Approximately 80% of diabetic patients will die of vascular disease, despite strong clinical trial evidence to support lowering low-density lipoprotein cholesterol (LDL-C) levels in diabetic patients. This article reviews the subgroup analyses of the major HMG-CoA reductase inhibitor (statin) trials, which show significant benefit in clinical outcomes (ie, vascular event, coronary heart disease mortality) in diabetic patients treated with statin therapy. Results from the recently published Heart Protection Study also suggest that treatment is beneficial in patients regardless of their LDL-C level; even patients with low baseline LDL-C levels can benefit from lipid-modifying therapy. Fibrates demonstrate benefit in coronary heart disease. However, further study is needed, as there is less clinical trial evidence regarding the effect of fibrates in diabetes. In addition, 1 report suggests that statins may also prevent the onset of diabetes, but this must be confirmed by other studies.


The relationship between diabetes and vascular disease is clear: 80% of patients with diabetes will die of vascular disease—a 2- to 3-fold higher risk of death by vascular disease than in people without diabetes. The clinical trial evidence to support the importance of lowering low-density lipoprotein cholesterol (LDL-C) levels in diabetic patients is strong, notwithstanding the multiple other atherosclerotic risk factors in diabetes (eg, glycemia, advanced glycosylation end products, hypertension, modified LDL particles).

**Indirect Clinical Trial Evidence for Statins**

The large primary and secondary prevention trials using HMG-CoA reductase inhibitors (statins) included patients with diabetes, but the diabetic patients were generally only a small subset of the cohort (ie, 5%) (Table 1) despite the fact that in a typical coronary population, the prevalence of diabetes is usually 20% to 25%. The bias against diabetes was based on the inclusion and exclusion criteria of the studies. In fact, the Diabetes Atherosclerosis Intervention Study (DAIS) is the only clinical trial completed to date that was specifically designed to study lipid modification in diabetic patients. Overall, however, the studies show that statins are able to significantly reduce LDL-C levels in diabetic patients, and to approximately the same degree as observed in individuals without diabetes. The relative risk for coronary events is also reduced to a similar extent in both diabetic and non-diabetic populations.

The Scandinavian Simvastatin Survival Study (4S) showed similar reductions in risk for total mortality,
coronary heart disease (CHD) mortality, major CHD event, cerebrovascular event, and any atherosclerotic event for diabetic and non-diabetic cohorts (Figure 1). It should be noted, however, that the definition of diabetes used in this trial was less strict than current definitions (ie, they included patients with fasting sugars only above 140 mg/dL). When the current definition of diabetes is applied to the study cohort, the diabetic population increases from 202 to 483 patients, yet the risk reduction of 30% to 40% is maintained. If individuals with impaired fasting glucose are included (n = 678), the risk reduction is even greater, at 40% to 50%.

In the Cholesterol and Recurrent Events (CARE) trial, which followed patients with heart disease with relatively average LDL-C levels, the extent of risk reduction and LDL-C lowering in patients with diabetes was virtually identical to the nondiabetic participants. With regard to primary prevention, the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), showed a risk reduction in the diabetic subset of the same magnitude as that observed in other subgroups (Figure 2).

One of the recent emerging questions regarding LDL-C is, “Is lower better?” Epidemiologic analyses certainly support the concept that lower is better, but there has been only 1 clinical trial completed to date that has randomized patients to differing LDL-C levels: the post-Coronary Artery Bypass Graft (Post-CABG) trial. In Post-CABG, about 1300 patients with a history of bypass surgery were given LDL-C-lowering therapy, with one group receiving aggressive treatment to a mean LDL-C level of approximately 100 mg/dL and the other group receiving a moderately aggressive treatment plan to a mean LDL-C level of about 130 mg/dL. The study showed that those receiving aggressive therapy had less progression of atherosclerosis than those who had the moderate LDL-C-reduction therapy. Of note, this difference between the 2 treatment groups was also observed in the diabetic subgroup compared with the nondiabetic participants (Figure 3). Several studies are currently under way to examine the potential benefits of LDL-C targets lower than 100 mg/dL, but these results will not likely be available for another 2 to 3 years.

