Statin Use and Risk of Gallstone Disease Followed by Cholecystectomy

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Context  Gallstone disease is a leading cause of morbidity in western countries and carries a high economic burden. Statins decrease hepatic cholesterol biosynthesis and may therefore lower the risk of cholesterol gallstones by reducing the cholesterol concentration in the bile. Data on this association in humans are scarce.

Objective  To study the association between the use of statins, fibrates, or other lipid-lowering agents and the risk of incident gallstone disease followed by cholecystectomy.

Design, Setting, and Participants  Case-control analysis using the UK-based General Practice Research Database. Incident patients between 1994 and 2008 and controls per each patient were identified and matched on age, sex, general practice, calendar time, and years of history in the database. The study population was 76% women and the mean (SD) age was 53.4 (15.0) years at the index date. Conditional logistic regression was used to estimate the odds ratio (OR) of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents, stratified by exposure timing and duration. The ORs and 95% confidence intervals (CIs) were adjusted for smoking, body mass index, ischemic heart disease, stroke, and estrogen use.

Main Outcome Measure  The adjusted OR (AOR) for developing gallstone disease followed by cholecystectomy in relation to exposure to lipid-lowering agents.

Results  A total of 27,035 patients with cholecystectomy and 106,531 matched controls were identified, including 2,396 patients and 8,868 controls who had statin use. Compared with nonuse, current statin use (last prescription recorded within 90 days before the first-time diagnosis of the disease) was 1.0% for patients and 0.8% for controls (AOR, 1.10; 95% CI, 0.95-1.27) for 1 to 4 prescriptions; 2.6% vs 2.4% (AOR, 0.85; 95% CI, 0.77-0.93) for 5 to 19 prescriptions, and 3.2% vs 3.7% (AOR, 0.64; 95% CI, 0.59-0.70) for 20 or more prescriptions. The AORs for current use of statins defined as 20 or more prescriptions were similar (around 0.6) across age, sex, and body mass index categories, and across the statin class.

Conclusion  Long-term use of statins was associated with a decreased risk of gallstones followed by cholecystectomy.

ORIGINAL CONTRIBUTION

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Two small studies reported conflicting results; one found no association between statin use and gallstone risk, and the other reported a risk reduction with limited statistical power. Fibrates affect lipid metabolism mainly by acting as synthetic ligands of the peroxisome proliferator–activated receptor α. Activation of peroxisome proliferator–activated receptor α affects numerous metabolic pathways including glucose and lipid metabolism, reducing level of plasma triglycerides and glucose concentration, and increasing high-density lipoprotein cholesterol levels. Studies in humans demonstrated that short-term fibrate treatment is associated with decreased bile acid synthesis and biliary excretion. In a randomized controlled trial, a higher incidence of cholecystectomy was noted in patients taking fibrates, and another study reported a higher prevalence of gallstones in patients taking fibrates.

Therefore, currently available clinical studies on the possible effect of statins on gallstone formation and the risk of cholecystectomy are limited by either small sample size, lack of long-term follow-up, sex restriction, or methodological drawbacks. We conducted a large long-term observational study to explore the association between statin use and the risk of developing an incident diagnosis of gallstone disease followed by cholecystectomy.

METHODS

A case-control analysis was conducted using the UK-based General Practice Research Database (GPRD). The UK-based GPRD was established around 1987 and encompasses data on approximately 5 million patients who are registered with selected general practitioners. The general practitioners provide anonymized medical information for research purposes, which are recorded in a standard manner. Patients enrolled in the GPRD are representative of the United Kingdom with regard to age, sex, geographic distribution, and annual turnover rate. The information recorded includes patient demographics and characteristics (eg, age, sex, height, weight, smoking status), symptoms, medical diagnoses, referrals to consultants, and hospitalizations. Because physicians generate drug prescriptions directly with the computer using a coded drug dictionary, all recorded prescriptions include the name of the preparation, route of administration, dose of a single unit, number of units prescribed, and intake regimen (in most instances). The database has been described in detail elsewhere, and has been validated extensively, and has been the source for numerous epidemiological studies published in peer-reviewed journals.

The study protocol was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database for Research. Informed consent by patients was not needed for this database study.

