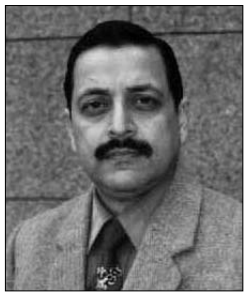

# Statins in Diabetes

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## ABSTRACT

For patients with Type 2 diabetes mellitus, lipid lowering interventions remain the cornerstone of treatment to reduce the risk of vascular complications. According to the UKPDS report, eventhough intensive glucose control significantly reduced microvascular events such as retinopathy, it produced only a modest and nonsignificant reduction in macrovascular events such as myocardial infarction and stroke. LDL-C is accepted as the strongest predictor of CHD risk in persons with diabetes and the treatment goal for LDL-C in Diabetes is <100 mg / dl. It has been observed that even after effective management of blood glucose, there is only a modest improvement in the plasma levels of LDL-C and this improvement frequently does not meet the recommended target levels. Current evidence favours statins as first-line drugs to reduce LDL-C in the treatment of diabetic dyslipidemia. Higher dose statins may also help reduce elevated plasma triglycerides. One of the major advantages with statins is that they are well-tolerated drugs with excellent safety record and large clinical trials have clearly demonstrated their beneficial effect in diabetes. Statins are effective in primary prevention of CHD in patients with diabetes and in patients who had a history of peripheral or carotid atherosclerosis but not CHD. For secondary prevention too, the utility and benefit of statins has been clearly established. Some studies recommend that use of statins should be considered routinely for patients with diabetes. Statins are more than just hypolipidemic agents. The pleiotropic benefits of statins include improved endothelial function and stabilization of atheromatous plaque. There is also some evidence suggesting a positive effect of statins on insulin resistance. Considerable interest has been generated by the experimental reports stating that statins carry the potential to decrease proteinuria and progressive decline in renal function. In addition, there is also evidence that statins play a useful role in osteoporosis, dementia and immunomodulation.

The risk of coronary heart disease (CHD) death and serious nonfatal CHD events is markedly increased in diabetic patients in comparison to non-diabetic individuals. This is a well established fact hardly requiring any reiteration.[1-4] Furthermore, clinically manifest CHD has a worse prognosis in diabetic patients than in nondiabetic patients.[5,6]

An important initial step, therefore, in reducing the overall burden of atherosclerotic disease as well as various microvascular and macrovascular complications of diabetes is to prevent progression to Type 2 diabetes mellitus in individuals at risk. Great success in this endeavour can be achieved through lifestyle changes including reduced intake of saturated fats and cholesterol, increased intake of fiber, reduction in body weight and increase in physical activity. This is evident from recommendations of, among others, the widely quoted National Cholesterol Education Program, the Joint European Studies and the US trial conducted by the Diabetes Prevention Program Research Group.[7-9]

For patients already having Type 2 diabetes mellitus, lipid lowering interventions remain the cornerstone of treatment to reduce the risk of diabetic vascular complications. According to the UKPDS, even though intensive glucose control significantly reduced microvascular events such as retinopathy, it produced only a modest and nonsignificant reduction in macrovascular events such as myocardial infarction and stroke.[10]

## STATINS - THE FIRST CHOICE

Statin therapy to reduce low-density lipoprotein (LDL) cholesterol is the first choice in treatment of diabetic dyslipidemia.[11]

The term diabetic dyslipidemia essentially refers to atherogenic dyslipidemia occurring in persons with Type 2 diabetes mellitus.[12] It is characterised by elevated triglycerides, small LDL particles and low high density lipoprotein (HDL) cholesterol concentrations. Diabetic dyslipidemia must be considered as one component of the metabolic syndrome, which is exceedingly common in persons with Type 2 diabetes.

