Pravastatin and the Development of Diabetes Mellitus
Evidence for a Protective Treatment Effect in the West of Scotland Coronary Prevention Study

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Background—We examined the development of new diabetes mellitus in men aged 45 to 64 years during the West of Scotland Coronary Prevention Study.

Methods and Results—Our definition of diabetes mellitus was based on the American Diabetic Association threshold of a blood glucose level of $7.0 \text{ mmol/L}$. Subjects who self-reported diabetes at baseline or had a baseline glucose level of $\geq 7.0 \text{ mmol/L}$ were excluded from the analyses. A total of 5974 of the 6595 randomized subjects were included in the analysis, and 139 subjects became diabetic during the study. The baseline predictors of the transition from normal glucose control to diabetes were studied. In the univariate model, body mass index, log triglyceride, log white blood cell count, systolic blood pressure, total and HDL cholesterol, glucose, and randomized treatment assignment to pravastatin were significant predictors. In a multivariate model, body mass index, log triglyceride, glucose, and pravastatin therapy were retained as predictors of diabetes in this cohort.

Conclusions—We concluded that the assignment to pravastatin therapy resulted in a 30% reduction ($P=0.042$) in the hazard of becoming diabetic. By lowering plasma triglyceride levels, pravastatin therapy may favorably influence the development of diabetes, but other explanations, such as the anti-inflammatory properties of this drug in combination with its endothelial effects, cannot be excluded with these analyses. (Circulation. 2001;103:357-362.)

Key Words: diabetes mellitus • prevention • lipids • trials • risk factors

Factors that influence the development of diabetes mellitus have been the subject of considerable research.1–4 Blood lipid and lipoprotein levels have been confirmed as important predictors of this pathology,4,5 and more recently, markers of low-grade inflammation have been shown to predict the occurrence of type 2 diabetes.4 Interestingly, despite these strong associations, there have been very few investigations into the effects of drugs that influence the blood lipid profile or that have anti-inflammatory actions on the development of diabetes. One such drug that exhibits potentially beneficial pleiotropic effects on both plasma lipids and the inflammatory response is pravastatin.

Pravastatin is an HMG Co-A reductase inhibitor that has significant effects on the plasma lipid and lipoprotein profile, lowering total and LDL cholesterol and triglyceride levels and raising HDL cholesterol levels.6–8 In addition to these lipid effects, pravastatin has been shown to have a range of other antiatherothrombotic effects, including the restoration of endothelial function9 and anti-inflammatory effects.10

Pravastatin therapy has been shown unequivocally to reduce cardiovascular risk in a series of large-scale, randomized, controlled clinical trials.6–8 In a diabetic/glucose-intolerant subgroup analysis of one study, pravastatin significantly reduced coronary events, but no attempt was made to examine the effects of pravastatin on glucose control over time.11

The West of Scotland Coronary Prevention Study (WOSCOPS) database provided an opportunity to study prospectively the effects of pravastatin therapy on the risk of developing diabetes in subjects with follow-up ranging from

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Methods

Subjects
All study subjects were participants in WOSCOPS, and their characteristics have been summarized in detail elsewhere. Briefly, these subjects were all men aged 45 to 64 (mean age 55.2 years) with a mean baseline plasma total cholesterol level of 7.0 mmol/L (SD 0.6), LDL cholesterol level of 5.0 mmol/L (SD 0.4), HDL cholesterol level of 1.1 mmol/L (SD 0.3), and triglyceride level of 1.9 mmol/L (SD 0.8). They also had normal renal and hepatic function with no history of myocardial infarction or organ transplantation. With the exception of plasma cholesterol levels and the absence of a history of myocardial infarction, unstable angina, or coronary revascularization, the study recruits had a similar risk factor profile and demographic distribution as the group of 81 000 screenees from which they were selected.

Laboratory Methods
Glucose was measured according to an automated enzymatic method, and plasma lipids and lipoproteins were measured according to the protocols of the Lipid Research Clinics. Blood counts, including white blood cell count (WBC), were performed with a Coulter STKR or S+1 automated cell counter.

Definition of Diabetes
Fasting venous blood glucose measurements were performed at baseline and at 6-month intervals throughout WOSCOPS. We used the ADA definition of diabetes mellitus, which requires a fasting blood glucose level of ≥7.0 mmol/L. Two important additional criteria were imposed. Although all glucose measurements were intended to be performed on fasting samples in WOSCOPS, inevitably in such a large group during 5 years, some patients may have failed to fast. Because a single, nonfasting glucose measurement may result in the misclassification of a subject as diabetic, a minimum of 2 glucose measurements of ≥7.0 mmol/L were required. In addition, because we were primarily interested in examining subjects who experienced significant deterioration in their glucose control, a further restraint was incorporated into the definition, whereby one glucose measurement must be ≥2.0 mmol/L above baseline. The value of 2.0 mmol/L was chosen to represent an average increment of 5.0 mmol/L to a diabetic value of 7.0 mmol/L.

