Statin Use and Clinical Osteoarthritis in the General Population: A Longitudinal Study

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BACKGROUND: One hypothesis has posited whether abnormal lipid metabolism might be a causal factor in the pathogenesis of osteoarthritis (OA). Routine statin use in clinical practice provides the basis for a natural experiment in testing this hypothesis.
OBJECTIVE: To test the hypothesis that statins reduce the long-term occurrence of clinically defined OA.
DESIGN: Cohort design with a 10-year follow-up.
PARTICIPANTS: 16,609 adults cardiovascular disease cohorts aged 40 years and over from the UK General Practice Research Database with data available to 31 December 2006.
INTERVENTION: Statins were summarised as annual mean daily dose and dose change over two-year time periods.
MAIN MEASURES: Incident episode of clinically defined osteoarthritis was assessed within 2 years, and at 4-year and 10-year follow-up time periods, using Cox and discrete time survival analysis. Covariates included age, gender, deprivation, body mass index, cholesterol level, pain-modifying drug co-therapies, and duration and severity of cardiovascular disease.
KEY RESULTS: Higher therapeutic dose of statin, with a treatment duration of at least 2 years was associated with a significant reduction in clinical OA compared to non-statin users in the follow-up time period. The estimated adjusted rate ratios were as follows: lowest statin dose quartile 1: 2.5 (95 % CI 2.3, 2.9); quartile 2: 1.3 (1.1, 1.5); quartile 3: 0.8 (0.7, 0.95); and highest statin dose quartile 4: 0.4 (0.3, 0.5). The largest statin dose increments were associated with significant reductions estimated at 18 % in OA outcome within 2 years and 40 % after 4 years, compared to non-statin users.
CONCLUSIONS: This longitudinal study from a national clinical practice setting provides evidence that higher statin dose and larger statin dose increments were associated with a reduction in clinically defined OA outcome.

KEY WORDS: drug therapy; osteoarthritis; cardiovascular diseases.
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BACKGROUND

Osteoarthritis (OA) is a complex disease that encompasses change in articular, bone and cartilage structures.[1] Current clinical and research focus has been modification of mechanical loading as a causal factor, or treatment of psychosocial factors, or treatment and replacement of intra-articular cartilage.[2] Yet, studies of generalised osteoarthritis suggest the potential role of systemic processes,[3,4] and from this framework, it has been hypothesised that disorder of lipid metabolism may play a role in the pathogenesis of osteoarthritis.[5,6] The hypothesis is generated from different evidence in the cellular and bio-molecular pathways. First, adipocytes share mesenchymal origin with articular cells, providing a potential cellular link between lipid metabolism and osteoarthritis.[7,8] Second, in vitro studies have shown that excessive lipid levels in the synovial fluid induce arthritic changes, and higher levels of leptin found in obesity has also been shown in joint cartilage destruction.[9,10] Supporting epidemiological studies indicate that these two chronic diseases commonly co-occur,[11] share similar risk factors,[12,13] and are both associated with higher mortality.[14]

Recent literature suggests that statins may have a modifying role in osteoarthritis.[15] Our previous work has shown that the risk factors for cardiovascular disease are also associated with OA over a 30 year time period of follow-up,[16] and smaller studies have established "proof of principle" for such a link, in radiographically confirmed subgroups of OA.[17,18] However, the full public health potential of statins remains to be investigated, as well as whether there is an association with the larger group presenting with clinical OA. For populations at risk, statins are a key drug preventative therapy and form the basis of quality care guidelines to prevent long-term cardiovascular events.[19] The objective of this study was to use large data sets available from the primary care population, where OA is a common presenting problem and statin use is routine, for investigating the hypothesis of whether statins are associated with a reduction in OA occurrence.

METHODS

We used the General Practice Research Database (GPRD) on over 300 practices, which links clinical diagnosis to

other data, such as prescribed drugs, test results and measurements such as body mass index (BMI). The GPRD is representative of England and Wales population, since most people are registered with a General Practitioner (GP), and such data on a large scale population over a longitudinal time period provides the basis for a variety of hypothesis-testing epidemiological studies.[20,21] All data is routinely computer recorded, with diagnostic data coded as patients present their clinical complaints, using a standard clinical classification to record chronic diseases such as cardiovascular disease and osteoarthritis.[22] Permission to access the GPRD data was given by the Independent Scientific Advisory Committee.

