ABSTRACT

Diabetes is a recognized risk factor for coronary heart disease (CHD), among diabetologists and the entire medical community. As per the National Cholesterol Education Program Third Adult Treatment Panel guidelines, people at high risk for CHD should undergo aggressive lipid-lowering and antihypertensive therapy, including diabetic patients. The major clinical trials for HMG-CoA reductase inhibitors (statins) and fibrates have shown that they are both effective but different in producing the beneficial lipid changes needed to reduce CHD risk, both in diabetic and nondiabetic populations. Statins have their most pronounced effect on low-density lipoprotein (LDL) cholesterol levels, while fibrates affect high-density lipoprotein cholesterol, triglycerides, and LDL particle size to a greater extent. The combination of statin + fibrate therapy appears to be more effective in diabetic patients than either therapy alone, but the studies have been small and warrant further evaluation, including safety, although the combinations of currently available fibrates and statins seem to be virtually as safe as monotherapy. According to the most recent data niacin also appears to be a safe addition to statin therapy in patients with established diabetes. While the statins as a class are considered very effective, they differ in their metabolism and tissue distribution, which can have serious ramifications in patients taking multiple medications. Lifestyle intervention is a very important part of the CHD risk reduction equation, by lowering CHD risk and possibly reducing the chances of developing diabetes to begin with. (Advanced Studies in Medicine. 2002;2(22):800-807)

Dyslipidemia in diabetes is characterized by normal or increased total cholesterol, normal or increased low-density lipoprotein cholesterol (LDL-C), elevated very-low-density lipoprotein cholesterol, elevated triglycerides, and low high-density lipoprotein cholesterol (HDL-C). The American Diabetes Association (ADA) has published their recommendations for treating dyslipidemia in diabetic patients. As with nondiabetic patients, the primary target is LDL-C lowering and the treatment strategy employed is defined by LDL-C levels at the start of therapy. Table 1 summarizes the ADA recommendations for adults with diabetes. The LDL-C goal is lower than 100 mg/dL. For those with LDL-C of 100 to 129 mg/dL at baseline, therapeutic lifestyle changes (TLC) should be intensified and a lipid-lowering drug
may be added. Risk factor control should also be intensified. For those with very high LDL-C levels (ie, ≥130 mg/dL), treatment should begin with simultaneous TLC and LDL-C-lowering drugs. If the triglyceride levels go to 200 mg/dL or beyond, non–HDL-C becomes a secondary target. Non–HDL-C is a measure of LDL-C and intermediate density Lipoprotein cholesterol (IDL-C) and very low density Lipoprotein cholesterol (VLDL-C). It is a measure of all potentially atherogenic Lipoprotein particles and correlates highly with apo Lipoprotein B.

In the United States, diabetes is now approaching epidemic proportions, and the metabolic syndrome is also increasing at an alarming rate. The National Cholesterol Education Program (NCEP) Third Adult Treatment Panel (ATP III) has defined the metabolic syndrome as shown in Table 2. The World Health Organization (WHO) has issued a definition that is basically similar to the NCEP ATP III definition, but also includes microalbuminuria levels. The metabolic syndrome is a strong risk factor for diabetes. Dyslipidemia in metabolic syndrome patients should also be treated aggressively and, as will be discussed later, can be achieved through common lipid-lowering treatment strategies.

As discussed in Dr Leiter’s article, elsewhere in this issue, the HMG-CoA reductase inhibitors (statins) as a class have shown a remarkable ability to influence outcomes in diabetic and nondiabetic populations. Statins are able to reduce the risk for total mortality, stroke, coronary heart disease (CHD), and the progression of atherosclerosis.

However, the practicing clinician is guided by the parameters published by the major organizations (eg, ADA, NCEP, the European Society of Cardiology, International Atherosclerosis Society, WHO). Their measure of success is LDL-C lowering so it is important to examine how the statins and other lipid-lowering drugs (eg, fibrates, niacin) affect LDL-C levels in diabetic patients.

### Efficacy in Major Trials

Figure 1 provides an overview of the effect of statins used in the major clinical trials on lipid levels in diabetic populations. These data are from subgroup analyses; the studies were not originally designed to stratify patients based on the presence of diabetes. As can be seen in Figure 1, all of the statins were able to

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**Table 1. 2002 ADA Recommendations Based on LDL-C in Adults With Diabetes**

<table>
<thead>
<tr>
<th>Status</th>
<th>Medical Nutrition Tx Initiation LDL-C Level (mg/dL)</th>
<th>LDL-C Goal (mg/dL)</th>
<th>Drug Tx Initiation LDL-C Level (mg/dL)</th>
<th>LDL-C Goal (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With CHD, PVD, or CVD</td>
<td>≥100</td>
<td>&lt;100</td>
<td>≥100</td>
<td>&lt;100</td>
</tr>
<tr>
<td>Without CHD, PVD, or CVD</td>
<td>≥100</td>
<td>&lt;100</td>
<td>≥130*</td>
<td>&lt;100</td>
</tr>
</tbody>
</table>

* Some authorities recommend drug initiation between 100-130 mg/dL. If high-density lipoprotein <40 mg/dL, fibric acid may be used.

