Pattern of risks of systemic lupus erythematosus among statin users

Citation for published version (APA):

De Jong, H. J. I., van Staa, T. P., Lalmohamed, A., de Vries, F., Vandebriel, R. J., Van Loveren, H., Klungel, O. H., & Tervaert, J. W. C. (2017). Pattern of risks of systemic lupus erythematosus among statin users: a population-based cohort study. *Annals of the Rheumatic Diseases*, 76(10), 1723-1730. <https://doi.org/10.1136/annrheumdis-2016-210936>

Document status and date:

Published: 01/10/2017

DOI:

[10.1136/annrheumdis-2016-210936](https://doi.org/10.1136/annrheumdis-2016-210936)

Document Version:

Publisher's PDF, also known as Version of record

Document license:

Taverne

Please check the document version of this publication:

- A submitted manuscript is the version of the article upon submission and before peer-review. There can be important differences between the submitted version and the official published version of record. People interested in the research are advised to contact the author for the final version of the publication, or visit the DOI to the publisher's website.
- The final author version and the galley proof are versions of the publication after peer review.
- The final published version features the final layout of the paper including the volume, issue and page numbers.

[Link to publication](#)

General rights

Copyright and moral rights for the publications made accessible in the public portal are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

- Users may download and print one copy of any publication from the public portal for the purpose of private study or research.
- You may not further distribute the material or use it for any profit-making activity or commercial gain
- You may freely distribute the URL identifying the publication in the public portal.

If the publication is distributed under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license above, please follow below link for the End User Agreement:

www.umlib.nl/taverne-license

Take down policy

If you believe that this document breaches copyright please contact us at:

repository@maastrichtuniversity.nl

providing details and we will investigate your claim.

EXTENDED REPORT

Pattern of risks of systemic lupus erythematosus among statin users: a population-based cohort study

Hilda J I De Jong,^{1,2,3} Tjeerd P van Staa,^{3,4} Arief Lalmohamed,^{3,5} Frank de Vries,^{3,6,7} Rob J Vandebriel,¹ Henk Van Loveren,^{1,8} Olaf H Klungel,³ Jan Willem Cohen Tervaert^{2,9}

For numbered affiliations see end of article.

Correspondence to

Dr Olaf H Klungel, Department of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, 3508 TB Utrecht, The Netherlands; o.h.klungel@uu.nl

Received 7 December 2016

Revised 30 April 2017

Accepted 20 May 2017

Published Online First

6 July 2017

ABSTRACT

Objectives To examine the association between the use of statins and the risk of systemic lupus erythematosus (SLE) with focus on describing the patterns of risks over time.

Setting A population-based cohort study using the UK Clinical Practice Research Datalink.

Participants All patients aged 40 years or older who had at least one prescription of statins during the period 1995–2009 were selected and matched by age, sex, practice and date of first prescription to non-users. The follow-up period of statin users was divided into periods of current, recent and past exposure, with patients moving among these three exposure categories over time. Current statin users were also stratified into ≤ 1 year or > 1 year of use.

Main outcome measures Time-dependent Cox models were used to calculate HRs of SLE, adjusted for disease history and previous drug exposure.

Results We included 1 039 694 patients, of whom 519 847 were statin users. Current statin users did not have an increased risk of developing SLE among patients aged ≥ 40 years (HR_{adjusted} 0.75, 95% CI 0.53 to 1.07). Current statin users who continued the therapy for > 1 year had a 38% lower risk of developing SLE (HR_{adjusted} 0.62, 95% CI 0.42 to 0.93). When more specific definitions for SLE were used, this latter finding, however, was not observed.

Conclusions Our findings showed no effect of statins on the risk of developing SLE among patients aged ≥ 40 years. Further research is needed to study the long-term effects of statins on SLE.

INTRODUCTION

Statin users are effective in reducing the risk of cardiovascular morbidity and mortality in patients with hyperlipidaemia, hypertension or diabetes.^{1–3} Besides their cholesterol-lowering activity, several studies have shown that statins have anti-inflammatory and immunomodulatory properties and may suppress the expression of ongoing autoimmune responses. Specifically, several studies have shown that statins decrease the proinflammatory biomarkers and/or disease activity scores in patients with SLE.^{4–7} Alternatively, we previously suggested that statins may facilitate the development of autoimmunity.^{8–10} In these studies, however, we used different study designs, study populations, study outcomes and definitions of the exposure to statins.^{8–10} Four studies that included analyses of reports of adverse drug reactions suggested that statins could trigger the development of lupus-like

syndrome.^{10–13} The mean time from statin exposure to the onset of SLE has been described as 12.8 ± 18 months (range 1 month–6 years).¹² However, one study showed that statin use was associated with a decreased risk of connective tissue disease (CTD), including SLE.¹⁴ To date, there is no robust evidence of whether statins have an effect on the development of SLE. We examined the association between the use of statins and the risk of SLE with focus on describing the pattern of risk of SLE over time.

METHODS

Data source

Data were derived from the Clinical Practice Research Datalink (CPRD), an ongoing primary care database of anonymous medical records from general practitioners. CPRD contains the computerised medical records of 625 general practices, representing approximately 8% of the population in the UK and has been described in detail elsewhere.¹⁵ The data recorded in the database include demographic information, diagnoses, prescription details, preventive care provided, referrals to specialist care, hospital admissions and related major outcomes.¹⁵ Several independent validation studies have shown that the CPRD database has a high level of completeness and validity.¹⁶ The current study was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database Research.

