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-

adjusted dosing using insulin detemir and a simplified algorithm (Group 1) was non-inferior to physician-directed standard-of-care dosing (Group 2). Detemir was started in either group once daily at bedtime as an add-on therapy to any other glucose-lowering regimens, or as a replacement of previous basal insulin in patients with type 2 diabetes. The primary outcome measure was HbA1c reduction from baseline.

Randomization was done at the site level. Patients from sites assigned to Group 1 adjusted their detemir dose every 3 days based on mean fasting blood glucose (FBG) values using the following simplified algorithm: mean FBG <4.4 mmol/L, reduce dose by 3U; FBG between 4.4 and 6.1 mmol/L, no change; FBG >6.1 mmol/L, increase by 3U. Detemir dose for Group 2 patients was adjusted by physicians according to the standard of care.

Mean baseline HbA1c was 8.5%. At 26 weeks, mean HbA1c was 7.9% for patients in Group 1 and 8.0% in patients in Group 2 group ($p=0.01$ between groups; $p<0.0001$ vs baseline for both groups). FBG, which was 9.7 mmol/L (178 mg/dL) at baseline, dropped to 7.8 mmol/L (143 mg/dL) in patients in Group 1 and to 8.4 mmol/L (154 mg/dL) in Group 2 patients ($p<0.0001$ between groups; $p<0.0001$ versus baseline for both groups). As expected, the reductions in HbA1c observed in the insulin-naïve subjects in Group 1 and Group 2 were substantially greater, with no significant differences between groups (-1.1% vs -1.0%, respectively; $p=0.09$ between groups; $p<0.0001$ vs baseline for both groups)

At 26 weeks most patients (88%) remained on once-daily insulin detemir (91% in Group 1, 85% in Group 2). The mean daily insulin detemir dose at 26 weeks was 0.7 and 0.5 U/kg, in Groups 1 and 2, respectively. Among insulin-naïve patients, rates of once-daily insulin detemir dosing were higher (95% in Group 1, 92% in Group 2).

At study end, the overall rates of daytime and major hypoglycemia (event/patient/year) were significantly reduced in both groups versus baseline ($p<0.05$). Daytime, nocturnal and overall hypoglycemia were significantly lower Group 2 versus Group 1 ($p<0.0001$). Weight remained constant in Group 1 but dropped from 98.2 kg to 97.9 kg in Group 2.

In summary, Prof. Meneghini said that basal insulin titration was successfully carried out in primary care practices. “Compared with standard-of-care, the 303 Algorithm resulted in better or equal improvement in glycemia with slightly greater incidence of non-major hypoglycemia, and no significant weight gain.”

MITRE: No Benefit for Continuous Glucose Monitoring Devices

The MITRE (Minimally Invasive Technology Role and Evaluation) Study, a randomized controlled trial of continuous glucose monitoring device use, showed them to be of no greater benefit than standard care. Stanton Newman, PhD, University College, London, UK, reported that all groups, including controls, had a sustained reduction of HbA1c.

Prof. Newman said that prior to MITRE, clinical trial evidence regarding the use of continuous glucose monitoring devices was limited by small sample size, the inclusion primarily of type 1 diabetes patients, and the increased attention given to those receiving the continuous glucose monitoring device. The objective of MITRE was to compare the benefits of using the GlucoWatch® G2™ Biographer (Animas) and the Continuous Glucose Monitoring System (CGMS®, MiniMed) on HbA1c versus attention control and standard treatment in a randomized controlled trial. Percentage change in HbA1c from baseline to 6, 12, and 18 months was the primary endpoint.

Patients were randomly assigned to one of MITRE’s four study arms (~100 patients each). The groups differed as follows:

- Standard Control (baseline visit only asked to test capillary blood glucose at normal frequency with Lifescan Onetouch Ultra Meter®), continued with standard care.
- Attention Control (feedback based on self-monitoring of blood glucose)
- GlucoWatch (used at times of patient choice; recommended minimum of 4x/month and maximum of 4x/week)
- CGMS (fitted at 3, 6, and 12 weeks and worn for 72 hours each time)

The participants in the two treatment groups and the attention placebo group attended three research visits. The attention control group was included to control for the impact of increased levels of contact with health care professionals in the two device groups. Planned visits were conducted with nurses trained specifically on use of the MITRE devices, interpretation of blood glucose results and delivery of appropriate feedback to patients.

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