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Statins and newly diagnosed diabetes

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Aims
In order to evaluate a hypothesized protective effect of the use of HMG Co-A reductase inhibitors (statins) on the development of Type 2 diabetes, we conducted a nested case–control study based on data from the UK-based General Practice Research Database (GPRD).

Methods
We identified a population of adults 30–79 years of age between 1 January 1991 and 31 March 2002, who were being treated with a statin or who were diagnosed with hyperlipidaemia but were not being treated with a lipid-lowering drug. From this population we identified all incident cases of Type 2 diabetes. We conducted a nested case–control study encompassing 588 cases and 2063 matched controls.

Findings
We observed an adjusted odds ratio (OR) of 1.1 [95% confidence interval (CI) 0.8, 1.4] for current statin users compared with non-exposed subjects and adjusted ORs for pravastatin use alone and simvastatin use alone compared with non-exposed of 0.7 (95% CI 0.4, 1.2) and 1.0 (95% CI 0.7, 1.3), respectively. There was little evidence for a duration effect for simvastatin in these data, though there is a slight suggestion of a long-term protective effect with pravastatin.

Conclusion
The current study results are most consistent with the conclusion that there is little if any protective effect of statins on the development of Type 2 diabetes.

Background

Research into the beneficial effects of lipid-lowering drugs such as the HMG Co-A reductase inhibitors (statins) has demonstrated a reduction in low-density lipoprotein (LDL)-cholesterol levels and the endogenous synthesis of cholesterol [1–3]. One specific statin, pravastatin, has been reported to reduce the risk of coronary heart disease [4, 5], improve the endothelium-dependent vasodilatation of the resistance coronary arteries [6] and the peripheral circulation [7], and to have potential anti-inflammatory effects through its interaction with cyclosporin [8] in patients with hypercholesterolaemia. Recently, the West of Scotland Coronary Prevention Study (WOSCOPS) reported a reduced risk of developing Type 2 diabetes for patients with high cholesterol levels who were treated with pravastatin compared with nonusers (RR = 0.7) [9], though studies of other statins have not found this effect [10, 11]. Since diabetes is associated with considerable morbidity and mortality, investigating the potential preventive effects of statins, and pravastatin in particular, is warranted. We studied users of all statin drugs, including pravastatin, to evaluate their effects on the development of Type 2 diabetes using the UK-based General Practice Research Database (GPRD).

Subjects and methods

This study was based on information derived from the GPRD, which has previously been described [12, 13]. Since 1987, over three million residents in the UK have

been enrolled with selected general practitioners (GPs) who use office computers and have agreed to provide data for research purposes to the GPRD. The GPs received 12 months of instruction on the standardized recording of medical information and they agreed to supply anonymized information to academic researchers on an ongoing basis. The information recorded includes patient characteristics, drugs dispensed, clinical diagnoses, notation of referrals to consultants, hospitalizations, certain historical information and other findings (e.g. smoking status, blood pressure, height and weight). Referral letters from consultants and hospitalizations are kept in a manual file. The GPs generate prescriptions directly from the computer, and these are automatically transcribed into the patient's computer record. The details of each prescription, including dose, instructions and quantity, are automatically recorded on computer and can be used to determine dose and duration of drug exposure. Validation studies have repeatedly demonstrated the high quality and completeness of these data [14–16].

This study used a nested case–control analysis. The study base population was comprised of all people aged 30–79 in the GPRD who were users of statins, or who had a diagnosis of hyperlipidaemia with no drug treatment between 1 January 1991 and 31 March 2002. We limited the study population to untreated and statin-treated hyperlipidaemics so that all subjects would have hyperlipidaemia and thus we could minimize the effects of hyperlipidaemia itself on the development of diabetes.

Case selection

From the base population we identified all cases of newly diagnosed Type 2 diabetes. Cases were required to have at least 2 years of history in their computerized medical record prior to the diagnosis date in order to insure that there was no prior history of diabetes or other diseases that would lead to exclusion from the study. All potential cases who had any diagnosis of myocardial infarction, angina, congestive heart failure, cancer, chronic renal or liver disease, or alcohol abuse prior to their first diagnosis of diabetes were excluded.