Case Definition and Ascertainment

Patients aged 20 years or older with a first-time diagnosis of gallstone disease or cholecystectomy between 1994 and 2008 were identified based on the Oxford Medical Information System and Read codes. All patients were required to have both a recorded diagnosis for gallstone disease or a complication thereof (such as bile duct obstruction, choledocholithiasis, or cholesterol gallstone) and a record of cholecystectomy within 2 years of the diagnosis or a cholecystectomy only. The date of the first-time diagnosis of gallstone disease or the date of cholecystectomy in patients without a recording of a gallstone diagnosis is referred to as the index date. Patients with less than 3 years of active history in the database prior to the index date, as well as those with a history of alcohol or drug abuse, cancer (except non–melanoma skin cancer), or human immunodeficiency virus prior to the index date were excluded.

A total of 300 potential patient profiles (selected at random) were reviewed to verify the validity of the patient selection criteria.

Controls

From the base population, 4 control patients were identified at random for each patient with cholecystectomy, matched on calendar time (same index date), age (same year of birth), sex, general practice, and number of years of active history in the GPRD prior to the index date. Controls had no recording of gallstones, clinical complications suggestive of gallstones, or cholecystectomy. The same exclusion criteria were applied to patients and controls.

Exposure to Statins and Other Lipid-Lowering Agents

From the computer record, exposure was assessed to statins, fibrates, or other lipid-lowering agents (anion-exchanger resin, probucol, acipimox, niacin, fish oil, or omega fatty acids) prior to the index date for patients and controls. Patients were classified as currently taking medications if the last prescription was recorded less than 90 days, or as formerly taking medications if the last prescription was recorded 90 or more days prior to the index date. Medication use was classified by duration of use prior to the index date based on the number of prescriptions (statins: short-term, 1-4; medium-term, 5-19; or long-term, ≥20; fibrates and other lipid-lowering drugs: short- to medium-term, 1-9; long-term, ≥10). Statin use was also classified according to the tablet dose. Finally, duration and timing of use were combined into 1 exposure variable.

Statistical Analysis

Conditional logistic regression analyses were conducted using SAS statistical software version 9.1 (SAS Institute Inc, Cary, North Carolina) to calculate relative risk estimates as odds ratios (ORs) with 95% confidence intervals (CIs) at a 2-sided P value of .05. With an assumed prevalence of exposure to statins of about 1%, the required sample size was about 19 000 patients (and 4 times as many controls) to detect an OR of 0.75 at the significance level of .05 with a power of greater than 90%.
The potential confounders age, sex, general practice, calendar time, and years of recorded history in the database were controlled for by matching and the ORs were further adjusted for smoking status (none, current, former, or unknown) and body mass index (BMI, which was calculated as weight in kilograms divided by height in meters squared) (BMI categories: <18.5, 18.5-24.9, 25.0-29.9, 30-34.9, ≥35, or unknown) in the multivariate model. The risk estimates were adjusted for a history of ischemic heart disease, ischemic stroke, transient ischemic attack, and use of opposed or unopposed estrogens (current or past use [defined as last prescription ≤180 days before the index date or thereafter] of 1-9 or ≥10 prescriptions). Further testing included whether other diseases (eg, liver cirrhosis, renal diseases, gastrointestinal tract ulcer, constipation, urinary dysfunction, hypertension, hypothyroidism, inflammatory bowel disease, or diabetes mellitus) or other drugs (eg, thiazides, contraceptives) confounded the main association of interest. Because this was not the case, these parameters were not included in the final model.

Various sensitivity analyses were conducted. In the first model, only patients with abdominal pain recorded within 90 days before the index date were included to reduce the likelihood of detection bias (ie, including patients who had gallstones detected by chance). In the second model, patients with cholecystectomy in the absence of a recorded gallstone diagnosis were excluded. In the third model, the index dates were shifted for all patients and their controls by 30, 90, and 180 days backward in time because gallstones may have been present prior to the actual first-time recording of the diagnosis; this was done to rule out potential protopathic bias (ie, the possibility that general practitioners may have stopped statin treatment in patients due to abdominal pain). In the fourth model, an analysis was restricted to patients and controls whose index date was before 2004 because 10 mg of simvastatin became available over-the-counter in August 2004.29 In the fifth model, current long-term statin use was compared with current short-term statin use to explore the association of interest in a population diagnosed as having hypercholesterolemia; this analysis likely excluded patients with normal cholesterol levels who may have a different gallstone risk than patients with hypercholesterolemia. The final sensitivity analysis was conducted taking another proxy for duration of statin use—the total number of statin tablets prescribed prior to the index date, which equals the total number of exposure days. This analysis was performed to estimate more precisely how much exposure time it takes to lower the risk of developing gallstones followed by cholecystectomy, and because many, but not all statin prescriptions, are issued for 28 days.

