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ORIGINAL ARTICLE

Statin-related adverse drug reactions in UK primary care consultations: A retrospective cohort study to evaluate the risk of cardiovascular events and all-cause mortality

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Aims: To investigate the risk of cardiovascular disease (CVD) events and all-cause mortality in patients with statin-related adverse drug reaction (ADR) consultation in primary care and examine whether different treatments following the ADR affect subsequent outcomes.

Methods: This was a retrospective cohort study of statin users between 2004 and 2019 using IQVIA Medical Research Data (formally known as the THIN database). Patients with statin-related ADR consultation were matched by propensity score (1:1) to statin users without ADR consultation based on demographics, comorbidities and concomitant medication. Cox proportional hazard regression was used to compare the risk of subsequent CVD event and all-cause mortality, stratified by history of CVD. In the secondary analysis among patients with statin-related ADR, treatment changes within a 1-year period following the ADR were examined and the outcomes were compared between different treatment groups.

Results: Among 1 564 687 statin users, 19 035 (1.22%) had a statin-related ADR consultation in primary care. The mean (standard deviation) follow-up time was 6.32 (3.74) years and 5.31 (3.83) years for CVD primary and secondary prevention cohorts, respectively. Statin-related ADR consultation was associated with subsequent CVD events in both cohorts (adjusted hazard ratio [HR] of 1.39 [95% CI 1.23, 1.57] and 1.34 [95% CI 1.25,1.42], respectively). In the secondary analysis among patients with statin-related ADR consultation, we found that (i) continued statin prescription or combination of any statin with additional lipid-lowering treatment (LLT) and (ii) other LLT only were associated with lower risks of CVD event (adjusted HR 0.71 [95% CI 0.64, 0.78] and 0.75 [95% CI 0.62, 0.92], respectively) and all-cause mortality (adjusted HR 0.46 [95% CI 0.42, 0.50] and 0.52 [95% CI, 0.43, 0.64], respectively), compared to discontinuation of all LLT.

The authors confirm that the Principal Investigator for this paper is Prof. Li Wei.

[Correction added on 12 July 2022, after first online publication: In Abstract, the last sentence in the Result section has been updated in this version.]

Conclusion: Statin-related ADR was associated with an increased risk of subsequent CVD event, indicating that these patients should be monitored more closely. Continued lipid-lowering medication is of importance to protect against CVD events and mortality.

KEYWORDS
adverse drug reactions, cardiovascular event, mortality, primary care, statin

1 | INTRODUCTION

Statins are among the most commonly prescribed medications worldwide.[1–3] Statin is the cornerstone of lipid-lowering treatment with established efficacy for primary and secondary prevention of cardiovascular disease (CVD).[4,5] O'Keeffe et al reported a sharp increase in statin initiation prescribing rate in the United Kingdom (UK) during 1995-2013, from 0.51 to 10.76 per 1000 person-years.[6] Clinical guidelines were recently revised to recommend lowering the threshold at which statins are initiated, particularly for individuals with 7.5-10% CVD risk at 10 years.[7,8]

Although statins are generally safe and well-tolerated, up to 6% of statin users might develop an adverse drug reaction (ADR), predominantly muscle-related symptoms with or without elevation of creatinine kinase (CK) level, gastrointestinal disturbances, cognitive impairment and liver enzymes abnormalities.[9,10] The risk of statin-related ADR is increased among patients on high-dose statin therapy or concomitant cytochrome CYP3A4 inhibitors with diabetes, hypothyroidism and liver impairment.[11–14] Using the general practice research database, Tsang et al showed that statin-related ADR consultations (6.91%) were among the most frequently recorded ADRs in the UK primary care setting.[15]

Previous studies showed that one-third of patients with statin-related ADR discontinued the medication, putting these patients at substantially higher risk of CVD.[16,17] By investigating a CVD secondary prevention cohort of 105 329 patients in the United States, Serban et al found that statin intolerance was associated with an increased risk of recurrent CVD events.[18] Clinical guidelines suggested several approaches for lipid management following statin-related ADR, including reducing statin dose within the same statin intensity group, switching to a different statin, using intermittent/nondaily statin dosing regimens, combining a statin with an additional lipid-lowering drug, and as a last resort using nonstatin treatment only for those unable to tolerate any statin.[7,19,20] A previous study in the United States found that over half (59.1%) of patients continued receiving a statin prescription following a statin-related ADR, with about 40% continuing to receive the same statin and the remainder switching to a different statin.[21]

Nevertheless, the impact of statin-related ADRs on clinical outcomes, particularly in the UK general population, remains limited. In addition, real-world evidence on treatment pattern changes following the statin-related ADR and its impact on subsequent patient outcomes are still under-investigated.[22] Therefore, this study aimed to investigate the risk of CVD events and all-cause mortality in patients with statin-related ADR and examine whether different treatments following the ADR affect subsequent outcomes. Such information may help improve understanding on the burden of ADRs for patients and better inform appropriate strategies following the occurrence of ADRs.

What is already know about this subject

- In addition to direct impact to physiological functioning, adverse drug reaction (ADR) may negatively affect patients' treatment outcomes due to medication nonadherence, prolonged discontinuation, and limited treatment options.
- Studies have suggested that statin-related ADR contributed significantly to treatment discontinuation, putting these patients at substantially higher risk of cardiovascular disease (CVD).
- However, there is limited evidence on the impact of statin-related ADR on patients' outcomes and treatment pattern changes following the ADR in a real-world clinical setting.

What this study adds

- Patients with statin-related ADR had an increased risk of a subsequent CVD event in both CVD primary and secondary prevention cohorts, indicating that these patients should be monitored more closely.
- Continued lipid-lowering medication was associated with a lower risk of CVD event and all-cause mortality compared to discontinuation of all lipid-lowering medication altogether following the occurrence of ADR.

2 | METHODS

2.1 | Data source

This study was conducted using primary care data from IQVIA Medical Research Data (IMRD) UK that incorporates data from the Health

Improvement Network. We used de-identified data provided by patients as a part of their routine primary care. UK primary care databases have previously been used to investigate ADR-related consultations and CVD events.[15,23,24] The study protocol was approved by IMRD Scientific Review Committee (reference number 21SRC008).

