# STATINS - A BOON OR A BANE

### Anandh K<sup>1</sup>, P. Venkata Krishnan<sup>2,\*</sup>

<sup>1</sup>Resident, Department of Medicine, LHMC & SSK Hospital, N. Delhi <sup>2</sup>Consultant, Division of Internal Medicine, Medanta - The Medicity, Gurgaon

# **Corresponding Author:**

E-mail: pvkdoc@gmail.com

# **Abstract:**

The role of HMG CoA Reductase inhibitors (Statins) in type 2 Diabetes Mellitus (DM) patients with hypercholesterolemia is undisputable. The ATP III guidelines suggests that diabetes should be considered as a CHD risk equivalent and it advocates that all patients with established CHD or diabetes should achieve a target goal of LDL - C < 100 mg/dl. Statins are considered as first-line drugs when LDL-lowering drugs are indicated to achieve LDL treatment goals. There is compelling evidence for the use of statin therapy for CHD risk reduction in such patients with diabetes based on large randomized control trials. The glycaemic status of patients on statin therapy is not a concern until recently. Evidence accrues that statin therapy impairs the glycaemic status. Although the causality is not well proven yet, it demands a focus because whether this is a class effect of all statins or limited to specific statins requires further clarifications. In this light, it becomes important to do a systematic review of the studies using statins and the effect on glycaemic status.

#### Introduction

Type 2 diabetes and Hyperlipidaemia are well known risk factors for coronary heart disease. Some persons without established CHD will have an absolute, 10-year risk for developing major coronary events (myocardial infarction and coronary death) equal to that of persons with CHD, i.e., >20 percent per 10 years. Such persons can be said to have a CHD risk equivalent. These persons belong in a high-risk category for primary prevention. Persons with type 2 diabetes have a 10-year risk for major coronary events (myocardial infarction and CHD death) that approximates the risk in CHD patients without diabetes. ATP III guidelines clearly states that persons with type 2 diabetes should be managed as a CHD risk equivalent. Lowering of LDL cholesterol is the main target in management of Dyslipidaemia. LDL lowering has been shown to produce marked benefit regardless of gender, age, and the presence of diabetes, smoking, and hypertension 1-7

Furthermore in persons with established CHD, LDL-Cholesterol lowering therapy reduces risk for stroke<sup>8-11</sup>. Thus with the available pool of evidence the central role of statins is indispensable with regard to the management of dyslipidaemia in patients with CHD or CHD risk equivalent (like Diabetes Mellitus).

However, the side effect profile of statin therapy includes myopathy, increased liver transaminase etc. There is evidence that it may also cause impairment in glycaemic status. This is brief review on literature available on Incidence of New Onset Diabetes in patients on statin therapy.

### **Systematic review of literature:**

The major secondary prevention trials with statins are the 4S  $^{12},\ CARE$   $^2,\ LIPID$   $^{10}$  studies. All these studies unequivocally proved that statin therapy in patients with CHD had a statistically significant reduction in major coronary events, coronary mortality and total mortality and stroke.

Study	Drug	CHD risk reduction in <b>Diabetes</b>	CHD risk reduction <b>Overall</b>			
Primary Prevention						
AFCAPS/TexCAPS 13	Lovastatin	-43 %	-37%			
Secondary Prevention						
CARE <sup>2</sup>	Parvastatin	-25%	-23%			
4S <sup>12</sup>	Simvastatin	-55%	-32%			
LIPID 10	Parvastatin	-19%	-25%			
4S- Extended <sup>14</sup>	Simvastatin	-42%	-32%			

These figures show that both in primary and secondary prevention statins has significantly influenced the CHD risk reduction percentages- more reduction seen in diabetic patients when compared to overall risk reduction. However, a new growing body of evidence in various analyses found that, the incidence of **new onset diabetes (NOD)** in patients with statin therapy is higher.

Randomized controlled trials evaluating the effect of statin use and risk of incident type 2 diabetes<sup>15</sup>

