Dyslipidaemia in diabetes - A GP guide (general practice physicians)

* How much more at risk of CHD are diabetic patients compared to the general population?

* Which are the most important modifiable risk factors?

* What are the best treatment options for diabetic dyslipidaemia?

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Patients with diabetes have a significantly increased risk of CHD, and cardiovascular events may occur in these patients without warning signs or symptoms - the risks are sufficiently great that even diabetic patients with borderline high cholesterol should be treated with lipid-lowering medication following evaluation of their CHD risk.

Effective management of CHD in patients with diabetes is now an important priority for GPs. This has been highlighted in the National Service Framework (NSF) for CHD,1 which includes cholesterol targets for patients who have or are at high risk of CHD, including all people with diabetes. An NSF for diabetes expected soon is likely to provide further guidance on managing CHD in these patients.

* The risks A patient with type 2 diabetes has a two- to five-fold increase in age-adjusted risk of mortality from CHD2 - and the current thinking is that a patient with diabetes, but without a previous history of cardiovascular disease, is considered to be at the same cardiovascular risk as a non-diabetic patient who has sustained an MI.

When a diabetic patient develops cardiovascular disease (CVD), their prognosis for survival is much worse than for a non-diabetic CVD patient,3 and more than 70 per cent of patients with diabetes die from CVD.2

In fact, although patients with diabetes account for only 3-5 per cent of the population, they represent 10-15 per cent of those admitted to hospital with MI and up to 20 per cent of those who die.4

Moreover, atherosclerosis can be well advanced before symptoms of CHD are apparent and therefore before treatment is initiated.3

When managing patients with diabetes, all risk factors for CHD need to be taken into account. The UK Prospective Diabetes Study (UKPDS) ranked dyslipidaemia as the most important modifiable risk factor for CHD in people with type 2 diabetes, ahead of hyperglycaemia, hypertension and smoking.5

* Dyslipidaemia in diabetes patients Lipid profiles in patients with diabetes are characterised by low levels of high-density lipoprotein (HDL) cholesterol, and elevated low- and very low-density lipoproteins (LDL and VLDL). This combination is often termed diabetic dyslipidaemia, and represents a set of lipoprotein abnormalities that promote atherosclerosis.3

The American Diabetes Association recommends a hierarchy of priorities for the management of diabetic dyslipidaemia, starting with lowering LDL cholesterol, then increasing HDL cholesterol and thirdly lowering triglycerides.6

* LDL cholesterol Total and LDL cholesterol levels are similar in both diabetic and non-diabetic people. It was therefore originally thought that dyslipidaemia was not responsible for the increased cardiovascular risk seen in patients with diabetes and that cholesterol-lowering therapy might not be of benefit.

However, statin trials clearly demonstrated that LDL cholesterol levels were important and in fact a borderline high LDL cholesterol level (3.4-4.1 mmol/L) in a diabetic patient is equivalent, in terms of risk, to a much higher LDL cholesterol in a patient without diabetes.

Diabetes patients with a raised LDL cholesterol level, therefore, experience an even greater risk of CHD than non-diabetic people with the same level of cholesterol. One trial showed that for every 1mmol/L increase in LDL cholesterol there was a corresponding 1.57-fold greater risk of coronary artery disease for patients with diabetes.5

* HDL cholesterol Low HDL cholesterol is a risk factor for CHD in patients both with and without diabetes. In a study involving 313 type 2 diabetes patients, HDL cholesterol levels were shown to be the most powerful predictor of future CHD.7

* Triglycerides Another risk factor for CHD in the diabetic and non-diabetic population is increased plasma triglyceride.8 Evidence suggests that increased triglyceride levels may lead to increased small dense LDL cholesterol, which promotes atherosclerosis.9

* Cholesterol targets in diabetes Guidelines for the management of CHD include the Joint British Recommendations (JBR) on Prevention of CHD in Clinical Practice10 and the NSF for CHD.1
Both the JBR and the NSF for CHD set targets for reducing total serum cholesterol concentrations either to less than 5mmol/L,1,10 (or by 20-25 per cent, whichever is greater1) and LDL cholesterol to below 3mmol/L,1,10 (or by 30 per cent, whichever is greater1), in patients with or at high risk of CHD, which includes people with diabetes.

* Treatment options Many patients with diabetes die from CHD, so it is important to find methods to reduce this risk. Improving glycaemic control and treating hypertension are obvious management options, although the former has only a small effect (if any) in decreasing CHD.11

Recent trials using aggressive LDL cholesterol-lowering therapy (4S and CARE) have shown that patients with diabetes treated with statins have reductions in morbidity and mortality that are equivalent to the results achieved in patients without diabetes.12,13

* Statins Statins are the first-line therapy for lowering LDL cholesterol.1,10 They are effective at lowering total and LDL cholesterol without altering glycaemic control in diabetic patients.

The ability of statins to achieve defined cholesterol targets in as many patients as possible is now a key factor. The ideal statin is one that meets all the above criteria with a minimum need for dose titration - that is, it is one that is effective at its starting dose. This will improve compliance, as well as making life easier for the clinician.

Although all the statins are effective at reducing cholesterol, there are significant differences in the scale of that reduction. Table 1 summarises the efficacy of each of the five statins at their starting dose in lowering LDL and total cholesterol. Data on the percentage of hypercholesterolaemic patients who could be expected to achieve a target LDL cholesterol of below 2.8mmol/L at each of the starting doses is also included17 (although this is lower than the NSF’s target of 3.0mmol/L for LDL cholesterol).

In addition to their well-established efficacy in lowering LDL cholesterol, statins also achieve significant increases in HDL cholesterol levels, which are of similar magnitude across the class. Two of the statins, atorvastatin and simvastatin, are licensed in the UK to raise HDL cholesterol levels.

Many of these patients also have hypertriglyceridaemia. In fact the American Diabetes Association suggest that the first line of treatment of a patient with diabetes and combined hyperlipidaemia is improved glucose control plus a high-dose statin. If this does not achieve the lipid targets, the addition of a fibrate is then recommended.6

* Fibrates are the first-line treatment for raising HDL cholesterol and for lowering triglyceride levels in patients with dyslipidaemia. Results from the recent Diabetes Atherosclerosis Intervention Study (DAIS) have shown that fenofibrate reduced angiographic progression of focal lesions by 40 per cent over three years, compared with placebo in patients with type 2 diabetes (presented at the International Atherosclerosis Society meeting, Stockholm, 2000).

There is a good case for the addition of fibrates to statin therapy to optimise management of lipids in patients with type 2 diabetes. However, fibrates are not recommended in people with impaired renal function, which is a relatively common problem in diabetic patients and linked with a very high risk of CHD.18

Safety note: Bayer has recently voluntarily withdrawn cerivastatin from the market. This is because of the increased risk of rhabdomyolysis when co-prescribed with gemfibrozil. This problem can present as muscle pain with elevated creatine phosphokinase (CPK), and can (rarely) lead to death. This can occur with all statins, particularly if there is associated renal impairment or hypothyroidism.
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The risk is increased if fibrates are taken concurrently, but is still small.

The risk of rhabdomyolysis with cerivastatin and gemfibrozil when co-prescribed appears significantly greater, however, than with the other statins. For this reason, marketing and distribution has been suspended while a risk:benefit assessment is made.

References


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