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Statins and Diabetes Risk

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Abstract

Statins are a class of drugs that inhibit the HMG Co-A reductase enzyme and subsequently reduce the cholesterol levels. HMG Co-A reductase enzyme is involved in the cholesterol synthesis in the liver and accounts for 70% of the production of total body cholesterol. High cholesterol levels attribute to cardiovascular disease in high-risk individuals. Statins have been found to reduce CVD endpoints in the initial stages of the disease (secondary prevention) but evidence is still weak to support statin therapy in those without CVD but with high cholesterol levels (primary prevention). Statins are also associated with certain adverse effects like muscle pain, incident diabetes and elevated liver enzymes and occasionally muscle damage; although very rare. In this review I shall explore one of these adverse effects of statin therapy particularly the link between statins and incident diabetes in the following report and try to shed some light into this controversial topic.

Keywords: Diabetes; Statins; Cardiovascular Disease

Introduction

There is an increased risk of incident diabetes with statin use, which may be limited to those with diabetes risk factors.

I. These patients may benefit additionally from diabetes screening when on statin therapy.

II. In an analysis of one of the initial studies suggesting that statins are linked to increased risk of diabetes, the cardiovascular event rate reduction with statins outweighed the risk of incident diabetes even for patients at highest risk for diabetes [1].

III. The absolute risk increase was small (over 5 years of follow-up, 1.2% of participants on placebo developed diabetes and 1.5% on rosuvastatin) [2].

IV. A meta-analysis of 13 randomized statin trials with 91,140 participants showed an odds ratio of 1.09 for a new diagnosis of diabetes, so that (on average) treatment of 255 patients with statins for 4 years resulted in one additional cause of diabetes, while simultaneously preventing 5.4 vascular events among 255 patients [3-4].

V. The relative risk-benefit ratio favoring statins is further supported by meta-analysis of individual data of over 170,000 persons from 27 randomized trials. This demonstrated that individuals at low risk of vascular disease, including those undergoing primary prevention, received benefits from statins that included reductions in major vascular events and vascular death without increase in incidence of cancer or deaths from another causes [5-6].

In this review I shall explore one of these adverse effects of statin therapy particularly the link between statins and incident diabetes in the following report and try to shed some light into this controversial topic.

Discussion

Classification, Mechanisms and Recommendations for Statin Therapy

Several statin preparations are available in the market like atorvastatin, rosuvastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. All of these agents are equally effective at reducing cholesterol and vary only in their adverse effects with simvastatin and pravastatin exhibiting a slight superiority [5]. The various statins also differ in their pharmacokinetics and dosing and are outlined in the tables below (Table 1 & 2) [7-8].

Table 1: Pharmacokinetics of statins.

	Isoenzyme	Lipophilic	Protein binding (%)	Active metabolites	Half Life (hr)
Lovastatin	3A4	Yes	>95	Yes	3
Simvastatin	3A4	Yes	95-98	Yes	2
Pravastatin	None	No	~50	No	1.8
Fluvastatin	2C9	Yes	>90	No	1.2
Atorvastatin	3A4	Yes	96	Yes	7-14
Rosuvastatin	2C9/2C19	No	88	Yes	13-20
Pitavastatin	UGT1A3/ UGT2B7	Yes	99	No	12

Table 2: Dosing of statins.

Atorva	Fluva	Pitava	Lova	Prava*	Rosuva*	Simvastatin + Ezetimibe	Simvastatin	%LDL
.....	40mg	1 mg	20 mg	20 mg	.....	.....	10 mg	30%
10 mg	80 mg	2 mg	40 or 80 mg	40 mg	.....	.....	20 mg	38%
20 mg	.....	4 mg	80 mg	80 mg	5 mg	10/10 mg	40 mg	41%
40 mg	.....	.....	.....	.....	10 mg	10/20 mg	80 mg	47%
80 mg	.....	.....	.....	.....	20 mg	10/40 mg	.....	55%
.....	.....	.....	.....	.....	40 mg	10/80 mg	.....	63%

Atorva= Atorvastatin; Fluva= Fluvastatin; Pitava= Pitavastatin; Lova= Lovastatin; Prava= Pravastatin; Rosuva= Rosuvastatin; Simva= Simvastatin; *Hydrophyllic agents

Mechanisms of Action

Statins competitively inhibit the HMG CoA reductase enzyme which is involved in the biosynthesis of cholesterol. They are molecularly similar to the enzyme and inhibit the conversion from HMG CoA to mevalonate which further leads to inhibition of cholesterol synthesis and ultimately cholesterol reduction via several pathways. The following figure demonstrate how statins affect cholesterol biosynthesis (Figure 1) [9]. Statin therapy is initiated after failure of lifestyle modifications by determining risk category (Table 3) [10].

Figure 1: Mechanisms of action of statins.

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Table 3: Risk category determination for statin therapy.

Risk Category	LDL Goal	LDL Level at Which to Initiate TLC	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL <70 mg/dL optional	≥ 100 mg/dL	≥ 130 mg/dL (100-129 mg/dL: drug optional)
2+ Risk factors (10-year risk <20%)	<130 mg/dL	≥ 130 mg/d	10-year risk 10-20%: >130 mg/dL 10-year risk <10%: >160 mg/dL
0-1 Risk factor	<160 mg/dL	≥ 160 mg/dL	>90 mg/dL (160-180 mg/dL: LDL- lowering drug optional)

Evidence for the Benefits of Statin Therapy

Diabetes is associated with a two to four-fold increased risk of CVD compared to non-diabetics and intensive management of all CVD risk factors, including dyslipidemia, is of paramount importance in diabetics [11]. Additionally, the beneficial effects of LDL-C lowering with statins apply to people with and without diabetes [12]. Several trials have demonstrated the efficacy of statins for the primary and secondary prevention of CVD in diabetic individuals with the latter showing significant reductions in CVD associated mortality and morbidity.