Selection of Cohort Population

Cardiovascular disease (CVD) cohort populations aged 40 years and over were identified on the basis of a 2-year time period (1 January 1995 to 31 December 1996) with no clinical record of OA during this time period and in any available patient records in the preceding time period. This cohort (n=16,609) had linked records to drugs prescribed and to any incident clinically defined OA outcome in the following 10-year time period (1 January 1997 to 31 December 2006).

Within the overall cohort, there were six exclusive subgroups of CVD, ordered as follows: (1) hypertension, (2) atrial fibrillation, (3) angina, (4) myocardial infarction and (5) heart failure. Groups were allocated to the most 'severe' diagnostic category, irrespective of other CVD multimorbidity; for example, if a patient has heart failure and hypertension, then they were allocated to the heart failure cohort group. The sixth group consisted of any 'other' CVD symptoms and morbidities outside of the five specific categories. This broader 'other CVD' cohort, with some aspect of vascular disorders in their clinical records, was chosen to provide validation for the specific diagnostic groups.

Measures of Statin Use

Within the overall cohort, prescribed drugs had been coded using the standard British National Formulary (BNF) classification.[23] Lipid-regulating drugs within this classification were used to categorise statin users and other statins were standardised to the equivalent Simvastatin dose.[24] Statin dose was then summarised as the mean daily dose in each 12-month time period, which equates to the prescription dose x frequency of daily dose x quantity of tablets, divided by 365 days. This process was done for the each of the total 12 years of observation. For the overall cohort, data was organised into statin users, and non-users were classified on the basis of the whole of the 12-year time period.

Clinically Defined OA Outcome

In the 10-year follow-up period, the incident outcome of "OA" was defined on the basis of any coded clinical entry irrespective of joint site, and there were 147 OA-related diagnostic categories from a standard clinical classification.[22] OA diagnoses were recorded by GPs in the actual consultations, when it was the primary presenting problem care. These diagnostic codes focus on the specific use of the term "osteoarthritis", and not diffuse pain complaints or syndromes. Previously, we have shown that these OA categories are a marker of health severity, representing distinct diagnostic application when OA is established.[25] These clinical definitions represent a different measure from radiographic definitions of OA, but they are an important epidemiological clinical measure in large general populations consulting over time,[26,27] which provides the setting for an *a priori* natural experiment. Current evidence also shows that OA can be viewed primarily as a clinical joint pain syndrome, since clinical and radiographic features are not always concordant.[28,29]

Other Factors

Duration of each CVD in years was also estimated on the basis of time between the age at first diagnosis and the date of diagnosis in the cohort sampling window, and was used as a proxy marker of the 'immortal' time in which an OA event might have occurred.[30] Other measures included serum cholesterol levels (mmol/l) and obesity, as summarised by BMI (kg/m^2). We used the first recorded cholesterol level or a BMI record for an individual as a measure of baseline status, and repeated measures were not used in analyses, because this type of data was not fully available over the follow-up time period.

We also wanted to consider the potential role of other pain-modifying drug co-therapies, such as analgesia (non-opioids, opioids and non-steroidal anti-inflammatories) and anti-depressants, which might be associated with a reduction in OA presentation.[31] These drug co-therapies based on BNF classification were summarised into either analgesia users or non-users in the six 2-year time periods for the whole period of observation. Deprivation was measured by the Index of Multiple Deprivation (IMD) for each practice, and was based on the 2004 UK census and is an area-level measure of deprivation. IMD is based on the postcode, and is a weighted score of seven sub-domains relating to income; employment; health; education, skills and training; barriers to housing, and access to local services; crime; and living environment.[32]

STATISTICAL ANALYSIS

Modelling Statin Dose and Latency Period

In terms of hypothesising the time that it might take for a person to be on statin to reduce the clinical occurrence of OA

(potential 'latency' treatment time period), we estimated that a minimum time period of 2 years of statin use was required. This hypothetical time period for 'treatment effect' is based on evidence from other studies, which show this is the duration of statin use required in order to achieve a significant reduction in cardiovascular disease outcomes.[33,34]

The statin daily dose measure was modelled in two ways. In the overall cohort Cox regression analysis, statins were defined as mean daily dose per year, to categorise statin users of more than 2 years in the 10-year follow-up period. The four quartile dose categories, ranging from quartile 1 (low dose) to quartile 4 (high dose). If any drug users had had less than 2 years of statin, they were allocated to the non-user group (n=556).

