflammatory cells and tissues by various stimuli, suggesting that it has a key role in the process of inflammation. Nonsteroidal anti-inflammatory drugs (NSAIDs) have both therapeutic and toxic effects that are mediated by their ability to reduce PG biosynthesis through inhibition of COXs [23].

COX-2 mRNA expression was reported to be significantly higher in synovial tissue from RA patients than in tissue from osteoarthritis (OA) patients [24]. It has also been reported that cytokine-activated cells, such as synovial cells, chondrocytes and macrophages/monocytes, are the primary source of PGs in arthritic joints. Furthermore, PG production at sites of inflammation coincides with the upregulation of COX-2 expression in activated articular cells [25].

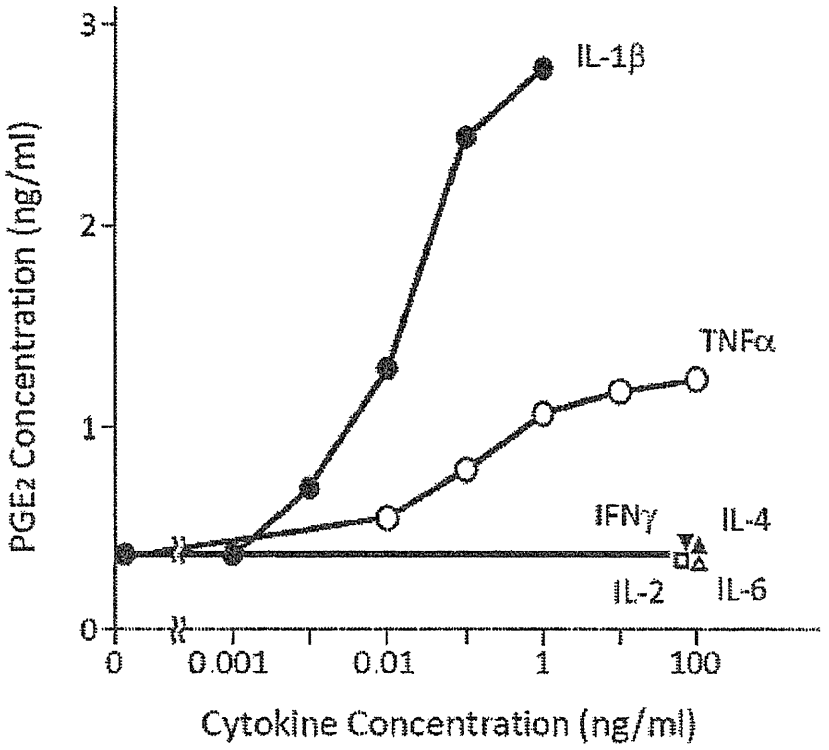

Figure2. Effects of various cytokines on COX activity in human synovial cells. Synovial cells were treated with cytokines at 37°C for 24 h. After washing the cells, 3 μM arachidonic acid was added for 30 min and then the prostaglandin E_2 (PGE_2) concentration of the medium was measured. Each point represents the mean value of three samples. IL, interleukin; TNFα, tumor necrosis factor-a; IFNγ, interferon-γ. Reproduced from Kawai et al., [28], with kind permission from European Journal of Pharmacology.

PGE_2 in RA

AA is transformed into PGG_2 by COX, and then is further catalyzed to an unstable intermediate (PGH_2) by the peroxidase activity of COX. PGH_2 is a substrate for the production of PGE_2, PGD_2, $PGF_2\alpha$, PGI_2, and TXA_2 (Figure1). Among them, PGE_2 is a key mediator of immunopathology [26]. High concentrations of PGE_2 have been detected in the synovial fluid of

patients with RA [27], and IL-1β and TNFα have been shown to induce PGE_2 production by RA synovial fibroblastsin a dose-dependent manner [28]. In contrast, IL-2, IL-4, IL-6, and interferon-γ (IFNγ) have no influence on PGE_2 production by human synovial cells (Figure 2). Since IL-1β and TNFα are key cytokines associated with the pathophysiology of RA, induction of COX and the resulting over production of PGE_2 induced by these cytokines may play an important role in rheumatoid synovial inflammation. PGE_2 has numerous biological actions (Table 1), some of which contribute to joint destruction in RA.

Table 1. Effects of PGE_2 on joint inflammation and destruction

Outcome	Mechanism	Reference
Pain	Reduction of the temperature threshold for TRPV1 activation	[62]
	Activation of the TTX-R Na^+ channel	[63]
	Induction of hypersensitivity via voltage-gated sodium channel Nav1.9	[64]
	Activation of the purinergic P_2X_3 receptor channel	[65]
	Facilitating spinal release of excitatory neurotransmitters	[66,67]
	Enhancement of AMPAR and NMDAR	[68]
	Blocking the glycinergic receptor α3 subunit	[69]
Edema	Increasing vascular permeability	[70]
	Regulation of vascular tone	[71]
Bone destruction	Upregulation of RANKL expression	[72-76]
	Inhibition of OPG expression	[77,78]
	Induction of chondrocyte death	[79]
	Induction of MMPs	[80-82]
	Induction of ADAMTS1	[83]

ADAMTS1, a disintegrin and metallopeptidase with thrombospondin type 1;AMPAR, 2-amino-3-(5-methyl-3-oxo-1,2-oxasol-4-yl) propanoic acid receptor; MMPs, matrix metalloproteinases; NMDAR, N-methyl-D-aspartic acid receptor; OPG, osteoprotegerin; RANKL, receptor activator of NFκB ligand;TRPV1, transient receptor potential subtype V1; TTX-R, tetrodotoxin-resistant.