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

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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 great 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

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Diabetes mellitus, a metabolic disorder defined by fasting glucose concentration ≥7.0 mmol/l or by glycated haemoglobin ≥6.5 %,[1] represents an established risk factor for coronary artery disease;[2,3] the number of people who have diabetes mellitus is predicted to rapidly rise in coming years,[4] 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.[5,6] 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,[7] 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 (5, 6), 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).[8] 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.[9]

To achieve this goal, statins are the drugs of choice; fibrates or nicotinic acid are often used,[9] 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.[8] However, it can induce insulin resistance, thus worsening hyperglycaemia.[10]

A number of studies, including the Collaborative atorvastatin diabetes study (CARDS),[11] the Helsinki heart study (HHS),[12] the Scandinavian simvastatin survival study (4S)[13] and the Cholesterol and recurrent events (CARE) study,[14] have shown that lipid-lowering therapy in type 2 diabetes significantly reduced the number of cardiac events,[8] with a risk reduction of 22–50 % with statins and up to 65 % with fibrates,

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.[8] The Bezafibrate infarction prevention (BIP) trial,[15] the HHS,[16] and the Fenofibrate intervention and event lowering in diabetes (FIELD) trial[17] 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[18] 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.[19] In the analysed trials, the benefits of statin therapy were shown to be similar for both diabetic and non-diabetic patients (see *Table 1*); no differences were observed between type 1 and type 2 diabetic patients.[20]

Statins and the Risk of Incident Diabetes

Statin therapy is effective in reducing cardiovascular events and is safe and well tolerated;[19–21] 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[22] 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)[23] 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,[24–27] 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.[28] In experimental studies, atorvastatin reduces adipocyte maturation resulting in a lower GLUT4 and a higher GLUT1 expression in preadipocytes;[29] as a consequence, a significant reduction of insulin-mediated glucose uptake was observed, possibly increasing glucose intolerance.[30] 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.[31,32]

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

Major Cardiovascular Events	Events (%) Treatment	Control	Rate Ratio (99 % CI)
Major Coronary Event			
Diabetes	776 (8.3 %)	979 (10.5 %)	0.78 (0.69–0.87)
No diabetes	2,561 (7.2 %)	3,441 (9.6 %)	0.77 (0.73–0.81)
Coronary Revascularisation			
Diabetes	491 (5.2 %)	627 (6.7 %)	0.75 (0.64–0.88)
No diabetes	2,129 (6.0 %)	2,807 (7.9 %)	0.76 (0.72–0.81)
Stroke			
Diabetes	407 (4.4 %)	501 (5.4 %)	0.79 (0.67–0.93)
No diabetes	933 (2.7 %)	1,116 (3.2 %)	0.84 (0.76–0.93)
Major Vascular Event			
Diabetes	1,465 (15.6 %)	1,782 (19.2 %)	0.79 (0.72–0.86)
No diabetes	4,889 (13.7 %)	6,212 (17.4 %)	0.79 (0.76–0.82)

CI = confidence interval. Adapted from Kearney et al., 2008.[20]

Table 2: Association Between Statins and Incident Diabetes in Randomised Trials

Study	n	Statin (%)	Placebo/ Control (%)	Odds Ratio (95 % CI)
Atorvastatin				
ASCOT-LLA	7,773	154 (11.9 %)	134 (10.5 %)	1.14 (0.89–1.46)
Simvastatin				
HPS	14,573	335 (9.2 %)	293 (8.0 %)	1.15 (0.98–1.35)
4S	4,242	198 (17.3 %)	193 (16.8 %)	1.03 (0.84–1.28)
Rosuvastatin				
JUPITER	17,802	270 (16.0 %)	216 (12.8 %)	1.26 (1.04–1.51)
CORONA	3,534	100 (20.9 %)	88 (18.5 %)	1.14 (0.84–1.55)
GISSI-HF	3,378	225 (34.8 %)	215 (32.1 %)	1.10 (0.89–1.35)
Pravastatin				
WOSCOPS	5,974	75 (5.2 %)	93 (6.5 %)	0.79 (0.58–1.10)
LIPID	6,997	126 (6.0 %)	138 (6.6 %)	0.91 (0.71–1.17)
PROSPER	5,023	165 (20.5 %)	127 (15.8 %)	1.32 (1.03–1.69)
MEGA	6,086	172 (10.8 %)	164 (10.1 %)	1.07 (0.86–1.35)
ALLHAT-LLT	6,087	238 (16.4 %)	212 (14.4 %)	1.15 (0.95–1.41)
GISSI PREVENZIONE	3,460	96 (27.5 %)	105 (30.6 %)	0.89 (0.67–1.20)
Lovastatin				
AFCAPS/ TexCAPS	6,211	72 (4.5 %)	74 (4.6 %)	0.98 (0.70–1.38)
Overall				1.09 (1.02–1.17)