A person was considered a newly diagnosed Type 2 diabetic if they received a first-time diagnosis of diabetes accompanied by two or more prescriptions for a hypoglycaemic agent (insulin or oral hypoglycaemic), or if they had at least three recorded entries indicating that they were being managed by diet. Subjects were excluded from the study if they had a first-time diagnosis of diabetes that occurred within 90 days after the first treatment for hyperlipidaemia. This was done because it was found that a large number of people were diagnosed with both hyperlipidaemia and diabetes at around the same time. It is likely that routine blood tests taken at a scheduled examination resulted in the two diagnoses being made at approximately the same time. Since it is not biologically plausible that lipid-lowering drug use of <90 days could have an effect on the development of diabetes, and since it is possible that the diabetes preceded the hyperlipidaemia, we excluded these cases from further study to avoid any diagnosis bias resulting from the coincidence in timing of the diagnosis of these two diseases. The computer record of each potential case was reviewed by hand to insure that the case satisfied all eligibility criteria. Case selection was made without regard to exposure status.

Control selection

From the study population we identified up to four controls, with no prior diagnosis of diabetes, for each case, matched for age within 1 year (58%), 3 years (30%), or 5 years (12%), sex, general practice, index date, and date of first active computer recording within 1 year (85%), or 2 years (15%). Controls were subject to the same exclusion criteria as the cases.

Exposure

A subject was considered currently exposed to a statin (atorvastatin, cerivastatin, fluvastatin, pravastatin, or simvastatin) if they had received two or more prescriptions for a statin within 365 days prior to the index date. Past use was defined as any use that ended more than 365 days prior to the index date. Subjects who were never prescribed a statin (i.e. nontreated hyperlipidaemics), those who had only one prescription for a statin prior to the index date and those whose statins were received after the index date comprised the non-exposed (reference) group. We also assessed the effects of cumulative statin use.

Use of nonstatin lipid-lowering drug, such as fibrates, was not considered in this study. Only 15% of all study subjects had received a nonstatin lipid-lowering drug prescription at some time prior to the index date.

Statistical analysis

We used conditional logistic regression analyses using SAS, version 8.0 (SAS Institute Inc., Cary, NC, USA), to calculate odds ratios (ORs), and their 95% confidence intervals (CI), for developing Type 2 diabetes among statin users compared with people with nontreated hyperlipidaemia. We also analysed pravastatin and simvastatin users separately. Use of the remaining statins (atorvastatin, cerivastatin, and fluvastatin) was not suf-

ficient for them to be analysed independently. In addition to matching on age, sex, general practice, index date, and length of history in the database, the effects of other potential risk factors for diabetes, such as smoking (current, past, nonsmoker or unknown), body mass index (BMI) (<25, 25–29, 30+), history of steroid use (oral steroids or injectable steroids), hypertension, and the number of visits to the GP in the 3 years prior to the index date, were controlled for in the analyses. The effect of cumulative statin use was also evaluated by calculating the number of statin prescriptions received prior to the index date for each currently exposed subject. Duration was also calculated for each currently exposed subject as the time from first to last prescription for a statin before the index date. These latter two variables were coded as 'unknown' when the subject had a statin prescription at the beginning of their computerized medical record (within 90 days of the record's start date), and when the number of prescriptions was less than the highest value for the variable. If the subject's use was already in the highest category they were coded in that category regardless of the date of the first statin prescription.

Results

After exclusions were made, the study base population included 41 986 users of statins, and 27 862 nontreated hyperlipidaemics. From this population we identified 588 cases of newly diagnosed diabetes and 2063 matched controls. Fifty-one percent of subjects were male, 74% were between the ages of 50 and 69 and 55% were diabetics treated with oral hypoglycaemics compared with 2% treated with insulin and 43% who were managed by diet. The mean age among cases was 59.2 (SD 9.1) and 59.2 (SD 8.6) among controls. The mean BMI among cases was 30.1 (SD 5.6) and 26.9 (SD 4.4) among controls. These and other characteristics of the cases and controls are presented in Table 1. The adjusted OR for diabetes comparing current statin users with the non-exposed (reference) group was 1.1 (95% CI 0.8, 1.4), with BMI, hypertension, smoking, steroid use, and number of prior GP visits included in the model (Table 1). High BMI (OR 10.1, 95% CI 6.2, 16.3), hypertension (OR 1.8, 95% CI 1.4, 2.2), and 26 or more GP visits compared with nine or fewer visits (OR 2.8, 95% CI 2.0, 3.9) were independently associated with an increased risk of diabetes (Table 1).