2.2 | Study design

This was a retrospective cohort study that included statin users between January 1, 2004 and September 30, 2019. Patients with missing date of birth, sex, aged <18 years at the date of first statin prescription and who had a previous statin-related ADR consultation before 2004 were excluded. Patients who had a statin-related ADR consultation formed the exposed group. The index date was defined as the date of the first statin-related ADR consultation. Statin-related ADR consultations were defined using standardised designated codes for ADR-related consultations from electronic medical records in primary care which have been previously examined in previous studies.[15,23,25] In this study, we used designated codes specific to statin-related ADR consultation. Thus, it is estimated the ADR consultation is attributable wholly to statin therapy.[15,25] We excluded patients who were registered less than 1 year before the index date, had history of cancer and had statin-related ADR consultation before the commencement of statin therapy. As the previous history of CVD increased the risk of further such events, patients were classified as (i) CVD primary prevention cohort (ie, without a history of CVD) and (ii) CVD secondary prevention cohort (ie, with a history of CVD). CVD was defined as a previous diagnosis of coronary heart disease (myocardial infarction, angina), cerebrovascular disease (stroke and transient ischemic attack [TIA]), and peripheral arterial disease (PAD). Patients with congestive cardiac failure were included in the secondary prevention cohort due to their equivalent level of risk as people with an established CVD.[26,27]

For the primary analysis, a pool of potential control cohort was created by assigning index dates at random to a sample of 30% of unexposed patients by incidence density sampling from the distribution of index dates in the exposed group.[28] The control cohort was those who were on statin treatment but did not have statin-related ADR consultation during the study period. After excluding patients who died/transferred before or at the assigned index date, registered less than 1 year before the assigned index date, had history of cancer and had an assigned index date before the commencement of statin therapy, propensity score matching (1:1) was performed between the ADR and control cohorts. Propensity score was used to reduce potential bias due to exposure allocation, which aims to mimic the randomization process in randomized clinical trials (RCTs), thus matched samples with balanced characteristics across the exposed and unexposed groups could be produced.[29,30] The scores were estimated from a logistic regression model with covariates identified at the baseline. In this study, a greedy matching algorithm was used for the matching process, which has been shown to generate adequate performance.[31,32]

The covariates at baseline were age, sex, treatment duration between statin therapy initiation date and index date of ADR or assigned index date, comorbidities (recorded at any time before or on the index date), including dyslipidaemia, hypertension, diabetes mellitus, chronic kidney disease, chronic liver disease, chronic obstructive pulmonary disease and rheumatic disease, and the use of concomitant medication (recorded ≤ 180 days prior to the index date), including angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, calcium channel blockers, diuretics, β-blockers, antiplatelets/anticoagulants, antidiabetics, nitrates and nonsteroidal anti-inflammatory drugs.

The primary outcome was the first composite CVD event (myocardial infarction and stroke/TIA). All-cause mortality served as the secondary outcome. For the primary analysis, the follow-up for each patient commenced from the date of ADR consultation for the ADR-exposed patients or the assigned index date for the ADR-unexposed patients until the occurrence of the outcome of interest, patient transferred out, death or study end date, whichever occurred first.

For the secondary analysis, which included patients with statin-related ADR consultation, treatment pattern changes within a 1-year period following the ADR consultation were examined. Treatment patterns were identified based on the prescriptions data from the primary care. Treatment groups were classified as follows:

a) Continued with any statin, with the same statin, switched to a different statin or using a combination of any statin with additional lipid-lowering treatment (LLT).
b) Continued with other LLT only, eg, ezetimibe, fibrates, bile acid sequestrants, niacin, proprotein convertase subtilisin/kexin 9 inhibitor (PSCK9i), etc.
c) All LLT was discontinued.

To address immortal time bias, we excluded patients who died, transferred out of practice, had last day of follow-up or had a CVD event within 1 year following the index date. The follow-up commenced from 1 year after the ADR until the occurrence of the outcome of interest, the patient transferred out of practice, death or study end date, whichever occurred first. CVD events and all-cause mortality were compared between (i) the statin and discontinued all LLT groups, and (ii) the other LLT and discontinued all LLT groups, using inverse probability of treatment weighting (IPTW) based on the propensity scores. (Figure 1).

2.3 | Sensitivity analysis

To examine the robustness of our results, we performed sensitivity analysis by conducting IPTW based on propensity scores for the primary analysis. In the secondary analysis, we adjusted the window period from 1 year to a 6-month period following the statin-related ADR consultation to assess the treatment pattern changes. Competing risk analyses with death were conducted for all analyses with CVD outcome using Fine-Gray's subdistribution hazard model.