CI = confidence interval. Adapted from Sattar et al., 2010.[33]

A recent meta-analysis of 13 randomised statin trials showed that subjects treated with statins are at increased risk of developing diabetes, independently of the type of statin used.[33] Over a mean of four years, in 91,140 non-diabetic subjects, 2,226 treated with statins and 2,052 controls developed diabetes, with a 9 % increase in risk (see *Table 2*). The risk seems to be related to age, being present mainly in older patients and virtually absent in people under 60 years. However, this risk is small in absolute terms and the cardiovascular benefit for individuals who need statin therapy is still important. This means that patients with high or moderate cardiovascular risk should continue their statin therapy; on the other hand, patients with low cardiovascular risk should be followed for incident diabetes when treated with statins.

Table 3: Major Cardiovascular Events in Subgroups in the ACCORD Lipid Trial

Subgroup	Fenofibrate % of Events (n)	Placebo % of Events (n)	Hazard Ratio (95 % CI)	p-value for Interaction
Overall	10.52 (2,765)	11.26 (2,753)	0.92 (0.79–1.08)	
Sex				
Female	9.05 (851)	6.64 (843)	1.38 (0.98–1.95)	0.01
Male	11.18 (1,914)	13.30 (1,910)	0.82 (0.69–0.99)	
Race				
Non-white	9.70 (856)	8.22 (888)	1.15 (0.84–1.57)	0.09
White	10.90 (1,909)	12.71 (1,865)	0.84 (0.70–1.02)	
Lipoproteins				
High TG/ low HDL*	12.37 (485)	17.32 (456)	0.69 (0.49–0.97)	
All others	10.11 (2,264)	10.11 (2,284)	1.00	

**TG ≥204 mg/dl, HDL ≤34 mg/dl*
CI = confidence interval; HDL = high-density lipoprotein; TG = triglyceride.
Adapted from Ginsberg et al., 2010.[18]

Effects of Combination Lipid Therapy in Type 2 Diabetes

Type 2 diabetes mellitus is associated with an increased cardiovascular risk,[7,34–36] due in part to associated risk factors such as hypertension and dyslipidaemia. The ACCORD study[37] was designed to test the effect of an intensive control of glucose and blood pressure or plasma lipids on cardiovascular events. The study considered 10,251 patients with type 2 diabetes and high cardiovascular risk who were randomly assigned to either intensive or standard glycaemic control.

Fibrates are effective agents for raising serum levels of HDL and decreasing levels of TGs. A number of trials have demonstrated that, among patients with high TGs and low HDL, fibrate therapy reduces cardiovascular morbidity in diabetic and non-diabetic subjects. A subgroup of patients of the ACCORD study (5,518 patients) were enrolled in the ACCORD lipid trial,[18] designed to test whether combination therapy with a statin plus a fibrate would reduce cardiovascular disease, compared with statin monotherapy, in people with type 2 diabetes mellitus at high risk of cardiovascular disease. These patients had a glycated haemoglobin level of 7.5 % or more, LDL cholesterol between 60 and 180 mg/dl, HDL cholesterol level <55 mg/dl for women and blacks and <50 mg/dl for other individuals and TGs <750 mg/dl, if not receiving therapy, and <400 mg/dl, if receiving lipid therapy. Patients were randomly assigned to receive simvastatin alone or simvastatin plus fenofibrate, to test the hypothesis that the use of fenofibrate to increase HDL cholesterol levels and decrease TG levels in patients with type 2 diabetes taking simvastatin would increase the cardiovascular benefit compared with simvastatin alone, with a mean duration of follow-up of 4.7 years. The addition of fenofibrate to the statin therapy did not significantly improve the rates of the primary outcome (major fatal or non-fatal cardiovascular events) or any secondary outcomes, including major coronary events (coronary mortality, non-fatal MI or unstable angina), non-fatal MI, stroke, all-cause mortality or cardiovascular mortality. Subgroup analysis suggested a different effect according to sex, with a benefit in men and a trend towards an increased risk in women when fenofibrate was added to simvastatin (see *Table 3*). Differences were also observed according to baseline lipid levels: 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. This can be explained by the fact that fibrates reduce TG and raise 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 guidelines[38] for subjects with high TG level and low HDL cholesterol level persistent despite statin therapy.

The Study of heart and renal protection (SHARP) trial[39] compared the combination therapy of simvastatin and ezetimibe to placebo in 9,438 patients with chronic kidney disease (CKD). One-third of these patients required dialysis, and all had lost at least 50 % of their normal kidney function. People with CKD tend to have a very high cardiovascular risk; the SHARP trial showed that lowering LDL cholesterol with combination therapy decreased major atherosclerotic events by 17 % in these patients. This combined therapy may be particularly safe for kidney patients, as it avoids the possible side effects with high statin doses.

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. ■

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