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Treating Patients with the Metabolic Syndrome and Type 2 Diabetes: A Step Beyond Statins

Washington - In Canada, there are now more than 2 million patients with type 2 diabetes of whom about two-thirds will die of cardiovascular disease. Approximately 25% of Canadians have the metabolic syndrome, which by itself has been associated with a 38% increased risk of coronary events. The typical dyslipidemia in these patients is elevated triglycerides, suppressed HDL-C levels and near normal LDL-C levels. While statins exert most of their benefit by reducing LDL-C and have been associated with significant risk reductions in these patient groups, emerging data suggest important additional risk reductions can be achieved by raising HDL-C and reducing triglycerides. New data indicate most patients with type 2 diabetes or the metabolic syndrome can benefit from a combination lipid-lowering therapy. These data, generated by the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial, the largest lipid treatment study conducted in diabetic patients, are changing the standards of clinical practice.

It has long been recognized that individuals with type 2 diabetes or the metabolic syndrome have lipid abnormalities that are not addressed by statin therapy. In the third National Cholesterol Education Panel (NCEP III) guidelines, it is suggested that the "addition of a fibrate or nicotinic acid to LDL-C-lowering therapy can be considered" in these patients. In lipid abnormalities that are not well controlled with statins, use of a fibrate in the FIELD (Fenofibrate Intervention and Event Lowering in Diabetes) trial confirmed an 11% (P=0.035) reduction in total cardiovascular (CV) events. The benefit is expected to be incremental to the LDL-C-lowering effect provided by statins, making combination therapy a logical step to improving outcome.

Combination Therapy: The Next Logical Step

According to Dr. Kenneth Cusi, Diabetes Division, University of Texas Health Science Center, San Antonio, "Combination therapy will play an increasing role in the management of patients with type 2 diabetes and the metabolic syndrome, because of the opportunity it provides to better address the abnormalities of atherogenic dyslipidemias." Although statins have proven to reduce risk of CV events in diabetic patients and those with the metabolic syndrome, he emphasized that "statins are not fulfilling our needs" in regard to the other important dyslipidemias encountered in these populations.

The metabolic syndrome has been described as a prediabetic state with a constellation of CV risk factors including elevated fasting plasma glucose (>5.5 mmol/L), abdominal obesity (waist circumference in men >102 cm, in women >88 cm), triglycerides ≥1.7 mmol/L, HDL cholesterol in men <1.0 mmol/L and in women <1.2 mmol/L, blood pressure ≥130/≥85 mm Hg. Control of dyslipidemias in these patients provides one of the most important opportunities for CV risk reduction.

As a result of the FIELD trial, with support from a series of earlier studies that also evaluated therapies for hypertriglyceridemia and suppressed HDL-C, "we now have the data to determine how to address the specific dyslipidemias that we see in these specific patient populations [with type 2 diabetes or metabolic syndrome]," Dr. Cusi told delegates.

The FIELD Study: Important Findings

The FIELD study was an important analysis because it dramatically increased the outcome evidence with fibrates in CV disease in type 2 diabetes. While slightly more than 18,000 diabetic patients have participated in statin trials, there were only about 2000 patients evaluated in fibrate trials prior to the FIELD study. The additional 9795 patients in the study bring the total close to 12,000 patients. The design of the FIELD study was simple. Type 2 diabetic patients between the ages of 50 and 75 with triglyceride levels between 1.0 and 5.0 mmol/L or a total cholesterol/HDL ratio of >4.0 and a total-cholesterol concentration of 3.0 to 6.5 mmol/L were randomized to micronized fenofibrate 200 mg/day or placebo. Patients were excluded if they were on a lipid-lowering therapy at baseline, had a recent CV event, had renal impairment, known chronic liver disease or symptomatic gallbladder disease or had triglyceride levels >11.45 mmol/L.

At the end of an average of five years of follow-up, the 11% reduction in the primary end point of CV death or nonfatal myocardial infarction (MI) fell short of statistical significance (P=0.16), but this was attributed in part to the 47% increase (P<0.0001) in the proportion of patients in the placebo arm placed on statins over the course of the trial. When adjusted for statin use, the risk reduction was a statistically significant 19% reduction (P=0.01) in the primary end point in favour of

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active therapy. However, even without adjusting for statins, the fibrate was associated with a statistically significant 11% reduction (P=0.035) in the total number of CV events of any kind, a 24% reduction (P=0.01) in nonfatal MIs, and a 21% reduction (P=0.003) in coronary revascularizations. All of these relative advantages increased substantially in the active treatment arm when adjusted for statin use.