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**Table 2. NCEP ATP III Definition of the Metabolic Syndrome**

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Defining Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal obesity (waist circumference)</td>
<td></td>
</tr>
</tbody>
</table>
  - Men >40 in  
  - Women >35 in  
| TG | ≥150 mg/dL  
| HDL-C |  
  - Men <40 mg/dL  
  - Women <50 mg/dL  
| Blood pressure | ≥130/≥85 mm Hg  
| Fasting glucose | ≥110 mg/dL  

 TG = triglycerides; HDL-C = high-density lipoprotein cholesterol.
reduce LDL-C by 25% to 40% using the currently recommended doses. Total cholesterol and triglycerides were also reduced, but HDL-C increased relatively slightly (about 5% overall).3-6

Fibrates have also been shown to be very effective in correcting dyslipidemia in diabetic cohorts. As shown in Figure 2, fibrates have a significant impact on triglycerides, but their effect on LDL-C is very small. Thus far, the Diabetes Atherosclerosis Intervention Study (DAIS) is the only published outcome study to examine the effect of a lipid-lowering agent in a strictly diabetic population, even though this study was not designed for hard end points, but for changes in carotid atherosclerosis."7,9

**Comparing Fibrates With Statins and the Role of Combination Therapy**

Only 1 previous study has directly compared a statin to a fibrate in diabetic patients. Atorvastatin was compared with fenofibrate in 13 patients with type 2 diabetes and mixed hyperlipidemia (LDL-C >135 mg/dL, total triglycerides >200 mg/dL) in a prospective, randomized, open-label, crossover study. The treatments were given for 6 weeks each time with a 6-week washout period between. As shown in Table 3, the results on lipid levels in the 11 patients who completed the study were as expected for each therapy: atorvastatin was more effective in LDL-C lowering, whereas fenofibrate was more effective in total triglyceride lowering. In this study, fenofibrate also increased HDL-C by 11%, which is higher than expected.10

Given the complementary effects of statins and fibrates, recent clinical research is now evaluating combination therapy in diabetic cohorts. Although the studies are usually small, the data clearly indicate that combination therapy is more effective than either therapy alone.

Simvastatin monotherapy was compared with combination simvastatin + bezafibrate in 148 patients with type 2 diabetes stabilized over the preceding 3 months with diet and oral medication. This was an open-label study conducted over 21 months at 3 lipid clinics in tertiary care hospitals. The single drug (simvastatin or bezafibrate) was given for 6 months, followed by the combination for an additional year. The results...
show that the combination was at least as effective as either therapy alone in every lipid parameter, irrespective of whether the patient had been taking bezafibrate monotherapy or simvastatin mono-therapy before the combination therapy (Figure 3). Patients receiving combination therapy had higher creatine kinase levels than those receiving monotherapy, although all mean changes were in the accepted normal range for the laboratory and no cases of severe adverse effects were observed. Fibrinogen levels were also reduced to a greater extent with combination therapy.\textsuperscript{11}

Another combination therapy trial compared pravastatin (20 mg daily) with combination pravastatin (20 mg daily) + niacin immediate release (1.5 g daily) over a 4-week treatment period. Of the 23 diabetic patients who were recruited from a diabetes clinic (with \textit{LDL-C} $\geq 150$ mg/dL), 16 completed the study. The majority ($n = 14$) had type 2 diabetes. Niacin has been reported to induce diabetes in people with glucose abnormalities, but those with normal glucose levels seem not to be at a higher risk for diabetes with niacin treatment.\textsuperscript{12-16} This was an open-label, nonrandomized, sequential therapy study in which pravastatin alone was given for 4 weeks, followed by combination therapy for 6 weeks. The combination therapy had much greater effect on all lipid parameters than pravastatin alone (Figure 4). There were no clinically significant increases in uric acid or liver enzymes, and mild flushing was reported in 14 patients when the niacin treatment was initiated; however, only 3 discontinued. Of particular importance, no myopathy was reported and the mean fasting blood glucose and fructosamine concentration remained unchanged. Thus, niacin in combination with pravastatin appears to be safe and effective in diabetic patients, although larger, combination studies with niacin should be conducted.\textsuperscript{17}

