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ORIGINAL RESEARCH ARTICLE

Association Between an Acute, Drug-Induced Decrease in High-Density Lipoprotein Cholesterol Levels and Risk of Cardiovascular Events

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Abstract

Background and Objective The literature describing the long-term effect of an acute, drug-induced decrease in high-density lipoprotein cholesterol (HDL-C) and cardiovascular (CV) risk is limited. We aimed to further explore this potential association.

Methods A retrospective cohort study was conducted using the Clinical Practice Research Datalink (CPRD) between 2006 and 2014. The study enrolled patients who initiated statin therapy for a short term, to identify patients with an acute, short-term decrease in HDL levels rather than to assess sustained treatment. HDL-C measurements were assessed within 9 months before and after statin initiation and patients were followed up for up to 5 years for CV events, comparing those with a decrease in HDL-C with those with constant HDL-C levels. The primary composite endpoint of major adverse cardiac events (MACE) was defined as CV death, myocardial infarction, revascularisation, and hospitalised ischaemic stroke. We estimated crude and propensity score weighted 5-year cumulative risk differences and hazard ratios (HR) comparing both groups.

Results A total of 17,543 patients (HDL-C decrease group, $n=6454$; HDL-C constant group, $n=11{,}089$) were included in the study. The 5-year cumulative incidence of MACE in the HDL-C constant cohort was 5.91%. The corresponding risk differences for HDL-C decrease versus the constant group was 1.23% (95% confidence interval [CI] 0.28–2.18) and the HR was 1.20 (95% CI 1.04–1.39). This was mainly driven by an increased risk in ischaemic stroke (HR 1.44, 95% CI 1.08–1.90) and CV death (HR 1.23, 95% CI 0.93–1.63).

Conclusion Patients with a short-term, drug-induced decrease in HDL-C had a moderately increased long-term risk of CV events compared with those with constant HDL-C levels.

Trial Registration Number 207595 (GlaxoSmithKline Trial registry; https://www.gsk-studyregister.com/).

Key Points

A moderately increased long-term risk of cardiovascular (CV) events was observed in patients with an acute, drug-induced decrease in high-density lipoprotein cholesterol (HDL-C) in comparison with those with constant HDL-C levels.

The 5-year cumulative incidence of major adverse cardiac events (MACE) in the HDL-C constant cohort was 5.91%. The corresponding risk difference for HDL-C decrease versus the constant group was 1.23% (95% confidence interval [CI] 0.28–2.18) and the hazard ratio was 1.20 (95% CI 1.04–1.39).

The highest risk was found for ischaemic stroke, followed by the composite of MACE.

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1 Introduction

The association between high-density lipoprotein cholesterol (HDL-C) levels and the risk of cardiovascular (CV) disease is well known [1, 2]. Independent of low-density lipoprotein cholesterol (LDL-C) levels, low HDL-C levels have been identified as an important predictor of CV risk [3]. While a number of studies have demonstrated an inverse association between increased HDL-C and CV risk, the literature describing the effect of an acute decrease in HDL-C on long-term CV risk is limited.

HDL-C levels may be decreased in various disease states, and initiation of some medications may result in acute HDL-C reductions in otherwise healthy individuals. For example, although the majority of published trials of statin therapy for LDL-C reduction have observed a modest increase of 4–5% in HDL-C [4], a group of patients in these trials experienced a decrease in HDL-C along with the beneficial effects of LDL-cholesterol lowering. This phenomenon has also been reported in several observational studies [5–7].

Using data from the Framingham Offspring study, Grover et al. observed that approximately 25% of patients had a decrease in HDL-C after initiating a statin. Nevertheless, the authors did not relate this decrease to subsequent CV outcomes [5].

The present retrospective cohort study was conducted to assess the long-term CV event risk associated with an acute, drug-induced decrease in HDL-C compared with maintaining steady HDL-C levels. In order to identify patients with a short-term HDL-C decrease and comparable patients without decreased short-term HDL-C levels, we identified a cohort of patients who initiated treatment with statins for a short duration (≤9 months) and followed them up for up to 5 years.

