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Statins exposure and acute pancreatitis: a retrospective cohort study using a large national insurance database

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ABSTRACT

Objectives The association between the use of statins and the incidence of acute pancreatitis (AP) has yielded inconsistent findings. While statins have been implicated as an aetiology for drug-induced pancreatitis, more recent studies have found statin use is associated with a reduced risk of pancreatitis. We sought to examine the association between the use of any statin medications and the risk of AP using large real-world data.

Design All data were collected retrospectively, but individuals were prospectively followed forward in time to determine the outcome of interest using International Classification of Diseases, 10th Revision, Clinical Modification codes indicating a diagnosis of AP. A stratified Cox proportional hazards regression model was conducted to examine the association of statins use with AP.

Settings Merative MarketScan claims database 2017–2020.

Participants Individuals who filled any statin prescriptions with at least 80% proportion of days covered between 1 January 2017 and 31 December 2017 and were continuously enrolled in the database from 2016 to 2020. We also identified non-users of statins and constructed multiple strata of individuals based on the 14 confounders of interest.

Results Among 1 695 914 individuals, 226 314 had filled their statins prescription during the study period. Unadjusted incidence rates of AP generally showed higher rates among statins users. The unadjusted incidence rate and 95% CI per 1000 person-years of follow-up was 0.63 (95% CI: 0.61 to 0.66) for non-statin users, versus 0.92 (95% CI: 0.86 to 0.98) for statins users. However, a stratified Cox proportional hazards regression analysis yielded a HR of 0.92 (95% CI: 0.84 to 1.01) for statins users, indicating no difference between the two groups.

Conclusions In this large real-world analysis, use of statins was not associated with a higher risk of AP in this US healthcare setting.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Longitudinal data of a large sample of individuals with statins use and controls without statins use with 3 years of follow-up.
⇒ Large sample size of patients exposed to statins (nearly 250 000) among over 1.5 million individuals included in the final analysis. We were able to control for confounders and comorbidities, thereby minimising bias.
⇒ Observational study that used US claims data, and therefore causality cannot be implied.
⇒ Claims-based databases can misclassify patients based on misreporting or under-reporting of diagnoses or procedure codes.
⇒ MarketScan database did not include information on race or ethnicity, thus precluding any analysis of racial disparities in acute pancreatitis after statins use.

INTRODUCTION

Pancreatitis is one of the most common gastrointestinal diagnoses for hospitalisations in the USA. While gallstones and alcohol use are the most common aetiologies of acute pancreatitis (AP), a multitude of medications, including the 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors (commonly referred to as statins) class of drugs, have been implicated. Based on case reports, statins have been designated as Class Ia, indicating at least one case report describing a recurrence of AP with a rechallenge with the drug.[1]

Conversely, due to the immunomodulatory and anti-inflammatory effects of statins, these medicines also have been investigated as protective against AP or post-endoscopic retrograde cholangiopancreatography (ERCP)-related pancreatitis.[2 3] Data from basic and clinical observational studies suggest that statin use may prevent or truncate AP.[4–7]

Given the clinical uncertainty of the role of statins in AP, we sought to examine the association between the use of any statin medications and the risk of AP using large real-world data.

MATERIALS AND METHODS

Design and data source

We performed this retrospective cohort study using data from 2016 to 2020 from the Merative MarketScan Commercial Database on individuals who were continuously enrolled in the database for 5 years. MarketScan is a

national database that captures employer-based insurance claims. The Merative MarketScan Commercial database includes health insurance claims across the continuum of care (eg, inpatient, outpatient pharmacy and other claims) as well as enrolment data from large employers and health plans across the 50 states of the USA and the District of Columbia that provide private coverage for employees, their spouses and dependents. This administrative claims database includes a variety of fee-for-service, preferred provider organisations and capitated health plans that cover about 50 million privately-insured individuals every year.[8] Longitudinal tracking of detailed patient-level healthcare claims information provides comprehensive data, including demographic characteristics such as age, sex, diagnosis, procedures and medications. The database has been widely used in large epidemiological outcomes research and health economic studies.[9–11] This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.[12]

