Diabetes is considered a risk equivalent for coronary heart disease (CHD). The use of statins for primary and secondary prevention in patients with diabetes is well established and supported by robust data from randomized, controlled trials and national guidelines. The American Diabetes Association recommends that individuals with diabetes and a history of cardiovascular disease (CVD), as well as those > 40 years of age without CVD but with CVD risk factors, should be treated with a statin regardless of their baseline LDL cholesterol concentration. This review explains the rationale behind considering diabetes a CHD risk equivalent and summarizes the data for statin use in adults with diabetes without (primary prevention) and with (secondary prevention) established CVD. Although individuals with diabetes are at an increased risk for CVD and benefit from statin therapy, the risk of CVD in people with diabetes is heterogeneous. It therefore may be reasonable to match the intensity of statin therapy with patients' baseline CVD risk.
A uniform treatment approach for diabetes patients, may result in better treatment outcomes, fewer medication side effects, and a more cost-effective therapy regimen. Therefore, risk stratification remains vital to finding those patients at highest risk who could benefit from a more aggressive strategy.

An individualized risk approach is also important to optimize treatment in people who are already on drug therapy. One recent study found that 14% of Veteran Affairs patients were “over-treated” with statins without any indication of being at higher risk, implying the need for adjusting the intensity of treatment to the level of risk with the use of appropriate clinical performance measures.

Evidence for the Use of Statins in Patients With Diabetes

Primary prevention trials in diabetes

Current clinical practice is based on relatively few randomized, control trials. Among these studies are the Heart Protection Study (HPS), the Collaborative Atorvastatin Diabetes Study (CARDS), the Anglo-Scandinavian Cardiac Outcomes Lipid Lowering Arm (ASCOT-LLA), the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack (ALLHAT) study, and the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) trials. All of these studies included a substantial portion of subjects with diabetes. A few key primary prevention trials are summarized in Table 1.

The HPS provided initial evidence for the routine use of statin therapy in diabetes patients at risk for major CVD events. Patients with nonfasting total cholesterol > 135 mg/dl were randomized to 40 mg simvas-

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Publication Year</th>
<th>Age at Enrollment (years)</th>
<th>Study Group</th>
<th>Diabetes Subjects (n)</th>
<th>Statin Type and Dose</th>
<th>Mean Follow-Up (years)</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>WOSCOPS19</td>
<td>1996</td>
<td>45–64</td>
<td>Primary prevention (men)</td>
<td>8 68</td>
<td>Pravastatin, 40 mg</td>
<td>4.9</td>
<td>Scotland</td>
</tr>
<tr>
<td>AFCAPS20</td>
<td>2000</td>
<td>Male: 45–73 Female: 55–73</td>
<td>Primary prevention</td>
<td>0 155</td>
<td>Lovastatin, 20–40 mg</td>
<td>5.2</td>
<td>United States</td>
</tr>
<tr>
<td>HPS14</td>
<td>2003</td>
<td>40–80</td>
<td>High-risk</td>
<td>615 5,348</td>
<td>Simvastatin, 40 mg</td>
<td>5.3</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>PROSPER21</td>
<td>2002</td>
<td>70–82</td>
<td>Elderly</td>
<td>51 572</td>
<td>Pravastatin, 40 mg</td>
<td>3.2</td>
<td>Scotland, Ireland, and the Netherlands</td>
</tr>
<tr>
<td>ALLHAT17</td>
<td>2002</td>
<td>&gt; 55</td>
<td>Hypertension</td>
<td>0 3,638</td>
<td>Pravastatin, 20–40 mg</td>
<td>4.8</td>
<td>United States and Canada</td>
</tr>
<tr>
<td>ASCOT-LLA16</td>
<td>2003</td>
<td>40–79</td>
<td>Hypertension</td>
<td>0 2,527</td>
<td>Atorvastatin, 10 mg</td>
<td>3.3</td>
<td>United Kingdom, Ireland, and Nordic countries</td>
</tr>
<tr>
<td>CARDS15</td>
<td>2004</td>
<td>40–75</td>
<td>Type 2 diabetes</td>
<td>3 2,835</td>
<td>Atorvastatin, 10 mg</td>
<td>4.0</td>
<td>United Kingdom and Ireland</td>
</tr>
<tr>
<td>MEGA18</td>
<td>2006</td>
<td>40–70</td>
<td>Hyperlipidemia</td>
<td>0 3,866</td>
<td>Pravastatin, 10–20 mg</td>
<td>5.3</td>
<td>Japan</td>
</tr>
<tr>
<td>ASPEN22</td>
<td>2006</td>
<td>40–75</td>
<td>Primary prevention</td>
<td>0 2,410</td>
<td>Atorvastatin, 10 mg</td>
<td>4.0</td>
<td>Europe, Australia, and North America</td>
</tr>
</tbody>
</table>

