Effectiveness of Statins on Total Cholesterol and Cardiovascular Disease and All-cause Mortality in Osteoarthritis and Rheumatoid Arthritis

XIA SHENG, MICHAEL J. MURPHY, THOMAS M. MacDONALD, and LI WEI

ABSTRACT. ***Objective.*** There is increasing prevalence of hypercholesterolemia among patients with osteoarthritis (OA) and rheumatoid arthritis (RA). We examined the effectiveness of statins on total cholesterol (TC), cardiovascular (CV) morbidity, and mortality in patients with OA or RA.

Methods. A population-based cohort study was done using a record-linkage database in Tayside, Scotland. In total, 2024 OA or RA patients who had at least 2 separate TC measurements between 1993 and 2007 were studied. They were categorized into statin-exposed and statin-unexposed groups according to statin use status during followup. The main outcomes were TC concentration change from baseline, CV events, and all-cause mortality during the followup. Multivariate Cox regression models with a time-dependent variable for statins were employed to assess the risk of outcomes.

Results. Statin-associated TC concentrations in OA decreased by 15% in patients without CV disease (primary prevention, n = 1269) and 7% in patients with CV disease (secondary prevention, n = 247) from baseline of 5.30 mmol/l and 4.54 mmol/l, respectively. Correspondingly, in RA TC was reduced by 16% (n = 430) and 15% (n = 78) with baselines of 5.54 mmol/l and 4.95 mmol/l. In primary prevention, statins were associated with reduced CV events and all-cause mortality in RA patients [adjusted HR 0.45 (95% CI 0.20–0.98) and 0.43 (95% CI 0.20–0.92), respectively] and all-cause mortality in OA patients [adjusted HR 0.43 (95% CI 0.25–0.72)]. Statins were not associated with reduced risk of CV events or all-cause mortality in the secondary prevention of RA or OA patients [adjusted HR 0.68 (95% CI 0.30–1.54) and 0.52 (95% CI 0.20–1.34) for OA patients, and HR 0.58 (95% CI 0.07–4.79) and 0.79 (95% CI 0.18–3.53) for RA patients].

Conclusion. Statins reduced TC concentrations between 7% and 16% in patients with OA or RA. Statins were associated with reduced CV events and mortality in RA and mortality in OA in primary prevention. (J Rheumatol First Release Nov 1 2011; doi:10.3899/jrheum.110318)

Key Indexing Terms:
STATINS OSTEOARTHRITIS RHEUMATOID ARTHRITIS MORTALITY
TOTAL CHOLESTEROL CONCENTRATION CARDIOVASCULAR DISEASE

Osteoarthritis (OA) is the most common form of arthritis and is the leading cause of chronic disability worldwide[1]. Rheumatoid arthritis (RA) is a chronic, progressive, and disabling autoimmune disease that is the second most common type of arthritis, affecting 0.8% of the UK adult population. Patients with OA or RA are at significantly higher risk of cardiovascular (CV) morbidity and mortality compared with the general population[2,3,4,5,6,7,8]. Hypercholesterolemia is one of the established CV risk factors with an increased prevalence among patients with OA or RA. Statin use was associated with reduced risk of CV events and all-cause mortality in trial populations[9]. In addition, statins are suggested to have pleiotropic effects in patients with inflammatory diseases such as RA[10,11]. Recently, a large population-based cohort study had shown that high persistence with statin treatment was associated with a reduction of risk of developing OA or RA[12]. Studies have suggested that statins improve vascular function in RA[13,14,15]. But there are few data on the effectiveness of statins on CV events and all-cause mortality in these patients.

Low-density lipoprotein cholesterol (LDL-C) concentration is rarely measured in clinical practice in the UK. We have shown that total cholesterol (TC) can be used with confidence in the absence of LDL measurements to make decisions about statin titration in the management of coronary

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risk[16]. In addition, we have shown that in normal care, TC reductions with lipid-lowering drugs are comparable with reductions seen in the statin trials[17].

We investigated the effectiveness of statins on lowering TC in patients with OA or RA and on the subsequent risk of CV morbidity and mortality.

MATERIALS AND METHODS

We performed a cohort study in Tayside, Scotland, using the Medicines Monitoring (MEMO) Unit record-linked databases. The data collection methods have been described[18]. In brief, MEMO contains several datasets including all dispensed community prescriptions, hospital discharge data, biochemistry data, and other data; these data are linked by a unique patient identifier, the community health index number. Data are anonymized for the purposes of research as approved by the Caldicott guardians. This project was also approved by the Tayside Committee on Research Medical Ethics.

Study population. The study population consisted of residents of Tayside who were registered with a general practitioner between January 1993 and December 2007 and remained residents in Tayside or died during the study period.

