HMG-CoA Reductase Inhibitors and the Risk of Fractures

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Context Recent animal studies have suggested that 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins) increase bone formation, volume, and density. It is unknown whether use of statins is associated with a decreased risk of fractures in humans.

Objective To determine whether exposure to statins, fibrates, or other lipid-lowering drugs is associated with reduced bone fracture risk.

Design Population-based, nested case-control analysis.

Setting The UK-based General Practice Research Database (GPRD), comprising some 300 practices, with data collection from the late 1980s until September 1998.

Subjects Within a base population of 91611 individuals aged at least 50 years (28340 individuals taking lipid-lowering drugs, 13271 untreated individuals with a diagnosis of hyperlipidemia, and 50000 randomly selected individuals without diagnosis of hyperlipidemia), we identified 3940 case patients who had a bone fracture and 23379 control patients matched for age (±5 years), sex, general practice attended, calendar year, and years since enrollment in the GPRD.

Main Outcome Measures Use of statins, fibrates, or other lipid-lowering drugs in case patients vs control patients.

Results After controlling for body mass index, smoking, number of physician visits, and corticosteroid and estrogen use, current use of statins was associated with a significantly reduced fracture risk (adjusted odds ratio [OR], 0.55; 95% confidence interval [CI], 0.44-0.69) compared with nonuse of lipid-lowering drugs. Current use of fibrates or other lipid-lowering drugs was not related to a significantly decreased bone fracture risk (adjusted OR, 0.87; 95% CI, 0.70-1.08 and adjusted OR, 0.76; 95% CI, 0.41-1.39, respectively).

Conclusions This study suggests that current exposure to statins is associated with a decreased risk of bone fractures in individuals age 50 years and older. This finding has a potentially important public health impact and should be confirmed further in controlled prospective trials.

JAMA. 2000;283:3205-3210

We conducted a large nested case-control analysis using the UK-based General Practice Research Database (GPRD) to determine whether use of statins, fibrates, or other lipid-lowering drugs is associated with a reduced risk of bone fractures.
STATINS AND RISK OF FRACTURES

METHODS

Study Population and Data Source

Data were derived from the GPRD, which has been described in detail elsewhere.12–14 Since 1987, more than 3 million residents in the United Kingdom have been enrolled with selected general practitioners who have agreed to provide data for research purposes to the GPRD. The age and sex distribution of the patients enrolled is representative of the entire UK population. The general practitioners received 12 months of instruction on standardized recording via computer of anonymous information, which they agreed to supply continuously to academic researchers. The information recorded includes patient demographics and characteristics (eg, height, weight, and smoking status); symptoms; medical diagnoses; referrals to consultants; hospital admissions; and drug prescriptions, including the specific preparation, route of administration, dose, and number of tablets for each prescription. On request, hospital discharge and referral letters are available for review to validate the diagnoses recorded in the computer record. The GPRD currently encompasses some 30 million person-years of follow-up; it has been the source for numerous epidemiological studies in recent years, and the accuracy and completeness of these data have been well documented and validated.13,15,16 We analyzed data from the GPRD starting in the late 1980s through September 1998.

Cohort Definition and Follow-up

Within the GPRD, a base population consisting of 3 separate groups was identified: group 1 included all patients who received at least 1 prescription for a statin (ie, atorvastatin, cerivastatin, fluavastatin, pravastatin, or simvastatin), a fibrate (ie, bezafibrate, ciprofibrate, clofibrate, fenofibrate, or gemfibrozil), or a lipid-lowering drug other than statins or fibrates (ie, coleste- pol hydrochloride, cholestyramine, acipimox, or nicotinic acid) at age 50 through 89 years (at the time of the first prescription). Group 2 comprised patients with a computer-recorded diagnosis of hyperlipidemia (International Classification of Diseases, Eighth Revision [ICD-8], code 272.x) who did not receive any lipid-lowering drug treatment. Group 3 was a random sample of 50,000 patients who had neither a computer-recorded diagnosis of hyperlipoproteinemia nor a prescription for a lipid-lowering drug at any time. Within a base population consisting of these 3 groups, we followed each patient from the start of follow-up until the person developed a fracture, left the practice, or died. We defined start of follow-up as the date of the first prescription for any lipid-lowering study drug as defined above (group 1) or as the date exactly 1 year after computer recording of prescriptions began (groups 2 and 3). All patients were aged 50 through 89 years.