As reported by FIELD principal co-investigator, Dr. James D. Best, Professor of Medicine, University of Melbourne, Australia, fenofibrate was sufficiently well tolerated that the dropout rate of 20% at the end of the study was comparable in the active treatment and placebo arms, a result that "compares favourably to the statin trials." There was no evidence of myositis, rhabdomyolysis or liver enzyme abnormalities, all of which occurred in fewer than 1% of patients in both cohorts. The only significant differences in adverse events was a slight increase among those on fenofibrate in pulmonary embolism (P=0.022), of deep-vein thrombosis (P=0.074) and pancreatitis (P<0.05). Dr. Best noted that neither side effect is consistent with known mechanisms of fenofibrate.

According to lead author Dr. Anthony C. Keech, University of Sydney, New South Wales, Australia, a key finding in the FIELD study was that control of the dyslipidemias most strongly associated with type 2 diabetes led to significant reduction in some of the microvascular complications of diabetes. He reported that the time to first retinal laser therapy for retinopathies was increased by 30% (P=0.0003). Dr. Keech also provided data that was not included in the published results, such as a significant 38% reduction (P=0.011) in amputations in those receiving fenofibrate relative to placebo. Treatment with the fibrate was also associated with significantly more patients regressing or not progressing to albuminuria (P=0.002), suggesting a renoprotective effect.

Statin-Fibrate Combination Options

In the trial design, additional lipid-lowering therapies, including statins, were permitted. The higher rate of statin use in the placebo arm is likely to reflect the managing physician's concern about poorer dyslipidemia control. By the end of the study, close to 40% of patients in the placebo arm were taking a statin vs. approximately 20% in the fibrate arm. The absence of any signal of an increased risk of adverse events among patients taking both agents is consistent with other data demonstrating that these compounds are safe in combination.

"There have been studies of fenofibrate in combination with all of the major statins currently available, and no pharmacokinetic interactions have been reported. The clinical evidence to date suggests that this combination is very well tolerated," Dr. Cusi stated. In particular, fenofibrate does not share the interaction observed between statins and gemfibrozil, for which the maximum concentration is increased by two- to threefold when used with a statin. Although particular concern about this interaction was raised by reports of rhabdomyolysis in patients treated with gemfibrozil and cerivastatin, which has now been withdrawn from the market, an analysis published last year (Jones PH et al. *Am J Cardiol* 2005;95:120-122) demonstrated that gemfibrozil but not fenofibrate was associated with a large increased risk of rhabdomyolysis in combination with any statin. In this analysis, the estimated risk of rhabdomyolysis was 8.6 cases/million prescriptions with gemfibrozil and a statin was combined but only 0.58 cases/million when a statin was combined with fenofibrate.

For clinical management, there are now impressive data that the addition of fenofibrate to a statin substantially increases the proportion of patients who reach lipid goals as defined by the ADA. In a study evaluating a combination strategy, 80% of patients reached LDL-C goals of <2.55 mmol/L on atorvastatin alone but the addition of fenofibrate brought this proportion to 98%. While 93% reached the triglyceride goal of <3.9 mmol/L on fibrate monotherapy, this climbed to 100% with the addition of atorvastatin. For HDL-C, 18% were at the goal of >1.0 mmol/L on atorvastatin alone, 30% on fenofibrate alone, and 60% on the combination.

Summary

With consistency of benefits in the context of a benign safety profile demonstrated in the FIELD trial, the standard for optimal control of dyslipidemias in patients with type 2 diabetes or the metabolic syndrome is expected to become combination therapy with a statin and a fibrate. While statins have previously been associated with large risk reductions in type 2 diabetics, fibrates address the specific dyslipidemias typical of patients with type 2 diabetes more comprehensively. The FIELD trial has confirmed that treatment of these specific lipid abnormalities provides significant reductions in the risk of CV events. Since the benefits were particularly pronounced in patients without prior CV disease, it underlined the importance of initiating combination therapy early in the course of management. □

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