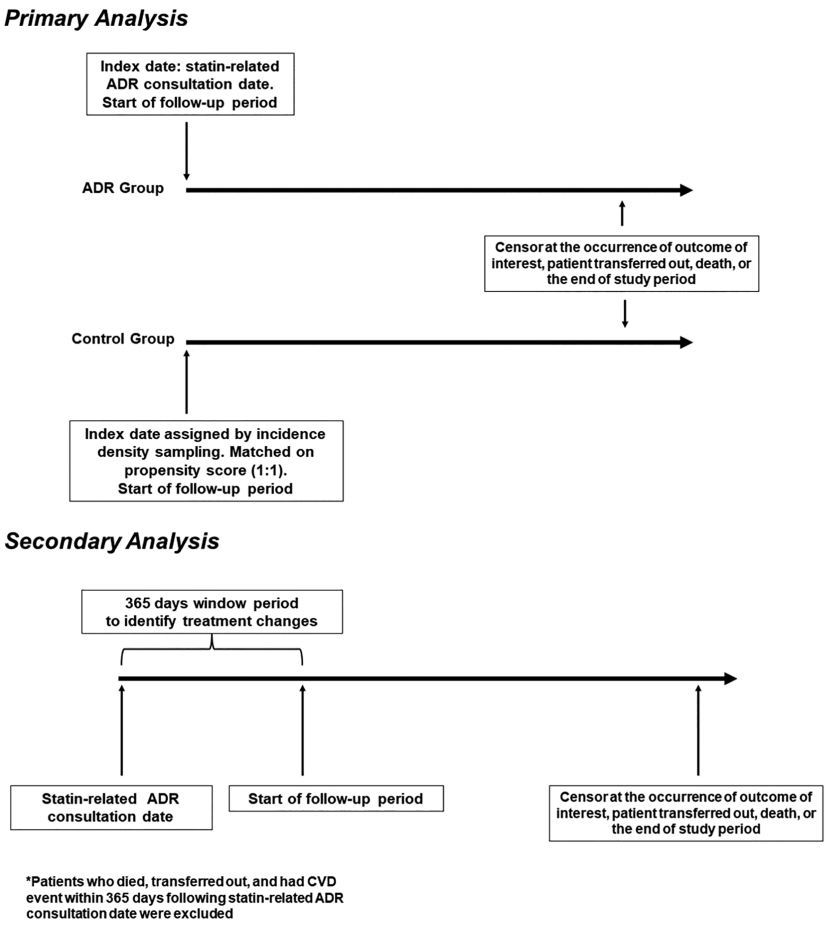

FIGURE 1 Study design in primary and secondary analysis. ADR, adverse drug reaction; CVD, cardiovascular disease

2.4 | Statistical analysis

Patient characteristics were presented as numbers (percentages) for categorical variables and as means (±SDs) for continuous variables. Cox proportional hazard regression was used to estimate the association between statin-related ADR consultation and the CVD event and all-cause mortality in the primary analysis, and different treatment groups following the ADR consultation and CVD event and all-cause mortality in the secondary analysis. Results were presented as hazard ratios (HRs) with 95% confidence intervals (CIs). A two-sided *P* value of less than .05 was considered as statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina, US).

3 | RESULTS

During the study period of 2004-2019, a total of 1 598 693 statin users were identified. We excluded 34 006 patients with invalid records (missing date of birth or sex, invalid registration date, invalid end date), aged below 18 years or had a previous statin-related ADR consultation. Among the remaining 1 564 687 eligible patients, 19 035 (1.22%) patients had a statin-related ADR consultation during the study period. After we applied exclusions, 15 039 patients remained in the exposed group. These patients were classified as the CVD primary prevention cohort (n = 6424) and the secondary prevention cohort (n = 8615). These patients were successfully matched to their respective control group (Figure 2). The distribution of the baseline covariates in each cohort are summarised in Table 1. The mean ages were 63.67 ± 11.64 for the CVD primary prevention cohort and 70.60 ± 10.86 for the secondary prevention cohort. In both cohorts, the ADR consulters were older and composed of more females, as compared to statin users without statin-related ADR consultation. After propensity scores matching, all baseline characteristics had standardised mean differences of less than 0.10, indicating comparability between the ADR and control group in both the primary and secondary prevention cohorts.

3.1 | Statin-related ADR and the risk of CVD event and all-cause mortality

3.1.1 | CVD primary prevention cohort

During the mean follow-up time of 6.32 ± 3.74 years, a total of 1056 composite CVD events occurred (596 [9.28%] in the ADR and 460 [7.16%] in the control group). The crude incidence rates (IRs) were 15.14 (95% CI 13.97, 16.40) and 10.99 (95% CI 10.03, 12.04)

