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# Strategies for the Management of Diabetic Dyslipidaemia

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## Abstract

Atherosclerosis, the complication most prominently associated with type 2 diabetes and cardiovascular disease, represents a major burden for both individuals and society. Mortality rates associated with cardiovascular disease among patients with type 2 diabetes are at least 3 times those in the general population, and although 'traditional' cardiovascular risk factors affect patients with this disorder as they do other individuals, they do not account for the excess risk attached to type 2 diabetes. There is a growing body of evidence to show that hyperglycaemia and dyslipidaemia are connected with this excess cardiovascular risk: hypertriglyceridaemia has been implicated in several prospective clinical studies, and available data suggest that low density lipoprotein (LDL)-cholesterol is more atherogenic in patients with type 2 diabetes than in other individuals. It is possible that this increased atherogenicity is associated with a preponderance of small, dense LDL particles that are more prone to oxidation and glycation than larger fractions and that may be involved in endothelial dysfunction. These findings lead to the recommendation of mandatory global risk assessment, accompanied by good glycaemic control, aggressive lowering of serum levels of LDL-cholesterol and maintenance of serum levels of triglyceride at the lowest possible level in patients with type 2 diabetes.

Cardiovascular disease accounts for approximately 75% of deaths among patients with diabetes, and mortality rates for coronary artery disease (CAD) are at least 3 times higher in these patients than in the general population.[1,2] There is also evidence to suggest that CAD is more prevalent in individuals with diabetes than in those who do not have the disease.[1]

Angiographic data from studies in 2273 patients with diabetes and 15 314 nondiabetic individuals[3-7] showed diabetes to be associated with significant increases in prevalence of multivessel disease (i.e. extensive atherosclerosis) [table I]. Furthermore, recently published data from nearly 4065 patients (620 with diabetes and 3445 without diabetes) with first myocardial infarction showed significantly higher short term (28-day) mortality rates in patients with than in those without diabetes; this excess mortality in patients with diabetes was associated with a higher incidence of congestive heart failure.[8] The same study also showed the 1-year mortality rate to be significantly higher ($p < 0.001$) in patients with diabetes. On the basis of these data, 44% of men and 37% of women with diabetes may be expected to die within 1 year of their first myocardial infarction, figures that carry profound implications in terms of burden of care to healthcare providers. Indeed, estimated hospitalisation costs of diabetic complications for the US in 1987 indicate that, of a total of $US5091 million, 74% was accounted for by cardiovascular disease (cardiac disease, stroke and arterial disease).[9]

**Table I.** Angiographic data in studies involving patients with diabetes

| Study | No. of patients with diabetes | No. of nondiabetic individuals | Multivessel disease as shown by angiography (%) | |
|---|---|---|---|---|
| | | | patients with diabetes | nondiabetic individuals |
| Granger et al.[3] | 148 | 923 | 65 | 46 |
| Mueller et al.[4] | 439[a] | 2900 | 40.8 | 26.8 |
| Orlander et al.[5] | 236 | 348 | 58.2 | 41.6 |
| Stein et al.[6] | 1133 | 9300 | 32.4[b] | 28.2 |
| Vigorito et al.[7] | 317 | 1843 | 85.8 | 77.7 |

a Not all patients underwent angiography.

b Patients selected for angioplasty.

## 1. Contribution of Risk Factors to Cardiovascular Disease in Diabetes

The presence of diabetes was associated with considerably higher rates of death due to cardiovascular disease in the Multiple Risk Factor Intervention Trial (MRFIT).[2] Data summarised in figure 1 show that although death rates increase in the general population with the presence of increasing numbers of 'traditional' risk factors (smoking, hypertension and high serum levels of cholesterol), consistently larger increases are seen in patients with diabetes. This suggests the presence of a factor related to diabetes that increases the risk of death from cardiovascular disease. Potential candidates include hyperglycaemia, diabetic dyslipidaemia, hyperinsulinaemia/insulin resistance, haemostatic abnormalities, oxidative stress, vascular dysfunction and the presence of advanced glycosylation end-products. Of these, hyperglycaemia and dyslipidaemia are the two that are most readily prevented or treated.