In the discrete time analysis, we wanted to assess change in statin dose use in individual patients over time, and this approach again incorporated 'immortal' time in which an OA event might have occurred.[30] Therefore, we split the 12 years into six 2-year time periods and summarised the dose changes for each individual from the baseline 2-year time period to each of the five respective follow-up time windows. This approach resulted in four incremental dose change groups, ranging from Group 1 (smallest dose change) to Group 4 (largest dose change), with the pooled estimate indicating that there was an increase in statin dose of 3.61 mg every 2 years (also see Fig. 1).

Analysis

First, for the four mean daily dose quartile groups compared to non-users, we estimated OA outcomes in the 10-year follow-up period using Kaplan Meier plots. Then, using Cox regression methods, with time to OA event, we adjusted for age, gender, IMD status, BMI, cholesterol level, other pain-modifying drug co-therapies and duration and category of cardiovascular disease group. Assumption of proportionality of hazard ratios was tested throughout.

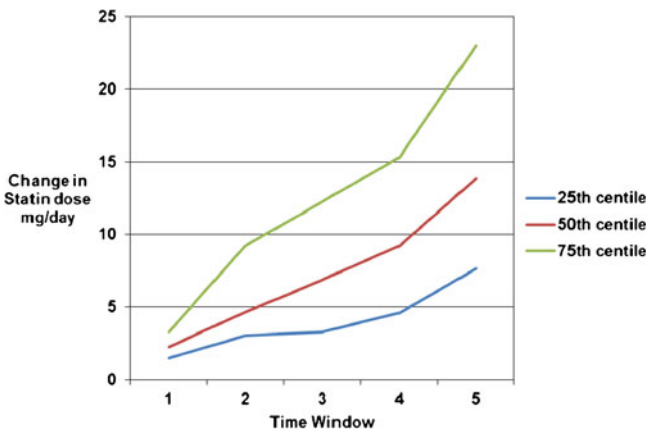

Figure 1. Statin dose increments over the 10-year follow-up period.

Second, using discrete time survival analysis, we wanted to assess the influence of incremental changes in statin dose in two shorter time periods of observation: (1) within each 2-year time window and (2) a temporal 4-year approach. For within each 2-year time period, we analysed the association between changing statin dose and OA outcome, which means there were six time windows. We then constructed a temporal element by linking each initial 2-year time period with the consecutive 2-year time period, to create five 4-year time windows. In this 'temporal approach', each initial 2-year time period was OA free, so that OA outcome was only assessed in the subsequent 2-year window. Individual follow-up time was first converted to 2-year blocks, and outcome and covariates status were determined for each block. Discrete time survival analysis was then used to model the risk of an OA event. This method treats time not as a continuous variable, but as being divided into discrete units. Within each time window, quartiles of statin exposure were determined and used as a time varying ordinal variable to reflect changing dose, which includes time without possible statin exposure. Logistic regression methods were used to compare changing dose groups with non-statin users for OA outcomes for these shorter time frames, adjusting for all covariates.

Finally, the statin analyses were repeated for each of the six exclusive CVD subgroups, using the chi-square test for trend. However, since the total number of statin users within each CVD group was small, the study groups were categorised into non-statin users, low dose statin users and high dose statin users, using the mean daily dose per year estimates. Statistical significance was defined as $p<0.05$, all hypothesis testing was two-tailed, and analyses were performed using SPSS (version 18.0) and MLwiN (version 2.21).

RESULTS

Cohort Population

Within the overall study population, there were 4,976 statin users who had been on at least 2 or more years of the statins with an mean daily dose of 15 mg, and 11,633 non-statin users (Table 1). Statins users were similar to non-users in terms of age, deprivation, BMI and cholesterol characteristics, but men were more likely to be on statins than women. Of the statin users, there were higher proportions with angina or myocardial infarction than non-users.