We excluded individuals with a computer-recorded diagnosis of osteoporosis, osteomala- cia, cancer (excluding nonmelanoma skin cancer), or alcoholism and patients who used bisphosphonates (considered an indicator for osteoporosis or bone metastases) prior to start of follow-up.

Case Definition and Nested Case-Control Analysis

Within the base population (ie, the 3 groups combined) we identified by ICD-8 codes all patients who developed a first-time diagnosis of a fracture of the femur; humerus; hand, wrist, or lower arm; vertebrae; clavicle; foot or malleolus; or an unspecified fracture after start of follow-up. The date of the fracture will subsequently be referred to as the index date. We reviewed a random sample of 200 case records by hand to verify the computer-recorded diagnosis and quantify the proportion of patients with fractures due to severe trauma (eg, vehicular collision). Within this sample, there was only 1 case patient with evidence for fracture due to severe trauma, a proportion that we considered negligible, so we included all cases of fracture identified on computer.

From the base population, we randomly selected up to 6 control patients per case patient matched for age (±5 years), sex, general practice attended, calendar time (by using the same index date as for cases; ie, the date of the first diagnosis of a bone fracture), and years of prior history in the GPRD (matching on the year of start of follow-up ±1 year). Furthermore, controls had to be alive and still enrolled at the index date. The same exclusion criteria were applied to control patients as to case patients.

Statistical Analysis

We conducted a matched analysis (conditional logistic regression) to explore the association between the risk of having a bone fracture and type of exposure (statins, fibrates, other lipid-lowering drugs, mixed use [switched between drug classes or used 2 or more drug classes concomitantly, regardless of timing of exposure] or none), exposure timing (current use, defined as having had the last prescription for a lipid-lowering drug <30 days preceding the index date; recent use, within 30–89 days; and past use, ≥90 days prior to the index date), and exposure duration (by number of prescriptions, in categories of 1–4, 5–9, 10–19, and ≥20 prescriptions). A prescription for a lipid-lowering drug usually lasts for 30 days.

In addition to matching for age, sex, general practice, calendar time, and years of history recorded in the GPRD prior to the index date, we controlled the analysis for the potential confounders smoking status (none, current, past, or unknown), body mass index (<25, 25–29.9, ≥30 kg/m², and unknown), exposure to oral or inhaled corticosteroids, hormone replacement therapy with estrogens, and number of general practice visits prior to the index date.

The analysis was performed using SAS, version 6.12 (SAS Institute Inc, Cary, NC). Odds ratios (ORs) are presented with 95% confidence intervals (CIs); P values are 2-tailed.

RESULTS

The base population comprised 91,611 individuals, consisting of 28,340 users of lipid-lowering drugs (group 1),
13,271 individuals with a diagnosis of hyperlipidemia who did not use lipid-lowering drugs (group 2), and 50,000 randomly selected individuals (group 3). During follow-up, 3940 individuals developed a bone fracture and were defined as cases: 705 in group 1 (2.5%), 681 in group 2 (5.1%), and 2554 in group 3 (5.1%). A total of 23,379 control patients were matched to the 3940 case patients, averaging 5.93 controls per case. For 7 cases (0.18%), no eligible control could be identified; more than 99.4% of cases had 6 matched controls. The average number of years of medical history recorded prior to the index date was similar for cases (3.3 years) and controls (3.2 years). The distributions of age and sex and the independent associations between patient characteristics (body mass index, smoking status, use of corticosteroids or estrogens, and number of general practice visits before the index date) and the risk of having a bone fracture (as assessed in univariate analyses) are displayed in Table 1. These covariates have been taken into account in all subsequent multivariate analyses.

When we compared cases with a diagnosis of hyperlipidemia who did not use lipid-lowering drugs with cases without a diagnosis of hyperlipidemia, the risk of having a bone fracture was almost identical in the 2 groups. Compared with the referent of normolipidemic nonusers of lipid-lowering drugs, the relative risk estimate for hyperlipidemic nonusers of lipid-lowering drugs was 0.95 (95% CI, 0.86–1.05). Since there was no material difference between normolipidemic and hyperlipidemic nonusers of lipid-lowering drugs, we combined all nonusers into 1 reference group for subsequent analyses.