### 1.1 Dyslipidaemia

Dyslipidaemia in type 2 diabetes consists of elevation of serum triglyceride levels, excessive postprandial lipaemia and accumulation of remnant particles,[10] a preponderance of small, dense low density lipoprotein (LDL) particles,[11,12] and reduced high density lipoprotein (HDL)-cholesterol levels with a preponderance of small, dense HDL particles.[13-16] All have atherogenic potential and together represent a constellation of interrelated risk factors.

Identification of the most atherogenic lipid component(s) is important for optimising treatment. Six studies in approximately 4500 patients with follow-up periods ranging from 7 to 13 years have shown a link between high serum levels of triglyceride and coronary events in patients with type 2 diabetes.[16] High serum levels of triglyceride were associated with coronary heart disease (CHD)-related events in 5 of these studies (H.S. Abu-Lebdeh et al. and G. Assmann et al., personal communications),[17-20] and with death in three.[17,18,20] In addition, 7-year data from Lehto and co-workers[20] indicate an association between increased serum triglyceride levels and decreased levels of HDL-cholesterol in relation to the incidence of CHD-related events and mortality in patients with type 2 diabetes (fig. 2).

Recently published results from the United Kingdom Prospective Diabetes Study (UKPDS)

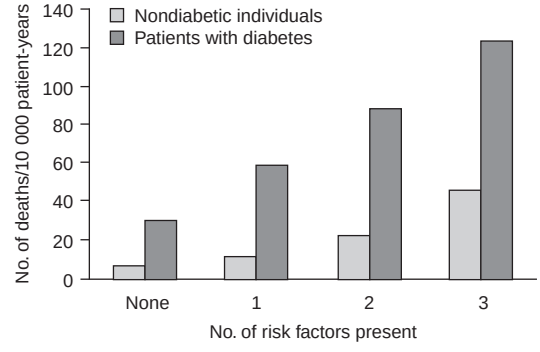


**Fig. 1.** Rates of death due to cardiovascular disease versus numbers of 'traditional' risk factors (smoking, hypertension and high serum levels of cholesterol) in the MRFIT study.[2]

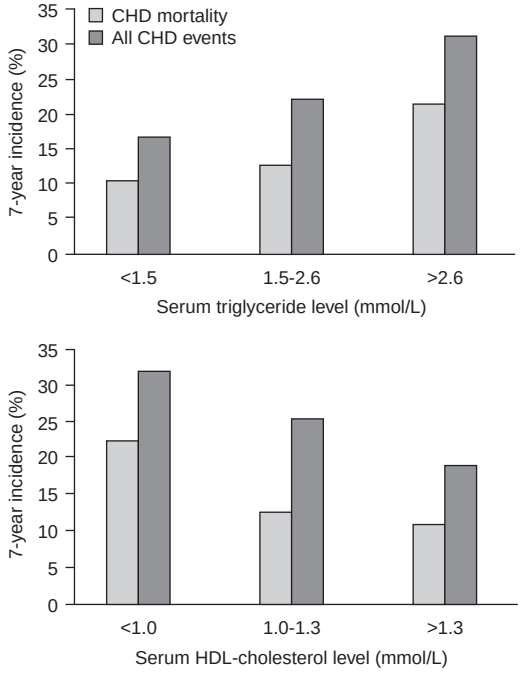


**Fig. 2.** Seven-year incidence of coronary heart disease (CHD)-related events and CHD-related mortality in patients with type 2 diabetes shown in relation to tertiles of serum levels of triglyceride and high density lipoprotein (HDL)-cholesterol.[20]

included data on risk factors for CAD in 3055 patients with type 2 diabetes (1564 men and 1129 women). Over a median duration of follow-up of 7.9 years, 355 (11%) of these patients had a myocardial infarction or developed angina. Relevant risk factors in terms of estimated hazard ratios were found to be increased age, increased serum LDL-cholesterol levels and decreased HDL-cholesterol levels. Glycaemic control, as shown by levels of haemoglobin $A_{1c}$ ($HbA_{1c}$), increased blood pressure and smoking were also found to contribute to increased risk of CAD.[21] Overall, the data show a quintet of modifiable risk factors for CAD in patients with type 2 diabetes:

- raised serum LDL-cholesterol levels
- low serum HDL-cholesterol levels
- raised blood pressure
- hyperglycaemia
- smoking.

