ABSTRACT

Aggressive lipid modification is warranted in patients with type 2 diabetes because cardiovascular disease has a profound impact on these patients as well as on those with the metabolic syndrome who have not yet developed diabetes. The primary treatment strategy to correct dyslipidemia in these groups of patients is to lower low-density lipoprotein cholesterol. The secondary strategies are to raise high-density lipoprotein cholesterol and lower triglyceride levels. Considerable evidence from trials evaluating treatment with statins and fibrates shows these strategies are effective in reducing the risk of coronary events in these patients. Although effective pharmacotherapy is available, the optimal treatment approach remains to be ascertained in a large prospective trial. Until then, early and aggressive management with available drugs to achieve target goals is recommended. (Advanced Studies in Medicine 2001;1(9):367-371)

RATIONALE FOR AGGRESSIVE LIPID MODIFICATION IN TYPE 2 DIABETIC PATIENTS

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The rationale for aggressive lipid modification in patients with type 2 diabetes is best and most succinctly expressed by a statement made many years ago: "With an excess of fat diabetes begins, and from an excess of fat diabetics die." Although this statement was made some time ago, numerous studies done in recent years confirm that dyslipidemia contributes heavily to atherosclerosis. In addition, national statistics indicate that cardiovascular disease is the major cause of death in patients with diabetes in the United States. As demonstrated in several large-scale trials, however, pharmacologic treatment of dyslipidemia is effective, in both diabetic and nondiabetic subjects, in reducing the risk of cardiovascular events and mortality from cardiovascular causes.

Because cardiovascular disease has such a profound impact on patients with diabetes, the need to implement early and aggressive treatment strategies aimed at correcting dyslipidemia, one of the major antecedents of atherosclerosis and cardiovascular disease, is critical. Such treatment would reduce the risk for cardiovascular events not only in patients with established heart disease, but also in prediabetic individuals, for whom the risk for coronary heart disease (CHD) begins before the onset of clinical diabetes.

TREATMENT STRATEGIES

The primary treatment strategy to correct dyslipidemia in patients with diabetes is to lower the level of low-density lipoprotein (LDL) cholesterol. The secondary strategies are to raise high-density lipoprotein

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*This article is based in part on a presentation given by Dr Ballantyne at the 61st Scientific Sessions of the American Diabetes Association.
In the most recent set of NCEP guidelines released in May 2001, diabetes is considered a CHD risk equivalent, warranting the same intensity of lipid-modifying therapy as is used in treating patients with known coronary disease. \[18\]

The number of diabetic subjects in the major statin trials is relatively small, which may have limited the study power. However, the findings demonstrating the benefits of statin therapy are consistent. The number of diabetic subjects in the Air Force/Texas Coronary Atherosclerosis Prevention Study, a primary prevention study involving a healthy population, was too small to draw any meaningful conclusions. However, somewhat higher numbers of diabetic subjects were included in 3 large secondary prevention trials evaluating statins: the Scandinavian Simvastatin Survival Study (4S) \[10\], the Cholesterol and Recurrent Events trial, and the Long-term Intervention with Pravastatin in Ischaemic Disease study. In these trials, LDL cholesterol levels were lowered by 25% to 36% in subjects with diabetes, with reductions in CHD events ranging from 19% to 55%. Overall, patients with diabetes showed consistent reductions in both relative and absolute risk with statin therapy.\[14\]

The need for aggressive risk reduction associated with the high morbidity and mortality in patients with diabetes and CHD was demonstrated in 4S, which showed that diabetic subjects who were randomized to placebo had a coronary event rate of more than 50%.\[15\]

The statin trials demonstrate that modification of risk factors unrelated to glucose are essential in reducing CHD events in diabetes. A subgroup analysis of 4S subjects with clinical diabetes (fasting plasma glucose level of 126 mg/dL or higher) and those with impaired fasting glucose (fasting plasma glucose levels of 110 to 125 mg/dL) found that the benefits of statin therapy in these groups were impressive.\[16\] An analysis of 4S that looked at the effect of statin therapy on hospital stay found that treatment also reduced the length of stay in patients with impaired fasting glucose or diabetes.\[17\] This finding, along with reduced event rates, may encourage managed care organizations to allocate more resources to early and aggressive lipid modification in patients with diabetes.

