



Safety of Combination Lipid Lowering Therapy

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INTRODUCTION

Patients with diabetes are twice as likely as non-diabetics to have abnormal serum lipid profile. Combined hyperlipidemia, a highly atherogenic lipid disorder characterised by increased LDL cholesterol, elevated triglycerides and low HDL cholesterol is common in patients with type 2 diabetes.¹ In some of these patients, dyslipidemia is secondary to derangement in intermediary metabolism caused by insulin deficiency and insulin resistance in which case, improved control of hyperglycaemia will mitigate the dyslipidemia. Consequently, some degree of dyslipidemia usually persists despite good glycaemic control.² Some diabetic patients will have concomitant genetic hyperlipidemia; in these patients, diabetes mellitus worsens the dyslipidemia, but correction of hyperglycaemia will not normalize lipid levels.³

Type 2 diabetic patients have a high frequency of dyslipidemia, which along with obesity, hypertension and hyperglycaemia may contribute significantly to accelerated coronary atherosclerosis.⁴ Because risk factors for coronary heart disease (CHD) are additive and perhaps multiplicative, even mild degrees of dyslipidemia may enhance CHD risk. Thus, managing dyslipidemia in patients with diabetes is essential for preventing cardiovascular events, which are increased two to four – fold in this population. Lipid modifying drugs are therefore recommended in this setting.

PREVALENCE OF DYSLIPIDEMIA

The prevalence of dyslipidemia in type 2 diabetic patients undoubtedly varies among different population. The World Health Organization Multinational Study of vascular disease in diabetic subjects revealed a high frequency of both

hypercholesterolemia and hypertriglyceridemia among adult diabetic individuals from many countries (Table 1).^{5,6} In many studies, the dyslipidemia in type 2 diabetic subjects relative to non-diabetic subjects is more severe in women than in diabetic men,^{7,8} which is consistent with the relatively greater risk of CHD in diabetic women than in diabetic men.^{9,10} The Diabetes Intervention Study found a two-fold increase hyperlipidemia in men and women with type 2 diabetes compared with the general population.¹¹ Like wise, the Framingham Heart Study noted that hypertriglyceridemia and reduced levels of HDL cholesterol were increased two fold in adult diabetic patients compared with non – diabetic subjects of both sexes.⁸ The Prospective Cardiovascular Munster Study further confirmed a two – to three fold increase in prevalence of hypertriglyceridemia, mixed hyperlipidemia and low levels of HDL cholesterol in middle – aged subjects with type 2 diabetes.¹²

LIPOPROTEIN RISK FACTORS

Relatively few prospective studies of lipids and lipoproteins as predictors of CHD have been reported in type 2 diabetic subjects. In the large Multiple Risk Factors Intervention Trial (MRFIT), total cholesterol as well as cigarette smoking and blood pressure predicted the development of cardiovascular disease in diabetic and non-diabetic subjects, suggesting that risk factors may be predictive in both groups. In a Finnish study, increased triglyceride levels and decreased HDL cholesterol levels (but neither LDL nor non HDL cholesterol) predicted CHD in well-characterized type 2 diabetic subjects. However, after adjustment for HDL cholesterol, neither total nor VLDL triglycerides predicted CHD. Baseline data from the United Kingdom Prospective Diabetes Study (UKPDS) showed that both decreased HDL and elevated LDL predicted CHD.¹³ Recent reports of the 11 – year follow – up of patients with type 2 diabetes or with impaired glucose tolerance from the Paris Prospective study indicate that hypertriglyceridemia may be the most potent lipid predictor for CHD mortality.¹⁴

LIPID LOWERING AGENTS

No specific studies have been done on the effects of lipid – lowering agents on subsequent CHD specifically in diabetic patients. However, a number of clinical trials have included small number of adult type 2 diabetic subjects. A sub group analysis on diabetic patients included in the Helsinki Heart Study, a 5 – year CHD primary prevention trial using gemfibrozil as a lipid – lowering drug, randomized to double – blind treatment

Table 1 : Prevalence of dyslipidemia in adults patients with diabetes: World Health Organization Multinational Study

