

Use of Statins in Treatment of Diabetes Mellitus

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Received: June 25, 2014

Revised: July 12, 2014

Accepted: July 15, 2014

Published online: August 10, 2014

ABSTRACT

Statins are the only lipid-lowering drugs that have been shown to reduce the incidence of cardiovascular events and mortality in patients with diabetes mellitus. This review article will discuss the studies demonstrating the efficacy of statins in reducing cardiovascular events and mortality in adults with diabetes mellitus and the current guidelines supporting this use of statins.

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Key words: Diabetes mellitus; Statins; Cardiovascular events; Dyslipidemia; Lipid-lowering therapy

Aronow WS. Use of Statins in Treatment of Diabetes Mellitus. *Journal of Cardiology and Therapy* 2014; 1(7): 160-162 Available from: URL: <http://www.ghrnet.org/index.php/jct/article/view/802>

INTRODUCTION

Numerous studies have demonstrated that diabetes mellitus is a risk factor for cardiovascular events and mortality^[1-6]. Elderly diabetics are more often obese and have higher serum low-density lipoprotein (LDL) cholesterol and triglycerides levels and lower serum high-density lipoprotein (HDL) cholesterol levels than do non-diabetics. These risk factors contribute to the higher incidence of cardiovascular morbidity and mortality in diabetics than in non-diabetics. Dyslipidemia must be treated in diabetics with or without

cardiovascular disease. Statins are the only lipid-lowering drugs that have been shown to reduce the incidence of cardiovascular events and mortality in patients with diabetes mellitus. This review article will discuss the studies demonstrating the efficacy of statins in reducing cardiovascular events and mortality in adults with diabetes mellitus and the current guidelines supporting this use of statins.

CLINICAL TRIALS

At 5.4-year median follow-up of 202 diabetics with coronary artery disease (CAD) and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with placebo, simvastatin reduced all-cause mortality 43% ($p=0.087$), major CAD events 55% ($p=0.002$), and any atherosclerotic event 37% ($p=0.018$)^[7]. At 5-year follow-up of 586 diabetics with CAD and a mean serum total cholesterol of 209 mg/dL in the Cholesterol and Recurrent Events trial, compared with placebo, pravastatin decreased fatal coronary event or nonfatal myocardial infarction 25% from 37% to 29% ($p=0.05$)^[8]. At 6.1-year follow-up of 782 diabetics with CAD and serum total cholesterol levels between 155 to 271 mg/dL in the Long-Term Intervention with Pravastatin in Ischaemic Disease study, compared with placebo, pravastatin insignificantly reduced all-cause mortality 19% from 23% to 19%^[9].

The Heart Protection Study randomized 20,536 men and women (5,806 of whom were aged 70 to 80 years) with prior myocardial infarction (8,510 persons), other CHD (4,876 persons), and no CHD (7,150 persons) and a serum total cholesterol level of 135 mg/dL or higher to simvastatin 40 mg daily or to double-blind placebo^[10]. At 5-year follow-up of the 5,963 diabetics in this study, compared to placebo, simvastatin significantly decreased first major vascular events from 25.1% to 20.2% ($p<0.0001$)^[10]. The significant reduction in major vascular events occurred regardless of initial levels of serum lipids, age, or gender^[10].

In the Collaborative Atorvastatin Diabetes Study, 2,838 patients (62% older than 60 years) with diabetes mellitus, no cardiovascular disease, and a serum LDL cholesterol less than 160 mg/dL were randomized to atorvastatin 10 mg daily or to double-blind placebo^[11]. At 3.9-year median follow-up, compared with placebo, atorvastatin significantly reduced time to first recurrence of acute coronary events, coronary revascularization, or stroke by 37% ($p=0.001$), acute coronary events by 36% (9% to 55%), stroke by 48% (11% to

69%), and all-cause mortality by 27% ($p=0.059$)^[11].

In an observational prospective study of 529 patients, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum LDL cholesterol of 125 mg/dL or higher, 53% of patients were treated with statins^[12]. At 29-month follow-up, compared with no treatment with statins, use of statins reduced coronary heart death or nonfatal myocardial infarction by 37% ($p<0.0001$) and stroke by 47% ($p<0.0001$)^[12]. In this study, 83% of diabetics treated with statins had hypertension. The lower the reduction in serum LDL cholesterol, the greater was the reduction in coronary events^[13] and in stroke^[14].

A meta-analysis was performed in 14 randomized trials of statins in 18,686 diabetics, mean age 63 years (1,466 with type 1 diabetes and 17,220 with type 2 diabetes)^[15]. Mean follow-up was 4.3 years. Compared with placebo, statins reduced all-cause mortality 9% per mmol/L reduction in serum LDL cholesterol ($p=0.02$), reduced cardiovascular mortality 13% per mmol/L reduction in serum LDL cholesterol ($p=0.008$), and reduced major cardiovascular events 21% per mmol/L reduction in serum LDL cholesterol ($p<0.0001$)^[15]. After 5 years, 42 (95% CI, 30-55) diabetics had major cardiovascular events reduced per 1,000 treated with statins^[15].