Statin Dose and OA Outcome

The mean quartile statin dose was as follows: quartile 1 (lowest dose), up to 5 mg daily; for quartile 2, up to 10 mg daily; for quartile 3, up to 18 mg daily; and for quartile 4 (highest dose), over 18 mg daily. The associations between statin dose quartiles and OA outcome in the follow-up period are shown in Kaplan Meier plots (Fig. 2).

Table 1. Characteristics of Statin Users and Non-Users Aged 40 Years and Over in the Cohort Population

	Statin users n=4,976	Non-statin users n=11,633*
Daily dose (SD) mg	14.6 (15.5)	n/a
Age (SD) years	65 (9.6)	70 (13.1)
Men: Women	2,925:2,051	5,402:6,231
Deprivation (SD)	26 (19.2)	27 (19.3)
BMI kg/m^2 (SD)	26 (5.1)	27 (5.1)
Cholesterol mmol/l (SD)	5.0 (0.9)	5.2 (1.2)
Hypertension† (%)	222 (4.5)	1,256 (11.3)
Atrial fibrillation† (%)	514 (10.3)	1,735 (15.7)
Angina† (%)	1,726 (34.7)	2,038 (18.4)
Myocardial infarction† (%)	1,410 (28.3)	1,166 (10.5)
Heart failure† (%)	265 (5.3)	2,096 (18.9)
Other cardiovascular diagnosis† (%)	839 (16.9)	2,786 (25.2)
Antidepressants (%)	1,154 (23.2)	2,172 (19.6)
Non-opioids (%)	1,313 (26.4)	2,488 (22.5)
Non-steroidals (%)	2,923 (58.7)	5,305 (47.9)
Opioids (%)	2,292 (46.1)	4,346 (39.2)

Percentage figures (%) represent the statin users in 10-year follow-up and non-users in the entire 12-year time period
**includes 556 statin users less than 2 years*
†Exclusive diagnostic categories

Over the 10-year follow-up period, higher mean daily statin dose was significantly associated with a decreased likelihood of clinical OA (Table 2), and the results showed a dose-gradient response. Compared to statin non-users, the relative adjusted estimates were as follows: quartile 1 (lowest dose), rate ratio 2.55 (95 % confidence interval 2.3–2.9); quartile 2, 1.31 (1.1–1.5); quartile 3, 0.82 (0.7–0.95); and quartile 4 (highest dose), 0.41 (0.3–0.5). Older age, female gender and higher BMI were significantly associated with increased clinical OA outcome, but disease categories, cholesterol levels, duration of disease and specified drug co-therapies did not influence the likelihood of clinical OA outcome.

Changing Statin Dose and OA Outcome

The influence of changing statin dose was also assessed for its impact on OA outcome. In the 10-year follow-up period, the 25th centile dose change was around 5 mg and the 75th centile dose change was over 20 mg, as shown in Fig. 2.

First, in the six shorter within 2-year time windows, larger dose change of statins was associated with a reduction in clinical OA, again showing a dose-gradient response (Table 3). Compared to statin non-users, the adjusted (for age, gender, deprivation and drug co-therapies) estimates were as follows: group 1 (smallest dose increment): odds ratio 1.07 (95 % confidence interval 0.9–1.3); group 2: 1.17 (0.9–1.4); group 3: 0.95 (0.8–1.2); and group 4 (largest dose increment): 0.82 (0.7–0.99). Second, in the temporal 4-year analyses, compared to the statin non-users, the relative adjusted estimates were: group 1 (smallest dose increment): odds ratio 1.7 (95 % confidence interval 1.5–1.9); group 2: 0.98 (0.8–1.2); group 3: 0.95 (0.8–1.1), and group 4 (largest dose increment): 0.60 (0.5–0.7). At around 2 years, in the group with the largest statin dose increment, there is a