	Men (%)	Women (%)	Both (%)
Plasma cholesterol (mM)*			
≥ 6.72	22.6	23.5	23.1
4.65 – 6.70	58.2	59.3	58.8
< 4.65	19.3	17.2	18.2
Plasma triglyceride (mM)#			
≥ 2.82			19.2
1.13 – 2.81			56.2
< 1.13			24.6
* Data on 3189 men and 3295 Women			
# Data from 5 of 14 centres on 1911 subjects			

showed a 5 – year incidence of major CHD events (CHD death or non- fatal myocardial infarction) in diabetic patients was 3.4% in the gemfibrozil group and 10.5% in the placebo group.¹⁵ The Scandinavian Simvastatin Survival Study (4S) trial reported that Simvastatin significantly reduced CHD incidence and total mortality in diabetic subjects with high LDL cholesterol and with previous clinical CHD.¹⁶ Pravastatin reduced CHD incidence significantly in diabetic subjects with average LDL levels and with previous clinical CHD, an outcome of Cholesterol and Recurrent Events (CARE) study. In the Veterans Affairs High – Density Lipoprotein Cholesterol Intervention Trial (VA – HIT), gemfibrozil was associated with a 24% decrease in cardiovascular events in diabetic subjects with prior cardiovascular disease.¹⁷

COMBINATION THERAPY

Although previous studies^{18,19} have shown that monotherapy can improve the lipid profile in patients with type 2 diabetes and combined hyperlipidemia, however these affect different aspects of lipoprotein metabolism. Hence, it is difficult to modify the lipid profile of the patients with type 2 diabetes and combined hyperlipidemia using monotherapy with either statin or fibrate.

Lipid-lowering combination regimens represent an emerging clinical paradigm to meet increasingly stringent consensus lipoprotein targets for coronary prevention. American Diabetes Association (ADA) and the National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III)^{20,21} guidelines suggests that combination therapy should be considered for patients with mixed dyslipidemia with inadequately controlled non-HDL cholesterol and / or triglyceride levels.

A number of studies have been focused on the efficacy, and safety of a statin – fibrate combination with combined hyperlipidemia. The combination of statin with a fibrate was given from a period varying between 16 weeks to 2 years in different studies.²²⁻²⁴ These studies demonstrated 28 – 42 % reduction in LDL cholesterol, 41 – 49% reduction in triglyceride and 8 – 25% increase in HDL cholesterol with the combination. In a study combining Simvastatin (20 mg / day) and Bezafibrate (400 mg/day) had moderate results on total (23%) and LDL (29%) cholesterol reduction, although drug combination significantly reduced triglyceride levels by 42% and increased HDL cholesterol by 25%.²⁵

Recently clinical studies^{24,26} have been conducted to compare the efficacy of concomitant therapy with atorvastatin and fenofibrate to monotherapy with either agent on diabetic and non-diabetic patients with combined hyperlipidemia. The concomitant administration proved to be well tolerated by the study population and there were no significant changes in the level of muscle and liver enzymes.

CONCLUSION

Type 2 diabetes is a metabolic syndrome associated with an increased risk for all manifestations of atherosclerotic vascular disease. As in non-diabetic individuals, lipid may be affected by factors unrelated to glycaemia or insulin resistance, such as renal disease, hypothyroidism and the frequent occurrence of genetically determined lipoprotein disorders (e.g. familial combined hyperlipidemia and familial hypertriglyceridemia). These genetic disorders may contribute to the severe hypertriglyceridemia seen

in some patients with diabetes. Furthermore, use of alcohol and estrogen may also contribute to hypertriglyceridemia. Good glycaemic control appears to improve but does not normalize these abnormalities.

The landmark survival trials, the Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Event Study (CARE) and The West of Scotland Coronary Prevention Study (WOSCOPS) showed that considerable reduction in LDL cholesterol levels induces clear clinical beneficial effects for high-risk patients. Therefore, patients with diabetes and combined hyperlipidemia will require pharmacotherapy or lifestyle modifications to correct their lipid abnormalities.

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