## TREATMENT GOALS

In case of diabetic dyslipidemia, although some observational studies suggest that low HDL-cholesterol and hypertriglyceridemia

may be more predictive than elevated LDL-cholesterol levels, the results of interventional clinical trials using statins strongly favour LDL-cholesterol lowering as the primary therapeutic aim.[13,14] LDL-C is generally accepted as the strongest predictor of CHD risk in people with diabetes.

Since diabetes falls in the category of CHD risk equivalent, the goal for LDL cholesterol in persons with diabetes, particularly Type 2 diabetes mellitus, is < 100 mg/dl. This opinion is supported by the American Diabetes Association recommendations.[15] Therapeutic lifestyle changes should be started in all persons when LDL cholesterol is ≥ 130 mg/dl. Most persons with diabetes will require an LDL-lowering drug to reach the LDL goal of <100 mg/dl. If the patient also has high triglycerides (≥ 200 mg / dl), non-HDL cholesterol will be a secondary target. Simultaneous control of other risk factors is essential.

Strict glycemic control and optimisation of metabolic control are important prerequisites in the management of diabetic dyslipidemia. Hepatic LDL receptors, the major regulators of plasma LDL level, are dependent on insulin and, total and LDL-cholesterol levels may therefore decline with improved glycemia. Elevated triglyceride levels may respond even more to the use of insulin to attain good glycemic control.

When the non-pharmacological measures to treat diabetic dyslipidemia prove inadequate, specific lipid-lowering drugs are indicated. These commonly include 1) 3-hydroxy-3methyl-glutaryl CoA (HMG-CoA) reductase inhibitors (STATINS) 2) Fibric acid derivatives (Fibrates) 3) Bile acid sequestrants (Resins) 4) Nicotinic acid (Niacin) 5) Probucol 6) Gugulipid 7) Combination of estrogen and progesterone and 8) Selective estrogen receptor modulators (SERMs).

## ADVANTAGE WITH STATINS

The HMG-CoA reductase inhibitors (statins) reduce intracellular cholesterol synthesis, thereby upregulating the expression of hepatic LDL receptors and leading to increased clearance of LDL – cholesterol from the circulation. LDL cholesterol and apoprotein B concentration then decline by about 25-30%.

One of the major advantages with statins is that they are well-tolerated drugs with excellent safety record and large clinical trails have clearly demonstrated their beneficial effect on LDL-cholesterol levels.

Reductions of approximately 25% have generally been observed in coronary events with the use of statins.

Higher dose statins, particularly in diabetic dyslipidemia, may also reduce elevated plasma triglyceride levels and other effects such as improved endothelial function and stabilization of atheromatous plaques may also be important.

Improvements in low HDL-cholesterol are less marked, but current clinical trial evidence favours statins as first-line drugs for patients with a total cholesterol concentration more than 195 mg / dl. The most recent data indicate that the effects of these drugs are additive to those of oestrogen and progesterone in post-menopausal women.

In addition, statins have non-lipid-lowering properties also and hence the benefits in diabetes may be beyond lipid control.

## ROLE IN PRIMARY AND SECONDARY PREVENTION

Statin-related data suggests that simvastatin 40 mg was effective in primary prevention of CHD in patients with diabetes and in patients who had a history of peripheral or carotid atherosclerosis but not CHD. It was also effective in patients who had a baseline LDL < 116 mg / dl (both diabetics and non-diabetics).

For the secondary and tertiary end-points, strokes were reduced as were cardiovascular procedures, total coronary events and chronic stable angina.

In contrast to primary prevention trials, the use and benefit of statins for secondary prevention has been clearly established due to convincing clinical data among diabetics as much as among non-diabetics.

The AVERT study suggests that aggressive statin therapy is as efficacious as percutaneous intervention in patients with stable angina.

Pravastatin and simvastatin have been found to significantly reduce the coronary events even among the diabetics.[14]

Based on the results of Heart Protection Study,[16] simvastatin 40 mg daily should be considered routinely for patients with diabetes mellitus. It has been shown to

1) Reduce the risk of major coronary events. 2) Reduce the risk of stroke. 3) Reduce the risk of both coronary and non-coronary revascularization. 4) Reduce the risk of developing peripheral macrovascular complications including peripheral revascularization, limb amputations and leg ulcers.

