



Treatment of Dyslipidemia in Diabetics

Wilbert S. Aronow*

¹Cardiology Division, Department of Medicine, New York Medical College, New York, USA

*Corresponding author: Wilbert S. Aronow, MD, FACC, FAHA, Cardiology Division, New York Medical College, Macy Pavilion, Room 138, Valhalla, NY 10595, USA, Tel: (914) 493-5311, Fax: (914) 235-6274, E-mail: wsaronow@aol.com

Abstract

Dyslipidemia in diabetics should be treated with lifestyle measures. Statins are the only lipid-lowering drugs that have been demonstrated to lower the incidence of cardiovascular events and mortality in patients with diabetes mellitus. This review article will discuss the treatment of dyslipidemia in diabetics and the current guidelines supporting the use of statins in the treatment of diabetics.

Keywords

Diabetes mellitus; Statins; Cardiovascular events; Dyslipidemia; Lipid-lowering therapy

Introduction

Numerous studies have found that diabetes mellitus is a risk factor for cardiovascular events and mortality [1-6]. 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 nondiabetics. These risk factors contribute to the increased incidence of cardiovascular morbidity and mortality in diabetics. Dyslipidemia must be treated in diabetics with or without cardiovascular disease. Statins are the only lipid-lowering drugs that have been demonstrated to lower the incidence of cardiovascular events and mortality in diabetics. This article will discuss the treatment of dyslipidemia in diabetics and the current guidelines supporting the use of statins in diabetics.

Lifestyle Measures

Lifestyle measures are important in the treating dyslipidemia in persons with diabetes mellitus [7,8]. 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 with a hemoglobin A1c level of less than 7.0%. Secondary causes of dyslipidemia should be treated.

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 to placebo, simvastatin lowered all-cause mortality 43% ($p = 0.087$), major CAD events 55% ($p = 0.002$), and any atherosclerotic event 37% ($p = 0.018$) [9]. 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 to placebo, pravastatin lowered fatal coronary event or nonfatal myocardial infarction 25% from 37% to 29% ($p = 0.05$) [10]. 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 to placebo, pravastatin insignificantly reduced all-cause mortality 19% from 23% to 19% [11].

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 patients), other CAD (4,876 patients), and no CAD (7,150 patients) and a serum total cholesterol level of 135 mg/dl or higher to simvastatin 40 mg daily or to double-blind placebo [12]. At 5-year follow-up of the 5,963 patients with diabetes mellitus in this study, compared to placebo, simvastatin significantly lowered first major vascular events from 25.1% to 20.2% ($p < 0.0001$) [12]. The significant decrease in major cardiovascular events occurred regardless of initial levels of serum lipids, age, or gender [12].

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 [13]. At 3.9-year median follow-up, compared to placebo, atorvastatin significantly lowered 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% ($p = 0.059$) [13].

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 the patients were

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treated with statins [14]. At 29-month follow-up, compared with no lipid-lowering drug therapy, treatment with statins lowered coronary heart death or nonfatal myocardial infarction by 37% ($p < 0.0001$) and stroke by 47% ($p < 0.0001$) [14]. In this study, 83% of diabetics treated with statins had hypertension. The lower the serum LDL cholesterol by treatment with statins, the greater was the decrease in coronary events [15] and in stroke [16].

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

Randomized placebo-controlled trials have not demonstrated a significant lowering of cardiovascular events and mortality in patients with diabetes mellitus treated with 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 reduce cardiovascular events in patients with type 2 diabetes mellitus at high risk for cardiovascular events [18]. In this study, 5,518 patients with type 2 diabetes mellitus 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 lower the primary outcome of first occurrence of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes or any secondary outcome [18].

In the Fenofibrate Intervention and Event Lowering in Diabetes study, 9,795 patients with diabetes mellitus were randomized to fenofibrate or to placebo [19]. 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 with placebo [19]. On the basis of a Food and Drug Administration review and committee deliberations, the benefit of adding a fibrate to statin therapy in decreasing cardiovascular events in diabetics is unproven [20].

Niacin has been used in clinical practice to reduce cardiovascular events in diabetics with dyslipidemia. 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 [21]. Niacin increased serum HDL cholesterol 25%, lowered serum LDL cholesterol 12%, and lowered 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% ($p = 0.11$) [21].

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 decrease 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% ($p < 0.0002$).

The 2013 American College of Cardiology (ACC)/American Heart Association guidelines on treatment of hypercholesterolemia support the use of statins in treating patients with diabetes mellitus [8]. These guidelines recommend that patients with diabetes mellitus and clinical atherosclerotic cardiovascular disease should be treated with high-dose statins. High-dose statins lower serum LDL cholesterol 50% or more and include atorvastatin 40 to 80 mg daily and rosuvastatin 20 to 40 mg daily. These guidelines also recommend that diabetics with a serum LDL cholesterol of 190 mg/dl or higher 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 7.5% or higher, these guidelines recommend that high-dose statins should be used to treat these diabetics [8].

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