Study population

We conducted a matched cohort study with prospectively collected data among patients who had at least one prescription of statins during the period 1995–2009. The date of the first prescription of statins was defined as the index date. Statin users were matched to a single control (non-users of statins) randomly selected from patients of the same age (± 5 years) and sex at index date, with the index date of the control being the same as that of the statin user (ie, matching on calendar time). Statin users and non-users were also matched on practice as they had to be registered at the same general practice as the statin user to control for differences in prescribing regimens per practice.

Statin users and non-users had to have at least 1 year of data collection before the index date. After this matching, statin users and non-users who had ever been diagnosed with SLE, had used disease-modifying anti-rheumatic drugs (DMARDs) and/or were younger than 40 years

CrossMark

To cite: De Jong HJ, van Staa TP, Lalmohamed A, et al. *Ann Rheum Dis* 2017;**76**:1723–1730.

Figure 1 Three examples of time-dependent exposure to statins in patients A, B and C. During follow-up of the patients who initiated statin therapy, time was divided into periods of current, recent and past exposure to statins, with patients moving between these three exposure categories over time. We illustrated this pattern of statin exposure by three examples. Patient A: the follow-up of statin use of patient A was divided into periods of current, recent and current exposure to statins. Patient B: the follow-up of statin use of patient B was divided into periods of current, recent and past exposure to statins. Patient C: the follow-up of statin use of patient C was divided into periods of current, recent, past and current exposure to statins. Black arrow: current exposure, time from the start date of a prescription until 3 months after its expected duration of use. The expected duration of use was defined as 3 months (run-out period). When the consecutive prescription of statins was prescribed within these 3 months, the exposure to statins was defined as current exposure. Dark grey arrow: recent exposure, time from 3 to 12 months after the end date of the most recent prescription of statins. Light grey arrow: past exposure, time from 12 months or longer after the end date of the most recent prescription of statins.

before or at the index date were excluded. Patients aged ≥ 40 years were considered more likely to receive a statin than patients < 40 years.

Exposure to statins

All prescriptions for statins were identified. Each prescription length was calculated by dividing the number of prescribed tablets by the prescribed daily dose. Since statin therapy compliance declines substantially over time,¹⁷ the time of follow-up was divided into periods of current, recent and past exposure to statins, with patients moving between these three exposure categories over time.¹⁸ Current exposure was defined as the time from the date of a prescription until 3 months after its expected duration of use. The expected duration of statin use was defined as 3 months. When the consecutive prescription of statins was prescribed within these 3 months, patients continued to be 'current users'. Since patients can move between different categories of exposure to statins over time, patients can be defined more than once as 'current users'. Current statin users were also classified as ≤ 1 year or > 1 year of use. Recent exposure was defined as the period of time from 3 to 12 months after the end date of the most recent prescription, and past exposure was the period of time from 12 months or longer after the end date of the most recent prescription of statins (figure 1).

Clinical outcome

Each patient was followed from the index date up to the date of the first record, diagnosis, of SLE (identified from CPRD's Read coded data)¹⁹ or the date when the patient left the general practice, died or the end date of data collection, whichever date came first. When a patient was referred to a rheumatologist before the date of the first SLE code, the date of the first referral was defined as the event date.

Risk factors

Potential risk factors for SLE were derived from the literature, including studies investigating the effects of statins on SLE, comorbidities in patients with early SLE and comedication with anti-inflammatory and immunomodulating effects which may potentially result in SLE.^{20–22} The risk factors in the year before the index date included body mass index (BMI), smoking and alcohol status (currently smoking or drinking, ex-smoker or ex-drinker, or never smoked or drank) and a history of hypertension, diabetes mellitus, hyperlipidaemia, cardiovascular disease, asthma, inflammatory bowel and thyroid disease.²³ Diabetes mellitus was defined as having a diagnosis of diabetes mellitus or using antidiabetic therapy. Patients were classified as hypertensive if they received a prescription for antihypertensive drugs or had a diagnosis of hypertension. Comedications with anti-inflammatory and immunomodulating properties within 6 months before the index date were non-steroidal

anti-inflammatory drugs, aspirin, proton pump inhibitors (PPIs), antibiotics, hormone replacement therapy, antidepressants, anti-convulsants, antipsychotics, antiarrhythmic and other lipid-lowering agents.²⁴

Statistical analysis

The incidence rate was estimated by dividing the number of patients with incident SLE by the total follow-up time. We estimated the HRs and 95% CIs for the risk of developing SLE among statin users. A multivariate time-dependent Cox proportional hazards model was used to assess the risk of SLE in current, recent and past users compared with non-users of statins. Potential risk factors were only included in the final model if they independently changed the estimated effect for statin use by at least 5%. Multiple imputation was used to address missing data for BMI (missing: 12.9%), smoking (9.2%) and alcohol status (17.9%). Missing data were imputed by the multiple imputation method using the fully conditional specification method.²⁵ All original exposure, outcome and co-variables as presented in tables 1 and 2 were included in the imputation model. Twenty imputations were created, analysed and pooled. Results from the complete and multiple imputation analyses were compared, and multiple imputation analyses are presented.