2 Methods

2.1 Data Source

A retrospective cohort study was chosen to assess the association between an acute, drug-induced decrease in HDL-C and the long-term risk of CV events.

The study population was selected from the Clinical Practice Research Datalink (CPRD), linked to Hospital Episodes Statistics (HES) and Office for National Statistics (ONS) data sources. The CPRD is an observational electronic health record database that contains de-identified patient data collected from a network of general practitioners across the UK [6].

2.2 Study Population

This cohort included patients aged between 18 and 85 years who initiated treatment with statins for primary or secondary prevention from 2006 to 2014 and discontinued the treatment within 9 months. We wanted to study patients with a relatively abrupt decrease in HDL levels. Knowing from the literature that some patients have paradoxical HDL-C decreases at the time of statin initiation, we chose those who were receiving short-term statin therapy, as a way to identify them. Statin initiation was defined as the first observed statin prescription during the study period following 1 year of up-to-standard medical history without statin use. Patients were required to have two HDL-C measurements—within 9 months before and after statin initiation. A 9-month period was selected to allow accumulation of enough sample size while still being considered 'short-term'. Patients were also required to discontinue statin therapy within 9 months of initiation. Patients with an ongoing malignancy and those experiencing any of the prespecified study outcomes during the period of statin use were excluded. The follow-up period began after statin discontinuation and continued until patients left the medical practice participating in CPRD, occurrence of a major adverse cardiac event (MACE) event, death, or the end of 2015. Patients were followed for up to 5 years, and those with a decrease in HDL-C were compared with those with constant HDL-C levels.

The primary endpoint was the occurrence of MACE, consisting of the following events: CV death, fatal and non-fatal MI, revascularisation, and hospitalised ischaemic stroke. Each MACE endpoint was considered separately and as a combined composite endpoint. Validated outcome definitions were employed [6, 7].

2.3 Exposure Definition

The primary exposure was reduction in HDL-C levels after statin initiation. A variation of ≤8% was considered as the cut-off point to define the exposure groups: the decrease group consisted of those with a decrease of >8%, and the constant group consisted of those with a change of ≤8%. This cut-off point was derived from the distribution of HDL-C change within the study sample after statin initiation. The percentiles of the distribution corresponding to the 25th percentile (p25), median value (p50) and 75th percentile (p75) were −9.09, 0.00 and 8.33, respectively. The constant group served as the comparator.

The distribution of baseline characteristics of the exposure groups, including the distribution of post statin initiation LDL-C levels and change in LDL-C levels, were calculated in the crude and weighted study population. As the objective of the study was to evaluate the effect of decreases in HDL-C levels versus maintaining constant HDL-C levels, those with increasing HDL-C levels were not included in the analyses.

2.4 Statistical Analyses

An inverse probability of treatment weighting (IPTW) approach was employed in this analysis, where a weight was calculated for each patient based on a propensity score, and these weights were applied to the study population to minimise the impact of observed confounding [8]. Propensity scores were estimated for the HDL-C constant and HDL-C decrease groups using logistic regression models; HDL-C decrease (yes/no) was used as the response variable, with potential confounders used as the explanatory variables. LDL-C and triglycerides levels were not included in the logistic model for estimating the propensity score due to a large amount of missing values and the fact that the distribution of LDL-C and triglycerides did not appear to differ between the exposure groups.

IPTW was defined as the inverse of the estimated propensity score for patients with a decrease in HDL-C and the inverse of one minus the estimated propensity score for patients with constant HDL-C levels, multiplied by the marginal prevalence of the actual HDL-C response. Once the IPTW was applied to the study population, the balance of the covariates included in the propensity score was assessed by examining the covariate values in the IPTW weighted population versus the original study population.