### Statins and Insulin Resistance

Even as the effect of statins on insulin resistance still remains unclear, there is some evidence suggesting improvement in carbohydrate metabolism.

Recent data from the West of Scotland study shows that more recent statins like pravastatin reduced the risk of new cases of Type 2 diabetes mellitus by 30 percent.[17]

### Safety Plus Efficacy

Based on the clinical trial data indicating safety plus efficacy of LDL-cholesterol lowering treatment, current American Diabetes Association recommendations identify reduction in LDL-cholesterol levels as the highest priority in managing dyslipidemia in patients with diabetes and statins are recommended as the first choice of treatment.[11]

Other aims in treatment include raising levels of HDL-cholesterol and reducing triglycerides. Herein, fibrates can be combined with statins to improve the overall lipoprotein pattern.[18]

The dose of statin administered should usually be low initially and titrated upward, if necessary. The lipid profile should be monitored every 3 months for the first 6 months, then every 6-12 months thereafter. However, very high-dose therapy e.g. simvastatin 80 mg or atorvastatin 40 mg or above, should be used only when absolutely necessary because of statins' greater association with side effects at these dosages.[15]

In the Heart Protection Study, substantial elevations of liver enzymes and creatinine kinase were not significantly higher in diabetics.[16]

### Renoprotection

Atherosclerosis and chronic renal failure share several common risk factors including hypercholesterolemia. This fact assumes particular significance in the background of diabetes mellitus which in itself happens to be a major risk factor for both atherosclerosis as well as chronic renal disease.

Experimental evidence suggests that statins decrease proteinuria and the progressive decline in renal function in these patients.[19,20]

Although the mechanism responsible for this renoprotective effect is not clear, considerable interest in the concept of renoprotection with lipid-lowering treatment exists in the medical community.[21,22]

### Pleiotropic Effects

The pleiotropic effects of statins have been attributed to the ubiquitous presence of mevalonate pathway and the diversity of end-products affected by isoprenoid synthesis. It implies that modulation of this pathway can have far-reaching consequences in a range of body tissues and in a range of clinical conditions. The effect of statins in two diseases of ageing which are somewhat distinct from macrovascular atherosclerosis e.g. osteoporosis and dementia have been studied. In addition, statins have been observed to have immunomodulating properties.

The pleiotropic benefits of statins reported in diabetics include

1) Improved endothelial function. 2) Inhibition of LDL oxidation. 3) Inhibition of release of cytokines. 4) Lowering of C-reactive protein levels. 5) Stabilizing the plaque and preventing its rupture. 6) Inhibition of migration and proliferation of smooth muscle cells. 7) Inhibition of platelet activation. 8) Inhibition of release of tissue factor. 9) Inhibition of matrix metalloproteinases. 10) No effect on fibrinogen levels and 11) Reduction in overall mortality.

### Osteoporosis in Diabetics

Osteoporosis can be considered to result from an imbalance between bone formation and resorption, at a cellular level. The LDL receptor-related protein-5, core binding factor and osteoprotegerin have been recently shown to be involved in the borne remodeling process.[23]

Statins inhibit bone resorption by affecting mevalonate synthesis.[24,25]

### Strokes and Dementia

It is well recognised that statins reduce the incidence of brain stroke in diabetics as well as non-diabetics, as evident from large randomised controlled trails. The 4S and CARE study have reported significant reduction in stroke rates by 19 to 31%.[13,14]

The reduction in stroke would probably also reduce the macrovascular dementia and possibly lessen the severity of Alzheimer's disease (AD) pathology too.

### AS Immunomodulators

It has been observed that diabetic patients with nephropathy who undergo renal transplant and who develop hyperlipidemia are more likely to develop chronic allograft rejection.

Statins have been found to improve the survival of the transplant.

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