Inevitably, this strategy restricted the number of subjects classified as newly diabetic but increased our level of confidence that the subjects labeled in this study as newly diabetic were truly thus. In addition, individuals who had been newly prescribed hypoglycemic agents (oral hypoglycemic agents or insulin) during the study were accepted as having become diabetic.

Importantly, because this analysis was designed to examine the development of new diabetes, subjects who were self-reported diabetics at baseline (76 subjects) or had elevated fasting blood glucose levels of ≥7.0 mmol/L and were neither self-reported diabetics nor had elevated fasting glucose levels ≥7.0 mmol/L at baseline. Of these, 139 subjects were later classified as diabetic.

Values for continuous measurements are mean±SD, and values for categorical measurements are numbers of subjects (percent) with the stated attribute.

Results

Study Subjects
The WOSCOPS cohort consisted of 6595 men, of whom 5974 had ≥2 postrandomization blood glucose measurements and were neither self-reported diabetics nor had elevated fasting blood glucose levels ≥7.0 mmol/L at baseline (Table 1). With the definition of diabetes outlined in Methods, 139 of the 5974 subjects included were classified as having a transition from normal glucose control to overt diabetes mellitus during the study.

Univariate Predictors of Diabetes
As shown in Table 2, body mass index (BMI), HDL cholesterol, log triglyceride, total cholesterol, log WBC, baseline glucose, and systolic blood pressure were all univariate predictors of the development of diabetes. Age, alcohol intake, and smoking status were not significant predictors of development of diabetes. Interestingly, pravastatin treatment

| TABLE 1. Baseline Characteristics of the Study Cohort (n=5974)* |
|------------------|------------------|------------------|
| Diabetic Subjects | All Subjects*    |
| (n=139)          | (n=5974)         |
| Age, y           | 55.6±5.7         | 55.2±5.5         |
| Glucose, mmol/L  | 5.49±0.69        | 4.72±0.51        |
| BMI, kg/m²       | 27.7±3.6         | 25.9±3.1         |
| Natural log[WBC], log(10⁵ cells/L) | 1.93±0.26 | 1.84±0.27 |
| Systolic blood pressure, mm Hg | 138±18       | 135±17           |
| Diastolic blood pressure, mm Hg | 85±10         | 84±10            |
| Natural log[triglyceride], log(mmol/L) | 0.78±0.39  | 0.52±0.40        |
| Total cholesterol, mmol/L | 7.17±0.60   | 7.02±0.58        |
| HDL cholesterol, mmol/L | 1.05±0.20   | 1.14±0.24        |
| Total to HDL cholesterol ratio | 7.10±1.46   | 6.42±1.37        |
| Alcohol, U/wk    | 11±15            | 11±13            |
| Pravastatin therapy, n (%) | 57 (41)    | 2999 (50)        |
| Smoking (Y/N), n (%) | 64 (46)      | 2584 (43)        |
| Hypertension (Y/N), n (%) | 36 (26)     | 930 (16)         |

*These 5974 subjects had ≥2 postrandomization measurements of glucose and were neither self-reported diabetics at baseline nor had a fasting glucose level ≥7.0 mmol/L at baseline. Of these, 139 subjects were later classified as diabetic.
ide level. In addition to establishing these variables as predictors of loss of glucose control such as BMI and plasma triglyceride, we were able to confirm well-recognized predictors based on serial fasting glucose measurements and the ADA criteria, we were able to confirm well-recognized predictors of loss of glucose control such as BMI and plasma triglyceride. In addition to establishing these variables as independent predictors, we identified for the first time a clinically important association between pravastatin therapy and a reduced risk of developing diabetes. It should be noted that these analyses were not predefined as part of WOSCOPS and as such should be interpreted cautiously. Nevertheless, they raise important new clinical possibilities, which should now be explored in further studies.

The definition of diabetes mellitus according to the ADA requires a fasting blood glucose of $\geq 7.0$ mmol/L. We have used this cutoff to define diabetes, but to avoid the mislabeling of patients as diabetic on the basis of single nonfasting samples, we used more rigorous additional criteria by requiring two blood glucose levels of $\geq 7.0$ mmol/L and one level of $\geq 2.0$ mmol/L than baseline. The finding that BMI and plasma triglyceride, both well-recognized risk factors for insulin resistance and glucose intolerance, were strong independent predictors of the loss of glucose control in this group is reassuring.