Crude and weighted risk differences for each individual endpoint, as well as for the composite endpoint, were calculated using the Proc lifetest procedure. Hazard ratios (HRs) were calculated using Cox proportional hazard regression models in both ways, censoring and accounting for competing events. Incidence proportions for each individual endpoint as well as the composite endpoint were estimated using 1-year intervals based on Kaplan–Meier curves. Crude HRs were estimated within individual propensity score deciles to see if there was any heterogeneity of the treatment effect by the propensity score.

Other secondary and sensitivity analyses were performed, including the following: stratifying by use of statins for secondary and primary prevention; censoring patients who restarted their statin over the follow-up period; restricting to patients with non-missing LDL-C and triglyceride values and including LDL-C and triglyceride values in the propensity score model; and examining outcomes in those with a $\geq 20\%$ decrease in HDL-C.

3 Results

A total of 429,223 patients who initiated statin treatment during the observation period were identified in the CPRD. After applying the inclusion/exclusion criteria, a total of 17,543 patients (HDL-C decrease group, $n = 6454$; HDL-C constant group, $n = 11{,}089$) were included in the final study population. The main reasons for exclusion were continued use of statins beyond 9 months of treatment and the lack of recorded lipid measurements 9 months before and after statin initiation (Fig. 1).

3.1 Baseline Characteristics

After excluding patients with missing values, 6114 patients were included in the HDL-C decrease group versus 10,588 in the HDL-C constant group. Both groups had similar baseline characteristics, although a higher proportion of patients had a history of MI, diabetes and coronary artery disease (CAD) in the HDL-C decrease group (2.3% vs. 1.6%; 21.5% vs. 19.1%; 8.0% vs. 7.3%, respectively). The distribution of covariates across cohorts was well-balanced after IPTW weighting (Table 1). Additionally, there were no meaningful differences between the IPTW-weighted HDL-C decrease and HDL-C constant groups for any of the potential confounding factors when LDL-C

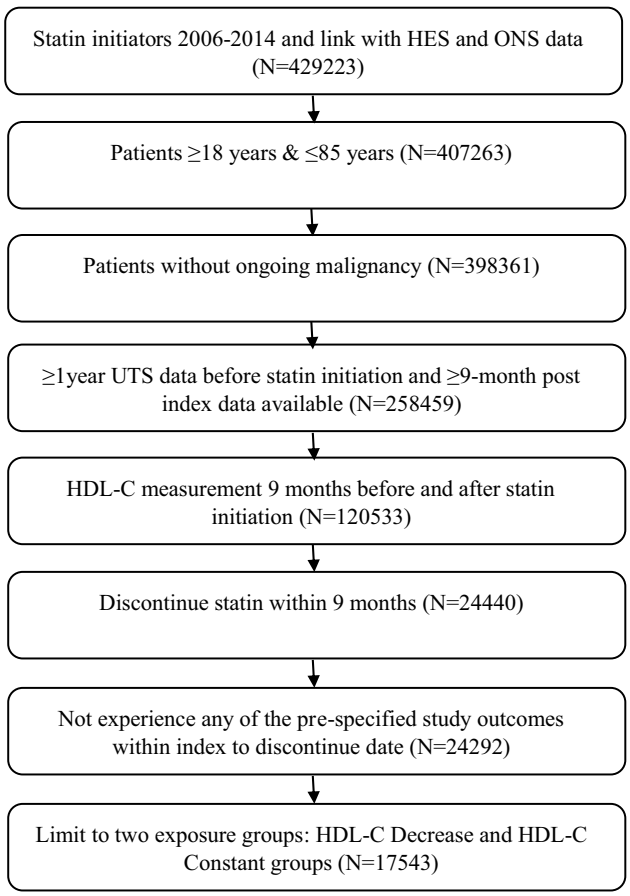

Fig. 1 Study flowchart. *HES* Hospital Episodes Statistics, *ONS* Office for National Statistics, *HDL-C* high-density lipoprotein-cholesterol, *UTS* up to standard

and triglycerides were included in the model (Online Resource 1). Details of the year of initiation, and type and dose of statin initiation in the overall population are provided in Online Resource 2. In brief, more patients initiated their treatment during the first years of the observation period (2006–2009; approximately 60%) than over the last 3 years (2012–2014; approximately 20%). Most of these patients initiated simvastatin 40 mg (44%) or 20 mg (33%) [Online Resource 2].