Study population

We identified patients who had been prescribed and filled any statin medications (atorvastatin, cerivastatin, fluvastatin, lovastatin, mevastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin) from 1 January 2017 to 31 December 2017 and were continuously enrolled in the database from 2016 through 2020. The index date for a statin user was defined as the earliest date of a statin prescription. We used the proportion of days covered (PDC) to measure adherence to any statin prescriptions. For the present study, we restricted our study population to regular statins users with at least 80% adherence threshold (PDC≥80%) (online supplemental figure 1). More detailed information on the PDC calculation is described elsewhere.[13] We also identified non-users during the same year who were continuously enrolled for 5 years, and we constructed multiple strata of individuals based on the 14 confounders of interest mentioned below. For these patients, we randomly assigned a pseudo-index date from 1 January 2017 to 31 December 2017. Both statin and non-statin users did not have International Classification of Diseases, 10th Revision (ICD-10) diagnosis codes of AP prior to the index date or diagnosis of pancreatic cancer, chronic pancreatitis and cytomegalovirus at any time during the study period (online supplemental figure 1).

Patient and public involvement

Patients and the public were not involved in the design or planning of this secondary data analysis.

Assessment of outcome

The outcome of interest was incident AP cases, identified by ICD-10 codes, occurring during the follow-up period from 1 January 2018 to 31 December 2020. AP events were defined by the presence of ICD-10 code K85 in the database.

Covariates

Demographic variables such as age (years), sex (male/female), place of residence (urban/rural) and US census region (South, West, North Central, Northeast) were directly extracted from the database. Based on a comprehensive literature review, the following non-demographic variables and potential confounders, representing risk factors for AP development, were also captured using their corresponding ICD-10, or Current Procedural Terminology codes (online supplemental table 1): overweight or obese, tobacco use, alcohol use, non-alcoholic fatty liver disease (NAFLD), gallstones, ischaemic heart disease, congestive heart failure, hypertension, diabetes, chronic kidney disease (CKD), each coded as (yes/no).

Statistical analysis

Patient characteristics were summarised as percentages (for categorical variables) and means and SDs (for continuous variables), as applicable. For each participant, person-years were calculated from the index dates to the date of AP or end of enrolment, or 31 December 2020, whichever date came first. The use of any statin medication with PDC≥80% was deemed as the primary exposure. The proportional hazards assumption was violated ($p<0.001$), which could be due to the large sample size of the current study. Thus, we applied a stratified Cox proportional hazards regression analysis to calculate HRs and corresponding 95% CIs. To construct the fully adjusted model, the first step was to construct strata based on the 14 confounders (age group, gender, region, gallstones, alcohol use, tobacco use, diabetes, hypertension, obesity, NAFLD, ischaemic heart disease, congestive heart failure and CKD). Because there were numerous sparse strata, we only included those strata that had at least two statin users and two statin non-users. In the second step, we applied a stratified Cox proportional hazards regression analysis with 2394strata.

As a secondary analysis, we conducted subgroup analyses by calculating the unadjusted incidence rates and corresponding 95% CIs per 1000 person-years of follow-up for the two cohorts within each subgroup.

To further test the robustness of our results, we conducted a sensitivity analysis using a meta-analysis approach that included the 25 largest stratums with respect to statins users. The 25 largest strata were constructed based on the 14 confounders mentioned above.

Data were analysed in SAS Software V.9.4 (SAS Institute; Cary, North Carolina, USA) using a two-tailed alpha level of 0.05.

RESULTS

In total, 1 695 914 individuals (mean (SD) age 52.0 (6.3) years) were included in the final analysis. Among 1 695 914 individuals, 226 314 had filled their statin prescriptions during the study period. During 3 years of follow-up, we identified 4066 incident AP cases. Compared with participants without statins use, individuals with statins use were