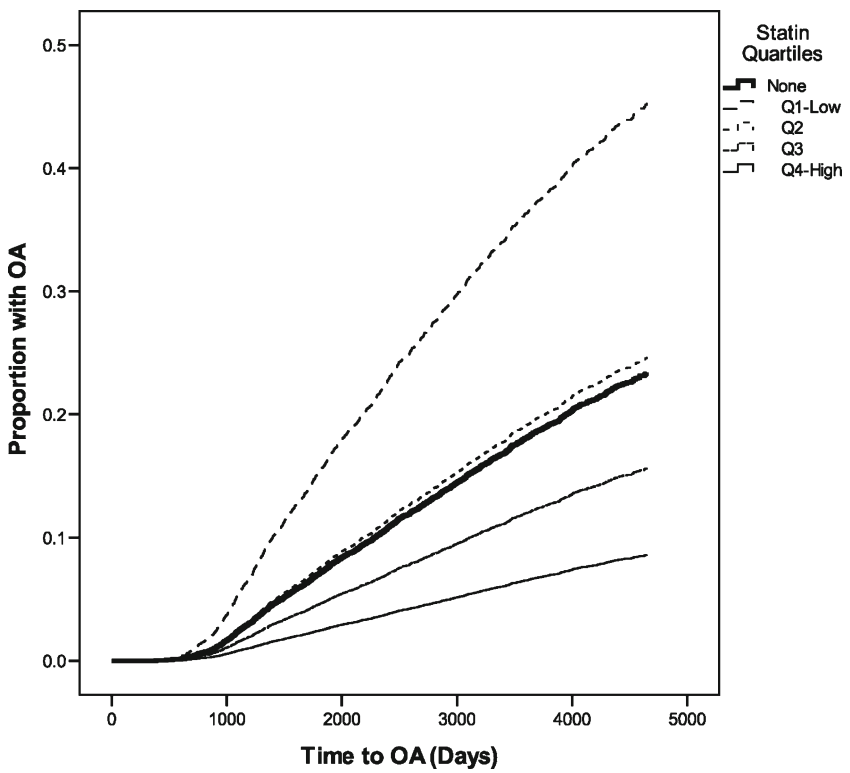

Figure 2. Cumulative Kaplan-Meier plots for statin dose quartile groups and osteoarthritis (OA) outcome over 10-year follow-up.

Table 2. Statin Dose Quartile Groups and Osteoarthritis (OA) Outcome Over 10-year Follow-Up

Factors	Subgroups	OA		Estimates		Rate ratio[#] (95 % CI)
		Yes	No	β	SE	
Sociodemographic	Older age	1,068	6,808	0.021	0.003	1.02 (1.01, 1.03)
	Female	898	7,181	0.495	0.050	1.64 (1.5, 1.8)
	Higher deprivation**	1,170	7,085	−0.001	0.001	1.00 (0.99, 1.01)
	Higher body mass index[††]	580	2,255	0.039	0.004	1.04 (1.0, 1.1)
Clinical status[†]	Hypertension	155	1,323	n/a		1.0
	Atrial fibrillation	314	1,940	0.040	0.139	1.04 (0.8, 1.4)
	Angina	646	3,122	0.189	0.128	1.21 (0.94, 1.6)
	Myocardial infarction	360	2,206	0.107	0.137	1.11 (0.9, 1.5)
	Heart failure	202	2,168	−0·077	0.169	0.93 (0.7, 1.3)
	Other CVD	583	3,050	0·085	0.134	1.09 (0.8, 1.4)
	Longer disease duration[†††]	678	3,999	−0.007	0.008	0.99 (0.98, 1.0)
	Higher cholesterol level[††]	265	894	−0.091	0.027	0.91 (0.9,1.0)
	Specific drug co-therapies[‡]	1,438	8,050	0.085	0.049	1.09 (0.98, 1.2)
Statin dose	None[‡‡]	1,383	9,779	n/a		1.0
	Quartile 1 (0.01–4.6 mg/day)	226	883	0.934	0.061	2.55 (2.3, 2.9)
	Quartile 2 (4.7–9.9 mg/day)	274	881	0.266	0.70	1.31 (1.1, 1.5)
	Quartile 3 (10.0–18.4 mg/day)	251	1,094	−0.204	0.076	0.82 (0.7, 0.95)
	Quartile 4 (18.5 mg/day or more)	126	1,172	−0.889	0.100	0.41 (0.3, 0.5)

