

Question: What is the risk of pancreatitis with long-term statin use?

The class of cholesterol-lowering drugs commonly referred to as “statins” are formally known as 5-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors, named for their ability to inhibit an enzyme involved in the synthesis of cholesterol. Since the first statin was approved by the Food and Drug Administration (FDA) in 1987,^{1,2} statins have become among the most widely prescribed drugs in the United States (US)³ and continue to be the pharmacologic standard of care for primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD).⁴⁻⁸ As summarized in Table 1, product labeling for 1 of the 7 currently available statins lists pancreatitis as an adverse event reported in short term clinical trials in <2% of patients,⁹ while labeling for 5 of the statins lists pancreatitis as an adverse effect identified only with postmarketing experience,^{2,10-13} and labeling for the remaining statin does not report any occurrences of pancreatitis.¹⁴

Table 1: Manufacturer reported incidence of pancreatitis with currently marketed statin drugs.^{2,9-14}

Generic Drug Name (Current Trade Name)	FDA-Approval Date	Incidence of Pancreatitis
Lovastatin (Altoprev®)	1987	Postmarketing experience only
Pravastatin (Pravachol®)	1991	Postmarketing experience only
Simvastatin (Zocor®)	1991	Postmarketing experience only
Fluvastatin (Lescol XL®)	1993	Postmarketing experience only
Atorvastatin (Lipitor®)	1996	Postmarketing experience only
Rosuvastatin (Crestor®)	2003	<2% reported in clinical studies
Pitavastatin (Livalo®)	2009	Not reported

FDA=Food & Drug Administration

A search of the literature identified a systematic review,¹⁵ a meta-analysis,¹⁶ and 2 additional case-control studies^{17,18} that may help shed some light on the risk of pancreatitis with long-term statin use.

Systematic review

In 2006, Singh and Loke conducted a two-part systematic review of observational cohort studies and spontaneous case reports of pancreatitis with statin use.¹⁵ Case control and/or cohort studies identified via a search of PubMed were included if they reported relative risk (RR) or odds ratios (OR) of pancreatitis in patients treated with statins. Case reports identified from searches of MEDLINE/PubMed, EMBASE, Scopus, Cochrane Library and Google Scholar were included if they described any “suspected, possible, probable or definite” cases of pancreatitis associated with use of any statin. Additionally, unpublished case reports of pancreatitis attributed to statin use through September 2005 were retrieved from the Canadian Drug Reaction Monitoring Program (CDRMP). Two case control studies were identified, one conducted in the United Kingdom (UK)¹⁹ and one in Denmark.²⁰ The UK study used cases of acute pancreatitis, defined by International Classification of Diseases (ICD)-9 code, and matched controls identified in the UK General Practice Research Database and evaluated prescription data for statin exposure within 360 days prior to the index event. The Denmark study used computerized hospital discharge records linked to prescription registries to identify cases of acute pancreatitis with matched controls, and evaluated statin exposure in both groups at any time prior to the index event. A meta-analysis of the pooled data from these 2 studies was conducted, resulting in an OR of 1.41 [95% confidence interval (CI) 1.15, 1.74] for the risk of acute pancreatitis in patients who had received a statin within the previous year. The I² statistic was 0%, indicating low heterogeneity between the results of the 2 studies.

Singh and Loke also identified a total of 53 case reports (20 published and 33 from the CDRMP) which they included in their review.¹⁵ Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin were all involved in at least 1 case. Their findings included the following: for the 46 cases that provided statin dosing, pancreatitis occurred at both low and high statin doses (normalizing data around a daily dose of simvastatin 20 mg); for the 28 cases that reported length of statin use, pancreatitis occurred anywhere from <24 hours >1 year of exposure to a statin, with the highest frequency of cases occurring after months to years of exposure (duration of therapy reported in the 20 published case reports ranged from 8 hours to 7 years). The investigators noted the absence of a dose-time response (i.e., patients on low dose statins could experience pancreatitis early on and patients on high dose statins did not appear to experience the reaction any earlier), suggesting pancreatitis is dose-independent and unpredictable. Though severity of pancreatitis was not reported in all cases, the majority of cases were presumed to be mild and resolved when the statin was stopped. Five of the 53 cases (9%) were fatal. Taking into account the limitations of case control studies and the inability to determine incidence or estimate risk based on case reports, the authors concluded that statin-induced pancreatitis appears to be a genuine adverse reaction that can occur with all statin drugs and is more likely to develop after long-term exposure. They noted that well-conducted prospective cohort studies are needed to better define the association.