Table 1 Basic characteristics according to use of statins at baseline

Characteristics	Participants, no. (%)	
	No statins use (N=1 469 600)	Statins use (N=226 314)
Age, years, mean (SD)	51.8±6.3	53.7±6.0
Age groups		
19–34	17 777 (1.2)	1779 (0.8)
35–44	175 932 (12.0)	17 595 (7.8)
45–54	693 278 (47.2)	84 025 (37.1)
55–61	582 613 (39.6)	122 915 (54.3)
Sex, %		
Male	801 232 (54.5)	142 272 (62.9)
Female	668 368 (45.5)	84 042 (37.1)
Rural residence, %	199 693 (13.6)	35 426 (15.7)
Region of USA, %		
South	641 847 (43.7)	105 160 (46.5)
West	193 815 (13.2)	25 149 (11.1)
North Central	360 306 (24.5)	53 842 (23.8)
Northeast	273 632 (18.6)	42 163 (18.6)
Lifestyle factors		
Tobacco use, %	47 290 (3.2)	9512 (4.2)
Alcohol use, %	9952 (0.7)	1426 (0.6)
Baseline comorbidities		
Diabetes, %	83 037 (5.7)	69 433 (30.7)
Hypertension, %	298 441 (20.3)	109 749 (48.5)
Overweight/obesity, %	118 629 (8.1)	31 774 (14.0)
Gallstones, %	9435 (0.6)	1638 (0.7)
NAFLD, %	18 304 (1.3)	4660 (2.1)
Ischaemic heart diseases, %	14 883 (1.0)	23 548 (10.4)
Congestive heart failure, %	7495 (0.5)	4601 (2.0)
CKD, %	9140 (0.6)	4740 (2.1)

CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease.

older, more likely to be male, had a higher proportion of living in rural areas and were from the South region of the USA. Moreover, compared with non-statins users, statins users had higher proportions of chronic disease conditions (eg, diabetes, hypertension, obesity, gallstones, NAFLD, ischaemic heart diseases, congestive heart failure and CKD), and tobacco use (table 1). Among women, the unadjusted incidence rates of AP were higher among statins users as compared with those without statins use. In regards to the lifestyle factors, among individuals with tobacco use, the unadjusted incidence rate of AP was higher among statins users as compared with non-statins users. In contrast, among individuals with alcohol use, the unadjusted incidence rate of AP was higher among non-statins as compared with statins users (table 2). We next examined multiple canonical risk factors for AP in these two cohorts (table 2). Among individuals with CKD, the unadjusted incidence rate of AP was higher among statins users as compared with non-statins users. Conversely, among individuals with NAFLD, diabetes and congestive heart failure, the unadjusted incidence rate of AP was higher among non-statins users as compared with statins users (table 2). Overall, the unadjusted incidence rate of AP was higher among statins users (0.92 per 1000 persons-years (PY)) compared with non-statins users (0.63 per 1000-PY) (table 3).

In the fully stratified Cox proportional hazards regression model with all 14 confounders, we found that statins use was not significantly associated with AP (HR=0.92; 95% CI: 0.84 to 1.01; table 3).

In our sensitivity analysis based on the 25 largest strata with respect to statins users (online supplemental table 2), we found that statins use was associated with higher risk of AP in stratum 9 (HR=1.92; 95% CI: 1.16 to 3.17). Stratum 9 consisted of the age group 55–61, male, living in the urban area and from the South region

Table 2 Subgroups analysis results showing the unadjusted incidence rates of acute pancreatitis, and 95% CIs, per 1000 person-years of follow-up within the two groups of statins use status

