Numerous studies have shown that statins reduce cardiovascular events including stroke and mortality in diabetics. The American Diabetes Association 2013 guidelines recommend that diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol reduced to <70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to <100 mg/dL. The 2013 American College of Cardiology/American Heart Association lipid guidelines recommend giving high-dose statins to adult diabetics aged ≤75 years with atherosclerotic vascular disease (ASCVD) unless contraindicated with a class I indication and moderate-dose or high-dose statins to diabetics with ASCVD ≥75 years with a class IIa indication. Diabetics ≥21 years with a serum LDL cholesterol of ≥190 mg/dL should be treated with high-dose statins with a class I indication. For primary prevention in diabetics aged 40 to 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins should be given with a class I indication. For primary prevention in diabetics aged 40 to 75 years, a serum LDL cholesterol between 70 to 189 mg/dL, and a 10-year risk of ASCVD of ≥7.5% calculated from the Pooled Heart Equation, high-dose statins should be given with a class IIa indication. For primary prevention in diabetics aged 21 to 39 years or older than 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins or high-dose statins should be given with a class IIa indication.

There is no additional ASCVD reduction from adding nonstatin therapy to further lower non-high-density lipoprotein (HDL) cholesterol once an LDL cholesterol goal has been reached. Clinical trials have found no lowering of cardiovascular events or mortality in diabetics treated with statins by addition of nicotinic acid, fibric acid derivatives, ezetimibe, or drugs that raise serum HDL cholesterol.

At 5.4-year median follow-up of 202 diabetics with coronary artery disease and hypercholesterolemia in the Scandinavian Simvastatin Survival Study, compared with double-blind placebo, diabetics randomized to simvastatin 20 to 40 mg daily had a 43% reduction in all-cause mortality (p = 0.087), a 55% reduction in major coronary events (p = 0.002), and a 37% reduction in any atherosclerotic event (p = 0.018) [2]. At 5-year follow-up of 586 diabetics with coronary artery diseases and a mean serum total cholesterol level of 209 mg/dL in the Cholesterol and Recurrent Events trial, compared with double-blind placebo, pravastatin 40 mg daily decreased the incidence of fatal coronary events or nonfatal myocardial infarction 25% from 37% to 29% (p = 0.05) [3].

In the Collaborative Atorvastatin Diabetes Study, 2,838 diabetics with 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 [4]. At 3.9-year median follow-up, compared with placebo, atorvastatin significantly reduced time to first occurrence 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) [4].

In an observational prospective study of 171 men and 358 women, mean age 79 years, with prior myocardial infarction, diabetes mellitus, and a serum low-density lipoprotein (LDL) cholesterol of 125 mg/dL or higher, 279 of 529 diabetics (53%) were treated with statins [5]. At 29-month follow-up, compared with no treatment with statins, use of statins significantly decreased in elderly persons coronary heart disease death or nonfatal myocardial infarction by 37% and stroke by 47% [5]. The greater the reduction in serum LDL cholesterol, the greater the reduction in new coronary events [6] and in stroke [7].

A meta-analysis was performed of 14 randomized trials of statins used to treat 18,686 diabetics (1,466 with type 1 diabetes and 17,220 with type 2 diabetes), 258,798 patients, and medication exposure varied from 5 to 65%. The risk of having a cardiovascular event is 11% lower in diabetics with type 2 diabetes compared to diabetics with type 1 diabetes (p = 0.05).

**Abstract**

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics. The American Diabetes Association 2013 guidelines recommend that diabetics at high risk for cardiovascular events should have their serum low-density lipoprotein (LDL) cholesterol reduced to <70 mg/dL with statins. Lower-risk diabetics should have their serum LDL cholesterol reduced to <100 mg/dL. The 2013 American College of Cardiology/American Heart Association lipid guidelines recommend giving high-dose statins to adult diabetics aged ≤75 years with atherosclerotic vascular disease (ASCVD) unless contraindicated with a class I indication and moderate-dose or high-dose statins to diabetics with ASCVD ≥75 years with a class IIa indication. Diabetics ≥21 years with a serum LDL cholesterol of ≥190 mg/dL should be treated with high-dose statins with a class I indication. For primary prevention in diabetics aged 40 to 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins should be given with a class I indication. For primary prevention in diabetics aged 40 to 75 years, a serum LDL cholesterol between 70 to 189 mg/dL, and a 10-year risk of ASCVD of ≥7.5% calculated from the Pooled Heart Equation, high-dose statins should be given with a class IIa indication. For primary prevention in diabetics aged 21 to 39 years or older than 75 years and serum LDL cholesterol between 70 to 189 mg/dL, moderate-dose statins or high-dose statins should be given with a class IIa indication. There is no additional ASCVD reduction from adding nonstatin therapy to further lower non-high-density lipoprotein (HDL) cholesterol once an LDL cholesterol goal has been reached. Clinical trials have found no lowering of cardiovascular events or mortality in diabetics treated with statins by addition of nicotinic acid, fibric acid derivatives, ezetimibe, or drugs that raise serum HDL cholesterol.