Meta-analysis

In 2012, Priess et al published a meta-analysis of large randomized trials to investigate the association between lipid-modifying therapy with statins or fibrates and incident pancreatitis.¹⁶ Literature searches of PubMed, EMBASE and Web of Science were conducted to identify relevant published studies, from which available pancreatitis data were extracted; unpublished data were also obtained from investigators. Randomized controlled trials evaluating the effect of fibrates or statins on cardiovascular endpoints were included, and only studies with at least 1000 participants followed up for a mean of at least 1 year were included. A total of 28 trials were included in the meta-analysis, 21 statin trials (2 with published and 19 with unpublished data on incident pancreatitis) and 7 fibrate trials (4 with published and 3 with unpublished data on incident pancreatitis). The 21 statin trials included 16 trials that compared a statin to either placebo or active control and 5 trials that compared intensive vs. moderate doses of statins in a total of 153,414 participants. Average baseline triglyceride levels ranged from 118 mg/dL to 187 mg/dL. Mean duration of follow-up was 4.3 years (standard deviation [SD], 1.6 years). Trials were rated as high quality with 100% agreement among reviewers. Of the 16 trials comparing statin to placebo or active control, a total of 113,800 participants were followed up for a median of 4.1 years (SD, 1.5); 309 developed pancreatitis (0.27%), 134 with a statin compared to 175 with a control [RR, 0.77 (95% CI, 0.62-0.97; P=0.03)]; $\chi^2 = 9.11$ and $I^2 = 0\%$, indicating low heterogeneity for trials comparing incident pancreatitis; number needed to treat (NNT)=1175 (95% CI, 693-9195) over 5 years. In the 5 trials comparing moderate to intensive statin doses, a total of 156 (0.39%) of 39,614 participants developed pancreatitis, 70 with intensive dose vs. 86 with moderate dose [RR, 0.82 (95% CI, 0.59-1.12; P=0.21)]; $\chi^2 = 1.29$ and $I^2 = 0\%$. Analysis of the 21 statin trials combined yielded 465 (0.30%) cases of pancreatitis, 204 with statin/intensive dose statin vs. 261 with placebo/active control/moderate dose statin [RR, 0.79 (95% CI, 0.65-0.95; P=.01)]; $\chi^2=10.48$; $I^2=0\%$; NNT=1187 (95% CI, 731-4768) over 5 years. Investigators reported no evidence of publication bias. The authors concluded that these results suggest that statin therapy is associated with a *reduced* risk of pancreatitis in patients with normal or mildly elevated triglycerides. A key limitation of this meta-analysis is the fact that pancreatitis was not a pre-specified endpoint in the clinical trials but authors noted that the limited statistical heterogeneity between study results adds confidence to the findings. They also noted that analyzing randomized trial data avoids the potential bias of unmeasured confounders present in observational studies; this may explain the contrast in the findings from the systematic review described above.

More recent case-control studies

Citing the continued rise in statin use and the conflicting results of previously published observational studies compared to the meta-analysis of randomized controlled trial data (both described above), Kuoppala et al conducted a more recent population-based case-control study examining the risk of acute pancreatitis with statin use.¹⁷ Using a nationwide population-based register, investigators in Finland conducted a retrospective case-control study of all subjects diagnosed with their first non-alcohol induced acute pancreatitis between January 1, 2008 and December 31, 2010. Adult patients with a hospitalization for incident pancreatitis, defined by ICD-10 code, were included; patients with biliary or alcohol-induced pancreatitis were excluded as were patients with any prior hospitalization for acute pancreatitis. Each case was matched to 5 controls. Exposure to statins was defined by the date of first prescription purchase to the last day of use, assuming an administration schedule of 1 tablet per day. Adherence was calculated based on dividing adherent time by total exposure time. Statin use was considered current if the index date of the pancreatitis occurred within 180 days of last use, otherwise the participant was classified as a former user. Data on other medications and hospitalizations with a look back to January 1, 2003, were used to evaluate comorbidities that may have contributed to the pancreatitis (e.g., gallstone disease, alcohol abuse, hypertriglyceridemia, diabetes, fibrate use, angiotensin converting enzyme (ACE) inhibitor use). Association of statin use with pancreatitis was modelled using conditional logistic regression.

