New Strategies for the Treatment of Diabetic Dyslipidemia

Type 2 diabetes is associated with a marked increase in coronary heart disease (CHD) (1). In some cases, the magnitude of the increase in CHD in diabetic subjects without preexisting CHD is as great as that in nondiabetic subjects with CHD (2,3). The possible equivalent risk of diabetes and prevalent CHD has led to the suggestion that diabetic subjects be treated as CHD-risk equivalents by a variety of organizations, including the American Diabetes Association (ADA) (4) and the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (5). Further amplifying the importance of early and aggressive risk factor interventions is the increased case fatality rate in diabetic subjects who have a myocardial infarction (6). In the latter report, 50% of diabetic men died prior to hospitalization before their first myocardial infarction, suggesting that a strategy based on secondary prevention may not be completely effective.

Given that diabetic subjects have a marked increase in CHD, what are appropriate strategies to reduce their risk of CHD? Diabetic subjects tend to have markedly increased triglyceride levels and decreased HDL cholesterol (7). In addition, LDL cholesterol levels in diabetic subjects are often similar to those of nondiabetic subjects. Additionally, diabetic subjects have an increased proportion of smaller, denser, potentially more atherogenic LDL particles than nondiabetic subjects (8). In early prospective studies (9), increased triglyceride levels and decreased HDL cholesterol levels were more powerful predictors of CHD than LDL cholesterol. Based on these observations, earlier recommendations for the treatment of diabetic dyslipidemia often focused on correction of the abnormal triglyceride HDL cholesterol levels in diabetic subjects (10). The initial strategy focused on the use of fibrates because nicotinic acid was felt to be relatively contraindicated due to its effects on worsening glycemic control (11). Indeed, Koskinen et al. (12) showed that the fibric acid gemfibrozil was associated with a 60% reduction in the incidence of cardiovascular disease among 135 diabetic subjects, although the results were not statistically significant because of low power.

However, over the last few years, increasing emphasis has been put on the use of statins in diabetic subjects, despite the fact that diabetic subjects do not have particularly high LDL cholesterol levels. A number of factors are behind this change in attitude. In the U.K. Prospective Diabetes Study (UKPDS) (13), LDL cholesterol was the first variable entered into a Cox proportional hazards multivariate model, with CHD as a dependent variable. HDL cholesterol was entered second, and triglyceride levels were not a predictor of CHD. Because this was a very large study (nearly 2,700 subjects) that followed subjects for an average of 10 years, these data were given considerable weight in the ADA technical review (14). Furthermore, a variety of articles (15–18) have suggested that diabetic subjects receive as much benefit from lipid lowering as nondiabetic subjects. More recently, the Heart Protection Study (HPS) (19) has suggested that in nearly 6,000 diabetic subjects, statin use reduced vascular disease. Indeed, simvastatin reduced vascular disease in the overall study, even if their baseline LDL cholesterol level was <100 mg/dl, implying that all high-risk patients might possibly benefit from statin therapy. (This analysis has not yet been presented for the diabetic subgroup.) Statin therapy reduces vascular events equally in diabetic subjects as in nondiabetic subjects. The evidence supporting statin use in terms of number of subjects and effect size is now more impressive for statins than for fibrates. Thus, the ADA has suggested statins as an initial therapy followed by an emphasis on HDL cholesterol (45 mg/dl) and, lastly, triglyceride levels (200 mg/dl) (4). The NCEP ATP III also suggests an initial focus on LDL cholesterol (<100 mg/dl) in diabetic subjects, followed by a secondary emphasis on non-HDL cholesterol (130 mg/dl) if the triglyceride level is elevated (200 mg/dl) (Table 1). There is not, at the present time, a large body of evidence supporting a specific goal of LDL lowering to <100 mg/dl in diabetic subjects. Perhaps the most convincing data from this area comes from the diabetic subgroup analysis of the Post–Coronary Artery Bypass Graft Study, in which subjects were randomized to high versus low doses of lovastatin. Subjects achieved an LDL of ~95 versus 135 mg/dl. Subjects who were randomized to high-dose lovastatin had less progression of atherosclerosis than subjects randomized to low doses of lovastatin (20).

Given that there is a general consensus for LDL lowering as a first priority for lipid therapy in diabetic subjects and that many of these recommendations suggest an LDL <100 mg/dl, what further inter-