3.2 Primary Endpoints

Patients were followed for up to 5 years, with a total median follow-up of 4.2 years for the composite MACE outcomes. In general, the proportion of CV events was higher in the HDL-C decrease group, except for the number of MI events, which was higher in the HDL-C constant group (data not shown).

In the IPTW-weighted analysis, there was a gradual increase in the cumulative risk from years 1–5 in composite

Table 1 Characteristics of the overall population and the IPTW-weighted population

Characteristics	Overall population[a]		IPTW-weighted[a]	
	HDL-C decrease group (%) [$n=6114$]	HDL-C constant group (%) [$n=10{,}588$]	HDL-C decrease group (%) [$n=6119$]	HDL-C constant group (%) [$n=10{,}583$]
Age, years [mean (SD)]	61.39 (11.85)	62.63 (11.47)	62.16 (11.63)	62.18 (11.62)
Females	3110 (50.87)	5479 (51.75)	3127 (51.11)	5427 (51.28)
BMI, kg/m^2 [mean (SD)]	28.54 (5.91)	28.40 (5.56)	28.46 (5.64)	28.46 (5.85)
Current smoker	1157 (18.92)	1895 (17.90)	1120 (18.31)	1936 (18.29)
Current drinker	4490 (73.44)	7887 (74.49)	4527 (73.99)	7837 (74.05)
Pre-statin initiation, triglyceride levels, mmol/L [mean (SD)][b]	1.96 (1.62)	1.95 (1.41)	2 (1.55)	1.92 (1.40)
Pre-statin initiation, HDL-C levels, mmol/L [mean (SD)]	1.51 (0.49)	1.42 (0.39)	1.45 (0.45)	1.45 (0.42)
Pre-statin initiation, LDL-C levels, mmol/L [mean (SD)][b]	4.06 (1.04)	4.06 (0.99)	4.09 (1.03)	4.04 (1.00)
Post-statin initiation, LDL-C level, mmol/L [mean (SD)][b]	3.04 (1.04)	3.08 (1.03)	3.05 (1.04)	3.07 (1.03)
Change in LDL-C, mmol/L [mean (SD)][b]	−1.02 (1.03)	−0.98 (1.01)	−1.04 (1.03)	−0.97 (1.00)
Non-statin treatment for LDL-C	164 (2.68)	238 (2.25)	148 (2.42)	253 (2.39)
Medical history: MI	140 (2.29)	177 (1.67)	115 (1.88)	201 (1.90)
Revascularisation	68 (1.11)	87 (0.82)	56 (0.91)	97 (0.92)
Ischaemic stroke	53 (0.87)	87 (0.82)	51 (0.84)	88 (0.83)
Diabetes	1369 (22.39)	2088 (19.72)	1276 (20.85)	2200 (20.79)
Hypertension (including antihypertensive therapy)	3581 (58.57)	6186 (58.42)	3575 (58.42)	6185 (58.44)
Renal disease	389 (6.36)	716 (6.76)	406 (6.63)	703 (6.64)
PVD	150 (2.45)	230 (2.17)	139 (2.27)	239 (2.26)
CAD	505 (8.26)	794 (7.50)	474 (7.74)	821 (7.76)
Family history of familial hypercholesterolaemia	88 (1.44)	191 (1.80)	98 (1.60)	175 (1.66)
Familial hypercholesterolaemia	13 (0.21)	17 (0.16)	11 (0.18)	19 (0.18)
Family history of CVD	2239 (36.62)	3851 (36.37)	2234 (36.50)	3858 (36.45)
IMD (socioeconomic)				
1: least deprived	1407 (23.01)	2549 (24.07)	1450 (23.70)	2507 (23.68)
2	1374 (22.47)	2410 (22.76)	1389 (22.70)	2400 (22.67)
3	1236 (20.22)	2179 (20.58)	1245 (20.35)	2160 (20.41)
4	1168 (19.10)	1954 (18.45)	1144 (18.69)	1980 (18.70)
5: most deprived	929 (15.19)	1496 (14.13)	891 (14.56)	1538 (14.53)