**Introduction**

Numerous studies have demonstrated that statins reduce cardiovascular events including stroke and mortality in diabetics [1,8]. At 5-year follow-up of 5,963 diabetics aged 40 to 80 years in the Heart Protection Study randomized to simvastatin 40 mg daily or to double-blind placebo, simvastatin reduced first major cardiovascular event (coronary event, stroke, or revascularization) 22% from 25.1% to 20.2% compared with placebo (p<0.0001) [1]. Of the 2,912 diabetics without occlusive arterial disease at study entry, simvastatin reduced first major cardiovascular event by 33% (p = 0.0003) [1]. Of the 2,426 diabetics with a serum LDL cholesterol below 116 mg/dL at study entry, simvastatin reduced first major cardiovascular event by 27% (p = 0.0007) [1]. Treatment of diabetics without occlusive arterial disease for 5 years reduced 1 major vascular event in 45 patients per 1,000 treated and prevented 70 first or subsequent major vascular events per 1,000 patients treated [1].
17,220 with type 2 diabetes) [8]. Mean follow-up was 4.3 years. All-cause mortality was reduced 9% per mmol/L reduction in serum LDL cholesterol (p = 0.02). Major cardiovascular events were reduced 21% per mmol/L reduction in serum LDL cholesterol, p<0.0001. Statins caused in diabetes a 22% reduction in myocardial infarction or coronary death (p<0.0001), a 25% reduction in coronary revascularization (p<0.0001), and a 21% reduction in stroke (p = 0.0002). After 5 years, 42 fewer diabetics per 1,000 diabetics treated with statins had major cardiovascular events [8].

In the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study, 9,795 type 2 diabetics (2,131 with cardiovascular disease) were randomized to fenofibrate or double-blind placebo [9]. Mean follow-up was 5.0 years. The primary outcome of coronary events was not significantly reduced by fenofibrate. Fenofibrate insignificantly increased coronary heart disease mortality by19% [9].

In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, 5,518 type 2 diabetics at high risk for cardiovascular disease were randomized to simvastatin plus fenofibrate or to simvastatin plus double-blind placebo [10]. Mean follow-up was 4.7 years. Compared with simvastatin plus placebo, simvastatin plus fenofibrate did not lower the incidence of fatal cardiovascular events, nonfatal myocardial infarction, or nonfatal stroke [10]. Among 3,414 patients with atherosclerotic cardiovascular disease and low serum high-density lipoprotein (HDL) cholesterol levels treated with simvastatin plus ezetimibe if needed to maintain the serum LDL cholesterol less than 70 mg/dl, at 36-month follow-up, patients randomized to niacin had improvements in serum HDL cholesterol and triglyceride levels but no clinical improvement compared to patients randomized to placebo [11].

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 American Diabetes Association 2013 guidelines recommend that diabetics at high risk for cardiovascular events should have their serum LDL cholesterol reduced to less than 70 mg/dl with statins [12]. Lower-risk diabetics should have their serum LDL cholesterol reduced to less than 100 mg/dl [12]. Combination therapy of a statin with either a fibrate or niacin has not been found to provide additional cardiovascular benefit above statin therapy alone and is not recommended [12]. Hypertriglyceridemia should be treated with dietary and lifestyle changes [12]. Severe hypertriglyceridemia should be treated with drug therapy to decrease the risk of acute pancreatitis [12].

The 2013 American College of Cardiology/American Heart Association lipid guidelines recommend the use of high-dose statins (rosuvastatin 20 to 40 mg daily or atorvastatin 40 to 80 mg daily) to adults aged 75 years and younger with atherosclerotic vascular disease (ASCVD) with or without diabetes mellitus unless contraindicated with a class I indication [13]. Moderate-dose or high-dose statins are reasonable to administer to patients with ASCVD with or without diabetes mellitus older than 75 years with a class IIa indication. Persons aged 21 years and older with a serum LDL cholesterol of 190 mg/dl or higher with or without diabetes mellitus should be treated with high-dose statins with a class I indication. For primary prevention in diabetics aged 40 to 75 years and a serum LDL cholesterol between 70 to 189 mg/dl, moderate-dose statins should be given with a class I indication. For primary prevention in diabetics aged 40 to 75 years, a serum LDL cholesterol between 70 to 189 mg/dl, and a 10-year risk of ASCVD of 7.5% or higher calculated from the Pooled Heart Equation, high-dose statins should be administered with a class IIa indication. For primary prevention in diabetics aged 21 to 39 years or older than 75 years and a serum LDL cholesterol between 70 to 189 mg/dl, moderate-dose statins or high-dose statins should be given with a class IIa indication. These guidelines also state that there is no additional ASCVD reduction from adding nonstatin therapy to further lower non-HDL cholesterol once an LDL cholesterol goal has been reached. Clinical trials have demonstrated no lowering of cardiovascular events or mortality in persons treated with statins by addition of nicotinic acid, fibric acid derivatives, ezetimibe, or drugs that raise HDL cholesterol [13].

References