Elevated HbA1c Associated with Cardiovascular Events in Non-Diabetics

Several large studies have shown that in diabetic patients, HbA1c is a strong predictor of cardiovascular disease, while in non-diabetics, this association is less clear. Results of the first study to examine the association of HbA1c with non-fatal cardiovascular disease in non-diabetics were reported by Esther van 't Riet, VU University Medical Center, Amsterdam, the Netherlands. The results showed that, even in non-diabetics, HbA1c elevation significantly increases the risk for non-fatal cardiovascular events.

The Hoorn Study is a population based cohort study of a general population in the Netherlands. The current analysis of cardiovascular events was based on data from 1,674 non-diabetic subjects from the Hoorn Study for whom data on Hb1Ac level, glucose level, and morbidity were available. Over the course of approximately 10 years, 385 non-fatal and 113 fatal cardiovascular events had occurred.

Esther van 't Riet reported that whether adjusting only for age and gender or for age and gender plus other traditional cardiovascular risk factors (eg, hypertension, smoking, LDL-cholesterol, triglycerides, and waist-to-hip ratio), subjects with HbA1c >5.6% had a significantly increased risk of a non-fatal cardiovascular event ($p<0.05$).

This association with fatal cardiovascular events was significant in the model that included only age and gender, but not when adjusted for the other traditional cardiovascular risk factors.

"The clinical meaning of this is that, even in subjects without diabetes, it is very important to maintain optimal glycemic control," she said. She added, however, that control of blood pressure and cholesterol are still more important than addressing HbA1c.

The study also examined the relationship between fasting plasma glucose and 2-hour-plasma glucose, finding no significant associations with cardiovascular disease, after correction for age, gender and other cardiovascular risk factors. Miss. van 't Riet speculated that the reason there was no association with 2-hour-plasma glucose (a relationship that has been reported in prior epidemiological studies) was that diabetic patients were excluded in the current analysis, whereas they were included in the previous studies. In addition, previous research not always adjusted for traditional cardiovascular disease risk factors.

One-Year Data Show Combination Sitagliptin and Metformin Improves and Sustains Glucose Control in Type 2 Diabetes Compared to Metformin Alone

Debora Williams-Herman, MD, Senior Investigator at Merck Research Laboratories, Rahway, New Jersey, United States, presented results from a recent clinical trial that found that patients treated with a combination of sitagliptin and metformin achieved significant and sustained improvement in blood sugar control over a one-year period compared to metformin monotherapy, and that the combination therapy was generally well tolerated.

Following the initial 24-week placebo-controlled phase (n=1091) of the study, 748 subjects with a mean baseline HbA1c of 8.7% entered the open-label phase, continuing for another 30-weeks on their initial treatment regimens.

The groups were: sitagliptin 50 mg/metformin 1000 mg BID (n=157); sitagliptin 50 mg/metformin 500 mg BID (n=148); metformin 1000 mg BID(n=137); metformin 500 mg BID (n=122); and sitagliptin 100 mg once daily (n=106).

At 54 weeks, the investigators found a mean HbA1c reduction from baseline of 1.8% for subjects treated with combination sitagliptin 50 mg/metformin 1000 mg BID for up to 54 weeks (n=153). They also found mean HbA1c reductions from baseline of 1.4% for subjects treated with sitagliptin 50 mg/metformin 500 mg BID (n=147), 1.3% for subjects treated with metformin 1000 mg BID (n=134), 1.0% for subjects treated with metformin 500 mg BID (n=117), and 0.8% for subjects treated with sitagliptin 100 mg once daily (n=106).

In terms of achieving the target HbA1c of < 7%, 67% of the sitagliptin 50 mg/metformin 1000 mg BID subjects achieved the target A1c, compared to 44% on metformin 1000 mg BID monotherapy.

Dr. Williams-Herman reported that 48% of the subjects treated with sitagliptin 50 mg/metformin 500 mg BID, 25% of those treated with metformin 500 mg BID, and 23% of those treated with sitagliptin 100 mg once daily reached the target HbA1c goal.