Data are expressed as *n* (%) unless otherwise specified

BMI body mass index, *CAD* coronary artery disease, *CVD* cardiovascular disease, *HDL-C* high-density lipoprotein-cholesterol, *IMD* index of multiple deprivation, *IPTW* inverse probability of treatment weighting, *LDL-C* low-density lipoprotein-cholesterol, *MI* myocardial infarction, *PVD* peripheral vascular disease, *SD* standard deviation

[a]Only patients with non-missing variable values (except for LDL-C and triglyceride levels) were included

[b]LDL-C (pre, post and change) and triglycerides were not included in the logistic model for estimating the propensity score

MACE within the groups. While there was not much difference in the risk of MACE across the study groups until the end of the first year of follow-up, the difference gradually increased over time up to the fifth year. The risk difference between the HDL-C decrease and HDL-C constant groups in year 1 was 0.24 (95% confidence interval [CI] −0.11 to 0.58), and, in year 5, the risk difference was 1.23 (95% CI 0.28–2.18) (Table 2).

A gradual increase in the risk difference was observed in the time to first ischaemic stroke from year 1 (0.16, 95% CI −0.02 to 0.34) to year 5 (0.63, 95% CI 0.11–1.14) between study groups (Table 3). Similarly, for CV death, the risk difference between the HDL-C decrease and HDL-C constant groups increased from year 1 (0.02, 95% CI −0.12 to 0.17) to year 5 (0.41, 95% CI −0.13 to 0.94) [Online Resource 3]. For further details, please see Online Resource 4.

Consistent with the analysis of absolute risk, the IPTW-weighted analysis showed an increased long-term risk in the HDL-C decrease versus HDL-C constant groups. The highest risk was found for ischaemic stroke, with a hazard ratio (HR) of 1.44 (95% CI 1.08–1.90), followed by composite MACE (HR 1.20, 95% CI 1.04–1.39). An increased risk of CV death (HR 1.23, 95% CI 0.93–1.63) and a decrease in the risk of MI (HR 0.94, 95% CI 0.74–1.20) in the HDL-C decrease versus HDL-C constant groups was also observed (Table 4).

3.3 Secondary Analyses

A secondary analysis stratified by the use of statins for secondary and primary prevention was performed. From our total study population, 96.4% from the decrease group and 97.1% from the constant group were treated for primary prevention, therefore this analysis yielded similar results as the main analysis. Additionally, a number of sensitivity analyses were conducted. These analyses included censoring patients who restarted their statin over the follow-up period; rerunning analyses in the subset of patients with non-missing LDL-C and triglyceride values; and examining outcomes in those with a ≥ 20% decrease in HDL-C. The results in the secondary or sensitivity analyses were largely consistent with the primary analysis. The main difference was observed in the analysis of those with a ≥ 20% decrease in HDL-C. These results were in line with the main analysis; a higher risk of CV events was observed with a higher decrease in HDL-C levels (Online Resource 5).