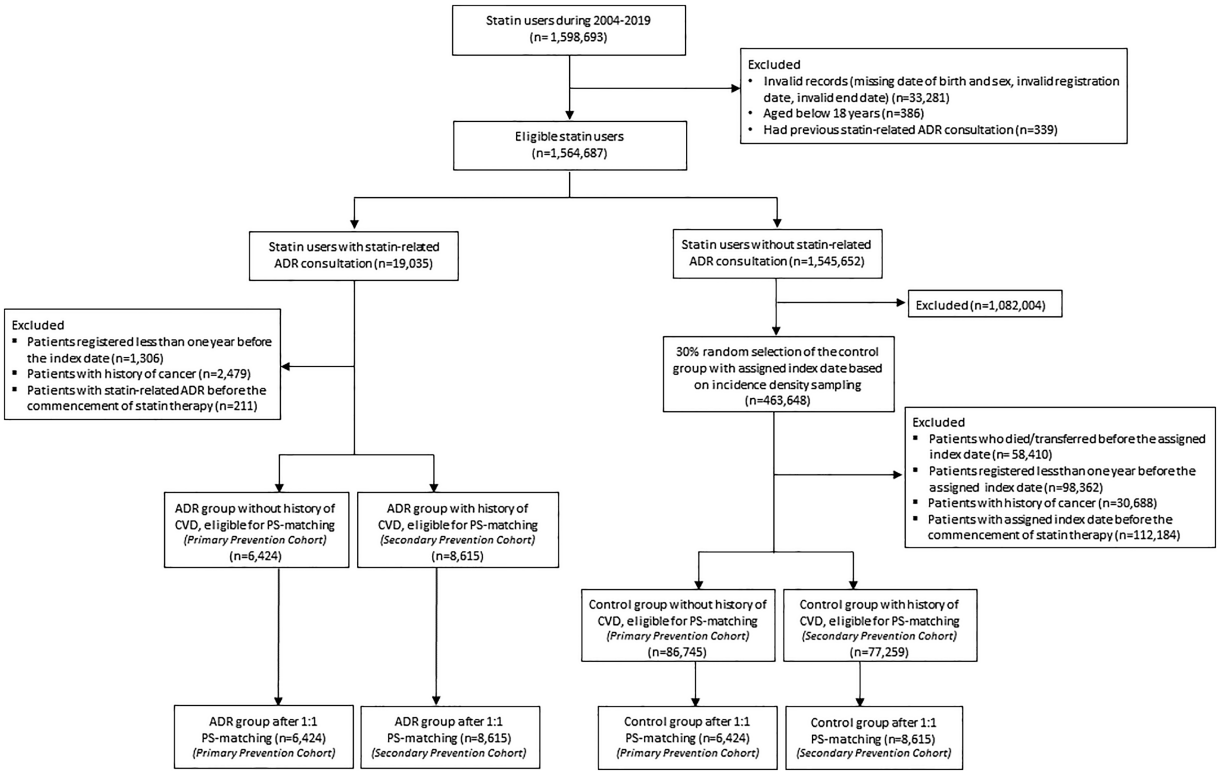

FIGURE 2 Flowchart of the study patient selection

per 1000 person-years in the ADR and control groups, respectively. Cox regression analysis showed that patients with statin-related ADR consultation had an increased risk of subsequent CVD event compared to statin users without statin-related ADR consultation, with an adjusted HR of 1.39 (95% CI 1.23, 1.57). For the secondary outcome, all-cause mortality, during the mean follow-up of 6.61 ± 3.76 years there were 1369 deaths (641 [9.85%] in the ADR group and 728 [11.18%] in the control group). The crude IRs were 15.09 (95% CI 13.95, 16.32) and 16.64 (95% CI 15.47, 17.90) per 1000 person-years in the ADR and control groups, respectively. No significant difference was observed in all-cause mortality between the two groups, with an adjusted HR of 0.93 (95% CI 0.83, 1.03).

3.1.2 | CVD secondary prevention cohort

During the mean follow-up time of 5.31 ± 3.83 years, 3980 composite CVD events occurred (2246 [26.07%] and 1734 [20.13%] in the ADR and control groups, respectively). The crude IR per 1000 person-years in the ADR group was 50.14 (95% CI 48.11, 52.26), while that of the control group was 37.15 (95% CI 35.44, 38.94). Statin-related ADR was associated with an increased risk of recurrent CVD events, with an adjusted HR of 1.34 (95% CI 1.25, 1.42). For the mortality outcome, during the mean follow-up of 6.26 ± 3.84 years, there were 4117 deaths (2015 [23.39%] and 2102 [24.40%] in ADR and control groups, respectively). All-cause mortality did not differ significantly between the two groups (crude IRs of 37.22 [95% CI 35.63, 38.88] and 39.08 [95% CI 37.45, 40.79] per 1000 person-years, respectively), with an adjusted HR of 0.95 (95% CI 0.90, 1.01) (Table 2 and Supporting Information Figure S1).

3.2 | Treatment pattern changes following the ADR consultation and CVD event and all-cause mortality

Treatment patterns within a 1-year period following ADR consultation are summarised in Figure 3. Over a third (38.86%, n = 5120) of patients continued receiving any statin prescriptions or a combination of any statin with additional LLT after statin-related ADR consultation. Approximately a fifth (19.64%, n = 2587) of patients received other LLT only and the remaining patients (41.50%, n = 5468) discontinued all LLT.

3.2.1 | Continued with any statin versus discontinued all LLT

During the mean follow-up time of 5.14 ± 3.45 years, a total of 1624 composite CVD events occurred (724 [14.14%] in the statin group and 900 [16.46%] in the discontinued all LLT group). The crude IRs per 1000 person-years were 26.30 (95% CI 24.46, 28.29) and 31.30

TABLE 1 Baseline characteristics of the study participants

Characteristics	Before propensity score matching			After propensity score matching		
	With statin-related ADR consultation n (%)	Without statin-related ADR consultationn (%)	SMD[a]	With statin-related ADR consultation n (%)	Without statin-related ADR consultationn (%)	SMD[a]
CVD primary prevention cohort	*n = 6424 (%)*	*n = 86 745 (%)*		*n = 6424 (%)*	*n = 6424 (%)*	
Age, mean ± SD	66.03 ± 10.59	63.49 ± 11.70	0.2278	66.03 ± 10.59	65.58 ± 11.15	−0.0004
Sex (male), n (%)	2706 (42.12)	44 229 (50.99)	−0.1784	2706 (42.12)	2715 (42.26)	−0.0145
Interval between commencement of statin therapy and index date in years, mean ± SD	3.13 ± 3.06	3.99 ± 3.14	−0.2781	3.13 ± 3.06	3.09 ± 2.84	−0.0468
Comorbidities, n (%)						
Dyslipidaemia	6424 (100.00)	86 737 (99.99)	0.0136	6424 (100.00)	6424 (100)	0.0000
Hypertension	4159 (64.74)	52 943 (61.03)	0.0768	4159 (64.74)	4195 (65.30)	0.0007
Diabetes	3151 (49.05)	26 396 (30.43)	0.3876	3096 (48.19)	3151 (49.05)	−0.0003
CKD	788 (12.27)	10 190 (11.75)	0.0160	788 (12.27)	724 (11.27)	0.0270
Liver disease	101 (1.57)	980 (1.13)	0.0383	101 (1.57)	73 (1.14)	0.0291
COPD	551 (8.58)	6616 (7.63)	0.0348	551 (8.58)	516 (8.03)	0.0209
Rheumatic disease	651 (10.13)	7812 (9.01)	0.0384	651 (10.13)	594 (9.25)	0.0225
Concomitant medications, n (%)						
ACEIs/ARBs	2967 (46.19)	37 839 (43.62)	0.0516	2967 (46.19)	2951 (45.94)	−0.0037
CCBs	1675 (26.07)	21 864 (25.20)	0.0199	1675 (26.07)	1624 (25.28)	0.0096
Diuretics	2030 (31.60)	25 491 (29.39)	0.0481	2030 (31.60)	2027 (31.55)	0.0080
Beta-blockers	1078 (16.78)	15 432 (17.79)	−0.0267	1078 (16.78)	1029 (16.02)	0.0236
Antiplatelets/ anticoagulants	1789 (27.85)	23 014 (26.53)	0.0296	1789 (27.85)	1778 (27.68)	0.0049
Antidiabetics	2192 (34.12)	21 011 (24.22)	0.2191	2192 (34.12)	2174 (33.84)	−0.0036
Nitrates	109 (1.70)	1118 (1.29)	0.0336	109 (1.70)	82 (1.28)	0.0431
NSAIDs	1065 (16.58)	13 554 (15.63)	0.0259	1065 (16.58)	993 (15.46)	0.0314
CVD secondary prevention cohort	*n = 8615 (%)*	*n = 77 259 (%)*		*n = 8615 (%)*	*n = 8615 (%)*	
Age (mean ± SD)	72.36 ± 10.08	70.40 ± 10.93	0.1865	72.36 ± 10.08	72.03 ± 10.47	0.0324
Sex (male), n (%)	3712 (43.09)	44 788 (57.97)	−0.3010	3712 (43.09)	3700 (42.95)	0.0028
Interval between commencement of statin therapy and index date, mean (year) ± SD	4.53 (3.76)	5.46 (3.75)	0.1865	4.53 (3.76)	4.47 (3.52)	0.0180
Comorbidities, n (%)						
Dyslipidaemia	8615 (100.00)	77 259 (100.00)	0.0000	8615 (100.00)	8615 (100.00)	0.0000
Hypertension	5784 (67.14)	50 877 (65.85)	0.0273	5784 (67.14)	5781 (67.10)	0.0007
Diabetes	1827 (21.21)	18 243 (23.61)	−0.0577	1827 (21.21)	1747 (20.28)	0.0229
CKD	1556 (18.06)	14 879 (19.26)	−0.0307	1556 (18.06)	1376 (15.97)	0.0556
Liver disease	99 (1.15)	724 (0.94)	0.0209	99 (1.15)	75 (0.87)	0.0279
COPD	1203 (13.96)	10 114 (13.09)	0.0255	1203 (13.96)	1133 (13.15)	0.0237
Rheumatic disease	1250 (14.51)	9933 (12.86)	0.0481	1250 (14.51)	1103 (12.80)	0.0497
Concomitant medications, n (%)						
ACEIs/ARBs	4535 (52.64)	45 349 (58.70)	−0.1221	4535 (52.64)	4511 (52.36)	0.0056
CCBs	2949 (34.23)	26 266 (34.00)	0.0049	2949 (34.23)	2953 (34.28)	−0.0010