[#]Cox regression rate ratio adjusted for all co-variates
***Based on IMD, which is the Index of Multiple Deprivation, a census based area-level measure*
[†]Patients with exclusive diagnostic categories in their clinical records for a 2-year time window (1995–1996)
[‡]Specific drug co-therapies relate to users of opioids, non-opioids, non-steroidal anti-inflammatories or anti-depressants in 2-year time windows over the total 12 year period of observation
[††]Values refer to the first available recorded date in an individual's clinical record and the (SD) summaries on available non-missing data
[††]includes 556 statin users less than 2 years
[†††]Time between age at first diagnosis and the date of diagnosis in the cohort sampling window

relative reduction estimated at 18 % in OA outcome compared to non-statin users, and after 4 years, the relative reduction was estimated at 40 %.

Statin Dose and OA Outcome by CVD Severity

Within all the CVD subgroups, except heart failure, higher dose of statin was associated with a reduction in clinical OA outcome (Table 4). The statistically significant trends ($p < 0.001$) in the association between higher dose of statin and reduction of OA outcome compared to non-statin users were significant for atrial fibrillation, angina, myocardial infarction, and 'other' CVD group.

DISCUSSION

Our study shows that increasing dose of statin use and larger statin dose increments were associated with a reduction in clinical OA compared to non-statin users. These findings were not explained by the duration or severity of associated cardiovascular disease, or pain-modifying drug co-therapies or age, gender, deprivation, or baseline cholesterol levels or BMI status. At the highest statin daily dose, which was a therapeutic dose of around 20 mg daily, there was approximately a 60 % relative reduction in clinical OA outcome, compared to non-statin users. Larger increments in the dose of statins were also associated with a 40 % relative reduction in clinical OA outcome compared to non-statin users over a 4-year time period.

Table 3. Change in Statin Dose and Osteoarthritis (OA) Outcome: Discrete Time Series Designs

Change in statin dose[†]	Within 2-year analyses[††]		Adjusted odds ratio** (95 % CI)	'Temporal' 4-year analyses[†††]		Adjusted odds ratio** (95 % CI)
	β	SE		β	SE	
None	ref	ref	1.0	ref	ref	1.0
Group 1 (Smallest)	0.067	0.083	1.07 (0.9, 1.3)	0.531	0.058	1.7 (1.5, 1.9)
Group 2	0.154	0.087	1.17 (0.9, 1.4)	−0.022	0.099	0.98 (0.8, 1.2)
Group 3	−0.046	0.106	0.95 (0.8, 1.2)	−0.056	0.082	0.95 (0.8, 1.1)
Group 4 (Largest)	−0.270	0.121	0.82 (0.7, 0.99)	−0.516	0.111	0.60 (0.5, 0.7)

[†]Increasing dose change, as measured by mean dose in a 2-year time-block to subsequent 2-year time periods in the following 10 years
***Adjusted for all covariates: age, gender, deprivation, BMI, cholesterol level, specific drug co-therapies (opioids, non-opioids, non-steroidal anti-inflammatories or antidepressants), and duration and diagnostic cardiovascular disease; specific drug co-therapies relate to users of opioids, non-opioids, non-steroidal anti-inflammatories or antidepressants in 2-year time windows over the total 12-year period of observation*
[††]Analyses applies to change in statin dose and OA event within the same 2-year time period, with estimates averaged for the five 2-year time windows in the 10-year follow-up
[†††]Analyses applies to change in statin dose estimated from the prior 2-year time period, with OA event in the subsequent 2-year follow-up (therefore again, five time windows, starting with 1995–1996 as the first window)

Table 4. Statin Dose and OA Outcome over 10 year Follow up by CVD Groups

Disease group†	Statin daily dose*	OA outcome		Adjusted rate ratio** (95 % CI)
		Yes	No	
Hypertension	None	130	1,126	1.0
	Low	15	96	0.91 (0.5, 1.8)
	High	10	101	0.50 (0.3, 1.0)
Atrial Fibrillation	None	214	1,521	1.0
	Low	5	263	0.99 (0.7, 1.4)
	High	12	234	0.69 (0.5, 1.0)
Angina	None	304	2,342	1.0
	Low	218	663	1.14 (0.9, 1.4)
	High	108	737	0.49 (0.4, 0.6)
Myocardial Infarction	None	140	1,006	1.0
	Low	115	578	1.36 (1.1, 1.8)
	High	46	671	0.61 (0.5, 0.8)
Heart failure	None	167	1,929	1.0
	Low	12	134	0.78 (0.4, 1.6)
	High	20	99	0.93 (0.5, 1.7)
Other CVD	None	416	2,370	1.0
	Low	95	338	1.25 (0.99, 1.6)
	High	55	351	0.70 (0.5, 0.9)