### Table 1. CHD Prevention Trials With Statins in Diabetic Subjects: Subgroup Analyses

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>N</th>
<th>Baseline LDL-C (mg/dL)</th>
<th>LDL-C Lowering</th>
<th>CHD Risk Reduction (Overall)</th>
<th>CHD Risk Reduction (Diabetes)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AFCAPS/TexCAPS³</td>
<td>Lovastatin</td>
<td>239</td>
<td>150</td>
<td>25%</td>
<td>37%</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Secondary Prevention</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CARE⁴</td>
<td>Pravastatin</td>
<td>586</td>
<td>136</td>
<td>28%</td>
<td>23%</td>
<td>25%*</td>
</tr>
<tr>
<td>4S⁵</td>
<td>Simvastatin</td>
<td>202</td>
<td>186</td>
<td>36%</td>
<td>32%</td>
<td>55%†</td>
</tr>
<tr>
<td>LIPID⁶</td>
<td>Pravastatin</td>
<td>782</td>
<td>150</td>
<td>25%</td>
<td>25%</td>
<td>19%</td>
</tr>
<tr>
<td>4S-Extended⁷</td>
<td>Simvastatin</td>
<td>483</td>
<td>NA</td>
<td>NA</td>
<td>32%</td>
<td>42%†</td>
</tr>
</tbody>
</table>

* P = .05  
† P = .002  
‡ P = .001  

CHD = coronary heart disease; LDL = low-density lipoprotein cholesterol; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CARE = Cholesterol and Recurrent Events; 4S = Scandinavian Simvastatin Survival Study; LIPID = Long-Term Intervention With Pravastatin in Ischaemic Disease.

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**Figure 1. 4S: Risk Reduction With Simvastatin in Diabetic vs Nondiabetic Patients**

By far, the largest and most important trial with regard to the potential benefits of improving lipid profiles in patients with diabetes is the Heart Protection Study (HPS). The objective of this study was to assess the effects of simvastatin 40 mg daily and/or an antioxidant vitamin cocktail consisting of vitamins E and C, and beta carotene (placebo) on total mortality and cause-specific mortality in a wide range of patients at high risk for vascular disease (ie, known coronary disease or other vascular disease, treated hypertension, or people with diabetes). Particularly interesting were the inclusion criteria, which were not specific with regard to LDL-C, high-density lipoprotein cholesterol (HDL-C), or triglycerides and included a broad age range of subjects aged 40 to 80 years, thus making the results of this trial very generalizable. The only lipid inclusion requirement was a total cholesterol level above 135 mg/dL. Follow-up was a minimum of 5 years.11,12

More than 20 000 patients participated in the HPS, of whom almost 6000 had diabetes (600 patients with type 1). About one third of the diabetic patients had known coronary disease, so this study provides important data on both primary and secondary prevention in patients with diabetes.11,12 Unfortunately, the results in patients with type 1 diabetes are not broken out from the entire diabetic subset.

The results show an overall 17% reduction in vascular mortality, 5% reduction in nonvascular mortality, and a 12% reduction in mortality for those receiving simvastatin. A 27% reduction in stroke was observed as well in the statin group, showing for the first time in a population without CHD that cholesterol reduction will reduce the risk for stroke as well as CHD.9,10 The results for major vascular events, total CHD, total stroke, or revascularization with simvastatin treatment are virtually identical with a 24% risk reduction for all variables. The results for those subjects with diabetes, with or without prior CHD, again were 24%.11,12

The most unexpected result from the HPS was the effect on vascular events when patients were stratified by LDL-C levels. The results (Figure 4) show that there was no baseline LDL-
C level below which a positive response was no longer observed. The relative and absolute risk reduction was independent of baseline LDL-C level. This has enormous implications in the way we manage dyslipidemia in patients with diabetes.\textsuperscript{11,12}

**Future Statin Studies**

Other statin trials currently under way should shed new light on the benefits of cholesterol reduction in diabetic patients with or without prior CHD, other risk factors, and those receiving renal dialysis.\textsuperscript{13,14} The future studies are briefly summarized in Table 2.

Of particular interest is the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study,\textsuperscript{15} which is evaluating the benefit of combined statin and fibrate therapy.

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**Table 2. Ongoing and Future Statin Trials**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>N</th>
<th>Drug Type</th>
<th>Duration</th>
<th>Primary End Point</th>
</tr>
</thead>
</table>
| ASPEN\textsuperscript{13} | Type 2 diabetics  
No prior MI:  
• LDL-C ≤160 mg/dL  
• TG ≤600 mg/dL  
Prior MI:  
• LDL-C ≤140 mg/dL  
• TG ≤600 mg/dL | 2421 | Atorvastatin  
Double-blind, placebo | 4 years | Time to CV event (CHD death, nonfatal MI, recanalization, CABG, stroke) |
| CARDS\textsuperscript{13} | Type 2 diabetics  
No prior MI or CHD  
Other risk factors + Lipid profile:  
• LDL-C ≤159 mg/dL  
• TG ≤600 mg/dL  
Collaboration in the UK with BDA and NHS | 2750 | Atorvastatin  
Double-blind, placebo | 4 years | Time to major CV event (CHD death, nonfatal MI, recanalization, CABG) |
| 4D\textsuperscript{14} | Type 2 diabetics  
Receiving renal dialysis | 1200 | Atorvastatin  
Placebo | 2.5 years | Combined end point: cardiovascular mortality rate and nonfatal MI |

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LDL-C = low-density lipoprotein cholesterol.