Notably, HbA1c percentage reductions at Week-54 for each active treatment group did not differ significantly from percentage reductions achieved at Week-24, suggesting that the treatment effect of each therapy held for a year and that the superior efficacy of combination sitagliptin/metformin was not diminished over a longer period of use.

Adverse events were generally comparable among the treatment groups. Rates of hypoglycemia were low across all groups, and rates of gastrointestinal adverse events were similar across all groups. There was a slight mean loss of body weight (less than 2 kg) in all groups except sitagliptin 100 mg (gain of less than 1 kg).

"In summary," said Dr. Williams-Herman, "in patients with type 2 diabetes inadequately controlled by diet and exercise, initial combination therapy with sitagliptin and metformin over one year showed consistent and substantial glycemic improvement, a small reduction in body weight, and a favorable safety profile."

Fenofibrate Treatment and Renal Function in Type 2 Diabetes: FIELD Helsinki Substudy

Results from a substudy of FIELD (Fenofibrate Intervention and Event Lowering in Diabetes), the largest study of fibrates to date, showed no evidence for direct nephroprotection from fenofibrate use [The Field Study Investigators. *Lancet* 2005]. There was, however, an increase in plasma creatinine, according to Anne Hiukka, MD, Helsinki University Central Hospital and Biomedicum, Finland.

FIELD included nearly 10,000 type 2 diabetes patients randomly assigned to fenofibrate 200 mg or placebo for 5 years. It showed no reduction in coronary heart disease events for fenofibrate, but did show some promise in spot samples of urinary albumin/creatinine ratio and self-reported retinal laser therapy, both markers for microvascular outcomes. Increases in plasma creatinine, through an as-yet unexplained mechanism, seem to be a class effect of the fibrates. While FIELD did show some significantly reduced progression of albuminuria for fenofibrate versus placebo, approximately three-fourths of patients in both groups had no change.

The current FIELD substudy, with evaluable results for 170 patients, investigated the effect of fenofibrate treatment on prespecified renal function parameters at baseline and at 2 and 5 years. Dr. Hiukka reported that in both groups after 5 years blood pressure dropped significantly and HbA1c remained unchanged. Fasting serum glucose dropped in both groups, but significantly only in the fenofibrate group (7.9 mmol/L baseline, 7.2 mmol/L 5-years; p=0.010). Although HDL-C remained unchanged in both groups, significant decreases in total cholesterol (~18%; p=0.001), LDL-C (~20%; p=0.001), and total triglycerides (~26%; p=0.001) were reported for fenofibrate treatment versus placebo.

In addition, plasma creatinine increased significantly with fenofibrate (p<0.001) versus placebo while urinary creatinine remained the same. Creatinine clearance decreased in both groups (Δ -2.0 mL/min/1.73m^2 placebo, Δ -8.5 mL/min/1.73m^2 fenofibrate; p=0.009 vs placebo). A similar pattern was observed for eGFR [estimated glomerular filtration rate]. While there were no differences in albuminuria and proteinuria rates between groups, nocturnal urinary albumin excretion rates decreased in both groups.

The suggestions of benefit in the overall FIELD study were not borne out in this substudy. Dr. Hiukka concluded, "The data provide no evidence for direct nephroprotection by fenofibrate. However, in clinical practice, increases in plasma creatinine with fenofibrate should be recognized and followed up." She noted that the clinical relevance of increased plasma creatinine with fenofibrate administration should be established through direct measures of renal function. "We can't speculate on the potential harm from this finding."

PREDICTIVE 303: Patient Self-Adjusted Dosing a Safe and Effective Alternative

In PREDICTIVE 303 (Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation), patient-directed insulin dose adjustments of once-daily insulin detemir appeared to be a safe and effective alternative to physician-directed dose adjustments in a primary care setting.

The primary objective of PREDICTIVE 303, stated lead investigator Luigi F Meneghini, MD, Diabetes Research Institute, University of Miami Miller School of Medicine, Florida, United States, was to show that patient self-