Study subjects. Study subjects were those with a primary diagnosis of OA or RA between January 1993 and December 2007. They were identified from 3 databases: the regional Rheumatoid Arthritis dataset[19], the Scottish Morbidity Record (SMR01) data coded either 715 according to the ninth revision of the *International Classification of Disease* (ICD9), or M15, M16, M17, M18, M19, or M47 according to the tenth revision (ICD10)[20], and patients with first disease-modifying antirheumatic drug (DMARD) use, who were identified from the prescription database. The date of their first diagnosis of OA or RA was used as the study entry date. These subjects had at least 2 different TC measurements with a minimum time interval of 30 days during the followup. They were divided into the statin-exposed group and statin-unexposed group according to statin use status during the followup. The statin-exposed group included prevalent statin-exposed patients (the statin use within 180 days prior to the entry date) or incident statin-exposed patients (the statin use after the entry date); and patients with no statin treatment during the followup were included in the statin-unexposed group. Subjects who were prescribed other lipid-lowering drugs after the entry date or within 180 days prior to the entry date were excluded. Patients were also classified into primary prevention (PP) and secondary prevention (SP) subcohorts in the analysis according to whether they had established CV disease [stroke, transient ischemic attack (TIA), myocardial infarction (MI), angina, heart failure (HF)] prior to the entry date.

Total cholesterol measurements. Serum TC measurements were obtained from the regional biochemistry database. Baseline TC concentration was the concentration measured on the nearest date to the entry date. This date was in the range of within 1 year before or within 30 days after the entry date. Followup TC concentration met the following criteria: (1) on or within 180 days prior to the CV admission; (2) the last available TC measurement during the followup in patients without CV admission; and (3) at least 30 days after statin treatment in the statin-exposed group.

Outcome variables. The primary study outcome was the TC concentration change from baseline and the secondary outcomes were incident or recurrent Anti-platelet Trialists' Collaboration (APTC) events and all-cause mortality during the followup. We used the APTC endpoint of nonfatal MI (ICD9: 410; ICD10: I21), nonfatal stroke (ICD9: 431, 434.9, 436; ICD10: I61, I63, I64), or vascular death (ICD9: 390-459; ICD10: I00-I99) as the primary CV endpoints. They were ascertained from SMR01 data according to the ICD9 or ICD10 codes and occurred at least 30 days after statin treatment in the statin-exposed group or after the entry date in the statin-unexposed group. All-cause mortality data were obtained from the General Register Office for Scotland. The same criteria of CV outcome were applied to the all-cause mortality outcome.

Statistical analysis. Data were summarized as mean (SD) for continuous variables and numbers of subjects (percentage) for categorical variables. To examine differences in baseline characteristics between the groups, chi-square and t tests were performed. TC concentration changes were calculated as baseline TC concentration minus followup TC concentration. A Cox regression model with a time-dependent variable for statin treatment was constructed to analyze the time to APTC, its components, and separately for all-cause mortality and adjusted for potential confounders. Data were expressed as hazard ratios (HR) with 95% CI. The Cox model assumptions were checked before the analysis. Covariates were age at entry to the study, sex, socioeconomic status, TC concentration change, comorbidities of diabetes mellitus, angina, transient ischemic attack, or heart failure, and use of medications including analgesics, corticosteroids, nonsteroidal antiinflammatory drugs (NSAID), drugs that suppress the RA process, and CV drugs of cardiac glycosides, diuretics, beta-adrenoceptor-blocking drugs, hypertension and heart failure drugs, nitrates, calcium-channel blockers, and other antianginal drugs, anticoagulants, and antiplatelet. The Scottish Index of Multiple Deprivation was used as a measure of socioeconomic status[21]. Sensitivity analyses were performed in patients who also had at least 2 high-density lipoprotein cholesterol (HDL-C) measurements or by excluding prevalent statin-exposed patients. A propensity score matched analysis was also conducted to balance the differences between statin-exposed patients and statin-unexposed patients. The propensity score is the conditional probability of exposure to a treatment given observed covariates. To determine the propensity score, a logistic regression model was constructed in which the dependent variable is the treatment group and the independent variables are predictors of treatment. Kaplan-Meier survival curves stratified by statins treatment were produced in OA or RA patients. All analyses were carried out using SAS version 9.1. All p values were 2-sided.

RESULTS

Primary prevention. Baseline characteristics. The PP cohort consisted of 1269 patients with OA (696 in the statin-exposed group, 573 in the statin-unexposed group) and 430 patients with RA (181 statin-exposed, 249 statin-unexposed). The mean followup period was 3.61 years in the statin-exposed group and 2.68 years in the statin-unexposed group in OA patients. The corresponding figures were 3.90 and 3.14 years in RA patients. Among OA patients, patients in the statin-exposed group were more likely to use analgesics, some CV drugs, corticosteroids, and NSAID, and have more diabetes and angina, TIA, or HF than the statin-unexposed group (Table 1). For the RA cohort, patients in the statin-exposed group were older, had a higher baseline TC concentration, had more diabetes, and used more analgesics, corticosteroids, and more CV drugs compared with those in the statin-unexposed group (Table 1).

TC reduction. In OA patients, statin-associated TC concentration fell by 15% [0.79 mmol/l (95% CI 0.70–0.89)] from the baseline of 5.30 mmol/l (SD 1.20; Figure 1A) and there was a 17% reduction in men (baseline TC 5.10 mmol/l) and 13% in women (baseline TC 5.43 mmol/l). In the OA statin-exposed group, there were 52 patients with prevalent statin use at the entry date in whom there was no TC change from baseline of 4.59 mmol/l. A total of 644 patients had incident statin use and TC reduced by 16% from baseline of 5.36 mmol/l.

In patients with RA, TC concentration reduced by 16% [0.91 mmol/l (95% CI 0.73–1.10)] with statins from a base-

Table 1. Characteristics of subjects in the primary prevention of cardiovascular disease. Data in parentheses are percentages.

