The Challenge of Lipid Management in Patients with Diabetes or Other Endocrine Disorders

Alberico L Catapano,1 Liliana Grigore2 and Angela Pirillo2

1. Professor of Pharmacology, Faculty of Pharmacy, Department of Pharmacological Sciences, University of Milan; 2. Research Fellow, SISA Centre for the Study of Atherosclerosis, Bassini Hospital, Milan

Abstract
Diabetes increases the risk of developing cardiovascular disease (CVD), and several guidelines suggest that subjects with diabetes are at high risk of developing CVD. The increased risk can be attributed, at least in part, to associated risk factors, including hypertension and dyslipidaemia. The role of statins in primary and secondary prevention of CVD is well established, and the positive effect has been clearly demonstrated also in patients with type 2 diabetes. A number of studies have evaluated the effect of statin therapy on incident CVD and shown that statin therapy produces a greater reduction in cardiovascular risk, but a recent meta-analysis revealed a slight increase in the risk of developing diabetes. Such risk is, however, low, especially when compared with the reduction in cardiovascular events and should not interfere with the choice of treating diabetic patients with a cholesterol-lowering therapy.

Keywords
Diabetes, low-density lipoprotein (LDL), cardiovascular risk, combination therapy, lipid-lowering, statins

Diabetes mellitus, a metabolic disorder defined by fasting glucose concentration ≥7.0 mmol/l or by glycated haemoglobin ≥6.5 %, represents an established risk factor for coronary artery disease; the number of people who have diabetes mellitus is predicted to rapidly rise in coming years, due to the increased incidence of type 2 diabetes. Furthermore, diabetes, particularly type 2 diabetes, is associated with a higher cardiovascular risk due to the association with other risk factors including dyslipidaemia, hypertension and obesity. Patients with type 2 diabetes without a history of myocardial infarction (MI) have the same cardiovascular risk as a patient without diabetes with a history of MI, and these observations have led to the recommendation that diabetic patients should be treated as high-risk patients in the control of low-density lipoprotein (LDL) cholesterol and blood pressure.

The principal alterations of the lipid profile in type 2 diabetes patients include low levels of high-density lipoprotein (HDL) cholesterol (with dysfunctional activity), high triglyceride (TG) levels and higher concentrations of small, dense LDL (S, D), which are associated with higher coronary heart disease (CHD) risk. The atherogenicity of small, dense LDL is attributed to its higher susceptibility to oxidation, but it also represents a marker for insulin resistance or the presence of atherogenic very-low-density lipoprotein (VLDL). Certainly, an insufficient control of glucidic metabolism worsens diabetic dyslipidaemia, while a rigid metabolic control could reduce the excess of free fatty acids and the overproduction of hepatic VLDL. The lipid disorders improve significantly with weight loss, physical activity and stopping smoking; therefore, lifestyle changes should be the first step in the treatment of diabetic dyslipidaemic patients. Anyway, in many cases, pharmacological treatment is absolutely necessary to reduce cardiovascular events as demonstrated in many intervention trials. Often, diabetic patients treated with hypolipidaemic drugs have a major benefit in terms of reduction of cardiovascular risk compared with non-diabetic patients. Lowering LDL levels is the first priority in treating diabetic dyslipidaemia. Current recommendations are for an LDL goal of less than 100 mg/dl (<70 mg/dl in high-risk patients), an HDL goal greater than 40 mg/dl for men and greater than 50 mg/dl for women and a TG goal less than 150 mg/dl.

To achieve this goal, statins are the drugs of choice; fibrates or nicotinic acid are often used, sometimes in combination with statins; resins and ezetimibe are added on top of the maximal tolerated therapy when goals are not achieved. In subjects with elevated TG levels, hyperglycaemia must be controlled first. If TG or HDL levels remain uncontrolled after this intervention, drugs should be considered. Fibrates are slightly more effective than nicotinic acid in lowering TG levels, but the latter increases HDL cholesterol levels appreciably more than fibrates do. Furthermore, in patients with type 2 diabetes, nicotinic acid can improve a vast array of lipoprotein abnormalities. However, it can induce insulin resistance, thus worsening hyperglycaemia.