AFCAPS, Air Force/Texas Coronary Atherosclerosis Prevention Study; ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack; ASCOT-LLA, Anglo-Scandinavian Cardiac Outcomes—Lipid Lowering Arm; ASPEN, Atorvastatin Study for Prevention of CHD Endpoints in Non-Insulin-Dependent Diabetes; CARDS, Collaborative Atorvastatin Diabetes Study; HPS, Heart Protection Study; MEGA, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS, West of Scotland Coronary Prevention Study.
Statin-treated diabetes patients had a 22% (95% CI 13–30%) relative risk reduction (event rate 20.2 vs. 25.1%). Similar reductions were seen in those without baseline occlusive arterial disease and those with baseline LDL cholesterol levels < 116 mg/dl.14

The ASCOT-LLA addressed lipid lowering in hypertensive patients in a 2 × 2 factorial analysis with atorvastatin, 10 mg, versus placebo. A baseline diagnosis of diabetes was present in 2,532 participants. Over a median follow-up of 3.3 years, there were 116 major CVD events (9.2%) in atorvastatin–allocated diabetes patients and 151 events (11.9%) in the placebo group (hazard ratio [HR] 0.77, 95% CI 0.61–0.98).16

The CARDS trial enrolled patients with type 2 diabetes with at least one additional risk factor, including hypertension, retinopathy, proteinuria, or smoking. This trial randomized 2,838 patients to atorvastatin, 10 mg daily, versus placebo. Relative risk reductions by individual outcomes were 36% for acute coronary events, 31% for coronary revascularizations, and 48% for stroke. Treatment would be expected to prevent 37 major vascular events (MVEs) per 1,000 patients treated for 4 years. Compared to placebo, the absolute risk reduction with atorvastatin was similar in patients with LDL cholesterol concentrations > 120 or < 120 mg/dl (reduction from 9.5 to 6.1% vs. reduction from 8.5 to 3.6%). Like HPS, CARDS supported treatment of patients with type 2 diabetes and other CVD risks with statin therapy regardless of their baseline LDL cholesterol level.15

The MEGA trial18 assigned 8,214 patients to atorvastatin, 10 mg, versus placebo. A total of 10.4% of the simvastatin and 80 mg atorvastatin, respectively (HR 0.83, 95% CI 0.71–0.98). The MEGA trial cautiously concluded that patients who have had an MI may benefit from intensive lipid lowering, even in patients with stable CHD.

In the TNT (Treating to New Targets) trial,27 1,501 patients with diabetes, stable CHD, and LDL cholesterol levels < 130 mg/dl were randomized to 10 or 80 mg atorvastatin and followed for a median of 4.9 years. A 25% reduction in rates of serious events was observed in the high-dose group (HR 0.75, 95% CI 0.58–0.97). This finding reinforced the benefit of intensive lipid lowering, even in patients with stable CHD.