†*Exclusive ordered groups, with hypertension as 'least severe' and heart failure 'most severe' category. Patients consulted for the diagnostic category in a 2-year time window (1995–1996). The exclusiveness of severity categories is that allocation of an individual to one of these was based on the most severe category; for example, if an individual had consulted for hypertension and heart failure, they would be classified into the heart failure category*

**Statin dose summarised as mean daily dose*

***Adjusted Cox regression rate ratios for all covariates: age, gender, deprivation, BMI, cholesterol level, specific drug co-therapies (opioids, non-opioids, non-steroidal anti-inflammatories or antidepressants), and duration and severity of cardiovascular disease*

Other emerging evidence over the life course is further adding to idea of shared pathogenesis for OA and cardiovascular disease. Studies have shown that the co-occurrence of OA and cardiovascular disease is common.[11,35,36] Severity of hand osteoarthritis is associated with atherosclerosis[37] and it has also been shown that OA is a predictor of all-cause mortality, particularly for cardiovascular disease-related mortality.[38] An additional relevant study suggests that diabetes, as part of the metabolic syndrome, may influence the onset of OA.[39]

It is postulated that statin modification of OA might be through two mechanisms, either through lowering of the cholesterol levels[5] or through anti-inflammatory properties.[15] There is evidence of local inflammatory processes that occur in osteoarthritis joints,[40] and it is thought that traumatic stimuli induce mechanical receptors in chondrocytes to produce cytokines[41] and matrix metalloproteinases, which lead to a degradation of articular cartilage.[42] Statins may modify these inflammatory mechanisms, and this may be separate to that of cholesterol lowering activity.

The study findings need to be placed within the context of the design and measurement issues. Statins measurement was based on prescribing by general practitioners, and in the United Kingdom they are still clinician prescribed-only drugs. This means the statin users and non-users were likely to be clearly defined, and the construction of dose quartile groups showed a gradient effect as hypothesised. The study design time frame from 1995 to 2006, during which there was increasing use of statins and statin doses, also provides the appropriate cardiovascular population at risk for investigating treatment hypothesis without indication.

The definition of OA was based on clinician-defined diagnosis as presented by patients, and the study findings for older age, female gender and body mass index associations show the validity of such a definition. This approach is reasonable, as in the UK it is largely presented to and managed by GPs, and the population-based database used has also been shown to have high clinical validity for a range of clinical conditions.[43] Finally, it is unlikely that clinical recording of OA diagnostic labels would have been influenced by statin prescribing, other than the random variation in the recording of clinically defined OA, but the large number of practices provide a reliable reflection of clinical OA in the general population.

We also considered the potential effects of disease severity and duration. Severity of cardiovascular disease may attenuate the potential impact of statins, and the associations between low dose statin groups and higher OA outcome compared to reference group seemed to suggest this, but our study showed that there was a gradient effect of statins within all but the heart failure cohort. It is probable that the heart failure group represents end-stage cardiovascular disease, when modification of OA pathogenesis is too late to take effect. The incorporation of duration of disease and statins modelled on change in dose over time, also addressed the issue of unexposed time, which can be an analytic bias[30] in pharmaco-epidemiology studies. An *a priori* treatment hypothesis was tested, and even though there may still be residual unmeasured confounders, it would be difficult to propose alternative explanations of the dose response gradient or the magnitude of statin effects that were shown.

CONCLUSIONS

This study provides evidence that therapeutic statin dose and larger statin dose increments were associated with a reduction in clinically defined OA outcome. These findings further support the hypothesis that biologic modification of OA may be plausible, and the potential clinical implication is that OA management may share preventative approaches with cardiovascular disease.

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