Characteristic	Osteoarthritis			Rheumatoid Arthritis		
	Statin-exposed	Statin-unexposed	p	Statin-exposed	Statin-unexposed	p
No. subjects	696	573	—	181	249	—
Age, yrs, mean (SD)	68.5 (8.9)	68.7 (11.4)	0.72	63.9 (11.5)	59.4 (15.3)	< 0.01
Male, n (%)	295 (42.5)	223 (38.9)	0.20	46 (25.4)	73 (29.6)	0.34
Baseline total cholesterol concentration, mmol/l, mean (SD)	5.30 (1.20)	5.27 (1.11)	0.69	5.54 (1.10)	5.05 (1.01)	< 0.01
Social economic status						
1 (most deprived)	141 (20.3)	115 (20.1)	0.08	46 (25.4)	61 (24.5)	0.93
2	135 (19.4)	110 (19.2)		40 (22.1)	49 (19.7)	
3	121 (17.4)	129 (22.5)		26 (14.4)	42 (16.9)	
4	146 (21.0)	92 (16.1)		34 (18.8)	50 (20.1)	
5 (most affluent)	139 (20.0)	108 (18.8)		30 (16.6)	40 (16.1)	
Concurrent use of drugs						
Analgesics	591 (84.9)	439 (76.6)	< 0.01	153 (84.5)	176 (70.7)	< 0.01
Positive inotropic drugs	17 (2.4)	25 (4.4)	0.06	3 (1.7)	11 (4.4)	0.11
Diuretics	416 (59.8)	306 (53.4)	< 0.05	97 (53.6)	95 (38.2)	< 0.01
Beta-adrenoceptor-blocking drugs	290 (41.7)	161 (28.1)	< 0.01	57 (31.5)	51 (20.5)	< 0.01
Hypertension and heart failure drugs	431 (61.9)	223 (38.9)	< 0.01	82 (45.3)	69 (27.7)	< 0.01
Nitrates and calcium-channel blockers	415 (59.6)	223 (38.9)	< 0.01	99 (54.7)	77 (30.9)	< 0.01
Anticoagulants	56 (8.1)	43 (7.5)	0.72	13 (7.2)	18 (7.2)	0.98
Antiplatelets	423 (60.8)	164 (28.6)	< 0.01	93 (51.4)	58 (23.3)	< 0.01
Corticosteroids	208 (29.9)	146 (25.5)	< 0.05	109 (60.2)	123 (49.4)	< 0.05
Nonsteroidal antiinflammatory drugs	342 (49.1)	249 (43.5)	< 0.05	110 (60.8)	144 (57.8)	0.54
Drugs that suppress RA process	—	—	—	142 (78.5)	193 (77.5)	0.41
Comorbidity						
Diabetes mellitus	131 (18.8)	50 (8.7)	< 0.01	36 (19.9)	14 (5.6)	< 0.01
Angina, TIA, heart failure	34 (4.9)	9 (1.6)	< 0.01	6 (3.3)	8 (3.2)	0.95

TIA: transient ischemic attack.

line of 5.54 mmol/l (SD 1.10) and decreased by 21% in men from 5.29 mmol/l at baseline and 15% in women from 5.63 mmol/l. Among statin-exposed RA patients, 16 patients were prevalent statin users and 165 patients were incident statin users. Correspondingly, TC decreased by 7% and 17% from baselines of 5.11 mmol/l and 5.59 mmol/l, respectively.

TC reductions with different followup periods of 180 days, 1 year, 2 years, 3 years, 5 years, 10 years, and 15 years varied from 10% to 15% in statin-exposed OA patients and from 13% to 17% in statin-exposed RA patients. TC concentration also fell by about 2% in both OA and RA statin-unexposed groups.

CV events and all-cause mortality. In OA patients there were 34 APTC events in the statin-exposed group and 34 in the statin-unexposed group during the 2513 and 1540 person-years of followup, respectively. Correspondingly, the crude incidences of APTC events per 1000 person-years were 13.5 (95% CI 9.7–18.9) and 22.1 (95% CI 15.8–30.9), respectively (Table 2). In addition, there were 12 nonfatal MI, 12 nonfatal strokes, 19 CV deaths, and 40 all-cause deaths in the statin-exposed groups and 10, 12, 27, and 64 in the statin-unexposed groups.

In RA patients there were 10 APTC events in the statin-exposed group and 19 in the statin-unexposed group, with crude event rates of 14.2 (95% CI 7.6–26.3) and 24.3 (95% CI 15.5–38.1), respectively (Table 2). There were 5 nonfatal MI, 3 nonfatal strokes, 6 CV deaths, and 23 all-cause deaths in the statin-exposed group and 9, 5, 13, and 38 in the statin-unexposed group.

The crude event rate for each component of APTC and the crude mortality rate are shown in Table 2. Figure 2 shows the Kaplan-Meier survival curves of APTC outcome for OA or RA.

In patients with OA, statin treatment had no influence on incident APTC events (adjusted HR 0.87, 95% CI 0.51–1.50) compared with the statin-unexposed groups (Figure 3A). These patients were older, male, used nitrates, calcium-channel blockers, and other antianginal drugs, and had hospital admissions for angina, TIA, or HF during the followup and had an increased risk of CV disease. The effect of statins on individual APTC events was significant only for CV mortality (adjusted HR 0.42, 95% CI 0.20–0.87; Figure 3A). However, statin use was associated with reduction of all-cause mortality of 57% (adjusted HR 0.43, 95% CI 0.25–0.72).