The most recently developed statin, rosuvastatin, is now under investigation in both diabetic and nondiabetic patients. A study comparing rosuvastatin monotherapy (5 or 10 mg) with rosuvastatin + fenofibrate in 216 hypercholesterolemic patients with type 2 diabetes was conducted in 2 phases. In phase 1, there were 4 treatment groups: 1 receiving rosuvastatin 5 mg, 1 receiving rosuvastatin 10 mg, and 1 corresponding placebo group for each rosuvastatin group; all 4 groups were treated for 6 weeks. Significant reductions in TG, \textit{LDL-C}, TC, \textit{VLDL-C}, and apolipoprotein B, as well as significant increases

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**Table 3. Atorvastatin vs Fenofibrate in Type 2 Diabetes**

<table>
<thead>
<tr>
<th></th>
<th>Atorvastatin</th>
<th>Fenofibrate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Chol</td>
<td>-24*</td>
<td>-16*</td>
</tr>
<tr>
<td>LDL-C</td>
<td>-29†</td>
<td>-11%</td>
</tr>
<tr>
<td>ApoB</td>
<td>-28%‡</td>
<td>-20%‡</td>
</tr>
<tr>
<td>Total TG</td>
<td>-4%</td>
<td>-39%*</td>
</tr>
<tr>
<td>HDL-C</td>
<td>10%†</td>
<td>11%</td>
</tr>
</tbody>
</table>

* $P < 0.05$; †$P < 0.01$; ‡$P < 0.05$; §$P = 0.06$.

Reprinted with permission from Excerpta Medica Inc., Frost RJ et al.\textsuperscript{10} Chol = cholesterol; \textit{LDL-C} = low-density lipoprotein cholesterol; ApoB = apolipoprotein B; TG = triglyceride; and HDL-C = high-density lipoprotein cholesterol.

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**Figure 3. Simvastatin (SIM) Alone vs SIM + Bezafibrate**

Reproduced with permission from J Intern Med. 2000;247(5):563-569.\textsuperscript{11} TG = triglyceride; Chol = cholesterol; \textit{LDL-C} = low-density lipoprotein cholesterol; \textit{HDL-C} = high-density lipoprotein cholesterol; CPK = creatine kinase.
in HDL-C, were observed with both doses of rosuvastatin after Phase 1 (P < .001 vs Placebo).

In Phase 2, patients who had LDL-C levels ≥50 mg/dL were force-titrated as follows over three 6-week intervals in an open-label fashion. Placebo group 1 received rosuvastatin 10, 20, then 40 mg daily. Placebo group 2 received fenofibrate 67 mg (od, bid, then tid). Those taking rosuvastatin 5 or 10 mg in phase 1 continued with their statin therapy in addition to a force-titration of fenofibrate to 67 mg (od, bid, then tid). The overall, combination therapy was more effective than rosuvastatin therapy alone (although a few parameters were not significantly different), and the effect appears to be dose dependent (Figure 5). Of note, fenofibrate had no effect on LDL-C; its effect was restricted to triglycerides and HDL-C.18

Rosuvastatin was also evaluated in hypercholesterolemic patients; a subset with metabolic syndrome was identified using a slightly modified version of the ATP III criteria (ie, waist circumference was replaced by body mass index [BMI]). Five different trials were conducted to evaluate treatment with rosuvastatin 10 mg over 12 weeks in hypercholesterolemic patients with and without the metabolic syndrome. The pooled analysis from all 5 trials showed that rosuvastatin was equally effective on all lipid outcomes in patients who had the metabolic syndrome compared with those who did not.19

SAFETY ISSUES IN DIABETIC POPULATIONS

STATINS AND FIBRATES

A review of the earlier clinical trial data for statins and fibrates currently in clinical use (discussed in the article) indicates no major differences in various potential adverse effects between the statins or fibrates and placebo. These include liver enzyme increases, myalgia, creatinine kinase, rhabdomyolysis, or the incidence of cancer, death from suicide or violence, and study withdrawals due to side effects with statins or fibrates.

ROSUVASTATIN AND A FIBRATE IN DIABETIC POPULATIONS

The combination of rosuvastatin and

Figure 4. Pravastatin + Niacin in Diabetic Patients

Data adapted from Gardner SF, et al.17
TC = total cholesterol; TG = triglyceride; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; Prav = pravastatin; N = niacin.