Randomized placebo-controlled trials have not demonstrated a significant reduction in cardiovascular events and mortality in diabetics treated by other lipid-lowering drugs. The Action to Control Cardiovascular Risk in Diabetes study investigated whether combination therapy with a statin plus a fibrate compared with statin monotherapy would decrease cardiovascular events in patients with type 2 diabetes at high risk for cardiovascular events^[16]. In this study, 5,518 type 2 diabetics treated with simvastatin were randomized to receive either fenofibrate or placebo. At 4.7-year follow-up, compared with simvastatin plus placebo, simvastatin plus fenofibrate did not reduce the primary outcome of first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes or any secondary outcome^[16].

In the Fenofibrate Intervention and Event Lowering in Diabetes study, 9,795 diabetics were randomized to fenofibrate or placebo^[17]. At 5-year median follow-up, there was no significant difference in the primary endpoint of CAD death or nonfatal myocardial infarction in patients treated with fenofibrate or placebo^[17]. On the basis of a Food and Drug Administration review and committee deliberations, the benefit of adding a fibrate to statin therapy in reducing cardiovascular events in diabetics is unproven^[18].

Niacin has been used in clinical practice to reduce cardiovascular events in diabetics. The AIM-HIGH (Niacin Plus Statins to Prevent Vascular Events) trial randomized 3,414 patients (34% with diabetes mellitus) with stable CAD and a low serum HDL cholesterol (median level of 35 mg/dL) treated with simvastatin or simvastatin plus ezetimibe to 1500 to 2000 mg of extended-release niacin or placebo^[19]. Niacin increased serum HDL cholesterol 25%, decreased serum LDL cholesterol 12%, and decreased serum triglycerides 29%. The trial was stopped by the National Heart, Lung, and Blood Institute data and safety monitoring board at 3 years because the primary endpoint of myocardial infarction, ischemic stroke, death due to CAD, hospitalization for an acute coronary syndrome, or symptom-driven revascularization was 16.4% in patients treated with niacin versus 16.2% in patients treated with placebo, and because niacin increased ischemic stroke by 61% ($p=0.11$)^[19].

At the American College of Cardiology Meeting on March 9, 2013, Dr. Jane Armitage presented results from the Heart Protection study 2-Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) study. In this study, 25,673 high-risk patients were randomized to treatment with simvastatin or simvastatin/ezetimibe

plus extended-release niacin plus the anti-flushing agent laropiprant or to treatment with simvastatin or simvastatin/ezetimibe. At 3.9-year follow-up, compared to treatment with simvastatin or simvastatin/ezetimibe, addition of niacin did not reduce the primary outcome of major vascular events but increased 31 serious adverse events per 1,000 niacin-treated patients. Excess diabetic complications were increased 3.7% ($p<0.0001$). Excess new diabetes was increased 1.8% ($p<0.0001$). Excess infection was increased 1.4% ($p<0.0001$). Excess gastrointestinal complications were increased 1% ($p<0.0001$). Excess bleeding (gastrointestinal and intracranial) was increased 0.7% ($p<0.0002$).

Lifestyle measures are important in the treatment of dyslipidemia in diabetics. The person should achieve and maintain a desirable weight. The diet should be low in cholesterol (less than 200 mg daily). Less than 30% of total caloric intake should be fatty acids. Saturated fatty acids should comprise less than 7% of total calories, polyunsaturated acids up to 10% of total calories, and monounsaturated fatty acids 10% to 15% of total calories. The diet should also be high in fiber and high in fruits and vegetables. There is no strong evidence to support any dietary supplements. A more liberalized diet is warranted in elderly persons prone to malnutrition. Moderate intensity exercise is recommended for 30 to 60 minutes daily. Smoking should be stopped, hypertension treated, and diabetes controlled. Secondary causes of dyslipidemia should be treated.

The 2013 American College of Cardiology (ACC)/American Heart Association guidelines on treatment of hypercholesterolemia support the use of statins in diabetics^[20]. Diabetics with clinical atherosclerotic cardiovascular disease should be treated with high-dose statins. High-dose statins reduce serum LDL cholesterol $\geq 50\%$ and include atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. Diabetics with a serum LDL cholesterol ≥ 190 mg/dL should also be treated with high-dose statins. The ACC/AHA guidelines recommend for primary prevention in diabetics with a serum LDL cholesterol between 70 to 189 mg/dL moderate-dose statins. If the 10-year risk of developing atherosclerotic cardiovascular disease (coronary heart disease, stroke, transient ischemic attack, or atherosclerotic peripheral arterial disease) by the Pooled Cohort Equations is $\geq 7.5\%$, high-dose statins should be given.

CONFLICT OF INTERESTS

There are no conflicts of interest with regard to the present study.

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- Peer reviewer:** Murat AYAZ, Selçuk Üniversitesi Tıp Fakültesi Biyofizik Ana Bilim Dalı E Blok Kat 3 Aleaddin Kampüsü, Selçuklu, Konya 42075, Turkey.