In patients with RA, statin use was associated with a borderline reduction of risk of APTC events (adjusted HR 0.45, 95% CI 0.20–0.98) and all-cause mortality (adjusted HR 0.43, 95% CI 0.20–0.92; Figure 3B). But there were no effects of statins on each APTC component.

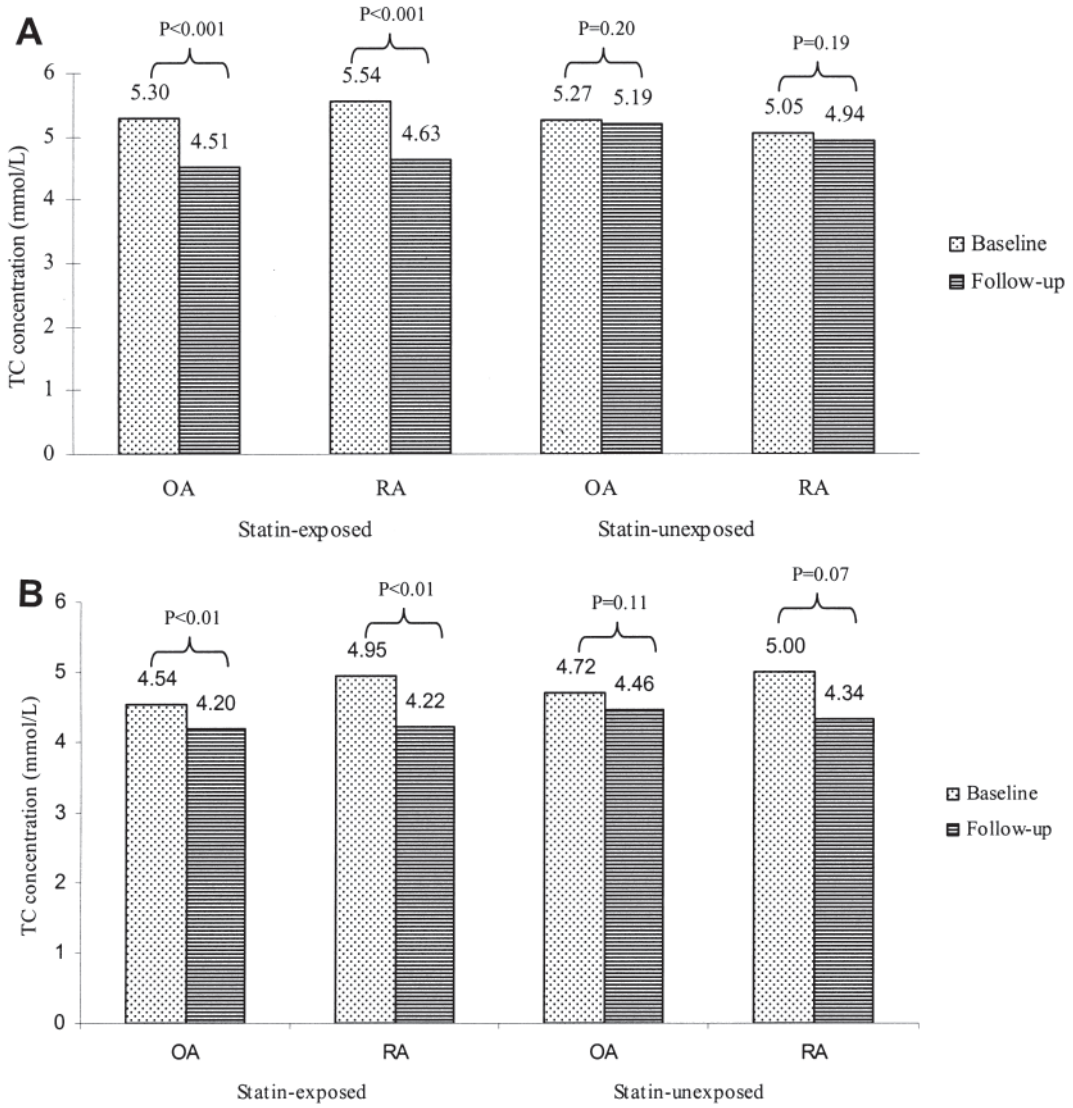

Figure 1. Changes in total cholesterol (TC) concentration in (A) the primary prevention and (B) secondary prevention groups of cardiovascular disease.

Table 2. The crude event rate per 1000 person-years (95% CI) for each endpoint in osteoarthritis and rheumatoid arthritis patients.