(Continues)

TABLE 1 (Continued)

Characteristics	Before propensity score matching			After propensity score matching		
	With statin-related ADR consultation n (%)	Without statin-related ADR consultationn (%)	SMD[a]	With statin-related ADR consultation n (%)	Without statin-related ADR consultationn (%)	SMD[a]
Diuretics	3461 (40.17)	30 546 (39.54)	0.0130	3461 (40.17)	3364 (39.05)	0.0230
Beta-blockers	3460 (40.16)	34 686 (44.90)	−0.0958	3460 (40.16)	3494 (40.56)	−0.0080
Antiplatelets/ anticoagulants	5917 (68.68)	55 419 (71.73)	−0.0667	5917 (68.68)	6073 (70.49)	−0.0394
Antidiabetics	1221 (14.17)	14 062 (18.20)	−0.1095	1221 (14.17)	1193 (13.85)	0.0094
Nitrates	2225 (25.83)	19 226 (24.89)	0.0217	2225 (25.83)	2107 (24.46)	0.0316
NSAIDs	1202 (13.95)	9774 (12.65)	0.0383	1202 (13.95)	1090 (12.65)	0.0383

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ADR, adverse drug reaction; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SMD, standardized mean difference.

[a]SMD indicates difference in mean or proportion of covariates in the exposed *vs* control group divided by the pooled standard deviation. SMD of less than 0.2 indicates a negligible difference in covariates between both groups.

(95% CI 31.30, 35.67), respectively. Cox regression analysis showed that continuing statin treatment was associated with a decreased risk of CVD event compared to discontinuation of all LLT (adjusted HR of 0.71 [95% CI 0.64, 0.78]). For the secondary outcome, all-cause mortality, during the mean follow-up of 5.67 ± 3.48 years there were 1711 deaths (694 [13.55%] in the continuing statin treatment group and 1077 [19.70%] in those who discontinued all LLT), with crude IRs per 1000 person-years of 22.97 (95% CI 21.33, 24.75) and 36.11 (95% CI, 34.01, 38.33), respectively. Continuing statin treatment also had a statistically significant effect on all-cause mortality compared to discontinuation of all LLT, with an adjusted HR of 0.46 (95% CI 0.42, 0.50).

3.2.2 | Continued with other LLT versus discontinued all LLT

During the mean follow-up of 5.23 ± 3.49 years, there were 1320 composite CVD events, (420 [16.24%] in patients who continued with other LLT only and 900 [16.46%] in those who discontinued all LLT), with crude IRs per 1000 person-years of 27.60 (95% CI 25.08, 30.37) and 33.41 (95% CI 31.30, 35.67), respectively. Patients who continued with other LLT had a decreased risk of CVD events, with an adjusted HR of 0.75 (95% CI 0.62, 0.92), as compared to patients who discontinued all LLT. A similar finding was observed for all-cause mortality. During the mean follow-up of 6.79 ± 3.54 years, there were 1486 deaths (409 [15.81%] in those who continued with other LLT and 1077 [19.70%] in those who discontinued all LLT), with crude IRs per 1000 person-years of 21.08 (95% CI 19.13, 23.23 and 30.51 (95% CI 28.74, 32.29), respectively. Patients who continued with other LLT had a low risk of all-cause mortality compared to those who discontinued all LLT altogether (adjusted HR 0.52 [95% CI 0.43, 0.64]) (Table 3 and Figure 4).