Table 1—Recommendations for the treatment of diabetic dyslipidemia

<table>
<thead>
<tr>
<th>1st Priority</th>
<th>2nd Priority</th>
<th>3rd Priority</th>
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<tbody>
<tr>
<td>EAS 1999 (28)</td>
<td>LDL-C &lt; 3.0 mmol (&lt;115 mg/dl)</td>
<td>TG &lt; 2 mmol (&lt;176 mg/dl)</td>
</tr>
<tr>
<td>ADA 2002 (4)</td>
<td>LDL-C &lt; 2.6 mmol (&lt;100 mg/dl)</td>
<td>HDL-C &gt; 1.2 mmol (&gt;45 mg/dl)</td>
</tr>
<tr>
<td>NCEP 2001 (5)</td>
<td>LDL-C &lt; 2.6 mmol (&lt;100 mg/dl)</td>
<td>If TG &gt; 2.3 mmol (TG ≥200 mg/dl) then Non-HDL-C &lt; 3.4 mmol (&lt;130 mg/dl)</td>
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</tbody>
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TG, triglyceride.
ventions might diabetologists provide, especially in diabetic subjects at a particularly high risk of CHD, such as those with prior vascular disease? One possibility is to further lower the LDL cholesterol to perhaps <75 mg/dl. Two clinical trials are actively testing the hypothesis that more aggressive therapy in patients with previous CHD may have more favorable outcomes. The Treatment of New Targets (TNT) Study has randomized 10,000 CHD patients to atorvastatin 10 versus 80 mg/dl day. The LDLs achieved in that study are ~100 versus 75 mg/dl. Another study is the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH), in which subjects with previous CHD are randomized to simvastatin 20 versus 80 mg/dl day. Furthermore, higher doses of more effective statins may be more effective in lowering triglyceride (and non-HDL cholesterol) levels, particularly in hypertriglyceridemic subjects. An alternate approach might be to add a fibric acid to a statin. The VA-HIT Study (21) has suggested a 24% reduction in cardiovascular events in both the diabetic subset (n = 627) and in the non-diabetic group (n = 1904). The DIAS Study (22) suggests similar reduction in vascular events (23%) in diabetic subjects treated with fenofibrate. To date, no clinical trial has reported outcomes in subjects with a combined fibric acid/statin trial, although the U.S. clinical trial Action to Control Cardiovascular Risk in Diabetics (ACCORD) study will ~5,000 diabetic subjects on simvastatin 20 mg who are randomized to fenofibrate 200 mg micronized or placebo.

The use of combinations of statin and fibric acids has been a matter of concern because of the possible increase in rhabdomyolysis. Recently, cerivastatin was withdrawn due to an increase in rhabdomyolysis, particularly in combination with gemfibrozil (23). The current report in this issue, by Athyros et al. (24), on atorvastatin 20 mg/dl plus 200 mg/dl micronized fenofibrate is therefore of considerable interest. The investigators randomized 120 subjects to fenofibrate, atorvastatin, or the combination of both for a period of 24 weeks. The investigation showed additive effects of atorvastatin and fenofibrate. No subject developed myositis. Furthermore, the effects of fenofibrate and atorvastatin were generally additive (in LDL cholesterol, HDL cholesterol, and apolipoprotein A_1), enabling patients who started with diabetes and combined hyperlipidemia to achieve the ADA goals for treatment in diabetic dyslipidemia. Although this study needs to be confirmed in larger populations, it suggests that in diabetic subjects with normal renal function, the combination of fenofibrate and atorvastatin might be both safe and effective. Clearly, combination therapy does further improve diabetic dyslipidemia, but definitive conclusions that the combination has additive benefits for cardiovascular disease prevention need confirmation in clinical trials.

One potentially attractive pharmacological agent in combination with statins might be nicotinic acid. Nicotinic acid increases HDL cholesterol more than fibric acids or statins. In the HDL-Atherosclerosis Treatment Study (HATS) (25), nicotinic acid plus low-dose simvastatin significantly reduced the progression of atherosclerosis. Although the number of subjects was small and included only a minority of diabetic subjects, there was an overall 90% reduction in vascular events in subjects treated with simvastatin and nicotinic acid. However, nicotinic acid has not generally been used in diabetic subjects because it may worsen insulin resistance and glycemic control (11). Yet, in a recent multi-center VA study (26), relatively low-dose (2–3 g/day) crystalline nicotinic acid significantly improved atherogenic dyslipidemia without an adverse effect on glycemic control. Similar results have been shown for Niaspan in the Assessment of Diabetes Control and Evaluation of the Efficacy of Niaspan Trial (ADVENT) (27). Because nicotinic acid is generally considered to have a lower risk of myositis in a combination of statins, this regimen may be attractive in patients who monitor glucose carefully.

A number of other options might be considered. This includes statins + fibric acids, colesevalam + fibrates, and ezetimibe + fibrates (+ colesevalam). The data in these combinations are limited, especially in diabetic subjects, to a few studies on lipoproteins, although there is little evidence of toxicity. Furthermore, there are no clinical trials involving hard CHD events or even progression of atherosclerosis.

Previous clinical trials have shown that both statins and fibric acids may reduce cardiovascular events by 20–40% in the majority of trials. However, this implies that 60–80% of subjects may continue to experience high rates of cardiovascular disease. To further improve outcomes, one possibility would be the combination of agents such as statins with fibric acids or even potentially nicotinic acid. These combinations need to be tested rigorously in clinical trials. It is hopeful, however, that the current report by Athyros et al. suggests that a combination of a statin (atorvastatin) and a fibric acid (fenofibrate) may be safe, at least in diabetic subjects with normal renal function (24).

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References