Compared with this reference group of nonusers of any lipid-lowering drugs, current, recent, or past exposure to statins, regardless of the total number of prescriptions, were 0.55 (95% CI, 0.44–0.69), 0.67 (95% CI, 0.50–0.92), and 0.87 (95% CI, 0.65–1.18), respectively (Table 2). As compared with the same reference group of nonusers of any lipid-lowering drugs, current, recent, or past exposure to fibrates (regardless of the

<table>
<thead>
<tr>
<th>Table 1. Characteristics of Case Patients and Control Patients and Association With Fracture Risk by Univariate Analyses†</th>
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</thead>
<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>---</td>
</tr>
<tr>
<td>Age, y</td>
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<td>60-69</td>
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<td>70-79</td>
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<td>Sex</td>
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<td>Women</td>
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<tr>
<td>Men</td>
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<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Nonsmoker</td>
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<tr>
<td>Current</td>
</tr>
<tr>
<td>Ex-smoker</td>
</tr>
<tr>
<td>Unknown</td>
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<td>Body mass index, kg/m²</td>
</tr>
<tr>
<td>&lt;25</td>
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<tr>
<td>25-29.9</td>
</tr>
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<td>≥30</td>
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<tr>
<td>Corticosteroid use</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Mixed</td>
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<tr>
<td>Oral (No. of prescriptions)</td>
</tr>
<tr>
<td>1-9</td>
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<tr>
<td>10-19</td>
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<td>20-29</td>
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<td>30-59</td>
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<tr>
<td>Inhaled (No. of prescriptions)</td>
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<tr>
<td>10-19</td>
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<td>20-29</td>
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<tr>
<td>≥30</td>
</tr>
<tr>
<td>Mixed</td>
</tr>
<tr>
<td>Estrogen use (No. of prescriptions)</td>
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<td>None</td>
</tr>
<tr>
<td>Current, 1-9</td>
</tr>
<tr>
<td>Current, 10-19</td>
</tr>
<tr>
<td>Current, ≥20</td>
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<tr>
<td>Past, 1-9</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval; ellipses, not applicable.
†Number of general practitioner visits indicate number of visits before the index date (date of fracture).
number of prescriptions) yielded adjusted ORs of 0.87 (95% CI, 0.70-1.08), 1.05 (95% CI, 0.79-1.41), and 0.85 (95% CI, 0.64-1.13), respectively. Current, recent, or past use of other lipid-lowering agents resulted in adjusted ORs of 0.76 (95% CI, 0.41-1.39), 1.19 (95% CI, 0.66-2.14), and 0.97 (95% CI, 0.71-1.34), respectively (Table 2).

We further stratified the analysis of current use of statins or fibrates by age (50-69 and 70-89 years), sex, and outcome (fracture of femur, humerus or arm, vertebrae, malleolus or foot, or other [including clavicle and unspecified fractures]) to detect possible effect modification. The results of these subanalyses did not suggest that the effects of statins on fracture risk differed materially by bones affected, age groups, or sex. Odds of fracture among those with current exposure to fibrates differed between men (OR, 0.50; 95% CI, 0.30-0.83) and women (OR, 1.01; 95% CI, 0.79-1.28) (Table 3). We also explored the effect of current exposure to individual lipid-lowering drugs on the risk of developing bone fractures. The effects were consistent within groups of lipid-lowering drugs; ie, all individual statins were associated with decreased fracture risks.

From the patient records, we assessed additional covariates that have been related to an altered risk of having a bone fracture and explored whether their inclusion in the multivariate regression model changed the results. There was no evidence of confounding of the association between lipid-lowering drugs and the bone fracture risk by including dichotomous variables for a history of chronic renal failure, hyperthyroidism, hyperparathyroidism, inflammatory bowel disease, malnutrition or malabsorption, or current exposure to benzodiazepines, neuroleptics, antidepressants, antihypertensives, calcium, fluoride, or vitamin D preparations, although current exposure to drugs affecting the central nervous system (ie, benzodiazepines, antidepressants, and antipsychotics) was associated with a slightly increased risk of bone fractures (OR, 1.20; 95% CI, 1.08-1.34).