Characteristics	No statins use	Statins use
Sex		
Men	0.62 (0.59 to 0.65)	0.97 (0.89 to 1.06)
Women	0.65 (0.62 to 0.68)	0.83 (0.74 to 0.94)
Age groups		
19–34	0.50 (0.35 to 0.71)	1.73 (0.98 to 3.04)
35–44	0.55 (0.49 to 0.61)	1.03 (0.82 to 1.30)
45–54	0.62 (0.59 to 0.65)	0.97 (0.87 to 1.09)
55–61	0.68 (0.65 to 0.72)	0.85 (0.78 to 0.94)
Residence		
Urban	0.62 (0.60 to 0.64)	0.89 (0.82 to 0.96)
Rural	0.73 (0.67 to 0.79)	1.10 (0.94 to 1.29)
Region of USA		
Northeast	0.55 (0.50 to 0.59)	0.69 (0.57 to 0.83)
North Central	0.68 (0.64 to 0.73)	0.88 (0.76 to 1.01)
South	0.67 (0.64 to 0.71)	1.05 (0.96 to 1.16)
West	0.54 (0.48 to 0.59)	0.83 (0.66 to 1.03)
Tobacco use		
No	0.61 (0.59 to 0.63)	0.89 (0.83 to 0.96)
Yes	1.42 (1.25 to 1.61)	1.59 (1.23 to 2.05)
Alcohol use		
No	0.62 (0.60 to 0.64)	0.91 (0.85 to 0.98)
Yes	2.62 (2.13 to 3.22)	2.34 (1.36 to 4.03)
Overweight/obesity		
No	0.60 (0.58 to 0.62)	0.89 (0.82 to 0.96)
Yes	1.03 (0.94 to 1.14)	1.11 (0.94 to 1.31)
NAFLD		
No	0.62 (0.60 to 0.64)	0.91 (0.85 to 0.98)
Yes	1.98 (1.66 to 2.32)	1.38 (0.93 to 2.04)
Hypertension		
No	0.54 (0.52 to 0.56)	0.76 (0.69 to 0.85)
Yes	1.00 (0.95 to 1.07)	1.09 (0.99 to 1.19)
Diabetes		
No	0.59 (0.56 to 0.61)	0.71 (0.65 to 0.78)
Yes	1.44 (1.30 to 1.58)	1.39 (1.25 to 1.53)
Ischaemic heart disease		
No	0.62 (0.60 to 0.65)	0.88 (0.82 to 0.95)
Yes	1.56 (1.25 to 1.93)	1.25 (1.04 to 1.50)
Congestive heart failure		
No	0.63 (0.61 to 0.65)	0.91 (0.85 to 0.97)
Yes	1.64 (1.22 to 2.22)	1.51 (1.03 to 2.20)
CKD		
No	0.63 (0.60 to 0.65)	0.88 (0.82 to 0.95)
Yes	1.91 (1.49 to 2.46)	2.60 (1.96 to 3.45)
Gallstones		
No	0.62 (0.60 to 0.65)	0.91 (0.85 to 0.98)
Yes	1.91 (1.50 to 2.45)	1.57 (0.84 to 2.91)

CKD, chronic kidney disease; NAFLD, non-alcoholic fatty liver disease.

without any presence of comorbid conditions. Contrarily, we also found that statins use was associated with lower risk of AP in stratum 20 consisting of age group 55–61, female, living in the urban are from the South region and had hypertension (HR=0.22; 95% CI: 0.05 to 0.94), stratum 22 made up of age group 55–61, female, living in the urban area and from the South region of the USA without any comorbid conditions (HR=0.38; 95% CI: 0.16 to 0.92). Lastly, no significant association between statins use and AP was found for the remaining 22 large stratums (figure 1).

DISCUSSION

In this large retrospective cohort study of 1 695 914 individuals using the MarketScan database and after controlling for comorbidities, statins use was not associated with the risk of AP. In our meta-analysis based on the 25 largest stratums with respect to statins users, we found that statins use was associated with higher risk of AP in stratum 9. Contrarily, we also found that statins use was associated with lower risk of AP in stratum 20 and stratum 22. Lastly, no significant association between statins use

Table 3 Incidence rates and stratified Cox hazard ratio (95% CI) for the association between statins use and acute pancreatitis in the MarketScan database from 2016 to 2020

Characteristics	No statins use	Statins use
Person-years	5 141 344	882 319
Acute pancreatitis cases, n	3255	811
*Incidence rate (95% CI) per 1000 person-years	0.63 (0.61 to 0.66)	0.92 (0.86 to 0.98)
Full model hazard ratio (95% CI)	(reference)	0.92 (0.84 to 1.01)

For the full model, the first step was to construct strata based on the 14 confounders (age group, gender, region, gallstones, alcohol use, tobacco use, diabetes, hypertension, overweight/obesity, non-alcoholic fatty liver disease, ischaemic heart diseases, congestive heart failure and chronic kidney disease). We only included those stratums that had at least two statin users and two statin non-users. In the second step we applied a stratified Cox proportional hazards regression analysis with 2394 stratums.
*Unadjusted incidence density rate per 1000 person-years.