Several meta-analyses have clearly shown the benefits of statin therapy for either short-term (< 5 years) or long-term (> 10 years) cardiovascular outcomes in primary prevention.36 These benefits not only apply to people at higher risk (> 10%) but also to the lower-risk population.37 This argument is especially valid in people with diabetes.38

In 2008, the Cholesterol Treatment Trialists (CTT) group39 analyzed 14 trials to ascertain the effects of statins on patients with diabetes.
tes. Four primary prevention trials (HPS, ASCOT-LLA, CARDS, and ALLHAT-LLT; see Table 1) accounted for 14,996 (83%) of the 18,686 patients with diabetes. During a mean follow-up of 4.3 years, per 39 mg/dl lowering of LDL cholesterol, the proportional reduction in all-cause mortality was 9% (rate ratio 0.91, 99% CI 0.82–1.01). This outcome was primarily driven by a significant 21% reduction in vascular mortality (rate ratio 0.87, 99% CI 0.76–1.00) with no effect on nonvascular mortality (rate ratio 0.97, 99% CI 0.82–1.16). However, this study did not include major adverse events from microvascular complications (neuropathy or retinopathy) or metabolic disturbances (incidence of diabetic ketoacidosis or nonketotic hyperglycemia). The proportional effects of statins in people with diabetes with vascular disease (secondary prevention) or without vascular disease (primary prevention) were similar. After 5 years, 42 (95% CI 30–55) fewer people had MVEs per 1,000 among those considered to be at high risk (> 10%).

A 2009 study reviewed 10 primary prevention trials for benefits of statins across age, sex, and lower-risk diabetes populations. Over a mean follow-up of 4.1 years, treatment with statins significantly reduced the risk of all-cause mortality (odds ratio [OR] 0.88, 95% CI 0.81–0.96), major coronary events (OR 0.70, 95% CI 0.61–0.81), and major cerebrovascular events (OR 0.81, 95% CI 0.71–0.93) similarly among all clinical subgroups.

A 2012 study explored the net effects of statins in people at low risk of vascular events. In this analysis, 7% of subjects with diabetes had a risk of < 5%, and 10% of subjects with diabetes had risk of 5–10%. There were significant reductions in MVEs in both lower-risk groups (among the < 5% group, rate ratio 0.61, 99% CI 0.45–0.81); among the 5–10% group, rate ratio 0.66, 99% CI 0.57–0.77) over a median of 5 years.

A recent review meticulously examined the patients with diabetes without known CVD in seven primary prevention trials. It showed that statin therapy was associated with a significant reduction of major CVD and cerebrovascular events (OR 0.79, 95% CI 0.66–0.95), but no statistical difference in all-cause mortality.

These three meta-analyses indicate that there likely are some benefits of treating even low-risk people with diabetes. Some experts have suggested that it may be important to revise guidelines to address the important population of patients at low to intermediate risk who could substantially benefit from statins.

In 2010, the CTT also analyzed the effects of intensive versus standard statin regimens (five trials, 39,612 individuals, median follow-up 5.1 years) and of statin versus control (21 trials, 129,526 individuals, median follow-up 4.8 years). Fourteen percent of people in the more versus less intensive regimen and 19% of people in the statin versus control group had diabetes. Among diabetes patients, an intensive regimen was associated with a significant reduction in CVD events compared to standard treatment in both type 1 (4.5 vs. 6.0%; rate ratio 0.77, 99% CI 0.58–1.01) and type 2