### Table 2. Exposure to Lipid-Lowering Drugs and Association With Fracture Risk in Multivariate Analysis*

<table>
<thead>
<tr>
<th>Exposure</th>
<th>No. of Case Patients (n = 3940)</th>
<th>No. of Control Patients (n = 23,379)</th>
<th>Unadjusted Odds Ratio (95% CI)</th>
<th>Adjusted Odds Ratio (95% CI)†</th>
<th>P Value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3235</td>
<td>19,223</td>
<td>1.0</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Statins only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>112</td>
<td>918</td>
<td>0.67 (0.53-0.84)</td>
<td>0.55 (0.44-0.69)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. of prescriptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>23</td>
<td>213</td>
<td>0.61 (0.38-0.95)</td>
<td>0.51 (0.33-0.81)</td>
<td>.004</td>
</tr>
<tr>
<td>≥20</td>
<td>55</td>
<td>404</td>
<td>0.76 (0.56-1.04)</td>
<td>0.62 (0.45-0.85)</td>
<td>.003</td>
</tr>
<tr>
<td>Recent use</td>
<td>53</td>
<td>373</td>
<td>0.79 (0.58-1.07)</td>
<td>0.67 (0.50-0.92)</td>
<td>.01</td>
</tr>
<tr>
<td>Past use</td>
<td>58</td>
<td>321</td>
<td>1.02 (0.76-1.38)</td>
<td>0.87 (0.65-1.18)</td>
<td>.37</td>
</tr>
<tr>
<td>Fibrates only</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current use</td>
<td>109</td>
<td>665</td>
<td>0.96 (0.78-1.19)</td>
<td>0.87 (0.70-1.08)</td>
<td>.19</td>
</tr>
<tr>
<td>No. of prescriptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>14</td>
<td>92</td>
<td>0.89 (0.50-1.57)</td>
<td>0.78 (0.44-1.39)</td>
<td>.39</td>
</tr>
<tr>
<td>≥20</td>
<td>35</td>
<td>235</td>
<td>0.88 (0.61-1.27)</td>
<td>0.79 (0.55-1.14)</td>
<td>.21</td>
</tr>
<tr>
<td>Recent use</td>
<td>58</td>
<td>296</td>
<td>1.16 (0.87-1.55)</td>
<td>1.05 (0.79-1.41)</td>
<td>.72</td>
</tr>
<tr>
<td>Past use</td>
<td>59</td>
<td>360</td>
<td>0.96 (0.72-1.28)</td>
<td>0.85 (0.64-1.13)</td>
<td>.27</td>
</tr>
<tr>
<td>Other lipid-lowering drugs only Current use</td>
<td>12</td>
<td>86</td>
<td>0.83 (0.45-1.52)</td>
<td>0.76 (0.41-1.39)</td>
<td>.37</td>
</tr>
<tr>
<td>No. of prescriptions</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-4</td>
<td>4</td>
<td>25</td>
<td>0.96 (0.33-2.76)</td>
<td>0.90 (0.31-2.58)</td>
<td>.84</td>
</tr>
<tr>
<td>≥20</td>
<td>3</td>
<td>32</td>
<td>0.55 (0.17-1.80)</td>
<td>0.49 (0.15-1.62)</td>
<td>.24</td>
</tr>
<tr>
<td>Recent use</td>
<td>14</td>
<td>60</td>
<td>1.38 (0.77-2.46)</td>
<td>1.19 (0.66-2.14)</td>
<td>.56</td>
</tr>
<tr>
<td>Past use</td>
<td>47</td>
<td>244</td>
<td>1.15 (0.84-1.58)</td>
<td>0.97 (0.71-1.34)</td>
<td>.87</td>
</tr>
<tr>
<td>Mixed use§</td>
<td>183</td>
<td>833</td>
<td>1.30 (1.10-1.55)</td>
<td>1.11 (0.93-1.32)</td>
<td>.25</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval. †Odds ratios are adjusted for body mass index, smoking, number of general practitioner visits, and steroid or estrogen use. ‡P values are for adjusted odds ratios. §For definition, see “Methods” section.