When pravastatin was evaluated separately the OR was 0.7 (95% CI 0.4, 1.2) comparing current use with the non-exposed, adjusting for BMI, hypertension, steroid use, smoking and prior GP visits. We also assessed current simvastatin use separately and found an adjusted OR of 1.0 (95% CI 0.7, 1.3) compared with the non-exposed (Table 2). There was no suggestion of an effect with past use.

When we examined cumulative statin use there was no suggestion of an effect with increased number of prescriptions received (Table 3). Nor was there an effect when we evaluated number of prescriptions received among users of simvastatin by itself. The effect of pravastatin at the highest level was consistent with a protective effect but the numbers are very small. Results for the effect of duration were similar (see Table 4).

Stratification by age at diagnosis (<65, ≥65), and by type of diabetes (treated with oral hypoglycaemics, treated with insulin, or managed with diet), did not yield material differences in diabetes risk. We stratified the data by number of visits to the GP in the 3 years prior to the index date to evaluate whether people who see the GP more often are more likely to receive lipid-lowering drugs and are more likely to be diagnosed with diabetes. While there was an association between number of visits and diagnosis of Type 2 diabetes, there was no difference in the effect of statins according to the number of GP visits.

When the data were stratified by sex the effect of pravastatin use was not materially different. However, among simvastatin users the adjusted ORs for current simvastatin use were 0.7 (95% CI 0.4, 1.1) in males and 1.3 (95% CI 0.9, 1.9) in females. Analyses of both duration of use and cumulative use of simvastatins demonstrated effects in males that became stronger with increased use of simvastatin. The effects were most protective at the highest level of use. There was no effect among females in these data where the ORs were ≥1.0 at all exposure levels. It should be noted that the numbers of exposed subjects in these analyses were small and in all instances the 95% CIs included 1.0 and were therefore not statistically significant.

Discussion

The results of this study are most consistent with the conclusion that there is no protective effect of the statin class of drugs on the development of Type 2 diabetes. BMI and hypertension were independently associated with an increased risk of diabetes, findings that are consistent with prior knowledge of diabetes epidemiology [17–19].

Since only a small proportion of the 588 diabetes cases were treated with insulin (2%), it was difficult to evaluate precisely the effect of exposure for insulin-treated cases separately. There was no material difference in the effect of exposure among those treated with hypoglycaemic medication compared with cases man-

Table 1
Characteristics of cases and controls and odds ratios for developing newly diagnosed diabetes using multivariable conditional logistic regression analysis

Exposure	Cases, *n*	Controls, *n*	Adjusted OR*	95% CI
Oral hypoglycaemics-treated diabetes	321	–		
Insulin-treated diabetes	11	–		
Diet-managed diabetes	256	–		
Males	303	1046	–	–
Females	285	1017	–	–
Age <50 years	86	282	–	–
Age 50–59 years	209	767	–	–
Age 60–69 years	214	773	–	–
Age ≥70 years	79	241	–	–
Non-exposed†	411	1462	1.0	–
Current statin use	156	504	1.1	0.8, 1.4
Past statin use	21	97	0.9	0.5, 1.6
BMI <25.0†	25	352	1.0	–
BMI 25.0–29.9	113	397	3.5	2.2, 5.6
BMI 30.0+	147	182	10.1	6.2, 16.3
Unknown BMI	303	1132	2.4	1.4, 4.1
No hypertension†	272	1313	1.0	–
Hypertension	316	750	1.8	1.4, 2.2
No steroid use†	549	1926	1.0	–
Current oral steroid use	21	40	1.5	0.8, 2.8
Current injectible steroid use	8	27	0.7	0.3, 1.9
Past steroid use	10	20	1.3	0.6, 3.1
Nonsmoker†	327	1201	1.0	–
Current	151	437	1.4	1.1, 1.8
Former	80	301	1.0	0.7, 1.3
Unknown	30	124	1.1	0.6, 1.8
GP visits: 0–9†	88	555	1.0	–
GP visits: 10–16	133	526	1.5	1.1, 2.1
GP visits: 17–25	143	477	1.9	1.3, 2.6
GP visits: 26+	224	505	2.8	2.0, 3.9
Total	588	2063	–	–