3.3 | Sensitivity analysis

The results of sensitivity analyses are provided in Supporting Information Table S1. Firstly, similar findings were observed in the primary analysis using IPTW based on propensity scores, with statin-related ADR consultation associated with an increased risk of CVD events but not all-cause mortality in both primary prevention (adjusted HR of 1.40 [95% CI 1.29, 1.53] and 0.95 [95% CI 0.87, 1.04], respectively) and secondary prevention cohorts (adjusted HR of 1.33 [95% CI 1.27, 1.39] and 0.96 [95% CI 0.92, 1.01], respectively). Secondly, similar results were observed in the analysis using the 6-month period following the ADR, as compared to that of analysis using the 1-year period for the secondary analysis (Supporting Information Figure S2 and Supporting Information Table S2). Thirdly, we found similar results using competing risk analysis with death for analysis with CVD outcome. In the primary analysis, after taking into account the competing risk of death, statin-related ADR consultation was associated with an increased risk of subsequent CVD events in both the primary prevention (adjusted HR of 1.40 [95% CI 1.24, 1.58]) and secondary prevention (adjusted HR of 1.35 [95% CI 1.26, 1.43]) cohorts. In the secondary analysis, continued statin prescription was associated with a reduced risk of CVD events, with adjusted HR of 0.76 (95% CI 0.69, 0.84), as well as continued with other LLT (adjusted HR of 0.83 [95% CI 0.72 0.95]).

4 | DISCUSSION

This is the first large UK study to report the impact of statin-related ADR on subsequent patient outcomes The key findings were (i) patients with statin-related ADR consultation had an increased risk of a subsequent CVD event in both primary and secondary prevention cohorts and (ii) continued lipid-lowering medication was associated

TABLE 2 Adjusted HR and incidence rate per 1000 person-years (95% CI) for CVD events and all-cause mortality

	CVD primary prevention cohort (n = 12 848)				
	Patients with statin-related ADR consultation (n = 6424)		Patients without statin-related ADR consultation (n = 6424)		
Outcome	Event (%)	IR (95% CI)	Event (%)	IR (95% CI)	Adjusted HR (95% CI)
Primary outcome					
Composite CVD events	596 (9.28)	15.14 (13.97, 16.40)	460 (7.16)	10.99 (10.03, 12.04)	1.39 (1.23, 1.57)
Myocardial infarction	214 (3.33)	5.26 (4.60, 6.01)	157 (2.44)	3.66 (3.13, 4.28)	1.45 (1.18, 1.78)
Stroke/TIA	406 (6.32)	10.14 (9.20, 11.17)	323 (5.03)	7.62 (6.83, 8.50)	1.35 (1.17, 1.56)
Secondary outcome					
All-cause mortality	641 (9.85)	15.09 (13.95, 16.32)	728 (11.18)	16.64 (15.47, 17.90)	0.93 (0.83, 1.03)

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; TIA, transient ischemic attack; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SMD, standardized mean difference.

TABLE 2 (Continued)

	CVD secondary prevention cohort (n = 17 230)				
	Patients with statin-related ADR consultation (n = 8615)		Patients without statin-related ADR consultation (n = 8615)		
Outcome	Event (%)	IR (95% CI)	Event (%)	IR (95% CI)	Adjusted HR (95% CI)
Primary outcome					
Composite CVD events	2246 (26.07)	50.14 (48.11, 52.26)	1734 (20.13)	37.15 (35.44, 38.94)	1.34 (1.25, 1.42)
Myocardial infarction	746 (8.66)	14.47 (13.47, 15.55)	501 (5.82)	9.61 (8.81, 10.49)	1.51 (1.34, 1.69)
Stroke/TIA	1662 (19.29)	35.41 (33.74, 37.15)	1333 (15.47)	27.72 (26.27, 29.25)	1.27 (1.18, 1.36)
Secondary outcome					
All-cause mortality	2015 (23.39)	37.22 (35.63, 38.88)	2102 (24.40)	39.08 (37.45, 40.79)	0.95 (0.90, 1.01)

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CVD, cardiovascular disease; IR, incidence rate; HR, hazard ratio; TIA, transient ischemic attack; NSAID, nonsteroidal anti-inflammatory drug; SD, standard deviation; SMD, standardized mean difference.

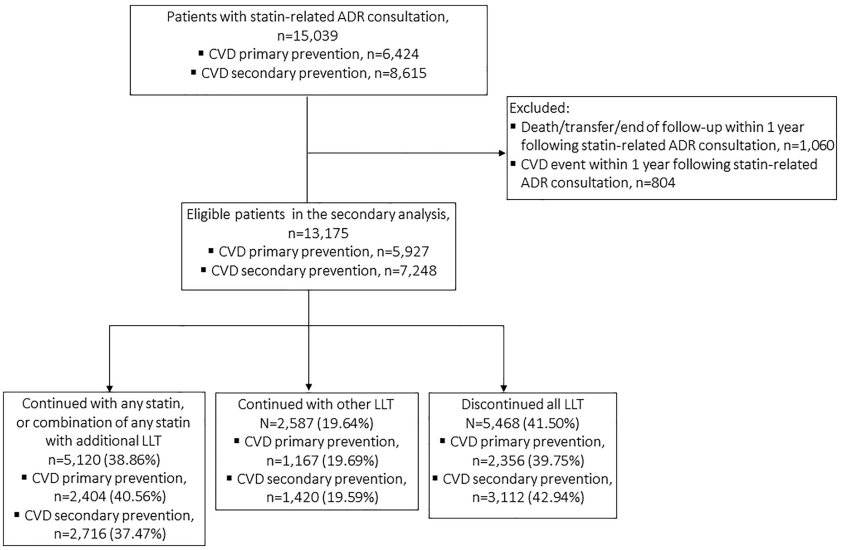

FIGURE 3 Treatment changes within a 1-year period following statin-related ADR consultation

TABLE 3 Adjusted HR for CVD events and all-cause mortality among different treatment groups within a 1-year period following statin-related ADR consultation

Treatment group	Event (%)	Adjusted HR (95% CI)
CVD event		
Continued with any statin or combination of any statin and additional LLT (total n = 5120, 38.86%)	724 (14.14%)	0.71 (0.64, 0.78),
Continued with other LLT only (total n = 2587, 19.64%)	420 (16.24%)	0.75 (0.62, 0.92)
Discontinued all LLT (total n = 5468, 41.50%)	900 (16.46%)	1.00
All-cause mortality		
Continued with any statin or combination of any statin and additional LLT (total n = 5120, 38.86%)	694 (13.55%)	0.46 (0.42, 0.50),
Continued with other LLT only (total n = 2587, 19.64%)	409 (15.81%)	0.52 (0.43, 0.64),
Discontinued all LLT (total n = 5468, 41.50%)	1077 (19.70%)	1.00

Abbreviations: ADR, adverse drug reaction; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; LLT, lipid lowering treatment.

with lower risk of CVD event and all-cause mortality compared to discontinuation of all LLT altogether following the occurrence of ADR.