In our multivariate analysis, baseline WBC failed to reach statistical significance ($P=0.063$) as a predictor of the loss of glucose control. The importance of baseline WBC as a predictor of the loss of glucose control has, however, been established by others and potentially lies in its association with low-grade chronic inflammation. Only very recently has it been appreciated that inflammatory markers linked with insulin resistance associate with the development of diabetes in adults. The mechanism by which inflammation leads to glucose intolerance and ultimately diabetes is unknown, but

### Table 2. Univariate and Multivariate Hazard Ratios With $P$ Values and Approximate 95% CIs for Baseline Predictors of Development of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>$P$</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (5 y)</td>
<td>1.04 (0.90–1.22)</td>
<td>0.58</td>
<td>1.05 (0.89–1.23)</td>
<td>0.58</td>
</tr>
<tr>
<td>BMI (3 kg/m²)</td>
<td>1.61 (1.42–1.84)</td>
<td>&lt;0.0001</td>
<td>1.29 (1.12–1.49)</td>
<td>0.0006</td>
</tr>
<tr>
<td>Natural log(WBC) [0.25 log(10² cells/L)]</td>
<td>1.36 (1.17–1.58)</td>
<td>0.0001</td>
<td>1.18 (0.99–1.41)</td>
<td>0.063</td>
</tr>
<tr>
<td>Systolic blood pressure (20 mm Hg)</td>
<td>1.23 (1.02–1.49)</td>
<td>0.028</td>
<td>1.04 (0.86–1.27)</td>
<td>0.69</td>
</tr>
<tr>
<td>Natural log(triglyceride) [0.5 log(mmol/L)]</td>
<td>2.25 (1.83–2.76)</td>
<td>&lt;0.0001</td>
<td>1.55 (1.14–2.09)</td>
<td>0.0048</td>
</tr>
<tr>
<td>Total cholesterol (0.5 mmol/L)</td>
<td>1.25 (1.09–1.42)</td>
<td>0.0011</td>
<td>1.00 (0.84–1.18)</td>
<td>0.95</td>
</tr>
<tr>
<td>HDL cholesterol (0.25 mmol/L)</td>
<td>0.62 (0.51–0.77)</td>
<td>&lt;0.0001</td>
<td>0.86 (0.67–1.11)</td>
<td>0.24</td>
</tr>
<tr>
<td>Alcohol (10 U/wk)</td>
<td>1.01 (0.88–1.14)</td>
<td>0.93</td>
<td>0.94 (0.82–1.09)</td>
<td>0.43</td>
</tr>
<tr>
<td>Pravastatin therapy (Y/N)</td>
<td>0.70 (0.50–0.98)</td>
<td>0.036</td>
<td>0.70 (0.50–0.99)</td>
<td>0.042</td>
</tr>
<tr>
<td>Smoking (Y/N)</td>
<td>1.15 (0.82–1.61)</td>
<td>0.41</td>
<td>1.11 (0.76–1.63)</td>
<td>0.59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose Quintile</th>
<th>Univariate Hazard Ratio (95% CI)</th>
<th>$P$</th>
<th>Multivariate Hazard Ratio (95% CI)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quintile I:&lt;4.3 mmol/L</td>
<td>†</td>
<td>†</td>
<td>†</td>
<td>†</td>
</tr>
<tr>
<td>Quintile II:&gt;=4.3–4.5 mmol/L</td>
<td>0.94 (0.33–2.63)</td>
<td>0.86 (0.31–2.42)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile III:&gt;=4.5–4.7 mmol/L</td>
<td>0.41 (0.11–1.51)</td>
<td>&lt;0.0001</td>
<td>0.37 (0.10–1.37)</td>
<td>&lt;0.0001*</td>
</tr>
<tr>
<td>Quintile IV:&gt;=4.7–5.0 mmol/L</td>
<td>1.74 (0.76–3.98)</td>
<td>1.50 (0.66–3.45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quintile V:&gt;=5.0 mmol/L</td>
<td>13.0 (6.60–25.8)</td>
<td>9.66 (4.83–19.3)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P value for the $\chi^2$ test on 4 df for the equality of the 5 quintiles of glucose.
†Referent level.

The given hazard ratio for continuous covariates is for an 1-SD change (indicated in parentheses); for example, for log(triglyceride), the hazard ratio is for a 0.5-unit change in the logarithm of triglyceride (with triglyceride measured in mmol/L). For categorical variables, the hazard ratio is with or without the stated attribute (eg, on pravastatin or not on pravastatin).
Proinflammatory cytokines, such as tumor necrosis factor (TNF)-α, and leptin may produce insulin resistance by influencing the function of the insulin receptor or impairing insulin action and inhibiting insulin secretion.