4 Discussion

Over a median follow-up of 4.3 years, the unadjusted percentage of patients with MACE events was larger in the HDL-C decrease group (5.2%) compared with the HDL-C constant group (4.4%). After adjustment for competing risks and confounding factors, the 5-year cumulative risk difference for MACE events across the study groups was 1.23%

Table 2 Cumulative risk and risk differences between the HDL-C decrease and HDL-C constant groups for the composite MACE endpoint up to 5 years (IPTW-weighted population)

Group	Risk difference (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
HDL-C decrease	1.25	2.54	3.96	5.44	7.14
HDL-C constant	1.01	2.10	3.44	4.75	5.91
Risk difference (95% CI)	0.24 (−0.11 to 0.58)	0.44 (−0.06 to 0.94)	0.52 (−0.13 to 1.18)	0.68 (−0.12 to 1.48)	1.23 (0.28–2.18)

CI confidence interval, *HDL-C* high-density lipoprotein-cholesterol, *IPTW* inverse probability of treatment weighting, *MACE* major adverse cardiac events

Table 3 Cumulative risk and risk differences between the HDL-C decrease and HDL-C constant groups for ischaemic stroke endpoint up to 5 years (IPTW-weighted population)

Group	Risk difference (%)				
	Year 1	Year 2	Year 3	Year 4	Year 5
HDL-C decrease	0.37	0.80	1.20	1.45	2.08
HDL-C constant	0.21	0.47	0.81	1.12	1.45
Risk difference (95% CI)	0.16 (−0.02 to 0.34)	0.33 (0.06–0.60)	0.39 (0.04–0.74)	0.33 (−0.08 to 0.74)	0.63 (0.11–1.14)

CI confidence interval, *HDL-C* high-density lipoprotein-cholesterol, *IPTW* inverse probability of treatment weighting

Table 4 Weighted HRs and 95% CIs comparing the HDL-C decrease group with the HDL-C constant group

Variable	CV outcome events	HR[a] (95% CI)	Subdistribution HR[b] (95% CI)
Composite MACE events			
HDL-C decrease	314	1.20 (1.04–1.39)	1.20 (1.04–1.39)
HDL-C constant	460		
MI			
HDL-C decrease	107	0.95 (0.75–1.21)	0.94 (0.74–1.20)
HDL-C constant	194		
Revascularisation			
HDL-C decrease	121	1.13 (0.90–1.42)	1.12 (0.89–1.41)
HDL-C constant	194		
Ischaemic stroke			
HDL-C decrease	90	1.44 (1.09–1.91)	1.44 (1.08–1.90)
HDL-C constant	111		
CV death			
HDL-C decrease	88	1.24 (0.94–1.64)	1.23 (0.93–1.63)
HDL-C constant	126		

HDL-C decrease, $n = 6114$; HDL-C constant, $n = 10,588$

Among the 17,543 patients in the crude population, 16,702 (95.2%) had variables with a non-missing value in the model

HR hazard ratio, *CI* confidence interval, *CV* cardiovascular disease, *HDL-C* high-density lipoprotein-cholesterol, *MACE* major adverse cardiac events, *MI* myocardial infarction

[a]HR: censoring competing events. A competing event precludes the events of interest; through censoring a competing event it is assumed that those with a censored record have the same probability of experiencing the event of interest if follow-up continues, and the model will overestimate hazard

[b]Subdistribution HR: accounting for competing events. Death is the only competing event considered in CV outcome for MI, revascularisation or ischaemic stroke. Non-CV death is the only competing event considered in CV outcome for composite MACE or CV death

(95% CI 0.28–2.18). We observed a gradual increase in the cumulative risk of the composite MACE outcome from years 1–5 between the groups. The difference started increasing from the second year onwards and continued up to the fifth year, although the magnitude of change in absolute risk was relatively small. In line with the analysis of risk difference, the HR for the composite MACE endpoint in the HDL-C decrease group compared with the HDL-C constant group was elevated 1.20 (95% CI 1.04–1.39) over the follow-up period. The elevated risk in the HDL-C decrease group was mainly driven by an increased risk in ischaemic stroke (HR 1.44, 95% CI 1.08–1.90) and CV death (HR 1.23, 95% CI 0.93–1.63).