	Primary Prevention		Secondary Prevention	
	Statin-exposed	Statin-unexposed	Statin-exposed	Statin-unexposed
Osteoarthritis				
APTC endpoint	13.5 (9.7–18.9)	22.1 (15.8–30.9)	37.7 (24.0–59.1)	86.7 (53.9–139.5)
Nonfatal MI	4.6 (2.6–8.1)	6.3 (3.4–11.7)	9.4 (3.9–22.7)	29.0 (13.0–64.5)
Nonfatal stroke	4.5 (2.6–8.0)	7.6 (4.3–13.5)	5.5 (1.8–16.9)	15.3 (4.9–47.5)
CV death	7.8 (5.0–12.2)	16.7 (11.4–24.3)	18.7 (9.7–35.9)	69.7 (41.3–117.6)
All-cause mortality	16.4 (12.1–22.4)	39.3 (30.8–50.2)	27.2 (15.8–46.8)	113.9 (75.7–171.3)
Rheumatoid arthritis				
APTC endpoint	14.2 (7.6–26.3)	24.3 (15.5–38.1)	47.6 (24.8–91.5)	81.6 (30.6–217.5)
Nonfatal MI	6.8 (2.8–16.2)	11.3 (5.9–21.8)	14.1 (4.5–43.7)	38.5 (9.6–153.8)
Nonfatal stroke	3.9 (1.2–12.0)	6.5 (2.7–15.6)	—	—
CV death	8.3 (3.7–18.5)	16.3 (9.4–28.0)	43.0 (21.5–86.0)	81.1 (26.1–251.4)
All-cause mortality	31.9 (21.2–48.0)	47.0 (34.2–64.6)	78.1 (47.1–129.6)	111.1 (41.7–296.1)

APTC: Anti-platelet Trialists' Collaboration; MI: myocardial infarction; CV: cardiovascular.

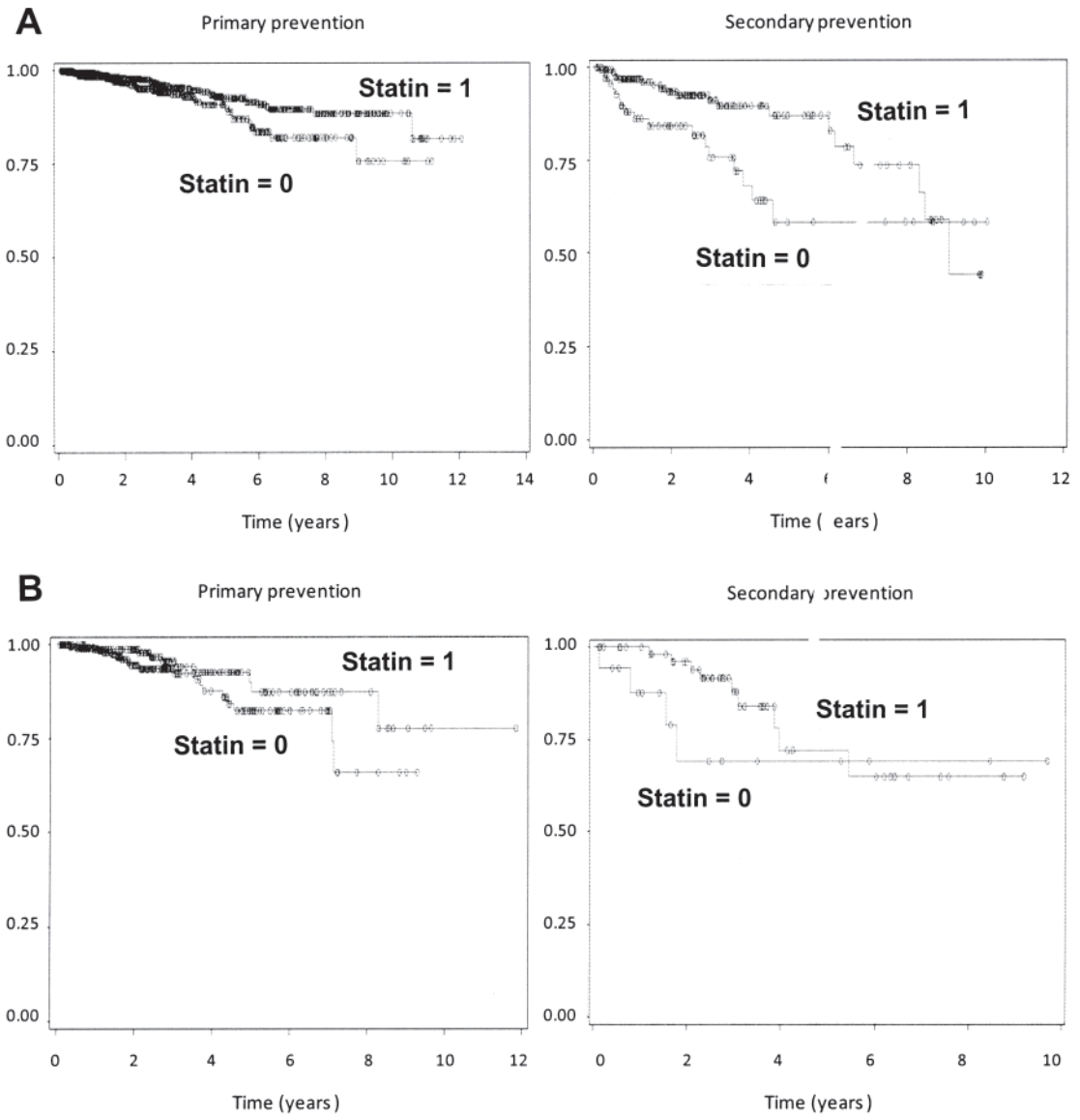

Figure 2. Kaplan-Meier survival curves stratified by statin treatment in subjects with (A) osteoarthritis and (B) rheumatoid arthritis.