Previous investigations into the effects of pravastatin on glucose tolerance have been equivocal. Most studies have been performed in small groups for a short duration and have yielded inconclusive results. In the present study, the benefits associated with pravastatin therapy are long term, and it should be noted that the subjects studied in WOSCOPS, on average, had normal triglyceride levels at baseline. The beneficial effects of pravastatin on glucose-intolerant subjects have been shown in a subgroup analysis of the CARE trial, in which significant reductions were observed in cardiovascular risk. The mechanism by which pravastatin may reduce a subject’s risk of developing diabetes mellitus is not clear from these analyses. One possibility that cannot be discounted with the present analysis is the impact of pravastatin on vascular events that lead to a secondary reduction in the need for the use of cardiovascular drugs that influence glucose control, such as thiazide diuretics and β-blockers.

The WOSCOPS database has information on concomitant medication but has insufficient resolution with respect to specific drugs to answer this question. Drug use at baseline was virtually identical between the placebo and pravastatin groups, and it may be argued that active treatment would actually increase the use of drugs such as thiazides and β-blockers by reducing the fatal event rate in the study.

We may, however, speculate that three known effects of pravastatin therapy may play a primary role, either individually or in concert in the development of diabetes. First, the triglyceride-lowering effect of pravastatin therapy may be important over the long term in reducing the risk of the development of insulin resistance. It has been known for many years that elevated triglyceride levels are associated with the development of diabetes. In WOSCOPS, pravastatin therapy reduced triglycerides by an average of 12%. Interestingly, when the on-treatment triglyceride values were put into the stepwise multivariate model, pravastatin therapy was no longer a statistically significant, independent predictor (data not shown). This, however, cannot be interpreted as necessarily explaining the pravastatin effect. On-treatment triglyceride levels, calculated as the average of the 6- and 12-month postrandomization values, are not independent of pravastatin therapy. Indeed, as stated earlier, pravastatin significantly decreases the plasma triglyceride level. The data
are therefore compatible with a treatment effect mediated through a change in plasma triglyceride levels but are not necessarily explained by this. It should also be noted that other lipid-lowering drugs, such as fibric acid derivatives, which have a greater lowering effect on plasma triglyceride than do statins, do not appear to improve insulin resistance.22 This would suggest that triglyceride lowering per se does not explain the observed effect.

Second, the anti-inflammatory effects of pravastatin may be key. Pravastatin has been shown to reduce circulating levels of the cytokines interleukin-6 and TNF-α.23 TNF-α and interleukin-6 are known to inhibit lipoprotein lipase activity24 and to stimulate lipolysis in adipose tissue.25 Indeed, it has been postulated that these cytokines, derived in part from adipose tissue, may be possibly responsible for the metabolic syndrome associated with insulin resistance.16 The anti-inflammatory properties of pravastatin may therefore interrupt the natural progression from central obesity to insulin resistance mediated by the adipose tissue–derived cytokines.

Finally, another effect of pravastatin that has been consistently demonstrated is the effect on endothelial function.9,26,27 This may be explained in part by the lipid-lowering effects of this statin, as dyslipidemia is known to impair endothelium-mediated vasodilatation.28 Impaired endothelial function has recently been shown to result in diminished capillary recruitment and in turn to correlate with the degree of insulin resistance.29 By restoring endothelial function, pravastatin may significantly influence selective tissue perfusion and thereby beneficially affect glucose and insulin transport.

These 3 mechanisms may all be operative, and together they may explain this important new finding that pravastatin therapy may reduce the propensity of subjects within WOSCOPS to develop diabetes. However, there may be other direct or indirect effects of pravastatin therapy on glucose control that have yet to be unraveled. Regardless of the mechanism or mechanisms, the prevention or delay of the onset of diabetes may contribute significantly to the observed cardiovascular benefits of pravastatin therapy.

These findings are generated from a post hoc analysis of WOSCOPS. As such, we must emphasize that our results should be treated as hypothesis generating and should now be confirmed in a prospective manner in other statin trials, such as the ongoing Prospective Study of Pravastatin in the Elderly at Risk (PROSPER).30

Appendix: WOSCOPS Group

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Computerized ECG Analysis
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Laboratory Operations
M. Anne Bell, Robert Birrell.

Company Liaison and General Support
Margot Millies, Joseph Meyer, Wendy Campbell.

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References


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