Prespecified subgroup analyses of patients with cardiovascular diseases or risk factors were performed. A previous study suggested different associations between statin use and the risk of developing SLE in patients with cardiovascular diseases, hypertension or diabetes.²⁶ Despite the increased lipid levels, statins could also have been prescribed to patients with only diabetes mellitus or a low socioeconomic status or a family history of cardiovascular disease or a high-risk ethnicity, as has been described in the National Institute for Health and Care Excellence clinical guideline lipid modification.²⁷ A subgroup analysis in patients with or without a medical history of hyperlipidaemia was conducted. In previous studies, it was found that older women were more likely to experience an adverse effect of statins.^{28 29} Therefore, the analyses were also stratified by age and sex. Data analyses were performed using SAS V.9.2 (SAS Institute, Cary, North Carolina, USA).

Sensitivity analyses

Five sensitivity analyses were carried out of which the first three were evaluating the impact of potential case misclassification by changing the definition of incident SLE into:

1. having at least two medical records of which the first record was used as the event date;
2. the first-time diagnosis of SLE with a referral to a rheumatologist or at least one prescription of the frequently prescribed drugs for SLE (azathioprine, cyclophosphamide, cyclosporine or methotrexate) and/or received at least two prescriptions of corticosteroids or (hydroxyl)chloroquine after the first medical record for SLE;
3. the required minimum of two physicians' claims for SLE at least 2 months apart within a 2-year span, an algorithm which has been proposed by Bernatsky and colleagues.³⁰
4. It is likely that there is a lag time between the onset of symptoms and the diagnosis of SLE, and therefore, we excluded the 2 years following initiation of statin treatment.³¹
5. We considered the date of SLE exactly 2 years before the first-time diagnosis of SLE because of the potential late manifestation of the clinically apparent symptoms of SLE.³¹

Table 1 Baseline characteristics of statin users and non-statin users

Baseline characteristics	Statin users (n=519 847)	Non-users (n=519 847)
Duration of follow-up (years)		
Mean (SD)	4.5 (3.4)	4.1 (2.6)
Sex, n (%)		
Female	250 608 (48.2)	250 608 (48.2)
Age (years)		
Mean (SD)	63.1 (12.1)	62.9 (12.5)
Age by category, years (%)		
40–49	70 047 (13.5)	74 647 (14.4)
50–59	148 461 (28.6)	158 441 (30.5)
60–79	242 331 (46.6)	221 013 (42.5)
80+	59 008 (11.3)	65 746 (12.6)
BMI (kg/m ²)		
Mean (SD)	26.9 (8.4)	21.0 (11.6)
Unknown BMI	28 284 (5.4)	105 970 (20.4)
Smoking status, n (%)		
Non-smoker	213 123 (41.7)	234 762 (45.1)
Ex-smoker	216 786 (31.6)	111 623 (21.5)
Smoker	164 492 (22.3)	100 837 (19.4)
Unknown smoking status	22 935 (4.4)	72 625 (14.0)
Drinking status, n (%)		
Non-drinker	65 250 (12.6)	54 528 (10.5)
Ex-drinker	32 799 (6.3)	20 856 (4.0)
Drinker	358 004 (68.8)	321 916 (61.9)
Unknown drinking status	63 794 (12.3)	122 547 (23.6)
Drug use within previous 6 months, n (%)		
Antihypertensive agents	323 170 (62.2)	124 169 (23.9)
Fibrates	8565 (1.6)	900 (0.2)
Ezetimibe	1969 (0.4)	133 (0.03)
Antidiabetic agents	122 185 (23.5)	18 603 (3.6)
Aspirin	145 039 (27.9)	36 945 (7.1)
Antiarrhythmic agents	20 625 (4.0)	11 301 (2.2)
NSAIDs	202 011 (38.9)	88 625 (17.0)
Proton pump inhibitors	84 995 (16.4)	48 211 (9.3)
Hormone replacement therapy or oral contraceptives	21 629 (4.2)	21 005 (4.0)
Oral corticosteroids	17 673 (3.4)	15 574 (3.0)
Antibiotics	47 321 (9.1)	36 493 (7.0)
Anticonvulsants	10 850 (2.1)	8126 (1.6)
Antipsychotics	5444 (1.0)	6190 (1.2)
Antidepressants	115 564 (22.2)	95 293 (18.3)
History of disease ever before, n (%)		
Hypertension*	323 170 (62.2)	124 169 (23.9)
Hyperlipidaemia	153 758 (29.6)	12 734 (2.4)
Diabetes†	122 515 (23.6)	18 762 (3.6)
Cardiovascular diseases	174 982 (33.7)	47 675 (9.2)
Cerebrovascular disease	59 891 (11.5)	17 077 (3.3)
Cancer	35 099 (6.8)	40 046 (7.7)
Psoriasis	20 182 (3.9)	16 544 (3.2)
Inflammatory bowel disease	5185 (1.0)	5155 (1.0)
COPD	21 113 (4.1)	20 849 (4.0)
Asthma	61 503 (11.8)	53 183 (10.2)
Dementia	5075 (1.0)	8610 (1.7)
Depression	72 446 (13.9)	49 371 (9.5)

*Diagnosis of hypertension or use of antihypertensive agents.

†Diagnosis of diabetes mellitus or use of antidiabetic therapy.

COPD, chronic obstructive pulmonary disease; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2 Risk of systemic lupus erythematosus in statin users compared with non-statin users

	SLE (n)	IR*	Age- and sex-adjusted HR (95% CI)	Fully adjusted HR (95% CI)†
No statin use	98	0.6	1.00	1.00
Past statin use	22	1.0	1.61 (1.01 to 2.56)	1.30 (0.79 to 2.13)
Recent statin use	20	1.1	1.67 (0.98 to 2.84)	1.31 (0.75 to 2.29)
Current statin use	117	0.6	0.98 (0.73 to 1.30)	0.75 (0.53 to 1.07)
≤1 year	64	1.9	1.31 (0.88 to 1.93)	1.01 (0.65 to 1.56)
>1 year	53	0.3	0.83 (0.59 to 1.16)	0.62 (0.42 to 0.93)

*Incidence rate is calculated for each recency of statin use by dividing the number of events by the person time within each given recency of use.