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ASPEN = Atorvastatin Study for the Prevention of Coronary Heart Disease Endpoints in Non Insulin Dependent Diabetes Mellitus; CARDS = Collaborative Atorvastatin Diabetes Study; 4D = Die Deutsche Diabetes Dialyse Studie; MI = myocardial infarction; CV = cardiovascular; CHD = coronary heart disease; CABG = coronary artery bypass graft; LDL-C = low-density lipoprotein cholesterol; TG = triglyceride; BDA = British Diabetic Association; NHS = National Health Service.
on vascular events in a planned population of 10,000 patients. The study objective is to determine whether a therapeutic strategy that raises HDL-C and lowers triglyceride levels (in the context of desirable levels of LDL-C and good glycemic control) reduce the rate of cardiovascular disease events, compared with a strategy that only achieves desirable levels of LDL-C and good glycemic control. Until now, there have been no data regarding patients with or without diabetes that show improved outcomes after receiving combination lipid-lowering therapy. The study strategy is to lower LDL-C levels with simvastatin, and then randomly assign subjects to receive either concomitant fenofibrate or placebo.

**Evidence for Fibrates**

Only 3 outcome studies involving the use of fibrates in diabetic patients have been conducted, with 1 specifically designed for diabetic patients only. The first trial was the Helsinki Heart Study published in the late 1980s. It was a primary prevention trial in which patients received either gemfibrozil 1200 mg daily or placebo. Overall, gemfibrozil produced a 55% reduction in the incidence of myocardial infarction or death compared with placebo, which was significant. Interestingly, when only the diabetic subgroups were analyzed, gemfibrozil offered a roughly 70% risk reduction relative to placebo, but it was not statistically significant, most likely because of the very small numbers of patients in this subgroup (135 diabetic patients vs 3946 nondiabetic patients).16

More recently, the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Trial (VA-HIT), a secondary prevention trial, has been published. Those subjects receiving gemfibrozil 1200 mg had relatively small increases in HDL-C (6%) with no change in LDL-C levels, but, again, demonstrated benefit in CHD risk reduction. In fact, in this trial, the risk reduction in the diabetic subset was identical to that which was observed in people without diabetes (ie, 24%).17

The DAIS is the only study designed to date that specifically evaluated the benefits of lipid modification in diabetic patients. A total of 418 patients with type 2 diabetes were randomized to receive either 200 mg daily fenofibrate or placebo, after 8 weeks on a Step-1 diet. The primary end point was progression or regression of coronary artery disease (CAD) on quantitative angiography. As shown in Figure 5, fenofibrate offered benefit of reduction of CAD based on minimum lumen diameter, percentage stenosis, and mean segment diameter. The benefit was significant for minimum lumen diameter and percentage stenosis but not for mean segment diameter. Interestingly, the investigators noted that, contrary to current beliefs, atherosclerosis in diabetes is focal and no more diffuse than what would be observed in a population without diabetes.8

The number of patients with at least 1 clinical end-point was 23% lower in those taking fenofibrate, but the difference was not significant. With 418 participants, however, the study was not powered to look at clinical outcomes, but the magnitude of the event reduction was similar to what has been observed in other larger studies.8,9

**Figure 5. DAIS: Angiographic Changes in Type 2 Diabetes**

Could Statins Prevent Diabetes?

An interesting benefit of statins is the possibility of preventing diabetes, given the interrelationship between lipid levels and risk of diabetes. Freeman et al analyzed the data from the West of Scotland Coronary Prevention Study (WOSCOPS) trial and found a 30% risk reduction for the development of diabetes associated with pravastatin treatment. The investigators suggested that pravastatin was able to reduce the risk of diabetes through lowering triglycerides. However, in the WOSCOPS, triglycerides were reduced only by 12%, so their role in this putative benefit is unclear. Other effects of statins (eg, anti-inflammatory effects) may also contribute. Nonetheless, other large statin trials completed to date have not shown a reduction in risk for diabetes.

Conclusion

Coronary risk is extremely high in diabetic patients. The benefits of lipid modification in intervention trials also apply to subgroups with diabetes in terms of reducing the risk of CHD. The HPS, however, may signal a need to redefine the target LDL-C goals and the LDL-C treatment criteria for diabetic patients. Finally, data from one trial suggest that statin therapy may also reduce the risk of developing diabetes.

References