The current study was designed to measure the effect of a short-term, drug-induced decrease in HDL-C compared with those patients with constant HDL-C levels, and therefore focused on patients discontinuing statin therapy within 9 months of initiation, as some patients are known to experience decreased HDL-C levels at statin initiation. This restriction to short-term statin users resulted in a study sample in which the majority of patients were being treated for primary prevention of CVD. Other research has investigated the CV risk associated with long-term HDL-C reductions, specifically in statin initiators. A recent study in Japanese patients with acute myocardial infarction (AMI) reported a decrease in HDL-C in approximately 14% of patients after statin initiation. The HR for the risk of CV events (death, recurrent myocardial infarction [MI], stroke) was 1.95 (95% CI 1.08–3.52) when those experiencing a decrease in HDL-C were compared with those with an increase in HDL-C after statin initiation for up to 7 years of follow-up [9]. Finally, Hasvold et al. [10] studied the effects of HDL-C decrease after statin initiation in a Swedish sample of patients initiating treatment for primary and secondary prevention of CV disease, where 20% of patients experienced a decrease in HDL-C after statin initiation. An HDL-C decrease was associated with a 56% higher risk of MACE, defined as MI, unstable angina pectoris, ischaemic stroke or CV mortality (HR 1.56, 95% CI 1.12–2.16) compared with patients with unchanged HDL-C for up to 7 years of follow-up. This association varied between the primary (HR 2.10, 95% CI 1.35–3.27) and secondary (HR 1.16, 95% CI 0.85–1.58) prevention subgroups [10].

When compared with previous studies evaluating the effects of longer-term statin therapy and longer-term HDL-C decreases [9, 10], the magnitude of effect observed in the current study was smaller than that seen in previous studies. In comparison, in the study by Hasvold et al. [10], the risk of CVD was doubled in patients with a decrease in HDL-C who were treated for primary prevention of CVD [10]. However, although we restrict our analysis to 'short-term' statin users, we could not rule out that some residual confounding might have affected our results. Furthermore, among those patients experiencing a decrease in HDL-C who had HDL-C measures available after the statin discontinuation (82%), 48% maintained a decrease > 8%, indicating that the decrease in HDL-C measured in this study may not have been 'short term' as originally planned, and may have extended further into the follow-up period for a subset of patients. This may also indicate that the decrease in HDL-C was not entirely due to initiation of statin therapy in all patients. There may be other reasons why HDL-C decreased, and it is not clear for how long such a decrease was maintained. In our study, the most robust data biologically for associating short-term decreases in HDL-C with CV outcomes is likely in the first year of follow-up. However, within a 1-year timeframe after an HDL-C decrease, no increased risk of CV events was found in this study population of patients being mainly treated with statins for primary prevention of CVD. Our results are more likely explained by

the presence of time-varying confounders such as body mass index, diet, and other lifestyle factors, rather than a biological relationship between short-term HDL-C decreases and CV risk. The interpretation of potential causal relationships between short-term changes in HDL-C and long-term CV risk becomes increasingly difficult over time. This study was designed to generate hypothesis, and definitive conclusions cannot be reached.

Patients who initiated statin treatment between 2006 and 2014 were included in this study, therefore the follow-up period for those selected at the end of 2014 might have differed considerably from those who initiated statins in 2006, giving different opportunity to develop the outcomes of interest. However, in our study, the majority of patients started statins during the first 3 years, with only 5% of the population starting in 2014. The mean follow-up period was over 4 years, and both exposure groups were affected in the same way, therefore we do not think this limitation has altered our findings.

The follow-up period for all patients began after statin discontinuation. Approximately 65% of patients had their second HDL-C measurement before discontinuing their statin medication, with 85% having this second measurement either before or within 2 months after discontinuation. Given that a vast majority of patients had their second HDL-C measurement in close proximity to their statin discontinuation date, this minimises, but does not exclude, the potential for immortal time bias (the inclusion of person-time during which a subject is not at risk of having the study outcome) in the study. Additionally, other sensitivity analyses were carried out to further assess our results, such as censoring subjects who restarted treatment with statins, as the CV risk in those subjects might differ after restarting the statin; however, the results from all exploratory analyses were similar to the main analysis.