†Adjusted for age, sex, practice, smoking, cardiovascular diseases, hyperlipidaemia, hypertension, diabetes and use of non-steroid anti-inflammatory drugs.

IR, incidence rate (per 10 000 person-years); SLE, systemic lupus erythematosus.

RESULTS

A total number of 1 107 988 statin users and controls were identified in the CPRD: 40 320 patients who were younger than 40 years, 3346 patients with a medical history of SLE and 24 628 patients with a prescription of DMARD before the index date were excluded. Of the remaining 1 039 694 patients, 519 847 were statin users and 519 847 were non-users (figure 2). Due to matching, statin users and non-users had similar distributions of age (statin users: mean age, 63.1 years and non-users: 62.9 years) and sex (statin users and non-users: 48.2% women). Compared with non-users, statin users were more frequently previous smokers and diagnosed with cardiovascular disease, hyperlipidaemia, hypertension and diabetes. Statin users were more likely to have a history of exposure to aspirin, antihypertensive, antidiabetic agents and PPIs compared with non-users (table 1).

In our study population, the incidence rate for SLE was 0.7 cases per 10 000 person-years. Current statin users had a risk of developing SLE among patients aged ≥40 years which was comparable to that of non-users (HR_{adjusted} 0.75; 95% CI 0.53 to 1.07) (table 2). Current statin users who continued the therapy for >1 year had a 38% decreased risk of developing SLE (HR_{adjusted} 0.62, 95% CI 0.42 to 0.93). Recent and past statin users had no increased risk of developing SLE. The HR_{adjusted} for recent and past statin users were 1.31 (95% CI 0.75 to 2.29) and 1.30 (95% CI 0.79 to 2.13), respectively.

Table 3 shows several potential factors that may have influenced the risk of developing SLE after statin exposure. No clear effect modifiers for the association among current, recent and past statin exposures and the risk of developing SLE were found. It seems that patients with a history of cardiovascular disease or diabetes who currently used statins, irrespective of the duration of use, had a decreased risk of developing SLE.

We observed also a tendency towards a decreased risk of developing SLE in patients aged 61–80 year and women who currently continued statin therapy for >1 year.

Table 4 shows the results of five different sensitivity analyses. Since our definition of SLE¹⁹ was rather unspecific, we subsequently used three more specific definitions. These analyses showed similar results. The decreased risk of SLE for current users who continued therapy for >1 year, however, was not found anymore. In addition, the sensitivity analysis where we excluded the first 2 years after initiation of statin treatment showed that current statin use, irrespective of the duration of the therapy, was associated with a decreased risk of SLE.

DISCUSSION

Our study demonstrated no association between current statin use and the risk of developing SLE among patients aged ≥40

Figure 2 Flow diagram showing the selection of the study population from the Clinical Practice Research Datalink.

Table 3 Confounding and modifying effects of systemic lupus erythematosus risk in statin users versus non-statin users

Adjusted HR (95% CI)*							
	SLE (n)	IR†	Past statin use	Recent statin use	Current statin use	Current statin use ≤1 year	Current statin use >1 year
By age, years							
40–60	109	0.7	1.44 (0.65 to 3.18)	2.23 (0.98 to 5.03)	1.07 (0.61 to 1.88)	1.35 (0.68 to 2.69)	0.92 (0.49 to 1.73)
61–80	137	0.7	1.12 (0.58 to 2.16)	0.69 (0.29 to 1.60)	0.51 (0.31 to 0.82)	0.75 (0.41 to 1.38)	0.40 (0.23 to 0.69)
>80	11	0.3	2.37 (0.22 to 24.73)	4.22 (0.56 to 31.80)	1.46 (0.29 to 7.53)	1.48 (0.23 to 9.31)	1.46 (0.21 to 9.99)
By sex							
Women	202	1.0	1.36 (0.79 to 2.33)	1.52 (0.82 to 2.82)	0.73 (0.49 to 1.10)	1.02 (0.62 to 1.68)	0.59 (0.38 to 0.94)
Men	55	0.3	1.01 (0.28 to 3.62)	0.73 (0.19 to 2.86)	0.79 (0.37 to 1.73)	0.94 (0.37 to 2.37)	0.71 (0.30 to 1.66)
By any previous history of disease							
No previous cardiovascular disease	191	0.7	1.62 (0.93 to 3.32)	1.75 (0.92 to 3.32)	0.96 (0.64 to 1.45)	1.32 (0.79 to 2.21)	0.77 (0.48 to 1.24)
Previous cardiovascular disease	66	0.6	0.45 (0.16 to 1.27)	0.39 (0.13 to 1.21)	0.27 (0.14 to 0.52)	0.32 (0.14 to 0.72)	0.24 (0.12 to 0.50)
No previous cardiovascular risk factor‡	102	0.6	1.69 (0.77 to 3.74)	0.60 (0.14 to 2.62)	0.63 (0.33 to 1.20)	0.71 (0.31 to 1.65)	0.56 (0.24 to 1.29)
Previous cardiovascular risk factor	155	0.7	1.49 (0.76 to 2.94)	1.87 (0.93 to 3.76)	0.95 (0.57 to 1.58)	1.37 (0.74 to 2.53)	0.80 (0.46 to 1.37)
No previous hyperlipidaemia	189	0.6	0.93 (0.47 to 1.82)	1.47 (0.75 to 2.85)	0.73 (0.49 to 1.10)	0.97 (0.58 to 1.61)	0.62 (0.38 to 1.00)
Previous hyperlipidaemia	68	0.8	5.33 (0.69 to 41.14)	2.73 (0.32 to 23.14)	2.02 (0.27 to 14.82)	2.69 (0.35 to 20.89)	1.71 (0.23 to 12.95)
No previous hypertension	139	0.7	1.61 (0.86 to 3.01)	0.56 (0.19 to 1.68)	0.71 (0.42 to 1.18)	0.85 (0.45 to 1.61)	0.61 (0.33 to 1.11)
Previous hypertension	118	0.7	1.01 (0.43 to 2.36)	1.99 (0.93 to 4.28)	0.80 (0.45 to 1.41)	1.16 (0.58 to 2.32)	0.66 (0.36 to 1.22)
No previous diabetes	218	0.6	1.21 (0.69 to 2.12)	1.42 (0.76 to 2.61)	0.88 (0.60 to 1.28)	1.26 (0.79 to 2.03)	0.68 (0.44 to 1.06)
Previous diabetes	39	0.7	1.10 (0.33 to 3.70)	0.71 (0.17 to 2.99)	0.29 (0.10 to 0.81)	0.29 (0.09 to 0.97)	0.29 (0.10 to 0.85)