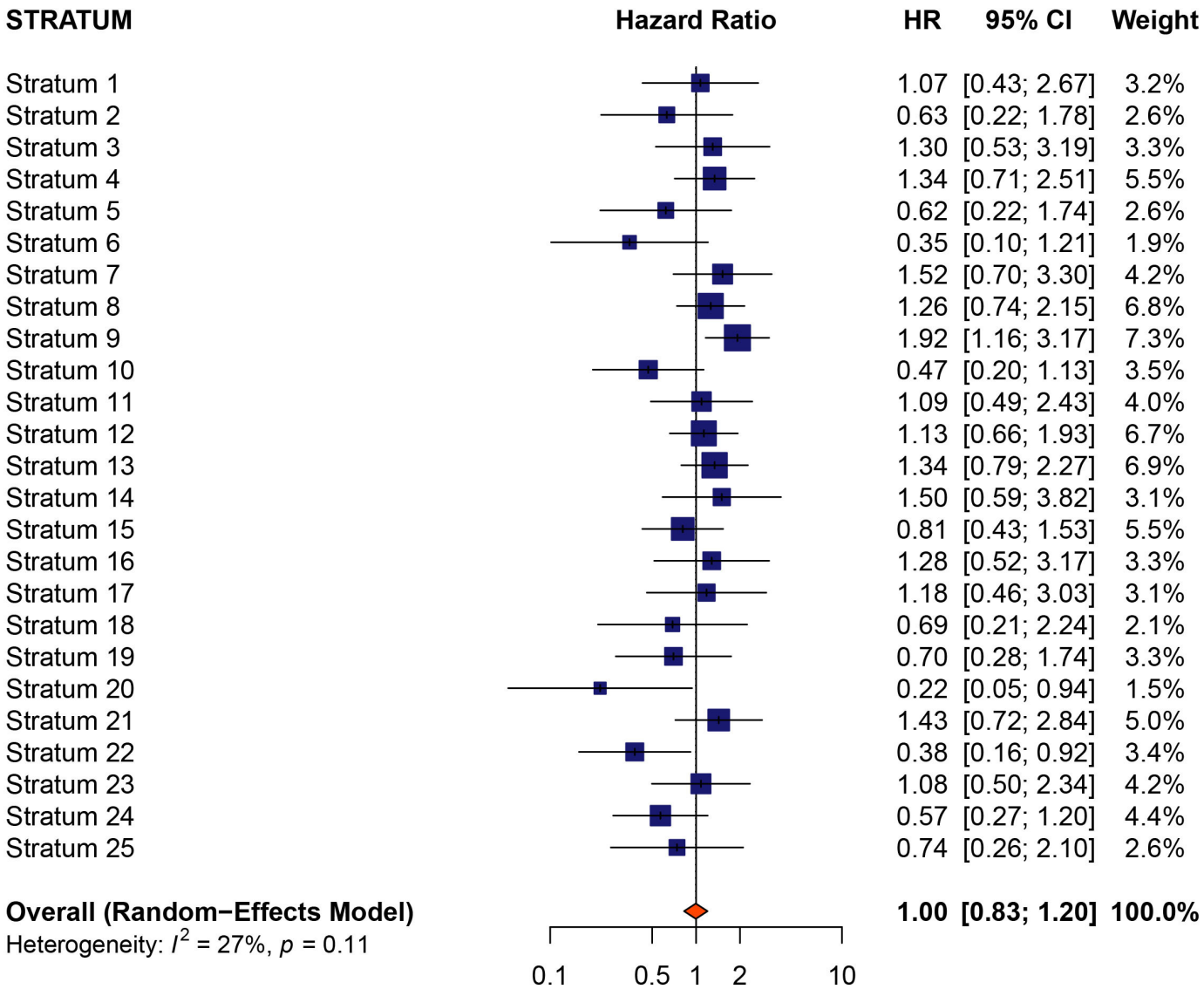

Figure 1 Forest plot of the 25 largest stratums with respect to any statin prescription analysis.

and AP was found for the remaining 22 large stratums and the overall random-effects models.