Figure 5. Rosuvastatin (ROS) vs ROS + Fenofibrate in Type 2 Diabetes: Phase II (Week 24)

* P<.017 vs ROS 40 mg od.
Data adapted from Durrington P, et al.18
ROS 10/20/40 po was Placebo Group 1 in Phase 1; FEN 67 mg tid was Placebo Group 2 in Phase I.
TG = triglyceride; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; HDL-C = high-density lipoprotein cholesterol; FEN = fenofibrate.
fenofibrate also appeared to have only mild adverse effects. The number of treatment-related adverse events occurring in at least 2 patients during the trial was very low for those taking rosuvastatin or fenofibrate alone. The number of adverse events increased in those taking the lower dose of rosuvastatin (5 mg), but the largest number of patients reporting adverse events was 5 (liver enzyme increases). Interestingly, when the rosuvastatin dose was increased to 10 mg in combination therapy, the incidence of adverse events dropped to less than half. Overall, the adverse effects appear to be mild (eg, headache, constipation, flatulence, nausea, vomiting, liver-enzyme increases) and infrequent, appearing in less than 2% of the diabetic patients.

**Pharmacologic Differences Among Statins**

While the efficacy and safety of the statins can be considered a class effect, the statins differ based on their lipophilicity, which can affect tissue distribution and metabolism. Differences in metabolism are of concern because they can cause drug-drug interactions, especially in older patients who are more likely to be taking polypharmacy.

The differences among the statins' lipophilicity and metabolism are summarized in Table 4. Whether these differences have major effects on the side-effect profile or efficacy is not yet known, but these characteristics should at least be considered when choosing the statin therapy.

In summary, drug therapy for dyslipidemia in diabetic patients consists primarily of statins and fibrates. Statins have their most pronounced effect on LDL-C levels and the amount of LDL particles, whereas fibrates affect primarily HDL-C levels, triglyceride levels, and LDL particle size. So, while fibrates may not necessarily reduce LDL-C levels, their influence on LDL-C particle size may be important for the prevention of progression of atherosclerosis.

The statins, as a class, are safe and similarly effective in both diabetic and nondiabetic hyperlipidemic patients. However, there are some differences among statins. For instance, lipophilicity and cytochrome P450 metabolism should be considered when choosing which statin to be used, especially in patients taking multiple medications. Also, niacin appears to be a safe and effective addition to statin therapy in diabetic patients, although careful monitoring of patients during such combination therapy is necessary.

**Prevention of Diabetes**

Dyslipidemia can be successfully treated with pharmacotherapy, but effective treatment of type 2 diabetes is notoriously unsuccessful. An ideal strategy would be to prevent diabetes initially, thus eliminating one of the risk factors for CHD. The Finnish Diabetes Prevention Study was a landmark study to determine whether lifestyle guidance of overweight (ie, BMI \( \geq 31 \) kg/m\(^2\)), middle-aged adults with impaired glucose tolerance will prevent or delay the development of type 2 diabetes. This was the first proper, randomized trial in prevention of type 2 diabetes.

Roughly 260 patients were in each of the intervention and control groups (N = 522). The intervention goals were to reduce weight by more than 5% (reducing BMI to less than 25 kg/m\(^2\)), reduce daily fat intake to less than 30% of total ingested calories, reduce daily saturated fat intake to less than 10% of total ingested calories, increase fiber intake to more than 15 g/1000 kcal, and participate in aerobic and muscle-strengthening exercise for more than 30 minutes daily.

After 1 year of treatment, those receiving lifestyle guidance had significant reductions in almost every endpoint measured (ie, weight, waist circumference, glucose, hemoglobin A\(_1c\), triglycerides, and systolic...
and diastolic blood pressure). Surprisingly, the total cholesterol and HDL-C levels did not change significantly, whereas triglycerides were reduced significantly. These lipid profiles were not expected, especially given that the intervention group had a 58% reduction in the risk of diabetes over the study period.

The success score (ie, the number of the above-mentioned targets achieved) was heavily dependent on intensive guidance, and the increase in success score had a dramatic effect on the risk of developing diabetes. So, lifestyle intervention is clearly effective in reducing the risk for diabetes in adults with impaired glucose tolerance, but additional strategies are necessary to affect cholesterol levels.21

CONCLUSION

Correction of lipid levels and blood pressure is even more important for prognosis than glycemic control alone in diabetic patients. In general, the primary aim of lipid management in type 2 diabetic patients is the same as in nondiabetic subjects: to lower LDL-C levels and thus lower the cardiovascular disease risk. Diet and exercise modifications are always needed but their effects on lipids may only be modest. Statins are much more efficient at lowering LDL-C than fibrates, whereas fibrates are somewhat more efficient in reducing triglycerides and increasing HDL-C. However, fibrates have no effect on LDL-C. Combination therapy with statins and fibrates appears to be the most efficient pharmacologic strategy in diabetic patients who have any form of dyslipidemia. The primary importance of concomitant lifestyle changes should always be kept in mind before starting antidiabetic or lipid-lowering drug treatment.

REFERENCES