Information on the use of statins was based on prescribing records rather than dispensing records, therefore it is unknown whether patients took their prescribed medications according to the physician's instructions. Information on diet and physical activity were not available in the data sources used for this study and are potential confounding factors; however, we would expect that few patients presenting for statin initiation would likely reach the physical activity levels needed to greatly affect HDL-C levels. Confounding was addressed using IPTW-weighted analyses; however, there is a possibility that unknown confounding factors might have influenced the association.

Finally, a relatively small proportion of the overall group of subjects initiating statin therapy during the study period was included in the study population. The patients included in our study were less likely to have a history of CVD compared with the overall group of patients initiating a statin over the study period. This may be because those who discontinued their statin after 9 months were less likely to have a history of CV events compared with those who remained on therapy. However, the objective of this study was to evaluate the effect of changes in HDL-C reduction, not statin use, and the results do not apply to all statins users. Additionally, these results may not be generalisable to patients with acute HDL-C decreases due to other medications or conditions.

As strengths, this study employed population-based data from a well-validated data source (CPRD linked with HES and ONS), allowing for a relatively large study sample and the most complete capture of events. Multiple validation studies have been performed in CPRD and specifically for the assessment of definitions of our outcomes of interest [6]. Separate analyses of primary and secondary prevention and several sensitivity analyses were performed to allow for the assessment of potential modification of the overall association between HDL-C decrease and MACE events.

5 Conclusion

An acute, drug-induced decrease in HDL-C levels > 8% was associated with a moderately increased long-term risk of subsequent MACE compared with those maintaining constant HDL-C levels. The risk difference between the HDL-C decrease and HDL-C constant groups increased gradually over time and became statistically significant at 5 years. The increase in risk in MACE events was mainly driven by an increase in ischaemic stroke and CV deaths. While this study adds to the body of scientific knowledge regarding the association between drug-induced decreases in HDL-C levels and long-term CV outcomes, the retrospective nature of the study, as well as the potential for unmeasured and time-varying confounding, limit the interpretation of the study findings. Future studies in prospective cohorts with systematically collected measures of HDL-C and confounding factors would help in further understanding the potential causal associations between acute decrease in HDL-C and long-term CV outcomes.

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Compliance with Ethical Standards

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Conflict of interest Gema Requena and Liyuan Ma are employees of GSK. Bradley Layton is an employee of RTI International, an independent, non-profit research institute that performs research on behalf of governmental and commercial clients, including pharmaceutical companies. Julia DiBello was an employee of GSK at the time of the writing of this publication, but is now an employee of Merck & Co., Inc., North Wales, PA, USA. Til Stürmer receives investigator-initiated research funding and support as Principal Investigator (R01 AG056479) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453; R01 HL118255, R21-HD080214), National Institutes of Health (NIH). He also receives salary support as Director of Comparative Effectiveness Research (CER), NC TraCS Institute, UNC Clinical and Translational Science Award (UL1TR002489), the Center for Pharmacoepidemiology (current members: GSK, UCB BioSciences, Merck, Shire), and from pharmaceutical companies (GSK, Amgen, AstraZeneca, Novo Nordisk) to the Department of Epidemiology, University of North Carolina at Chapel Hill. Dr. Stürmer does not accept personal compensation of any kind from any pharmaceutical company. He owns stocks in Novartis, Roche, BASF, AstraZeneca, and Novo Nordisk.

Ethics approval Not required for this retrospective study as only previously collected data were utilised. The study protocol was approved by the Independent Scientific Advisory Committee (ISAC), protocol number 17_004. The data used in this study were de-identified and compliant with privacy laws. Study investigators did not have access to patient-identifiable information.

Availability of Data and Material Anonymised individual participant data and study documents can be requested for further research from www.clinicalstudydatarequest.com.

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