A number of studies, including the Collaborative atorvastatin diabetes study (CARDS), the Helsinki heart study (HHS), the Scandinavian simvastatin survival study (4S) and the Cholesterol and recurrent events (CARE) study, have shown that lipid-lowering therapy in type 2 diabetes significantly reduced the number of cardiac events, with a risk reduction of 22–50 % with statins and up to 65 % with fibrates.

© TOUCH BRIEFINGS 2011
compared with placebo. These studies also showed that the risk of major coronary events in untreated diabetic patients is 1.5–1.7-fold higher than in untreated non-diabetic patients. In diabetic patients, gemfibrozil is more effective in decreasing TGs and increasing HDL cholesterol compared with statins; moreover, it increases LDL particle size without reducing LDL cholesterol levels. Yet statins are currently the preferred lipid-lowering drugs because LDL cholesterol remains the primary target of therapy. In fact, the diabetic patient may be more likely to benefit from statin therapy than the non-diabetic patient in terms of absolute risk reduction.

On the other hand, some trials have indicated a setting-dependent efficacy of some drugs in specific clinical conditions. This is the case with fibrates. The Bezaflibrate infarction prevention (BIP) trial, the HHS, and the Fenofibrate intervention and event lowering in diabetes (FIELD) trial indicated potential utility of fibrates in preventing the progression of cardiovascular disease, but only in a subgroup of patients and relative to secondary or tertiary endpoints (diabetic retinopathy, microalbuminuria). The data of the recent Action to Control cardiovascular risk in diabetes (ACCORD) lipid trial indicated the failure of combination therapy with fenofibrate and simvastatin to reduce the risk of fatal cardiovascular events, non-fatal MI or non-fatal stroke as compared with simvastatin alone, with the exception of a subgroup of patients with hypertriglyceridaemia and low HDL cholesterol levels.

### Statins and Diabetes

Statin therapy is appropriate in a wide range of individuals with diabetes. A collaborative meta-analysis of 14 randomised trials of statin therapy showed that lowering LDL cholesterol by 1 mmol/l decreases the risk of cardiovascular events by about one-fifth, and that a greater reduction in LDL cholesterol is associated with a greater proportional reduction of major vascular events. In the analysed trials, the benefits of statin therapy were shown to be similar for both patients with hypertriglyceridaemia and low HDL cholesterol levels.

### Statins and the Risk of Incident Diabetes

Statin therapy is effective in reducing cardiovascular events and is safe and well tolerated; however, six randomised trials reported conflicting results about the development of diabetes in patients treated with statins. The West of Scotland coronary prevention study (WOSCOPS) published in 2001 showed a 30% risk reduction for incident diabetes in subjects treated with pravastatin. A more recent study, Justifications for the use of statins in prevention: an intervention trial evaluating rosuvastatin (JUPITER) showed that rosuvastatin was associated with a mild but significant increased incidence of diabetes. Similar results were obtained in another four studies with different statins, suggesting a small but detectable increase of diabetes incidence in subjects treated with statins, regardless of the drug and the dose. The mechanisms by which statins can induce diabetes are unclear; it is possible that statins, in addition to their cardiovascular protective effects, interfere with glucose metabolism. In experimental studies, atorvastatin reduces adipocyte maturation resulting in a lower GLUT4 and a higher GLUT1 expression in preadipocytes; as a consequence, a significant reduction of insulin-mediated glucose uptake was observed, possibly increasing glucose intolerance. This statin-induced insulin resistance may result from the inhibition of isoprenoid synthesis, due to the block of cholesterol biosynthesis; moreover, some data suggested that statins can directly interfere with insulin secretion.