A total of 4376 cases and 19,859 controls were included in the final analysis.¹⁷ Median (range) exposure to a statin was similar between the groups, 2.12 (0.00-6.71) years for cases and 2.18 (0.01-6.77) years for controls. Median length of adherent time on statins was also similar, 1.4 years for cases and 1.5 years for controls, with 66% and 69%, respectively, exhibiting $\geq 80\%$ adherence. Statin use was associated with an increased incidence of acute pancreatitis (OR, 1.53 [95% CI, 1.39-1.67], adjusted for sex and age and OR, 1.25 [95% CI, 1.13-1.39], adjusted for potential confounders). Length of time on a statin was associated with an increased incidence of pancreatitis for current use of 4-12 months (OR, 1.32 [95% CI, 1.07-1.63] and former use ≤ 1 year (OR, 1.64 [95% CI, 1.33-2.03]) but did not reach significance for current use ≤ 3 months (OR, 1.37 [95% CI, 0.94-2.00]) or >1 year (OR, 1.11 [95% CI, 0.97-1.27]). Of the statins used (atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin), exposure to simvastatin was most common (536 cases), followed by exposure to 2 or more types of statins (197 cases), the next most common being atorvastatin (49 cases). Cumulative dosing of <1 year and ≥ 2 years was associated with increased pancreatitis (OR, 1.35 [95% CI 1.19–1.54] and OR, 1.26 [95% CI 1.06–1.51], respectively). The pancreatitis rate also increased with increased average daily dose equivalent to 20 mg or more of simvastatin. Taking into account limitations inherent to observational studies and using claims data, the authors concluded that statin use was associated with an increased risk of pancreatitis and was more apparent during the first year of use and at higher doses. They noted that their findings were more consistent with previously published case control studies reflecting real life scenarios than the randomized controlled trials.

In the most recently published observational study identified in this literature search, Lai et al investigated the association of pancreatitis with atorvastatin, using a national longitudinal health insurance database encompassing 99% of the population in Taiwan.¹⁸ Subjects aged 20 – 84 years with first time diagnoses of acute pancreatitis (defined by ICD-9 code) between 1998 and 2011 were identified as cases and matched by sex, age, and comorbidities to randomly selected controls without pancreatitis. Cases with codes for chronic pancreatitis, pancreatic cancer and/or with use of a statin other than atorvastatin or another lipid-lowering drug prior to the index date were excluded. A total of 5810 cases and 5733 controls were included in the analysis. Cases were similar to controls except for a higher proportion of current use (1.45% vs. 0.87%, $P=0.01$) and late use (1.89% vs. 1.66%, $P=0.01$) of atorvastatin compared to controls. Current vs. late use was defined as subjects possessing atorvastatin tablets ≤ 7 days or >7 days of the index date of pancreatitis, respectively. The univariable unconditional logistic regression model demonstrated that acute pancreatitis was associated with current use of atorvastatin compared to never use of atorvastatin (OR, 1.67 [95% CI, 1.18-2.38]), but the

association with late use of atorvastatin was not statistically significant. No other variable was significantly related to acute pancreatitis so the planned multivariable logistic regression analysis was not conducted. Authors noted in their discussion that a dose-response relationship was not found (data not included in the paper). They concluded that current use of atorvastatin is associated with a diagnosis of acute pancreatitis independent of other comorbidities, however these findings are limited by the lack of information regarding length of atorvastatin exposure.

Conclusion

There is conflicting evidence in the literature regarding the association of acute pancreatitis with statin use. Observational data, including a systematic review of published case reports, a meta-analysis of pooled results from 2 case control studies, and results of 2 more recent case control studies, have identified a significant association.^{15, 17-20} However, a meta-analysis of pancreatitis data extracted from large randomized control trials studying statins for cardiovascular outcomes failed to confirm this association, and even proposed a protective effect of statins against pancreatitis.¹⁶ A weakness of the meta-analysis, however, is the fact that acute pancreatitis was not a pre-specified endpoint of any of the randomized trials. The findings of the observational studies identified are even more limited and variable with regard to the association of acute pancreatitis and length of therapy on a statin. While the overall incidence of pancreatitis associated with statin use appears to be low, further prospective studies are needed to define the risk associated with long term statin use.

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