RESULTS
A total of 27 035 patients (n=9602 cholecystectomy only; n=17 433 cholecystectomy after a gallstone diagnosis or associated complications) and 106 531 matched controls were identified (TABLE 1). The study population was 76% women and the mean (SD) age was 53.4 (15.0) years at the index date. The OR of developing an incident gallstone diagnosis with cholecystectomy substantially increased with increasing BMI.

In the study population, 11 264 (2396 patients and 8868 controls) were...
taking statins, 1514 were taking fibrates, and 1038 were taking other lipid-lowering agents. The majority of patients (87%) treated with lipid-lowering agents were taking statins only (ie, not in combination [concurrently or subsequently] with other lipid-lowering agents). Compared with the reference group of patients who did not take statins, the adjusted OR (AOR) of developing gallstones with cholecystectomy was 0.78 (95% CI, 0.73-0.83) for current statin use and 1.19 (95% CI, 1.07-1.32) for past statin use (adjusted in the multivariate analysis for age, sex, general practice, and calendar time by matching). Further adjusted for body mass index (calculated as weight in kilograms divided by height in meters squared), smoking, history of ischemic heart disease, stroke, or transient ischemic attack, and use of estrogens, fibrates, and other lipid-lowering agents). Compared with nonuse of statins, the AOR for 1 to 4 current prescriptions was 1.10 (95% CI, 0.95-1.27), 0.85 (95% CI, 0.77-0.93) for 5 to 19 current prescriptions, and 0.64 (95% CI, 0.59-0.70) for 20 or more current prescriptions regardless of timing of use (Table 2). The findings were similar for men and women and for those younger than 60 years or for those aged 60 years or older. The analysis also was stratified by individual statin, with similar findings for all statins, with little statistical power for some of the newer compounds (Table 3). The AORs for current statin use of 20 or more prescriptions, stratified by dose, also were assessed and the results are displayed in Table 3. Current long-term use of fibrates was associated with a slightly increased AOR of 1.39 (95% CI, 1.12-1.72) for developing gallstones followed by cholecystectomy.

Because a comparison between patients with statin use and nonuse not only compares exposure to statins, but also patients with hypercholesterolemia to patients without hypercholesterolemia, the analysis was restricted to patients with statin use (ie, patients with hypercholesterolemia). Among these patients, long-term statin use was compared with short-term statin use, yielding an AOR of 0.58 (95% CI, 0.50-0.68). When this analysis was further stratified by BMI categories, the AOR associated with long-term statin use compared with short-term use was 0.58 (95% CI, 0.41-0.81) for normal weight (BMI, 20-24.9), 0.63 (95% CI, 0.48-0.83) for overweight (BMI, 25-29.9), and 0.65 (95% CI, 0.50-0.86) for obese patients (BMI ≥30).

Various sensitivity analyses (as described in the “Methods” section) related to statin use remained virtually unchanged in the subgroup of patients and their controls with abdominal pain before gallstone diagnosis with cholecystectomy, in patients with or without recorded gallstone disease prior to the cholecystectomy, for the analyses in which the index dates were shifted by 30, 90, and 180 days, as well as for patients and their controls with an index date before 2004. The analysis with the total number of tablets as a proxy for days of exposure suggested that the risk of gallstone disease followed by cholecystectomy starts decreasing after about 1 to 1.5 years of treatment with statins. Additional data are available in the eFigure and eTables 1 through 7 at http://www.jama.com.