**Adjusted for all other variables in the model. †Reference group. –, Odds ratios (ORs) not calculated as variable is a matching factor; BMI, body mass index.*

aged with diet only. There was no effect modification by age nor by number of GP visits in the 3 years prior to the index date, and no material difference in effect by sex.

Exposure recall bias is of little concern in this analysis because exposure information was recorded on computer at the time of prescription receipt, which preceded disease onset. Misclassification of disease and/or confounder status, though possible, is unlikely to have materially affected our risk estimates since all information on exposures, outcomes, and potential confounders was recorded on computer prior to the start of the study. To be considered a case of diabetes a subject was required to have multiple prescriptions for a hypoglycaemic agent, or multiple references to diabetes control through diet. Information on drug prescriptions and clinically significant medical events has been shown to be virtually complete in the GPRD [14–16].

Type 2 diabetes does not have an acute clinical onset and it is likely that some cases had the illness for some

Table 2
Risk of developing newly diagnosed diabetes in users of pravastatin alone and simvastatin alone using multivariable conditional logistic regression analysis

Exposure	Cases, *n*	Controls, *n*	Adjusted OR*	95% CI
Non-exposed†	411	1462	1.0	–
Pravastatin				
Current pravastatin use	25	108	0.7	0.4, 1.2
Past pravastatin use	17	28	2.4	1.2, 4.9
All other use‡	135	465	1.1	0.8, 1.4
Simvastatin				
Current simvastatin use	88	313	1.0	0.7, 1.3
Past simvastatin use	21	97	0.9	0.5, 1.6
All other use‡	68	191	1.2	0.8, 1.7

**Adjusted for body mass index, hypertension, steroid use, smoking and the number of GP visits within 3 years preceding the index date. †Reference group. ‡Other = use of another statin.*

Table 3
Risk of developing newly diagnosed diabetes in users of statins by number of prescriptions filled, using multivariable conditional logistic regression analysis

Exposure	Cases, *n*	Controls, *n*	Adjusted OR*	95% CI
Non-exposed†	411	1462	1.0	–
Number of prescriptions filled: all statins				
2–9 statin RXs	64	191	1.1	0.8, 1.5
10–19 statin RXs	36	126	0.9	0.6, 1.4
20–29 statin RXs	23	70	1.3	0.7, 2.2
30+ statin RXs	30	106	1.0	0.6, 1.6
Unknown no. of statin RXs	3	11	1.5	0.4, 6.6
Past users	21	97	0.9	0.5, 1.6
Number of prescriptions filled: pravastain				
2–9 pravastatin RXs	8	42	0.6	0.2, 1.3
10–19 pravastatin RXs	8	29	0.8	0.3, 2.0
20–29 pravastatin RXs	5	15	1.2	0.4, 3.6
30+ pravastatin RXs	4	20	0.6	0.2, 1.9
Unknown no. of pravastatin RXs	0	2	–	–
Other use	135	465	1.1	0.8, 1.4
Past users	17	28	2.5	1.2, 5.0
Number of prescriptions filled: simvastatin				
2–9 simvastatin RXs	41	120	1.1	0.7, 1.7
10–19 simvastatin RXs	17	69	0.8	0.5, 1.5
20–29 simvastatin RXs	9	45	0.8	0.4, 1.7
30+ simvastatin RXs	19	71	1.0	0.5, 1.7
Unknown no. of simvastatin RXs	2	8	1.0	0.2, 5.6
Other use	68	191	1.2	0.8, 1.7
Past users	21	97	0.9	0.5, 1.6