### Table 2. Summary of Seven Secondary Prevention Trials

<table>
<thead>
<tr>
<th>Clinical Trials</th>
<th>Publication Year</th>
<th>Age at Enrollment (years)</th>
<th>Study Group</th>
<th>Diabetes Subjects</th>
<th>Statin Type</th>
<th>Mean Follow-Up (years)</th>
<th>Sites</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S²⁹</td>
<td>1994</td>
<td>35–70</td>
<td>CHD</td>
<td>24</td>
<td>Simvastatin, 20–40 mg</td>
<td>5.4</td>
<td>Scandinavia</td>
</tr>
<tr>
<td>CARE³⁰</td>
<td>1998</td>
<td>21–75</td>
<td>Post-MI</td>
<td>193</td>
<td>Pravastatin, 40 mg</td>
<td>5</td>
<td>United States and Canada</td>
</tr>
<tr>
<td>Post-CABG³¹</td>
<td>1999</td>
<td>54–69</td>
<td>CABG</td>
<td>27</td>
<td>Lovastatin, 2.5–80 mg</td>
<td>4.3</td>
<td>United States</td>
</tr>
<tr>
<td>LIPID³²</td>
<td>1998</td>
<td>31–75</td>
<td>CHD</td>
<td>106</td>
<td>Pravastatin, 40 mg</td>
<td>6.1</td>
<td>Australia and New Zealand</td>
</tr>
<tr>
<td>GISSI-P³³</td>
<td>2004</td>
<td>60</td>
<td>Post-MI</td>
<td>120</td>
<td>Pravastatin, 20 mg</td>
<td>2</td>
<td>Italy</td>
</tr>
<tr>
<td>LIPS³⁴</td>
<td>2005</td>
<td>60–70</td>
<td>Post-PCI</td>
<td>39</td>
<td>Fluvastatin, 80 mg</td>
<td>3.9</td>
<td>Europe, Canada, and Brazil</td>
</tr>
<tr>
<td>ALERT³⁵</td>
<td>2003</td>
<td>40–60</td>
<td>Renal transplant</td>
<td>280</td>
<td>Fluvastatin, 40 mg</td>
<td>5.1</td>
<td>Europe and Canada</td>
</tr>
</tbody>
</table>

4S, Scandinavian Simvastatin Survival Study; ALERT, Assessment of Lescol in Renal Transplant; CABG, Coronary Artery Bypass Graft; CARE, Cholesterol and Recurrent Events; GISSI-P, Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico-Prevenzione; LIPID, Long-Term Intervention with Pravastatin in Ischemic Disease; LIPS, Lescol Intervention Prevention Study.
Diabetes (4.2 vs. 5.1%, rate ratio 0.80, 99% CI 0.74–0.86). Regardless of whether patients with at least one risk factor have documented CHD, the use of a higher-potency generic statin in lowering of LDL cholesterol to < 70 mg/dl appears to be both safe and efficacious. These benefits accrue without increasing noncoronary mortality.44

It should be noted that a 2010 review45 showed that there was no definite statistically significant difference in all-cause mortality across 11 primary prevention trials. In contrast to the 2008 analysis performed by the CTT, this review included the ASPEN trial, a negative clinical outcome trial in people with diabetes. Notably, this 2010 article did not examine nonfatal CVD or CHD outcomes. Because of methodological differences in the populations included and the statistical models, other recent meta-analyses46,47 do show a statistically significant decrease in total mortality with statin therapy in the primary prevention setting.

Non-LDL Targets of Statin Therapy in Diabetes

Although a 20–30% relative CVD reduction is impressive, this means that 70–80% of residual CVD risk persists despite statin treatment.48 The residual risk in treated patients with diabetes can be attributed to a number of factors, some of which may be potentially related to lipoproteins, including apolipoprotein B (Apo-B) or LDL particle concentration, but the vast majority of the residual risk is likely related to nonlipid factors. Apo-B is considered the key atherogenic moiety.49 In an analysis studying markers of CVD risk, Apo-B (risk ratio 1.43, 95% CI 1.35–1.51) outperformed non-HDL (1.34, 1.24–1.44), which outperformed LDL (1.25, 1.18–1.33).50

Patients with diabetes often have normal LDL levels but increased triglycerides, non-HDL cholesterol, and Apo-B, which may contribute to their high vascular risk despite largely normal LDL levels.51 This suggests that the risk in those patients with elevated levels of LDL particles may be underestimated by solely measuring cholesterol levels, although routinely calculated LDL for guiding treatment is less accurate compared to direct measurement, especially in hypertriglyceridemia.52 Apo-B or LDL particle concentration may be set as additional targets for many patients after lipoprotein cholesterol targets have been reached. An ADA and American College of Cardiology statement53 recommends consideration of measuring Apo-B in addition to LDL and non-HDL cholesterol in patients on lipid-lowering therapy. It further recommends an Apo-B target of < 80 mg/dl (Table 3).