Secondary prevention. Baseline characteristics. In total, 247 OA patients (175 statin-exposed, 72 statin-unexposed) were included in this cohort. There were 78 RA patients (60 statin-exposed, 18 statin-unexposed) in the SP cohort. The mean followup was 2.88 years in statin-exposed OA patients and 2.72 years in statin-unexposed OA patients. Correspondingly, the followup periods were 3.14 and 2.71 years, respectively, in RA patients. Statin-exposed OA patients were younger and used more CV drugs (Table 3). Statin-exposed RA patients were more likely to use beta-adrenoceptor-blocking drugs and drugs used in hypertension and heart failure (Table 3).

TC reduction. Figure 1B shows that there was about 7% TC reduction [0.34 mmol/l (95% CI 0.16–0.51)] in OA patients (men 6%; women 8%) and 15% reduction [0.73 mmol/l (95% CI 0.36–1.09)] in RA patients (men 15%; women 14%) with statin therapy from baseline TC of 4.54 mmol/l (SD 1.07) and 4.95 mmol/l (SD 1.28), respectively. In addition, a 5% and 13% reduction of TC was observed in statin-unexposed OA and RA patients. Among the statin-exposed OA group, 14 patients had prevalent statin use at study entry and had no TC reduction from baseline of 4.07 mmol/l. In total, 151 patients had incident statin use with a TC reduction of 7% from baseline, 4.56 mmol/l. In RA patients, 10 patients were prevalent statin users and 50 patients were incident users. Correspondingly, TC fell by 11% and 15% from 4.28 mmol/l and 5.08 mmol/l at the baselines. In patients with followup periods of 180 days, 1 year, 2 years,

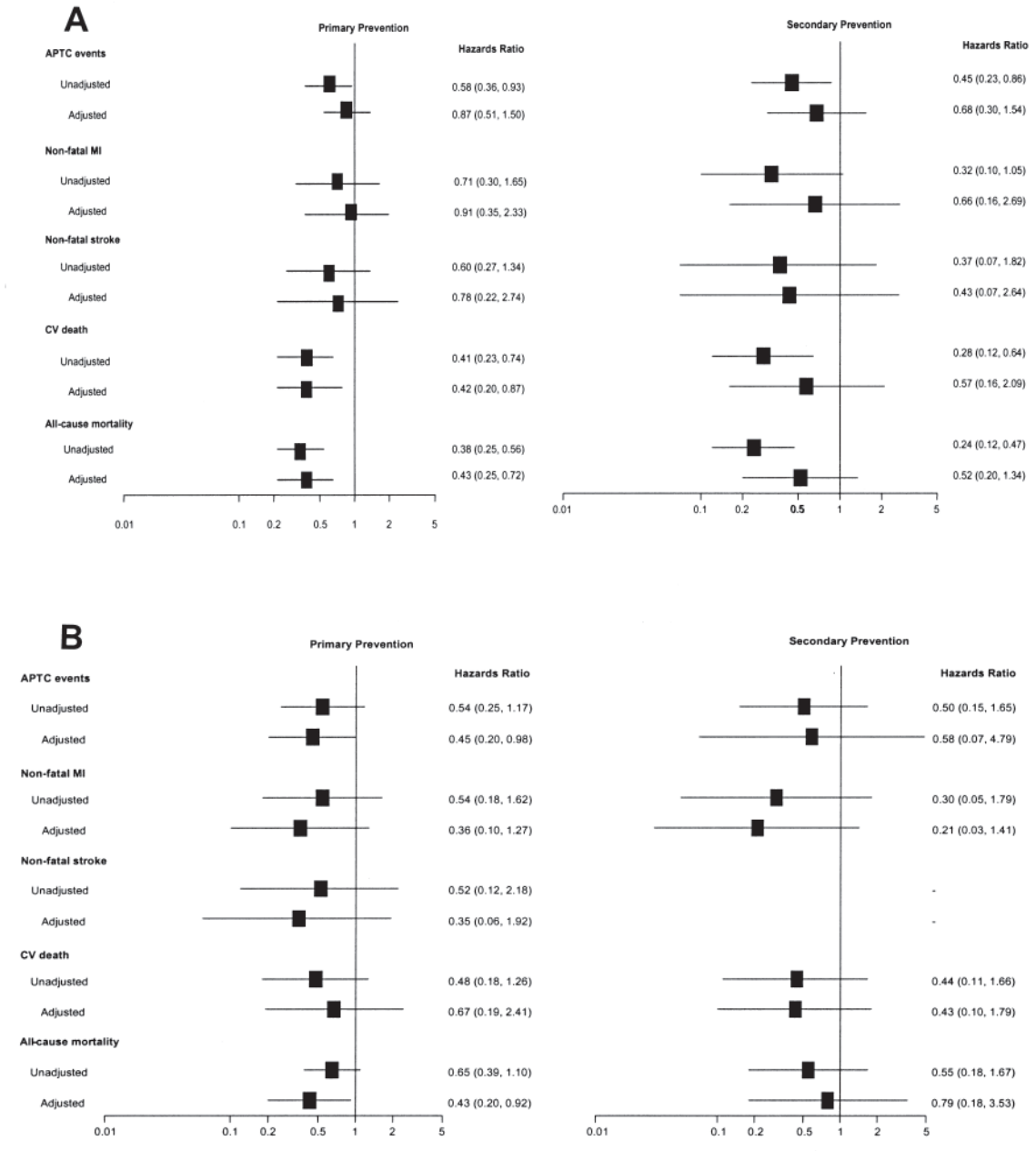

Figure 3. Unadjusted and adjusted hazard ratios of cardiovascular (CV) events and all-cause mortality associated with statin use in subjects with (A) osteoarthritis and (B) rheumatoid arthritis. APTC: Anti-platelet Trialists' Collaboration; MI: myocardial infarction.