**Adjusted for body mass index, hypertension, steroid use, smoking and the number of GP visits in the 3 years preceding index date. †Reference group.*

Table 4
Risk of developing newly diagnosed diabetes in users of statins by duration of use, using multivariable conditional logistic regression analysis

Exposure	Cases, *n*	Controls, *n*	Adjusted OR*	95% CI
Non-exposed†	411	1462	1.0	–
Duration of current statin use				
<1 year	49	171	0.9	0.6, 1.3
1–3 years	81	224	1.2	0.9, 1.7
4+ years	23	101	0.9	0.5, 1.5
Unknown	3	8	1.7	0.4, 7.5
Past use	21	97	0.9	0.5, 1.6
Duration of pravastatin use				
<1 year	7	42	0.5	0.2, 1.3
1–3 years	15	50	0.9	0.5, 1.7
4+ years	3	15	0.8	0.2, 2.9
Unknown	0	1	–	–
Other use	135	465	1.1	0.8, 1.4
Past use	17	28	2.5	1.2, 5.0
Duration of simvastatin use				
<1 year	32	99	1.0	0.6, 1.6
1–3 years	39	137	1.0	0.7, 1.5
4+ years	14	70	0.8	0.4, 1.5
Unknown	3	7	1.7	0.4, 7.8
Other use	68	191	1.2	0.8, 1.7
Past use	21	97	0.9	0.5, 1.6

**Adjusted for body mass index, hypertension, steroid use, smoking and the number of GP visits in the 3 years preceding index date. †Reference group.*

time prior to their diagnosis. This could result in some misclassification of exposure. The evaluation of the duration of use and cumulative use variables should clarify the effects of this potential misclassification, as those with the greatest exposure would be consistently classified as exposed and, if there were a true protective effect, it would be strongest with the heaviest use. We did not see evidence of a duration response in these data so this is not a likely explanation for our results.

The study population was limited to untreated and statin-treated hyperlipidaemics to maximize comparability between subjects who all have hyperlipidaemia. By doing this we have limited the ability to assess the effects of hyperlipidaemia itself on the development of diabetes. However, in a previous analysis we did look at people with no hyperlipidaemia ('healthy' subjects), and found no difference in the risk of diabetes between untreated hyperlipidaemics and the 'healthy' population (data not shown). Nevertheless, it is possible that there is some degree of confounding by indication present in these data. If people with severe hyperlipidaemia are more likely to develop diabetes and to receive statins the results could be biased towards the null. In additional analyses (data not shown), evaluating the effect of non-statin lipid-lowering drugs (i.e. fibrates and other drugs including colestipol, cholestyramine, acipimox, and nicotinic acid), compared with the nontreated hyperlipidaemics there was no elevated risk of developing Type 2 diabetes in any models, including a dose–response analysis, in the users of the nonstatin lipid-lowering drugs. This suggests that hyperlipidaemia itself is not a strong risk factor for developing diabetes. Thus, though we cannot completely rule out the influence of confounding by indication, it is unlikely to have materially affected our findings.

Also of concern is that subjects with untreated hyperlipidaemia are different from treated subjects, a possible result being that treated subjects see their GP more often than do untreated subjects. Those with greater GP contact could be more likely to be diagnosed with diabetes,

resulting in a risk estimate that is biased towards the null. In this study, we accounted for increased contact with a GP by categorizing subjects according to the number of GP visits before the diagnosis date and then controlling for this in the analysis. Although those with more GP visits were at higher risk of diabetes, this association did not confound the effect between statin use and the risk of diabetes.

There was limited use of pravastatin in this database and therefore estimates of relative risk of diabetes were imprecise. In particular, information on long-term use was sparse. Indeed, data on long-term use for all statins in this study were limited. Additional studies with long-term follow-up of statin use, pravastatin use in particular, would be useful to evaluate further the relation between statins and development of Type 2 diabetes.

In summary, these data do not provide evidence to support the hypothesis that statins, as a class, are protective against the development of Type 2 diabetes.

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