Primary Prevention

i. **HPS** Study [13]: In the diabetes subgroup, 40mg Simvastatin reduced CV events and stroke by 27% and 25% respectively compared to placebo.

ii. **CARDS** Study [14] (10 mg Atorvastatin): Statin therapy should be advocated for all patients with T2DM and other risk factors irrespective of their LDL levels.

iii. **CTT** Collaborators [15]: Diabetics had a 9% reduction in all-cause mortality and 21% reduction in major vascular events per mmol/L LDL-C reduction.

iv. **ASPEN** [16] (10 mg Atorvastatin): LDL-C was reduced by 29% with Atorvastatin compared to placebo but the primary endpoints of CVD were not significantly reduced. This poor showing was due to the study design and protocol changes.

Secondary Prevention

i. **PROVE-IT TIMI** [17] (40 mg Pravastatin vs. 80 mg Atorvastatin): Primary end point of CVD was reduced by 16% and CRP was also reduced which had positive benefit in CV event reduction irrespective of decreased LDL [18].

ii. **TNT** Study [19] (10 mg vs. 80 mg Atorvastatin): Significant 25% reduction in major cardiovascular events in the high dose group with LDL lowering to 2mmol/l compared to 2.5mmol/l in the low dose group.

iii. **A to Z** trial [20] (20 mg Simvastatin titrated to 80 mg): A reduction of 1.6mmol/l in the intensive group was seen with reduction in primary outcome (CVD, nonfatal MI, ACS and stroke) which, however, was not statistically significant.

iv. **IDEAL** trial [21] (Simvastatin 20 mg vs. Atorvastatin 80 mg): No significant reduction in major cardiovascular events but reduction in nonfatal AMI, coronary revascularization, and PVD.

Statins and Incident Diabetes

Recent meta-analyses point to a relative increase in diabetes with prolonged statin use with this increased risk being attributed to the statin dose [22-24]. US FDA issued a warning in 2012 linking statins with increased risk of new onset DM and worsening glycaemic status in pre-existing diabetic patients. Several trials have investigated the incidence of diabetes with statin therapy and they are outlined below:

1. **WOSCOPS** [25] study (Pravastatin 40 mg): 30% decreased incidence of diabetes with pravastatin therapy as compared to placebo.

2. **JUPITER** [26] study (Rosuvastatin 20 mg): Associated with significant reductions in the incidence of major coronary events. There was however a significant increase in the rate of physician-reported diabetes (26%) and an increase in median HbA1C.

3. **PROSPER** [27] study (Pravastatin 40 mg): Significant LDL-C reduction by 34% but incidentally a 32% higher incidence of diabetes.

4. Meta-analysis by Rajpathak et al [23]: studies were carried out to analyze the outcomes of the **WOSCOPS**, **ASCOT-LLA**, **JUPITER**, **HPS**, **LIPID** study and the **CORONA** study and showed an average 13% higher incidence of diabetes.

5. Meta-analysis by **Preiss** and **Waters**: high dose statins resulted in increased incidence of diabetes [24,28].

Statins differ in their lipophilic (atorvastatin, lovastatin, and simvastatin) as well as hydrophilic properties (pravastatin and rosuvastatin) and the results of the **CORALL** study showed a significant increase in HbA1C with high dose rosuvastatin and atorvastatin [29-30].

Mechanisms of Incident Diabetes and Statin use

- There is no clear-cut cause-effect relationship, but postulates include decreased insulin sensitivity with increasing statin doses and decreased adiponectin with loss of anti-proliferative and antiangiogenic properties.

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- Animal studies show decreased GLUT4 and increased GLUT1 expression with atorvastatin with defective insulin signaling and glucose transport defects in the adipocyte leading to insulin resistance.

- Abnormal regulation of cholesterol within the cell thereby impairing β cell function.

The results of these studies raised questions about the study design (associations rather than causation), more importantly, the fact that statins could well identify the patient already at risk of developing diabetes and concluded that the benefit from statin therapy in reducing CV events far outweighs the minor risk of incident diabetes and LDL-C reduction with statins lowered cardiovascular risk even in low-risk patients. However, caution should be exercised in the low-risk primary prevention groups without significant elevations in LDL-C, especially the elderly.

Conclusion and Future Perspectives

Statin therapy is advocated as a primary prevention of CVD for moderate to high-risk diabetic patients with dyslipidemia and as a secondary prevention for those with/without risk factors and the incidence of new-onset diabetes should not result in dose reduction or withdrawal in these patients. There appears to be only a slight increase in new-onset DM whereas the cardio-protective effects of statins clearly outweigh its risks. It would be reasonable to implement lifestyle changes like weight reduction, aerobic exercises, and dietary modification to prevent diabetes rather than to stop statins in moderate to high-risk patients like the elderly and in those with insulin resistance, metabolic syndrome and established CVD who are on therapy for the appropriate reasons.

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