**COMMENT**

This large observational study provides evidence that patients with long-term statin use have a reduced risk of gallstone disease followed by cholecystectomy compared with patients without statin use. However, the OR was not decreased for patients with short-term statin use but started to decrease after 5 prescriptions, reflecting approxi-
STATIN USE, GALLSTONE DISEASE RISK, AND CHOLECYSTECTOMY

Table 3. Long-term Use of Statins and Risk of First-Time Gallstone Disease Followed by Cholecystectomy

<table>
<thead>
<tr>
<th>Statin</th>
<th>Patients (n = 27,035)</th>
<th>Controls (n = 106,531)</th>
<th>Crudea</th>
<th>Adjustedb</th>
</tr>
</thead>
<tbody>
<tr>
<td>No statin use</td>
<td>24,639 (91.1)</td>
<td>97,663 (91.7)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>≥20 Current prescriptions</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>327 (1.2)</td>
<td>1,404 (1.3)</td>
<td>0.92 (0.81-1.04)</td>
<td>0.66 (0.58-0.76)</td>
</tr>
<tr>
<td>10 or 20 mg</td>
<td>232 (0.9)</td>
<td>990 (0.9)</td>
<td>0.69 (0.59-0.81)</td>
<td></td>
</tr>
<tr>
<td>40 or 80 mg</td>
<td>95 (0.4)</td>
<td>414 (0.4)</td>
<td>0.60 (0.47-0.76)</td>
<td></td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>14 (0.1)</td>
<td>94 (0.1)</td>
<td>0.59 (0.33-1.03)</td>
<td>0.41 (0.23-0.73)</td>
</tr>
<tr>
<td>20 mg</td>
<td>5 (0.02)</td>
<td>42 (0.04)</td>
<td>0.37 (0.14-0.95)</td>
<td></td>
</tr>
<tr>
<td>40 or 80 mg</td>
<td>9 (0.03)</td>
<td>51 (0.05)</td>
<td>0.43 (0.21-0.90)</td>
<td></td>
</tr>
<tr>
<td>Pravastatin</td>
<td>62 (0.2)</td>
<td>343 (0.3)</td>
<td>0.71 (0.54-0.94)</td>
<td>0.52 (0.39-0.68)</td>
</tr>
<tr>
<td>10 or 20 mg</td>
<td>34 (0.1)</td>
<td>176 (0.2)</td>
<td>0.58 (0.40-0.85)</td>
<td></td>
</tr>
<tr>
<td>40 mg</td>
<td>28 (0.1)</td>
<td>167 (0.2)</td>
<td>0.45 (0.30-0.68)</td>
<td></td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>32 (0.1)</td>
<td>134 (0.1)</td>
<td>0.93 (0.63-1.38)</td>
<td>0.68 (0.46-1.03)</td>
</tr>
<tr>
<td>5 or 10 mg</td>
<td>25 (0.1)</td>
<td>97 (0.1)</td>
<td>0.73 (0.46-1.16)</td>
<td></td>
</tr>
<tr>
<td>20 or 40 mg</td>
<td>7 (0.03)</td>
<td>37 (0.03)</td>
<td>0.54 (0.23-1.25)</td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>422 (1.6)</td>
<td>1,959 (1.8)</td>
<td>0.85 (0.76-0.95)</td>
<td>0.65 (0.58-0.73)</td>
</tr>
<tr>
<td>10 or 20 mg</td>
<td>277 (1.0)</td>
<td>1,209 (1.1)</td>
<td>0.71 (0.62-0.82)</td>
<td></td>
</tr>
<tr>
<td>40 or 80 mg</td>
<td>145 (0.5)</td>
<td>750 (0.7)</td>
<td>0.55 (0.45-0.66)</td>
<td></td>
</tr>
<tr>
<td>All statins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low dose</td>
<td>573 (2.1)</td>
<td>2,515 (2.4)</td>
<td>0.69 (0.62-0.77)</td>
<td></td>
</tr>
<tr>
<td>High dose</td>
<td>284 (1.1)</td>
<td>1,419 (1.3)</td>
<td>0.55 (0.48-0.63)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; OR, odds ratio.
aAdjusted for age, sex, general practice, and calendar time by matching.
bFurther adjusted for body mass index (calculated as weight in kilograms divided by height in meters squared), smoking, history of ischemic heart disease, stroke, or transient ischemic attack, use of opposed or unopposed estrogens, fibrates, and other lipid-lowering agents (anion-exchanger resin, probucol, acipimox, niacin, fish oil, or omega fatty acids).

The observed risk reduction of gallstone disease in patients with long-term statin use suggests a class effect for all statins, provided that the observed association is indeed causal. The stratification of current-long-term use of individual statins by dose further suggested a tendency toward a lower OR for high-dose compared with low-dose exposure.