*Adjusted for confounders as shown in table 2.

†Incidence rate is calculated for each recency of statin use by dividing the number of events by the person time within each given recency of use.

‡Cardiovascular risk factor included previous hyperlipidaemia, hypertension and diabetes.

IR, incidence rate (per 10 000 person-years); SLE, systemic lupus erythematosus.

years. However, we did find a 38% decreased risk of developing SLE in current users who continued their therapy for >1 year, although this finding of a decreased SLE risk disappeared in the sensitivity analyses.

We were unable to find any previous studies examining the association between statin use and the risk of developing SLE. However, a propensity score matched cohort study of 6956 pairs of statin users and non-users showed an association between statin use and a lower risk of CTD (approximately 13% of the CTD patients were patients with SLE) during a 1-year study period.¹⁴ In the first year of statin exposure, we found no decrease in the development of SLE which became only significant after 1 year of statin use. Differences between the study by Schmidt and colleagues and our study may be partially explained by the inclusion of other rheumatic diseases and defining statin exposure. In our study, statin exposure was defined by the recency of use and duration (≤1 year and >1 year) within the current statin users, whereas Schmidt and colleagues defined statin use as receiving at least a 90-day supply during a 1-year study period.¹⁴

Several clinical trials and open-label studies investigating the effects of statins in patients with SLE have found beneficial effects of statin therapy on lipid levels, proinflammatory biomarkers and the endothelial markers.^{4 6 32–36} It has been hypothesised that atherosclerosis often develops prematurely among patients with SLE in the setting of chronic inflammation in conjugation with the traditional cardiovascular risk factors.²⁶ Recently, a US population-based lupus cohort study demonstrated an increased number of cardiovascular events in the 2 years before the diagnosis of SLE, suggesting accelerated atherosclerosis before the onset or diagnosis of SLE.³⁷ Consistent with our finding

of no association between current statin use and the risk of developing SLE, several clinical trials and open-label studies evaluating the effects of statins in patients with SLE found no association between statin use and a change in disease activity score as measured by the Systemic Lupus Erythematosus Disease Activity Index.^{4 6 32–36}

Our findings did not show an increased risk of SLE after statin use. In a previous study conducted by our research group, it was found that statin use was more often reported in patients with lupus-like syndrome than in patients who experienced other adverse drug events.¹⁰ The findings of this study were consistent with the results of a study that used the French Pharmacovigilance database.¹³ Furthermore, two reviews, including studies of case reports of adverse drug reactions, found an increased risk of developing SLE in statin users.^{11 12} A major limitation of these studies was the use of data that were not population based but based on pharmacovigilance databases with selective reporting of adverse drug reactions.

The underlying mechanisms by which statins may interfere the risk of developing rheumatic autoimmune diseases^{4–10} are unknown and could not be investigated in our study. Statins are suggested to have anti-inflammatory and immunomodulating properties beyond their lipid-lowering effects.^{38 39} Importantly, statins may skew T cell differentiation toward regulatory T cells (Treg) and away from proinflammatory T helper (Th) 17 cells via geranylgeranylation of proteins, resulting in promoting Treg differentiation in the periphery, while blocking Th17 cell differentiation which may be protective against SLE.^{39 40} However, it has been suggested that statins may promote a shift in Th1/Th2 balance^{12 38} or lead to unstable peripheral Tregs^{41 42} and thus