3 years, 5 years, 10 years, and 15 years, TC decreased by 4% to 8% in OA patients and by 6% to 15% in RA patients after statin treatment.

CV events and all-cause mortality. In OA patients, recurrent APTC events occurred in 19 statin-exposed patients and in 17 statin-unexposed patients during 504 and 196 person-years of followup with crude event rates per 1000 person-years of 37.7 (95% CI 24.0–59.1) and 86.7 (95% CI 53.9–139.5), respectively (Table 2). For individual APTC endpoints, 5 nonfatal MI, 3 nonfatal strokes, 9 CV deaths, and 13 all-cause deaths happened in the statin-exposed group. Correspondingly, 6, 3, 14, and 23 events occurred in the statin-unexposed group.

In RA patients, 9 recurrent APTC events occurred in the statin-exposed group and 4 in the statin-unexposed group with event rates per 1000 person-years of 47.6 (95% CI 24.8–91.5) and 81.6 (95% CI 30.6–217.5), respectively (Table 2). For each APTC endpoint, 3 nonfatal MI, 0 nonfatal stroke, 8 CV deaths, and 15 all-cause deaths happened in the statin-exposed group and 2, 0, 3, and 4 in the statin-

Table 3. Characteristics of subjects in the secondary prevention of cardiovascular disease.

Characteristic	Osteoarthritis			Rheumatoid Arthritis		
	Statin-exposed	Statin-unexposed	p	Statin-exposed	Statin-unexposed	p
No. subjects	175	72		60	18	
Age, yrs	70.8 (9.6)	75.7 (9.6)	< 0.01	68.1 (9.9)	70.2 (9.4)	0.34
Male, n (%)	95 (54.6)	36 (50.0)	0.51	29 (48.3)	11 (61.1)	0.34
Baseline total cholesterol concentration, mmol/l	4.54 (1.07)	4.72 (1.05)	0.22	4.95 (1.28)	5.00 (1.15)	0.88
Social economic status						
1 (most deprived)	50 (28.6)	18 (25.0)	0.32	18 (30.0)	5 (27.8)	0.18
2	30 (17.1)	21 (29.2)		12 (20.0)	8 (44.4)	
3	29 (16.6)	9 (12.5)		9 (15.0)	1 (5.6)	
4	31 (17.7)	11 (15.3)		14 (23.3)	4 (22.2)	
5 (most affluent)	31 (17.7)	11 (15.3)		7 (11.7)	0	
Concurrent use of drugs						
Analgesics	156 (89.1)	58 (80.6)	0.07	55 (91.7)	14 (77.8)	0.11
Positive inotropic drugs	6 (3.4)	12 (16.7)	< 0.01	7 (11.7)	2 (11.1)	0.95
Diuretics	100 (57.1)	46 (63.9)	0.33	39 (65.0)	8 (44.4)	0.12
Beta-adrenoceptor-blocking drugs	94 (53.7)	22 (30.6)	< 0.01	41 (68.3)	6 (33.3)	< 0.05
Hypertension and heart failure drugs	124 (70.9)	40 (55.6)	< 0.05	48 (80.0)	8 (44.4)	< 0.05
Nitrates and calcium-channel blockers	130 (74.3)	54 (75.0)	0.91	51 (85.0)	13 (72.2)	0.22
Anticoagulants	13 (7.4)	13 (18.1)	< 0.05	13 (21.7)	3 (16.7)	0.65
Antiplatelets	152 (86.9)	49 (68.1)	< 0.01	45 (75.0)	14 (77.8)	0.81
Corticosteroids	46 (26.3)	21 (29.2)	0.64	32 (53.3)	14 (77.8)	0.06
Nonsteroidal antiinflammatory drugs	71 (40.6)	30 (41.7)	0.65	34 (56.7)	9 (50.0)	0.62
Drugs that suppress RA process	—	—	—	43 (71.7)	13 (72.2)	0.70
Comorbidity						
Diabetes mellitus	14 (8.0)	6 (8.3)	0.93	11 (18.3)	3 (16.7)	0.87
Angina, TIA, heart failure	17 (9.7)	10 (13.9)	0.34	9 (15.0)	5 (27.8)	0.22

TIA: transient ischemic attack.

unexposed group. Crude event rates per 1000 person-years for each outcome are shown in Table 2.

There was no significant reduction of risk in either recurrent APTC events or all-cause mortality in the secondary prevention of RA or OA patients (adjusted HR 0.68, 95% CI 0.30–1.54, and HR 0.52, 95% CI 0.20–1.34, for OA patients, and HR 0.58, 95% CI 0.07–4.79, and HR 0.79, 95% CI 0.18–3.53, for RA patients, respectively; Figure 3).