Our finding is in line with that of Serban et al, who focused on patients with previous history of myocardial infarction in the United States. Serban et al and our study found that statin intolerance increased the risk of CVD event.[18] An increased risk of medication nonadherence among those who reported statin-related symptoms was observed in a previous large survey among current and former statin users,[17] which partly explained the excess risk of CVD event. Furthermore, in the current study we found a large proportion (39.67-43.04%) of these patients discontinued receiving any LLT prescription, relatively higher than in previous studies (11.00-27.50%).[9,33] Although a similar risk of mortality was observed, patients' quality of life may be severely diminished due to an increased risk of CVD event after an ADR, confirming that lipid management for these individuals should be monitored more closely.[34] Another study performed by Zhang et al showed that patients who continued to receive statin prescriptions following a statin-related ADR had a 10-20% lower incidence of both CVD events and all-cause mortality, a finding that is supported by our results.[22] However, this previous study did not examine all possible treatment changes following an ADR, ie, continued with any statin, continued with other LLT and discontinued all LLT.

A previous study in the UK by Nair et al found that a large proportion (65%) of patients with a statin-related ADR were able to tolerate an alternative statin, requiring on average two switches of any statins to identify a tolerated statin.[35] However, our study result was different, as only 38.86% of these patients continued receiving any statins prescriptions within a 1-year period following an ADR. The difference could be due to the small sample size (40 patients) included in the study by Nair et al and different care settings. Statin rechallenge after an ADR, ie, stopping and restarting any statin to check whether the symptoms are related to statin, is of importance and this can be performed using either the same (lower dose within the same intensity) or a different statin.[7,20] A study by Zhang et al showed that using a different statin was one of the factors associated with a successful statin rechallenge, ie, 24 months without discontinuation after the ADR.[36] Three different statins should be considered before proceeding to another LLT.[7]

Another strategy included the use of an intermittent statin regimen.[37] Previous systematic reviews have shown that alternate-day dosing of statin, particularly using a statin with a long half-life, eg,

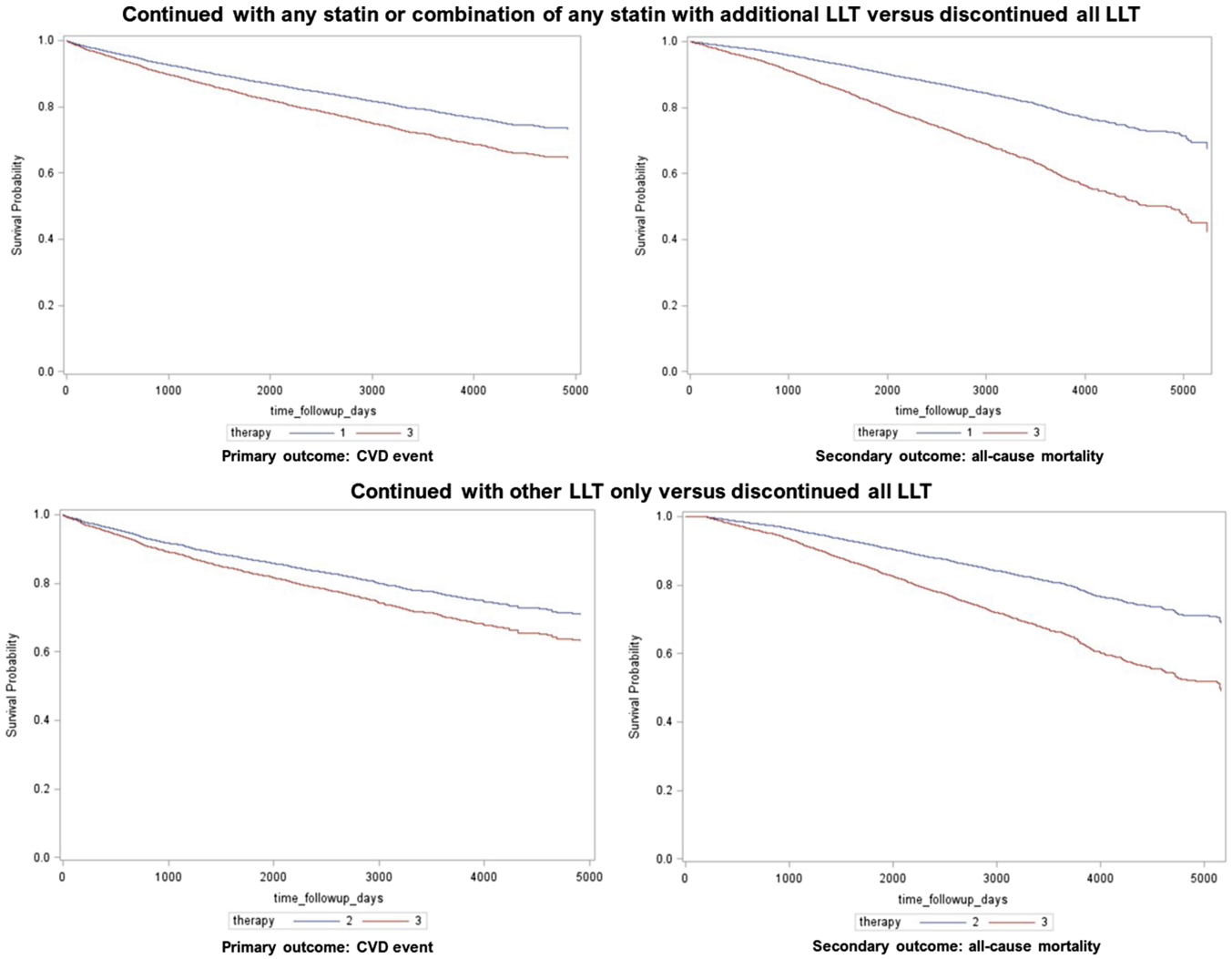

FIGURE 4 Kaplan-Meier survival curves for secondary analysis investigating the outcomes following statin-related ADR between different treatment groups. ADR, adverse drug reaction; CVD, cardiovascular disease; LLT, lipid lowering treatment