Table 4 Several sensitivity analyses to test the robustness of our findings

Sensitivity analyses	SLE (n)	IR†	Adjusted HR (95% CI)*			
			Past statin use	Recent statin use	Current statin use	Current statin use
1. Restrict to SLE patients with at least two medical records for SLE	83	0.2	2.11 (0.97 to 4.63)	1.83 (0.75 to 4.46)	0.80 (0.42 to 1.52)	>1 year 1.22 (0.58 to 2.56)
2. Restrict to SLE patients who were referred to a rheumatologist or received at least one prescription of azathioprine, cyclophosphamide, cyclosporine or methotrexate and/or received at least two prescriptions of corticosteroids or (hydroxy)chloroquine after the first-time diagnosis of SLE	121	0.3	2.37 (0.98 to 4.77)	1.74 (0.76 to 4.01)	1.19 (0.71 to 2.01)	≤1 year 1.54 (0.81 to 2.93)
3. Restrict to SLE patients with a minimum of two medical records for diagnosis of SLE at least 2 months apart but within a 2-year span.	44	0.1	3.85 (0.94 to 10.58)	2.72 (0.79 to 9.42)	1.13 (0.46 to 2.78)	1.87 (0.66 to 5.34)
4. Exclude 2 years after initiation of statin treatment	139	0.5	0.90 (0.50 to 1.63)	0.81 (0.37 to 1.82)	0.38 (0.23 to 0.63)	0.26 (0.13 to 0.53)
5. Shift the event (SLE) date exactly 2 years before the date of the first-time diagnosis of SLE	140	0.4	1.07 (0.54 to 2.13)	0.61 (0.23 to 1.65)	0.74 (0.46 to 1.20)	0.58 (0.31 to 1.06)
						0.84 (0.51 to 1.39)

*Adjusted for age, sex, practice, smoking, cardiovascular diseases, hyperlipidaemia, hypertension, diabetes and use of non-steroid anti-inflammatory drugs.

†Incidence rate is calculated for each sensitivity analysis by dividing the number of events by the person time within each given recency of use.

IR, incidence rate (per 10 000 person-years); SLE, systemic lupus erythematosus.

may promote autoimmunity. Statins may not cause autoimmunity by themselves, but they may promote a pre-existing autoimmune-prone condition to progress toward a clinical manifest disease.

Our study has several strengths including the large sample size, representativeness of the population, completeness of follow-up and information on matched non-users, and detailed information on confounders (eg, smoking status) was available. Furthermore, data are prospectively collected in the CPRD and thus not subjected to recall bias.

Our study has also some drawbacks. We used prescription data on statin exposure rather than on actual drug use, which could have resulted in an overestimation of statin use. Furthermore, we used a definition of incident SLE as has been previously used by Somers and colleagues.¹⁹ Although this definition was previously used in the CPRD database, it is rather unspecific for the diagnostic outcome (SLE). Therefore, we performed a series of sensitivity analyses regarding different more specific definitions of SLE. All analyses consistently showed no association between current statin use and the risk of developing SLE. The association between current statin use for >1 year and the decreased risk of developing SLE, however, disappeared when more specific definitions of SLE were used.

Since patients aged ≥40 years should be screened for cardiovascular risk,⁴³ we investigated the risk of SLE in patients aged ≥40 years using statins. SLE is typically a disease of young women, and we cannot conclude that there is no effect of statins on the risk of developing SLE in young women (ie, <40 years).

We had no information on dietary intake, physical activity and race/ethnicity. Since our study was performed in the UK with a predominantly Caucasian population, knowledge of race/ethnicity may be relevant in other studies as SLE occurs more frequently in blacks.⁴⁴ Also, we had limited data on lipid, blood pressure and glucose levels, and inflammatory markers (eg, C reactive protein) which all could be potentially confounders. Our subgroup analyses were limited by limited number of patients and statistical power, and it is likely that some patients with hyperlipidaemia, hyperglycaemia or high blood pressure levels were misclassified. This misclassification typically leads to an underestimate of the treatment effect. Also, ascertainment bias may have occurred as patients starting statin therapy may have had more visits to the general practitioner and blood tests than non-users, thereby increasing the likelihood of detecting more abnormalities (eg, SLE).^{45 46} Nonetheless, our study did not show an increased risk of developing SLE in current statin users who continued the therapy for ≤1 year. Another limitation was that SLE may have been present and was not well documented before the start of statin use. We defined the onset date of SLE by the first medical record for SLE, but the onset date of symptoms is unknown in our study. The median time between onset of symptoms to diagnosis of SLE of may be as long as 2 years.³¹ Our sensitivity analysis where we excluded the 2 years following the initiation of statin treatment showed similar results with regard to long-term statin use and the risk of developing SLE.

In summary, this is the first observational study assessing the risk of developing SLE with changes in statin exposure over time. We found that current statin use is not associated with an increased risk of developing SLE among patients aged ≥40 years. We observed a decreased SLE risk among current statin users who continued their therapy for >1 year, but further research is needed to substantiate this signal of a long-term effect of statin on SLE risk.

Author affiliations

- ¹Centre for Health Protection, National Institute for Public Health and the Environment, Bilthoven, The Netherlands
- ²School for Mental Health and Neuroscience, Maastricht University Medical Center, Maastricht, The Netherlands
- ³Division of Pharmacoepidemiology and Clinical Pharmacology, Department of Pharmaceutical Sciences, Faculty of Sciences, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
- ⁴Health eResearch Centre, Farr Institute for Health Informatics Research, University of Manchester, Manchester, UK
- ⁵Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, The Netherlands
- ⁶Department of Clinical Pharmacy & Toxicology, Maastricht University Medical Center, Maastricht, The Netherlands
- ⁷Care and Public Health Research Institute (CAPRI), Maastricht University, Maastricht, The Netherlands
- ⁸Department of Toxicogenomics, Maastricht University Medical Center, Maastricht, The Netherlands
- ⁹Department of Clinical and Experimental Immunology, Maastricht University, Maastricht, The Netherlands

Contributors HJIDJ contributed to the concept and design of the study, performed the data analysis, contributed to the interpretation of the results and drafted the manuscript. TVS initiated and obtained the funding for the project to which the study presented belongs, contributed to the concept and design of the study and interpretation of the results, provided background information for the study and reviewed the manuscript. AL and FDV contributed to the concept and design of the study, performed the data analysis and reviewed the manuscript. RJV provided background information for the study and reviewed the manuscript. HVL initiated and obtained the funding for the project to which the study presented belongs, provided background information for the study and reviewed the manuscript. OHK contributed to the concept and design of the study and interpretation of the results, provided background information for the study and reviewed the manuscript. JWCT contributed to the concept and design of the study and interpretation of the results, provided background information for the study and drafted and reviewed the manuscript.