While the statin trials have convincingly demonstrated the benefits of therapy versus placebo in diabetics and nondiabetics, only one study thus far, the Post Coronary Artery Bypass Graft study, has compared aggressive statin therapy with moderate statin therapy. Aggressive therapy was intended to lower LDL to less than 85 mg/dL, with moderate therapy intended to lower LDL to less than 130 mg/dL. The greatest benefit was seen with aggressive therapy in patients with diabetes, in whom a 51% reduction in coronary risk was noted.\[18\]

Evidence from Fibrate Trials: Diabetes and Combined Dyslipidemia

Trials evaluating fibrates to correct various lipid abnormalities have shown that these agents are effective in patients with diabetes or the metabolic syndrome. The Helsinki Heart Study, a primary prevention study involving subjects with elevated triglycerides and low HDL cholesterol, included a small number of diabetic subjects. The investigators found that fenofibrate reduced the relative risk for coronary events in the diabetic subjects, although the change was not statistically significant.\[14\] Patients with the combined abnormalities of high triglycerides and low HDL cholesterol who received placebo during this study had the highest event rate, but this subgroup also had the greatest event reduction with gemfibrozil.\[14\] In the Veterans Affairs High-Density Lipoprotein Cholesterol Intervention Study, triglycerides and low HDL cholesterol levels of less than 80 mg/dL in men or less than 50 mg/dL in women were associated with a substantial reduction in the risk of cardiovascular events.\[11\]

In quartile analyses of 4S,\[11\] patients in the highest triglyceride and lowest HDL cholesterol quartiles (lipid triad) had the highest event rate on placebo and the greatest event reduction on simvastatin, with a relative risk reduction of slightly more than 50%.

Baseline lipids in these patients were similar to those in the 4S guidelines for the metabolic syndrome, and this subgroup also had more diabet-ic, hypertensive, and obese patients as seen in the metabolic syndrome.

Although the major statin trials have shown reductions in coronary event rates with LDL, lowering of triglycerides and low HDL cholesterol in subjects whose only lipid abnormality was elevated LDL cholesterol, closer examination of the data reveals that subjects with low HDL cholesterol also benefit. This has also been observed in various angiographic trials. That patients with mixed dyslipidemia—high LDL cholesterol, low HDL cholesterol, and high triglyceride levels—benefit from statin therapy can be explained by the dose-dependent effects of some of the statins on these lipid abnormalities. In the Scandinavian Simvastatin Survival Study (4S), patients in the highest triglyceride and lowest HDL cholesterol quartile (lipid triad) showed a 25% to 36% reduction in triglycerides with simvastatin doses ranging from 10 to 40 mg.

The implications of post hoc analyses of 2 fibrate trials (Helsinki and BIP) and 1 statin trial (4S) are clear: patients with mixed hyperlipidemia are at highest risk for CHD events, and they benefit most from pharmacologic therapy. The challenge is to ascertain, through a large prospective trial, optimal therapy for these patients, be it high-dose statin therapy, fibrate therapy, or combination therapy.
Several studies investigating this point are currently in progress. They include the Heart Protection Study, which includes a large number of subjects with diabetes, the Atherosclerostin Study in Preventing Endpoints in NIDDM, and the Lipids in Diabetes Study, which is the only study comparing combination therapy (cerivastatin and fenofibrate) with monotherapy (each of these agents alone). The need for additional trials is obvious. Ideally, these studies would focus not only on persons with diabetes, but also on those with the metabolic syndrome.

Treatment guidelines for diabetic dyslipidemia from the American Diabetes Association call for lowering LDL to less than 100 mg/dL, raising HDL to more than 45 mg/dL, and lowering triglycerides to less than 200 mg/dL.11 Beginning with lifestyle modification, lowering LDL cholesterol to target levels can be accomplished by statin therapy alone or in combination with a bile acid resin or a fibrate. Raising HDL cholesterol to target levels requires behavioral intervention, combinations of lipid-modifying therapy, the addition of low-dose niacin, and more intensive glycemic control. Lowering triglyceride levels to less than 200 mg/dL can be accomplished by more intensive glycemic control, higher doses of statins, and the use of fibrates. Fish oils can be used as well because they are effective in lowering triglyceride levels and safe when used with statins.

CONCLUSION

The key to treating diabetic dyslipidemia is aggressive intervention with lifestyle modification and pharmacologic therapy. However, because the cardinal features of dyslipidemia are present in patients with the metabolic syndrome, who have a high probability of developing diabetes within a relatively short period of time, early intervention should be considered. Studies have shown that these patients benefit from pharmacologic lipid-modifying therapy, and they should receive it before diabetes develops.

Given that the major cause of death in persons with diabetes is cardiovascular disease, and given that clinical trials have shown convincingly that lipid-modifying therapy reduces coronary event rates in these patients, earlier and more aggressive pharmacologic treatment should result in even greater reductions in coronary risk.

REFERENCES