rosuvastatin (half-life 19 hours), has comparable efficacy with a to daily dosing regimen and is particularly beneficial for those patients who are intolerant to a daily statin regimen.[37,38] Approximately 70-72.5% of patients with a previous history of myopathy have been identified to tolerate an intermittent statin dosing strategy.[37,39] Mampuya et al showed that significant greater reduction of low-density lipoprotein (LDL-C) was observed in those using an intermittent statin dose regimen compared with those who discontinued any statin.[33]

The lipid solubility of different types of statins has been identified to play an important role in their metabolic properties and tolerability.[40–43] The most lipophilic statin, simvastatin, owing to its unselective penetration to extrahepatic tissues such as skeletal muscle, is most likely to induce muscular side effects, while hydrophilic statins (eg, pravastatin and rosuvastatin) have less muscle penetration, although muscle toxicity has been reported with all statins.[3,34,44] This was confirmed by a previous study showing that rosuvastatin and pravastatin were the most tolerated statin in patients with intolerance due to the nonsevere side effects of a previous statin.[35]

As statin therapy is superior in reducing CVD morbidity and mortality compared to other LLT, clinical guidelines recommend prioritising any statin use first following an ADR.[19,20] Other LLT should only be used and/or added for those with genuine intolerance to any statins, which is rare (<0.1%),[45] as well as those needing incremental lipid target improvement despite maximum tolerable statin dose use.[19,20,46] In a recent randomized trial of patients with confirmed statin intolerance due to muscle-related ADR (GAUSS-3 trials), the use of PSCK-9 inhibitor showed a significantly greater reduction of low-density lipoprotein (LDL) levels compared with ezetimibe after 24 weeks.[47] Nevertheless, the cardiovascular benefit of either PSCK-9 inhibitor or ezetimibe is still under-investigated, and conflicting results exist on the cost-effectiveness of PSCK9 inhibitor.[48,49] The use of nutraceuticals to complement LLT has been increasingly investigated, particularly for patients with statin intolerance who have not reached their lipid target with nonstatin therapy. A study by Cicero et al showed that the addition of several alternative treatments, including nutraceuticals, other LLT and an intermittent statin regimen

with ezetimibe, in patients with statin-related myalgia was effective to improve lipid therapeutic goals.[50] In our study, we found that those who continued with other LLT following the ADR consultation had a lower risk of CVD events and mortality compared to those who discontinued all LLT altogether. Several studies have suggested that LLT may improve systemic oxidative stress associated with arterial stiffness and endothelial function, independent of its hypolipidaemic activities.[50,51]

4.1 | Clinical implications

There are several implications from these findings. Firstly, as this study reveals that patients with statin-related ADR consultation had an increased risk of a subsequent CVD event, the monitoring of lipid target should be performed more closely for these patients. Even after switching, medication adherence of these patients could be compromised due to reduced quality of life and fear of ADR recurrence.[17] Secondly, this study showed that a large proportion of patients discontinued all LLT altogether within 1 year following the ADR and these patients had an increased risk of both CVD events and all-cause mortality. The decision of whether to continue any LLT should be balanced against the risk and adjusted based on the individual's circumstances.[19,22] Our study highlighted the subsequent burden of discontinuing potentially essential treatment for these individuals. Our findings strengthen the importance of continuing lipid-lowering management based on an individual's conditions to achieve optimal clinical outcomes.

4.2 | Strength and limitations

This study has several strengths. Firstly, to the best of our knowledge this is the first population-based study examining the impact of statin-related ADR consultations in the UK primary care setting. Secondly, we not only assessed the impact of ADR, but also investigated all possible treatment patterns following the ADR consultation and its associated outcomes. The previous study only compared the outcome between those continued and discontinued statin following the ADR occurrence.[22] This provides a better understanding of the burden of an ADR for patients and insight into the current practice of patient management following an ADR in a real-world clinical setting.

This study also has several weaknesses. Firstly, ADR-related consultations were identified using standardised designated codes, which may be prone to under-recording and varied assessment between clinicians.[15] In our study, statin-related ADR consultation was observed in 1.22% patients, which was lower than in previous studies.[9,10] Secondly, we could not identify the degree of severity of the ADR, which might influence the treatment changes in our secondary analysis. Thirdly, this study did not capture medication use prescribed in the secondary care setting. It was possible that patients with statin-related ADR consultations were referred to lipid specialists. Thus, under-estimation of treatment pattern changes would be possible as IMRD was not able to capture data from other healthcare settings. Lastly, information on medication use was limited according to the prescription records, thus it was not possible to confirm that the medications were taken by the patients.

5 | CONCLUSIONS

Statin-related ADR was associated with an increased risk of a subsequent CVD event in both primary and secondary prevention cohorts, indicating these patients should be monitored more closely. Continued lipid-lowering medication is of importance for these patients to protect against CVD events and all-cause mortality.

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CONFLICT OF INTEREST

There are no competing interests to declare.

CONTRIBUTORS

L.W., S.C. and W.N.I. conceived the idea. W.N.I., L.W. and C.W. designed the study. W.N.I. conducted the study and wrote the manuscript. C.J., K.K.C.M., H.A., A.A. and L.W. provided statistical advice on the data analysis. C.J. and L.W. validated the data analysis. C.W., C.J., K.K.C.M., H.A., A.A., S.C. and L.W critically reviewed the manuscript. All authors participated in the interpretation of the study result and approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

No additional data are available for sharing.

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SUPPORTING INFORMATION

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