Funding This work was supported by the research grant S340040 from the National Institute for Public Health and the Environment. The funder had no role in study design, in the analysis and interpretation of data, in the writing of the manuscript or in the decision to submit the manuscript for publication.

Competing interests All authors have completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf and declare financial support from the National Institute for Public Health and the Environment (RIVM; research grant S340040) for the submitted work. Dr Klungel has received funding for pharmacoepidemiological research from the Dutch private/public Top Institute Pharma (Grant T6.101 Mondriaan) and the Innovative Medicines Initiative Joint Undertaking under Grant Agreement No 115004, resources of which comprise financial contribution from the European Union's Seventh Framework Program (FP7/2007-2013) and EFPIA companies' in kind contribution. OHK had full access to all of the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis. All authors had final responsibility for the decision to submit the manuscript for publication.

Patient consent For the present study, a separate ethical approval was not required, since the patients were not directly involved in formulating the research question nor were patients actively involved in the design and/or conduct of the research. The CPRD Group has obtained ethical approval from a National Research Ethics Service Committee for all purely observational research using anonymised CPRD data, namely, studies which do not include patient involvement (which is the vast majority of CPRD studies).

Ethics approval National Research Ethics Service Committee (NRES); CPRD Independent Scientific Advisory Committee (ISAC)

Provenance and peer review Not commissioned; externally peer reviewed.

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- Baigent C, Keech A, Kearney PM, *et al.* Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet* 2005;366:1267–78.
- Colhoun HM, Betteridge DJ, Durrington PN, *et al.* Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial. *Lancet* 2004;364:685–96.
- Sever PS, Dahlöf B, Poulter NR, *et al.* Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian cardiac outcomes trial—lipid lowering arm (ASCOT-LLA): a multicentre randomised controlled trial. *Lancet* 2003;361:1149–58.
- Abud-Mendoza C, de la Fuente H, Cuevas-Orta E, *et al.* Therapy with statins in patients with refractory rheumatic diseases: a preliminary study. *Lupus* 2003;12:607–11.
- Ferreira GA, Navarro TP, Telles RW, *et al.* Atorvastatin therapy improves endothelial-dependent vasodilation in patients with systemic lupus erythematosus: an 8 weeks controlled trial. *Rheumatology* 2007;46:1560–5.
- Kotyla PJ, Sliwinski-Kotyla B, Kucharz EJ. Tumor necrosis factor- α as a potential target in the treatment of systemic lupus erythematosus: a role for the HMG-CoA reductase inhibitor simvastatin. *J Rheumatol* 2006;33:2361–3.
- Willis R, Seif AM, McGwin G, *et al.* Effects of statins on proinflammatory/prothrombotic biomarkers and on disease activity scores in SLE patients: data from LUMINA (LXXVI), a multi-ethnic US cohort. *Clin Exp Rheumatol* 2014;32:162–7.
- de Jong HJ, Klungel OH, van Dijk L, *et al.* Use of statins is associated with an increased risk of rheumatoid arthritis. *Ann Rheum Dis* 2012;71:648–54.
- de Jong HJ, Saldi SR, Klungel OH, *et al.* Statin-associated polymyalgia rheumatica. an analysis using WHO global individual case safety database: a case/non-case approach. *PLoS One* 2012;7:e41289.
- de Jong HJ, Tervaert JW, Saldi SR, *et al.* Association between statin use and lupus-like syndrome using spontaneous reports. *Semin Arthritis Rheum* 2011;41:373–81.
- Golomb BA, Evans MA. Statin adverse effects : a review of the literature and evidence for a mitochondrial mechanism. *Am J Cardiovasc Drugs* 2008;8:373–418.
- Noël B. Lupus erythematosus and other autoimmune diseases related to statin therapy: a systematic review. *J Eur Acad Dermatol Venereol* 2007;21:17–24.
- Moulis G, Béné J, Sommet A, *et al.* Statin-induced lupus: a case/non-case study in a nationwide pharmacovigilance database. *Lupus* 2012;21:885–9.
- Schmidt T, Battafarano DF, Mortensen EM, *et al.* Frequency of development of connective tissue disease in statin-users versus nonusers. *Am J Cardiol* 2013;112:883–8.
- Herrett E, Gallagher AM, Bhaskaran K, *et al.* Data resource profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol* 2015;44:827–36.
- Herrett E, Thomas SL, Schoonen WM, *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;69:4–14.
- Benner JS, Glynn RJ, Mogun H, *et al.* Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002;288:455–61.
- Gallagher AM, Smeeth L, Seabroke S, *et al.* Risk of death and cardiovascular outcomes with thiazolidinediones: a study with the general practice research database and secondary care data. *PLoS One* 2011;6:e28157.
- Somers EC, Thomas SL, Smeeth L, *et al.* Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. *Arthritis Rheum* 2007;57:612–8.
- Oglesby A, Korves C, Laliberté F, *et al.* Impact of early versus late systemic lupus erythematosus diagnosis on clinical and economic outcomes. *Appl Health Econ Health Policy* 2014;12:179–90.
- Sin E, Anand P, Frieri M. A link: allergic rhinitis, asthma & systemic lupus erythematosus. *Autoimmun Rev* 2016;15:487–91.
- De Jager PL, Graham R, Farwell L, *et al.* The role of inflammatory bowel disease susceptibility loci in multiple sclerosis and systemic lupus erythematosus. *Genes Immun* 2006;7:327–34.
- Bengtsson AA, Rylander L, Hagmar L, *et al.* Risk factors for developing systemic lupus erythematosus: a case-control study in southern Sweden. *Rheumatology* 2002;41:563–71.
- Rubin RL. Drug-induced lupus. *Toxicology* 2005;209:135–47.
- van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Stat Methods Med Res* 2007;16:219–42.
- Urowitz MB, Gladman DD, Anderson NM, *et al.* Cardiovascular events prior to or early after diagnosis of systemic lupus erythematosus in the systemic lupus international collaborating clinics cohort. *Lupus Sci Med* 2016;3:e000143.
- National Collaborating Centre for Primary Care. *Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. NICE clinical guideline 67.* London, UK: National Institute for Health and Clinical Excellence, 2008. reissued 2010.
- Bhardwaj S, Selvarajah S, Schneider EB. Muscular effects of statins in the elderly female: a review. *Clin Interv Aging* 2013;8:47–59.
- Walsh JM, Pignone M. Drug treatment of hyperlipidemia in women. *JAMA* 2004;291:2243–52.
- Bernatsky S, Joseph L, Pineau CA, *et al.* A population-based assessment of systemic lupus erythematosus incidence and prevalence—results and implications of using administrative data for epidemiological studies. *Rheumatology* 2007;46:1814–8.
- Pistiner M, Wallace DJ, Nessim S, *et al.* Lupus erythematosus in the 1980s: a survey of 570 patients. *Semin Arthritis Rheum* 1991;21:55–64.