The association between statins and AP has yielded inconsistent findings. A previous case report and literature review by Etienne and Reda suggested that statins may reduce the risk of developing an acute episode of pancreatitis through anti-inflammatory perturbation of the systemic inflammatory response pathway.[14] A number of studies have evaluated the role of statins in reducing the risk of PEP. A single-centre, retrospective cohort study by Hadi and colleagues including 1162 patients undergoing ERCP found that statin use was associated with a decreased risk of PEP, with an OR of 0.35.[2] A large retrospective study found that that statin use was a protective factor against PEP, with an OR of 3.18.[15] However, a large, multicentre, retrospective cohort study from Spain found that statin use was not associated with a decreased risk of PEP or a decrease in the severity of PEP.[16]

A systematic review of observational studies and case reports from Singh and Loke suggested that statins-induced pancreatitis can occur at any time but seems to be very uncommon early on and more likely to occur after many months of therapy.[17] A retrospective cohort analysis by Twohig and colleagues using a large clinical database assessed the association between statin use and AP, finding an increased risk of drug-induced pancreatitis among statins users. However, this study did not account for comorbidities and confounders to the extent performed in our analysis.[18] Conversely, a meta-analysis of observational studies including 13 studies with nearly 35 000 patients with AP and over 5 million controls found a prevalence of statin use of 9.8% among patients with AP versus 25% among controls.[7] Another meta-analysis by Preiss and colleagues using randomised controlled trials with cardiovascular endpoints including 16 studies and nearly 114 000 participants found that statin use was associated with a lower risk of patients with normal or mildly elevated triglyceride levels.[6]

Novel findings from our study were that our meta-analysis based on the 25 largest stratums according to the

statins' users, we found that statins use was associated with increased risk of AP in stratum made up of age groups 55–61, male, place of residence (urban), and US region (South) without any comorbid conditions. Conversely, we also found that statins use was associated with lower risk of AP in stratum that included age groups, gender, place of residence, US region and at least one comorbid condition. We did not find any significant association between statins use and AP for the remaining stratums made up of demographic variables and comorbid conditions and the overall pooled effect size.

Study strengths and limitations

Strengths of our study include an analysis based on longitudinal data of a large sample of individuals with statins use and controls without statins use with 3 years of follow-up. To the best of our knowledge, it is also the first study to examine the association between statins use and AP among a large sample of commercially insured patients using national real-world data. A main strength of our study is the large sample size of patients exposed to statins (nearly 250 000) among over 1.5 million individuals in the database. We were able to control for confounders and comorbidities, thereby minimising potential bias.

However, this study has important limitations that need to be addressed. This is an observational study that used US claims data and therefore causality cannot be implied. The study analysed only commercially insured individuals who had 5 years of continuous enrolment in their private insurance plan, and therefore our results may only be generalisable to a similar study population. We acknowledge that claims-based databases can misclassify patients based on misreporting or under-reporting of diagnoses or procedure codes. In addition, the MarketScan database did not include information on race or ethnicity, thus precluding any analysis of racial disparities in AP after statins use. Lastly, the database consists of a convenience sample of participants who are younger than 65 years, commercially insured and primarily work for large employers in the USA.

Despite these limitations, we believe this study provides new real-world evidence regarding the association between statins use and AP using large real-world data.

Conclusions

Findings from this large retrospective study indicate that use of statins was not associated with a higher risk of AP in this US healthcare setting. Future studies are warranted to further explore the association between statins use and AP.

Contributors Designed research (project conception, development of overall research plan and study oversight): DB, VMC and JM. Statistical analysis: DB and VMC. Analysed data: DB, VMC and YZ. Review and editing: All authors. DB is the guarantor and takes full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish. All authors have read and approved the final manuscript.

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Competing interests None declared.

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Patient consent for publication Not applicable.

Ethics approval The protocol of this study has received a determination of non-human subjects' research by the Penn State Institutional Review Board. The individual informed consent requirement was waived for this secondary analysis of de-identified data.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data may be obtained from a third party Merative and are not publicly available.

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