### 1.2 Enhanced Atherogenicity of LDL-Cholesterol in Persons with Diabetes

Data from the MRFIT study[2] have shown that, for any given serum level of cholesterol, the risk of cardiovascular mortality is higher in patients with type 2 diabetes than in those without diabetes (fig. 3). When viewed in the light of the data reviewed above, this indicates that LDL-cholesterol is more atherogenic in individuals with diabetes than in the general population. In support of this premise, it is known that there is a preponderance of small, dense LDL particles in the circulation of persons with type 2 diabetes,[11,12,16] and that LDL is modified in these individuals by glycation[22,23] and oxidation.[24] Furthermore, there are several mechanisms by which small, dense LDL particles may exert greater atherogenicity than larger, more buoyant particles.[11] These include increased oxidation, increased affinity for the arterial wall, and alteration of metabolic properties (interference with clearance via the LDL receptor pathway). Recent data also show an association between LDL particle size and endothelial dysfunction.[25] These data support the hypothesis that normal levels of LDL-cholesterol are associated with increased atherogenicity in patients with type 2 diabetes.

Evidence is also available from clinical studies to show cardiovascular benefit associated with lowering of LDL-cholesterol in patients with type 2 diabetes. Recent data from subgroup analyses in

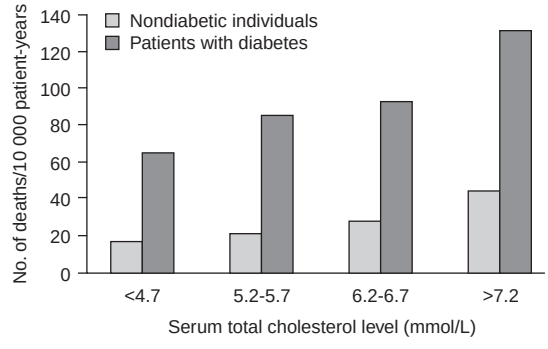


**Fig. 3.** Rates of death due to cardiovascular disease versus serum total cholesterol levels in individuals with and without diabetes who took part in the MRFIT study.[2]

**Table II.** Target serum lipid levels in patients with diabetes

| Lipid species or parameter | Target serum level |
|---|---|
| Triglycerides | <1.7 mmol/L |
| HDL-cholesterol | >1.1 mmol/L (males) |
| | >0.9 mmol/L (females) |
| LDL-cholesterol | <2.6 mmol/L |
| Total cholesterol : HDL-cholesterol ratio | <4.0 |

**HDL** = high density lipoprotein; **LDL** = low density lipoprotein.

trials in which patients received statin therapy to lower serum cholesterol levels (4S and CARE[26,27]) indicate these benefits to be at least as great in patients with type 2 diabetes as in nondiabetic individuals. Treatment with simvastatin in the 4S trial was associated with a 55% reduction in coronary risk in persons with diabetes, a reduction much greater than that seen in nondiabetic patients.

## 2. Priorities in the Management of Diabetic Dyslipidaemia

The data reported above suggest that the most important management strategies in diabetic dyslipidaemia should be lowering of serum levels of LDL-cholesterol and triglycerides and raising of serum levels of HDL-cholesterol. Recommended target serum levels for different lipid subtypes and fractions are summarised in table II.[28]

Lifestyle modification is the first stage in the treatment of dyslipidaemia in patients with type 2 diabetes, and should include dietary modification, increased physical activity and smoking cessation. This should be followed by improvements in glycaemic control and the use of lipid-lowering drugs, if necessary. Statins are highly effective in reducing serum LDL-cholesterol levels and do not affect glycaemic control, and reductions in serum triglyceride levels may be achieved with fibrins or high doses of statins.

The biguanide antihyperglycaemic agent metformin has been reported in several studies to exert beneficial effects on serum lipid profiles of both obese and lean patients with type 2 diabetes, hypertension and/or hyperlipidaemia (reviewed by Dunn & Peters[29]). It is also known that serum lipid profiles are improved by the achievement of better metabolic control.[14] However, there is a misconception that serum lipid levels will return to 'normal' if glycaemic control is improved. In fact, optimal lipid levels are rarely attained, even by patients who achieve excellent control of blood glucose levels.

Thus, to reduce the burden of cardiovascular disease in patients with type 2 diabetes, global risk assessment is mandatory. This should be accompanied by good glycaemic control, aggressive lowering of serum levels of LDL-cholesterol and maintenance of serum levels of triglyceride at the lowest possible level.

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