### Table 1: Major Cardiovascular Events in Diabetic and Non-diabetic Patients Treated with Statins in 14 Randomised Trials

<table>
<thead>
<tr>
<th>Statin</th>
<th>Placebo/Control (%)</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>154 (11.9%)</td>
<td>134 (10.5%)</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>335 (9.2%)</td>
<td>293 (8.0%)</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>270 (16.0%)</td>
<td>216 (12.8%)</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>225 (34.8%)</td>
<td>215 (32.1%)</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>75 (5.2%)</td>
<td>93 (6.5%)</td>
</tr>
<tr>
<td>LIPID</td>
<td>126 (6.0%)</td>
<td>138 (6.6%)</td>
</tr>
<tr>
<td>PROSPER</td>
<td>165 (20.5%)</td>
<td>127 (15.8%)</td>
</tr>
<tr>
<td>MEGAC</td>
<td>172 (10.8%)</td>
<td>164 (10.1%)</td>
</tr>
<tr>
<td>ALLHAT-LTT</td>
<td>238 (16.4%)</td>
<td>212 (14.4%)</td>
</tr>
<tr>
<td>GISSI-3</td>
<td>96 (27.5%)</td>
<td>105 (30.6%)</td>
</tr>
<tr>
<td>PREVENZIONE</td>
<td>72 (4.5%)</td>
<td>74 (4.6%)</td>
</tr>
<tr>
<td>Overall</td>
<td>1.09 (1.02–1.17)</td>
<td></td>
</tr>
</tbody>
</table>

CI = confidence interval. Adapted from Sattar et al., 2010.
The addition of fenofibrate to simvastatin seems to benefit a group of patients with dyslipidaemia, defined as HDL cholesterol level ≤34 mg/dl and TG level ≥204 mg/dl (see Table 3). This finding is relevant, as the use of a combination therapy may benefit patients with type 2 diabetes and dyslipidaemia. This finding is consistent with the results of three previous trials (HHS, BIP, and FIELD trials),15–17 which showed that the patient who may benefit from fibrate therapy has a high TG level and low HDL cholesterol. As fibrates do not represent an optimal approach for reducing LDL cholesterol, fenofibrate therapy offers no benefit in terms of cardiovascular risk reduction to patients with normal serum levels of TG and HDL cholesterol. In conclusion, the ACCORD lipid trial does not support use of the combination of fenofibrate and simvastatin compared with simvastatin alone to reduce cardiovascular disease events in the majority of patients with type 2 diabetes mellitus who have HDL cholesterol and TG levels that are close to the normal range. The use of combination fenofibrate/simvastatin in subgroups of patients with type 2 diabetes could be appropriate, as suggested by current guidelines34 for subjects with high TG level and low HDL cholesterol level persistent despite statin therapy.

The results from SHARP are also relevant for patients with normal kidney function who are at high risk of major atherosclerotic events, as the combination of ezetimibe and a statin produced similar benefits to those resulting from the same LDL reduction achieved with a high-dose statin. These results suggest that patients who have high risk of major atherosclerotic events despite maximal tolerated statin therapy may benefit from adding ezetimibe to their statin therapy. As patients with diabetes often present with an impairment of their renal function, the results from SHARP may also be relevant for them.40

Conclusions

LDL lowering remains the main goal in diabetic patients, and the benefit appears to depend only on the degree of LDL reduction. The diabetic patient often presents with complex derangements of lipoprotein metabolism that result in an increase in plasma TG and low HDL cholesterol; in these patients the association with fibrates and/or nicotinic acid appears to be rational. The association with fibrates, however, appears to be effective only in patients with this complex lipoprotein disorder. Statins might trigger insulin resistance. The development of diabetes is clinically relevant; however, cardiovascular complications account for almost two-thirds of deaths in diabetic patients and the risk of development of diabetes is low in absolute terms. For these reasons, the protective cardiovascular effects of statins should not be underestimated, despite the potential risk of developing diabetes.