**COMMENT**

The findings of this large nested case-control analysis indicate that exposure to statins (HMG-CoA reductase inhibitors) is associated with a substantially lower risk of developing fractures in humans. The association was mainly present for current users of statins (OR, 0.55; 95% CI, 0.44-0.69) and could be identified even after relatively short exposure duration (ie, 1-4 prescriptions, corresponding to a treat-
Current Use of Fibrates

†Odds ratios are for comparison with nonusers of lipid-lowering drugs (referent) and are adjusted for body mass index, smoking, number of general practitioner visits, and steroid treatment.17,18 Thus, a rapid change in bone remodeling significantly after 1 week of treatment. Other studies have shown that intervention with bisphosphonates reduces osteoclastic bone resorption significantly after 1 week of treatment. Thus, a rapid change in bone remodeling seems possible, but the dynamics of the effect of statins on bone remodeling needs further investigation.

As in previous investigations, we also found independent effects of several covariates on the fracture risk, such as a small decreased risk of osteoporotic fractures in relation to increasing body mass index, substantially decreased fracture risk associated with estrogen use, and increased fracture risk for longer-term use of oral corticosteroids and drugs affecting the central nervous system (ie, benzodiazepines, antidepressants, and antipsychotics) in the current study population.

As with all observational studies, biases or unknown confounders cannot be completely ruled out as alternative explanations for the findings. A limitation of this study is the lack of information on physical activity of cases and controls. However, the proposition that individuals may dramatically change their lifestyle habits and begin exercising after a diagnosis of hyperlipidemia cannot sufficiently explain the findings because physical activity has only a moderate effect in slowing age-related bone loss, and its effect in reducing the fracture risk can only be expected in the long-term.19,20 In addition, it seems unlikely that such substantial confounding would selectively affect statins but not other classes of lipid-lowering drugs.

Table 3. Association of Current Use of Statins or Fibrates With Fracture Risk, Stratified by Type of Fracture, Age, and Sex in a Multivariate Analysis*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Case Patients</th>
<th>Current Use of Statins</th>
<th>Current Use of Fibrates</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%) (n = 3940)</td>
<td>Cases Controls</td>
<td>Odds Ratio (95% CI)†</td>
</tr>
<tr>
<td>Type of fracture</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Femur</td>
<td>678 (17.2)</td>
<td>3</td>
<td>77</td>
</tr>
<tr>
<td>Hand, wrist, or arm</td>
<td>1906 (48.4)</td>
<td>58</td>
<td>465</td>
</tr>
<tr>
<td>Vertebral</td>
<td>98 (2.5)</td>
<td>2</td>
<td>26</td>
</tr>
<tr>
<td>Foot</td>
<td>748 (19.0)</td>
<td>24</td>
<td>197</td>
</tr>
<tr>
<td>Other‡</td>
<td>510 (12.9)</td>
<td>15</td>
<td>153</td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>50-69</td>
<td>2016 (51.2)</td>
<td>76</td>
<td>632</td>
</tr>
<tr>
<td>70-89</td>
<td>1924 (48.8)</td>
<td>36</td>
<td>286</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>984 (25.0)</td>
<td>36</td>
<td>286</td>
</tr>
<tr>
<td>Women</td>
<td>2956 (75.0)</td>
<td>76</td>
<td>632</td>
</tr>
</tbody>
</table>

*CI indicates confidence interval.
†Odds ratios are for comparison with nonusers of lipid-lowering drugs (referent) and are adjusted for body mass index, smoking, number of general practitioner visits, and steroid or estrogen use.
‡Includes clavicle and unspecified fracture.

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outcome of interest has been well documented in the computer records and left little room for misclassification. In conclusion, we found that current use of statins in men and women aged 50 years or older was associated with a reduced risk of fracture. This association was much weaker or not present for fibrates and other lipid-lowering drugs, and there was no risk difference between nonusers of lipid-lowering drugs with or without a recorded diagnosis of hyperlipidemia. Despite strong evidence from the current analysis, it is necessary to obtain additional information from controlled trials to further investigate a possible causal effect of statins on bone fracture risk, and, if an effect exists, further assess the timing of onset of such an effect.

REFERENCES