A substantially increased gallstone risk with cholecystectomy was found for patients with high BMIs and for patients with estrogen use, as well as a slightly increased risk for patients with current fibrate use, which is in accordance with the literature.21,22 These findings may be somewhat confounded by indication because most patients take fibrates to treat high levels of triglycerides and/or low levels of high-density lipoprotein cholesterol, which are both associated with gallstone formation.1,34,35

Our study has several strengths. First, it is based on a large validated database with documented high data quality and completeness. Second, it encompassed more than 27,000 patients with gallstone disease followed by cholecystectomy, yielding substantial statistical power even in stratified subgroup analyses. There also was long-term follow-up for all patients, which enabled the assessment of long-term statin use, and there were sufficient data for stratification by individual statins. Third, detailed information on important comorbidities, concomitant drug therapies, and BMI was available. Finally, sensitivity analyses allowed the addressing of a potential diagnostic or protopathic bias as an alternative explanation for the observed association between statin use and the risk of gallstone disease with cholecystectomy.

On the other hand, limitations included the possibility of some outcome misclassification because original medical records were not used to validate the gallstone diagnoses and/or cholecystectomy. However, in a previous GPRD-based study, González-Pérez and García-Rodríguez24 used a similar case definition and documented a high validity of gallstone diagnoses in the GPRD. They contacted general practitioners of a random sample of 263 patients and found a 90% confirmation rate for patients who underwent cholecystectomy and an 82% confirmation rate for patients who did not have cholecystectomy. Concerning misclassification, patients in this study also were required to have had a cholecystectomy, a well-defined clinical end point mostly due to gallstone
because of lack of understanding or information. Therefore, poor socioeconomic status could introduce a bias toward a decreased risk of gallstone disease among patients with statin use. However, such bias should lead to a reduced gallstone risk for all statin exposure groups, and not only for those with long-term statin use. In addition, cases and controls were matched on general practice that may, to some degree, control for socioeconomic status because patients from the same neighborhood tend to consult the same general practitioner. Although a large number of confounding factors were considered and other influences were attempted to be kept to a minimum, a statement about the causality between statins and gallstone disease with cholecystectomy cannot be made due to the observational nature of the data.

In summary, this large observational study provides evidence that long-term use of statins is associated with a decreased risk of developing a diagnosis of gallstone disease requiring cholecystectomy. Our findings may be of clinical relevance given that gallstone disease represents a major burden for health care systems.

Author Contributions: Dr Meier had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Drs Bodmer and Brauchli contributed equally to this article.

Study concept and design: Bodmer, Brauchli, Meier.

Acquisition of data: Bodmer, Brauchli, Jick, Meier.

Analysis and interpretation of data: Bodmer, Brauchli, Krähnénbühl, Meier.

Drafting of the manuscript: Bodmer, Brauchli.

Critical revision of the manuscript for important intellectual content: Krähnénbühl, Jick, Meier.

Statistical analysis: Brauchli.

Administrative, technical, or material support: Krähnénbühl, Jick, Meier.

Study supervision: Krähnénbühl, Meier.

Financial Disclosures: The Division of Clinical Pharmacology and Toxicology, University Hospital Basel (Drs Bodmer and Krähnénbühl), Basel Pharmacoepidemiology Unit, University of Basel (Drs Brauchli and Meier), and the Boston Collaborative Drug Surveillance Program (Drs Jick and Meier) reported having a research collaboration with various companies in the pharmaceutical industry. Regarding drug companies producing and selling statins, the Basel Pharmacoepidemiology Unit as well as the Boston Collaborative Drug Surveillance Program had or currently have a research collaboration with AstraZeneca and Novartis. The Division of Clinical Pharmacology and Toxicology at the University Hospital Basel currently receives an unconditional grant from AstraZeneca. All of these funded research collaborations are unrelated to this article. We have conducted numerous studies using the UK-based General Practice Research Database in the past, and we are presently working on several projects. Some, but not all of the studies are industry-sponsored. This particular study was not funded. Our group has been conducting research for the pharmaceutical industry for many years, and these collaborations involve numerous companies including Pfizer, Novartis, Bristol-Myers Squibb, AstraZeneca, and Merck Sharp & Dohme. Drs Brauchli, Jick, and Meier reported conducting research related to prasiodias in the past for MerckSerono, Switzerland.

Additional Information: The efigure and eTables 1 through 7 are available at http://www.jama.com.

REFERENCES
The new individual must work out the whole problem of science, letters and theology for himself; can owe his fathers nothing.

—Ralph Waldo Emerson (1803-1882)