RCT WOSCOPS	Study population  Men aged 45–67 years	Intervention (No. of patients)  Pravastatin 40 mg	Results of primary outcome RR (95% CI)	Incident diabetes (n in statin group/ n in placebo group)  57/82	RR (CI 95%) for diabetes (comparing statin treatment with placebo)  0.7 (0.50–0.99)
(2001)	(mean age 55.2 years) from West of Scotland with moderately Elevated cholesterol	(n _ 2,999) vs. placebo (n _ 2,975)	cardiovascular death, 0.69 (0.57–0.83)	37702	0.7 (0.50 0.55)
HPS (2003)	Adults (78% men) (mean age 62.1 years) with occlusive arterial disease	Simvastatin 40 mg ( <i>n</i> _ 7,291) vs. placebo ( <i>n</i> _ 7,282)	All-cause mortality, 0.87 (0.81–0.94)	335/293	1.14 (0.98–1.33)
ASCOT (2003)	Adults aged 40–79 years (mean age 63.2 years) with hypertension and at high risk for CVD	Atorvastatin 10 mg (n _ 3,910) vs. placebo (n _ 3,863)	Nonfatal MI, cardiovascular death, 0.64 (0.50–0.83)	154/134	1.15 (0.91–1.44)
LIPID (2003)	Adults aged 31–75 years (mean age 62 years) with CVD	Pravastatin 40 mg( <i>n</i> _ 3,970) vs. placebo ( <i>n</i> _ 3,967)	Cardiovascular death, 0.76 (0.65–0.88)	172/181	0.95 (0.77–1.16)
CORONA (2007)	Elderly adults (mean age 73 years) with heart failure	Rosuvastatin 10 mg (n _1,771) vs. placebo (n _1,763)	Cardiovascular death, nonfatal MI, and nonfatal stroke, 0.92 (0.83–1.02)	100/88	1.13 (0.86- 1.50)
JUPITER (2008)	Apparently healthy men and women (median age 66 years)	Rosuvastatin, 20 mg (n _ 8,901) vs. placebo (n _ 8,901)	Nonfatal MI and stroke, unstable angina, arterial revascularization, and cardiovascular death, 0.56 (0.46–0.69)	270/216	1.25(1.05–1.49)

In another population-based study from Taiwan in 2012, patients on statins had a higher rate of NOD during a median follow-up of 7.2 years, 2.4% versus 2.1%, but a reduced rate of MI, stroke and in-hospital mortality <sup>16</sup>. An analysis done in 2013 by Waters DD <sup>17</sup> et al, showed that the presence of baseline risk factors for development of diabetes with statin therapy includes Fasting blood glucose >100 mg/dl, Fasting triglycerides > 150 mg/dl, BMI >30 kg/m² and History of hypertension. The results of this analysis indicated that high-dose statin increased the risk of New Onset Diabetes (NOD) among patients with 2 to 4 diabetes risk factors, compared with lower-dose statins. No increased risk of NOD

was seen with high-dose statin treatment in patients with 0 to 1 risk factors for diabetes.

The mechanism by which statins increase the risk of NOD is not proven as yet. Atorvastatin has been shown to inhibit adipose cell maturation in cell culture and to increase insulin resistance in type 2 diabetic mice <sup>18</sup>. Atorvastatin and Rosuvastatin have been reported to increase insulin resistance during coronary bypass surgery in patients without diabetes <sup>19</sup>. It also seems that lipophilic statins (i.e., simvastatin, atorvastatin) have a more pronounced effect on insulin sensitivity compared with hydrophilic statins (i.e., pravastatin, rosuvastatin)<sup>20</sup>. A recent Meta-analysis done by David et al in 2011

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showed intensive-dose statin therapy was associated with an increased risk of new-onset diabetes compared with moderate dose statin therapy <sup>21</sup>.

Two large population based studies from United Kingdom (CPRD) <sup>22</sup> and United States (WHI) <sup>23</sup> have suggested increased risk of NOD with statins. Clinical Practice Research Datalink (CPRD) study from UK comprising population from age 30- 85 years starting statins (430890 individuals) compared to 5 times more non statin users (1585204 individuals) for 5.43 years vs 3.89 years in non-statin users, found that statin use was associated with type 2 DM and the relative risk was higher among people without Hypertension and CVD but more in individuals with high BMI <sup>22</sup>.

Another such population based study from US among post-menopausal women participating in Women Health Initiative (WHI) <sup>23</sup> comprising 1,61,808 post-menopausal women aged 50-79 years without DM reported 10242 incident cases of DM and statin use was found to be associated with higher risk of development of NOD. Women with lower BMI were found to be at higher risk than higher. Both the studies however referred to better lifestyle management in patients with pre-existing HT or high BMI as cause for decreased chance of development of NOD in them on statins.

#### **Conclusion:**

The results of meta-analysis shows clearly that statin therapy is associated with increase in new onset diabetes. Whether this adverse effect on glycaemic status is dose dependent or a class property of statins is still an unanswered question. Given this uncertainty of the available information it would be premature to decide against the use of statins in patients with high risk of CHD. Further studies focusing on this aspect of statins would provide a valuable insight regarding the management of dyslipidaemia.

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