- 32 Mok CC, Wong CK, To CH, *et al.* Effects of rosuvastatin on vascular biomarkers and carotid atherosclerosis in lupus: a randomized, double-blind, placebo-controlled trial. *Arthritis Care Res* 2011;63:875–83.
- 33 Costenbader KH, Liang MH, Chibnik LB, *et al.* A pravastatin dose-escalation study in systemic lupus erythematosus. *Rheumatol Int* 2007;27:1071–7.
- 34 de Kruif MD, Limper M, Hansen HR, *et al.* Effects of a 3-month course of rosuvastatin in patients with systemic lupus erythematosus. *Ann Rheum Dis* 2009;68:1654.
- 35 Norby GE, Holme I, Fellström B, *et al.* Effect of fluvastatin on cardiac outcomes in kidney transplant patients with systemic lupus erythematosus: a randomized placebo-controlled study. *Arthritis Rheum* 2009;60:1060–4.
- 36 Fatemi A, Moosavi M, Sayedbonakdar Z, *et al.* Atorvastatin effect on systemic lupus erythematosus disease activity: a double-blind randomized clinical trial. *Clin Rheumatol* 2014;33:1273–8.
- 37 Bartels CM, Buhr KA, Goldberg JW, *et al.* Mortality and cardiovascular burden of systemic lupus erythematosus in a US population-based cohort. *J Rheumatol* 2014;41:680–7.
- 38 Youssef S, Stüve O, Patarroyo JC, *et al.* The HMG-CoA reductase inhibitor, atorvastatin, promotes a Th2 bias and reverses paralysis in central nervous system autoimmune disease. *Nature* 2002;420:78–84.
- 39 Kagami S, Owada T, Kanari H, *et al.* Protein geranylgeranylation regulates the balance between Th17 cells and Foxp3+ regulatory T cells. *Int Immunol* 2009;21:679–89.
- 40 Shah K, Lee WW, Lee SH, *et al.* Dysregulated balance of Th17 and Th1 cells in systemic lupus erythematosus. *Arthritis Res Ther* 2010;12:R53.
- 41 Zhou X, Bailey-Bucktrout SL, Jeker LT, *et al.* Instability of the transcription factor Foxp3 leads to the generation of pathogenic memory T cells in vivo. *Nat Immunol* 2009;10:1000–7.
- 42 Komatsu N, Mariotti-Ferrandiz ME, Wang Y, *et al.* Heterogeneity of natural Foxp3+ T cells: a committed regulatory T-cell lineage and an uncommitted minor population retaining plasticity. *Proc Natl Acad Sci U S A* 2009;106:1903–8.
- 43 National Collaborating Centre for Primary Care. *Cardiovascular disease: risk assessment and reduction, including lipid modification. NICE clinical guideline 181*. London, UK: National Institute for Health and Clinical Excellence, 2014.
- 44 Feldman CH, Hiraki LT, Liu J, *et al.* Epidemiology and sociodemographics of systemic lupus erythematosus and lupus nephritis among US adults with Medicaid coverage, 2000–2004. *Arthritis Rheum* 2013;65:753–63.
- 45 Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010;340:c2197.
- 46 Mansi I, Mortensen E. The controversy of a wider statin utilization: why? *Expert Opin Drug Saf* 2013;12:327–37.