Sensitivity analysis. In patients with data for HDL-C measurements (OA: 656 statin-exposed and 520 statin-unexposed; RA: 169 and 214, respectively), HDL-C concentration increased by 4% with statins in PP in both OA and RA groups. In SP there was about 2% increase of HDL-C concentration in OA patients (n = 226, 167 statin-exposed and 59 statin-unexposed) and 4% increase in RA patients (n = 72, 56 and 16) after statin therapy. Similar results for the effects of statins on APTC events and all-cause mortality were observed in OA or RA patients who had HDL-C measurement.

In a sensitivity analysis that excluded prevalent statin-exposed patients, there were similar findings on the effect of statins on TC reduction, APTC events, APTC components, and all-cause mortality in both PP and SP in patients with OA or RA.

Propensity score-matched analysis. *Primary prevention*. A propensity score-matched analysis was conducted in 736 OA patients (368 in each group) and 216 RA patients (108 in each group). Statin use was associated with a decreased risk of all-cause mortality in both OA and RA patients (adjusted HR 0.59, 95% CI 0.35–0.97, and HR 0.48, 95% CI 0.25–0.92, respectively). There was no statistically significant reduction of risk of APTC events with statin therapy (adjusted OR 0.75, 95% CI 0.40–1.39, in OA patients, and OR 0.30, 95% CI 0.08–1.05, in RA patients).

Secondary prevention. In total, 116 OA patients and 22 RA patients were included in the analysis. Statin use was not associated with statistically significant reduction of risk of APTC events and all-cause mortality in either OA or RA compared with non-use of statins (adjusted HR 0.59, 95% CI 0.21–1.64, and HR 0.51, 95% CI 0.21–1.24, for OA patients, and HR 0.99, 95% CI 0.14–7.25, and HR 0.91, 95% CI 0.14–6.12, respectively).

DISCUSSION

To our knowledge, this is the first population study to investigate the effectiveness of statin use on TC concentration and CV outcome and all-cause mortality among patients with OA or RA. Statin-associated reductions of TC concentration were observed in both patient groups. There were protective effects of statins on CV mortality and all-cause

mortality in OA patients, and on APTC events and all-cause mortality in RA patients in primary prevention. Statins had no influence on CV disease and all-cause mortality in the secondary prevention in both OA and RA patient groups. The results were robust when sensitivity analyses and propensity score-matched analysis were performed by taking HDL-C into consideration or by excluding prevalent statin-exposed patients or by balancing the differences in baseline characteristics.

Reduction of TC concentration with statin treatment in PP (15%) was more than 2-fold that in SP (7%) in OA patients. There was no TC reduction in OA prevalent statin-exposed patients, while about 10% TC reduction was observed in RA prevalent statin-exposed patients. This might be explained by the small sample size (66 OA patients, 26 RA patients). Statins had a comparable effect on TC reduction in PP (16%) and in SP (15%) in RA patients. TC decreased by 13% in the statin-unexposed RA group in SP, and this might be because the group included a very small number of patients (n = 18). Compared with results from our previous studies of TC reduction with statin use in the general population (about a 24% reduction) or in PP and SP of statin trials (each 21% reduction, respectively)[15,16], the reductions of statin-associated TC concentration in patients with OA or RA were smaller, especially in the SP group in OA patients (7%). A lower baseline TC concentration in OA or RA patients than that in the general population appeared to be related to a lesser TC reduction with statin therapy. We calculated the average daily doses of simvastatin in OA or RA patients and the rest of the population excluding patients with OA or RA. They were comparable in the PP group (OA: 27 mg; RA: 28 mg; the rest of the population: 25 mg) and the SP group (OA: 35 mg; RA: 33 mg; rest of the population: 27 mg; both with $p > 0.05$). This indicated that despite higher doses of statins there were smaller TC reductions in patients with OA or RA compared to the remaining population.

Compared with our study, some randomized trials and crossover studies indicated a larger reduction of TC concentration with statin therapy in patients with RA. Three studies suggested that 20 mg or 40 mg simvastatin daily use was associated with a range of 18% to 24% TC reduction and resulted in an improvement in vascular function in patients with RA[13,14,15]. Another 3 studies showed that TC concentration decreased by 29%, 29%, or 33% with 20 mg/day, 40 mg/day, or 80 mg/day atorvastatin[10,22,23]. However, these studies had some important limitations, such as small sample size and relatively short treatment period. In addition, patients in the randomized controlled trials were strictly controlled in a trial setting and had good adherence and persistence to statin treatment. These patients may not be representative of RA patients in usual care, and those trials probably lacked external validity.

We recognize several potential limitations in our study. There were relatively small numbers of patients in both OA and RA groups who had an established CV disease and so there was limited power to provide meaningful results. Studies with larger sample sizes are required to confirm this relationship. Also, the persistence of statin treatment was not taken into consideration in our study. It is possible that other potential confounders not evaluated, such as smoking and body mass index, might have influenced the results. However, we used socioeconomic status as a surrogate marker for this, as data from Scotland have shown there is a significant correlation between smoking and body mass index and social deprivation[24].

Our study shows the evidence of statin-associated reductions of TC concentration and outcome of APTC events and all-cause mortality in patients with OA or RA in a real-world setting. Statins were protective of CV events and mortality in RA patients and protective of mortality in OA patients in primary prevention.

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