Approach to Statin Intensification, Statin Intolerance, and Patient Preference

When it is unclear whether a patient has CHD and might benefit from an LDL goal of < 70 mg/dl, one should assess whether there is potential benefit from statin intensification. Use of coronary artery calcium (CAC) may prove helpful in guiding the intensity of statin therapy in diabetes. CAC is related to ongoing disease burden44 and is an independent predictor of CVD in diabetes.35,36 The absence of CAC remains associated with an excellent 7-year prognosis, whereas CAC > 100 portends a worse prognosis.57 Prediction of CHD events in diabetes is improved by CAC compared to traditional risk factors (HR 6.2 vs. 2.9, P < 0.05).58 In patients reporting side effects in association with statin therapy or hesitating to initiate therapy, CAC might be used to better quantify CVD risk and guide more informed risk-benefit discussions between patients and providers.

For example, based on a recent meta-analysis,59 people with a CAC of < 10 are 6.8 times less likely to have a CVD event. These patients do not meet conventional criteria for high risk or even intermediate risk, reinforcing the heterogeneity of risk in diabetes. At this time, a CAC score of 0 among individuals with diabetes may lead a provider to withhold aspirin therapy.57 However, it should not lead to withholding of statin therapy based on the robust data at all levels of risk.36 A less potent statin may be a reasonable choice for people with mild intolerance and those who would not prefer statin therapy because of low CAC scores.

Role of Statins in Diabetes With Renal Disease

Dyslipidemia is common in people with diabetes and chronic kidney disease (CKD). CVD events are a frequent cause of morbidity and mortality in this population. A 2009 review60 showed that statins significantly reduce the risk of all-cause and CVD mortality in CKD patients who are not receiving renal replacement therapy. A 2011 trial61 suggested that lowering LDL with statins reduces the risk of major atherosclerotic events in patients with moderate to severe kidney disease, including those with diabetes. Guidelines62 recommend using statins to reduce the risk of major CVD events in patients with diabetes and CKD, including those who have received a kidney transplant. However, it is recommended that statins not be initiated in patients with diabetes who are already treated by dialysis, mainly because of a more than fivefold increased risk of hemorrhagic strokes in this population.63

### Table 3. ADA/ACC Consensus Targets: Lipoprotein Therapy

<table>
<thead>
<tr>
<th>Cardio-Metabolic Risk</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDL (mg/dl)</td>
<td>Non-HDL (mg/dl)</td>
</tr>
<tr>
<td>Highest-risk patients, including those with 1. Known CVD or 2. Diabetes plus one or more additional major CVD risk factors</td>
<td>&lt; 70</td>
</tr>
<tr>
<td>High-risk patients, including those with 1. No diabetes or known clinical CVD but two or more additional major CVD risk factors or 2. Diabetes but no other major CVD risk factors</td>
<td>&lt; 100</td>
</tr>
</tbody>
</table>

Other major risk factors (beyond dyslipoproteinemia) include smoking, hypertension, and family history of premature CAD.
Statin therapy is associated with an increase in the risk of hyperglycemia and diabetes. In one meta-analysis, statins were associated with a 9% increased risk (an absolute difference of about 0.4%) of developing diabetes. To cause a new case of diabetes, 255 patients would have to be treated for a mean of 4 years. Compared to low-dose therapy, intensive therapy is associated with a 12% increase in risk of diabetes with a number needed to harm of 498 per year. People of 65 years of age are more susceptible to this unwanted effect. In the JUPITER study, 77% of participants had impaired fasting glucose, and a significant number of participants had metabolic syndrome and prediabetes (A1C > 5.7%) at baseline in the rosuvastatin arm. In a review of three atorvastatin trials, four risk factors independently predicted new-onset diabetes: fasting glucose > 100 mg/dl, triglycerides > 150 mg/dl, BMI > 30 kg/m², and history of hypertension.

A recent study examined the incidence of diabetes and CVD events according to these baseline risk factors. Compared to lower-dose therapy, atorvastatin, 80 mg/day, did not increase the incidence of diabetes in patients with none or one risk factor but did, by 24%, among patients with two to four risk factors. However, the number of CVD events was significantly reduced with atorvastatin, 80 mg/day, in both risk groups. Several analyses have shown that cardiovascular and mortality benefits of statin therapy exceed the diabetes risk, including in participants at high risk of developing diabetes. From a clinical standpoint, there is no evidence that elevation in blood glucose while taking statins is associated with an increased risk of CVD events or that it attenuates the beneficial effects of the statin therapy. The evidence from individual clinical trials is mixed. Clinicians must interpret this information cautiously because many potentially confounding factors are involved. There is a lack of data for microvascular disease and glycemic control in patients with existing diabetes. All statin trials have been less than rigorous in terms of diagnosing diabetes. (Almost all relied on physician report or nontraditional means of diagnosis.) None of these trials was designed to look for diabetes.

Perhaps statin therapy uncovers diabetes only in people at risk for diabetes. Improved survival benefit with statins may allow more people at risk for diabetes to live long enough to actually develop and have it diagnosed, whereas those without statins may die before ever developing or being diagnosed with diabetes.

There is still no clear mechanism for the increased risk for diabetes. Although statin-prescribing practices should not change because of the modest diabetes risk, it is clear that patients being prescribed statins should be informed of their potential future diabetes risk, and this may provide added incentive to undertake sustained lifestyle changes. Following such advice could help to alleviate their diabetes risk and further reduce their CVD risk.

Table 4. Key Clinical Practice Points

- Statins provide risk reduction in a wide range of patients with diabetes who either have established CVD or are at high risk of developing atherothrombosis.
- All patients with diabetes and established CHD should be prescribed a statin unless contraindicated.
- All diabetes patients who are at a higher risk of CVD should receive a statin regardless of their baseline lipid levels. Men > 50 years and women > 60 years who have diabetes and one other CVD risk factor should probably get a statin.
- The main goal of statin therapy is to achieve an LDL level of < 100 mg/dl and, ideally, < 70 mg/dl using higher-dose statins or 30–40% LDL reduction when earlier targets cannot be met with maximum tolerated therapy.
- Diabetes patients at apparent low to low-intermediate risk could be considered for further risk stratification, for example, with coronary artery calcium scoring.
- At every patient encounter, lifestyle modification should be addressed emphatically to help reduce the incident diabetes risk from statins as well as overall CVD risks.
CAC testing, can integrate risk factor information and potentially identify patients for earlier intervention. Such risk stratification also has a potential role in the clinical approach to statin intensification, statin intolerance, and patient reluctance to take statins. Most patients in randomized clinical trials have been 40–80 years of age and had similar reductions in CVD morbidity and mortality irrespective of sex, race, geographical location, or other CVD risk factors. The absolute benefit will vary based on patients’ underlying risk.

Despite treatment with statins, a large burden of residual risk remains. Some degree of residual risk may be addressed by personalizing statin therapy through more accurate lipoprotein cholesterol assessment, using targets such as non-HDL, Apo-B, and LDL lipoprotein particle size. Nevertheless, residual risk may also be attributed to other risk factors. At this time, it is probably most cost-effective to strive for non-HDL targets with a potent generic statin.

Ultimately, careful risk-benefit analysis should guide the use of statin therapy. Regarding potential risks, there is evidence of mild hyperglycemia and a small risk of incident diabetes, particularly among patients with metabolic syndrome who are prescribed high-potency statins. However, pooled analyses from existing trials have demonstrated that the benefit accrued from statin therapy far outweighs the small potential risk of hyperglycemia or diabetes, particularly in those at the highest CVD risk.

(Kay clinical points are summarized in Table 4.)

References


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