between the treatments in other glycemic control outcomes.

The chief secondary endpoint was percentage of people with ≥1 severe or confirmed episodes of nocturnal hypoglycemia from Month 3 to Month 6. Fewer people assigned to Gla-300 experienced severe or confirmed nocturnal hypoglycemia during Months 3 to 6 (36.1% vs 46.0%, representing a 21% reduction in relative risk; p=0.0070). The occurrence of any hypoglycemic event during study period was numerically lower in the Gla-300 group than in the Gla-100 group.

There were no between-treatment differences in weight change, adverse events, serious adverse events, adverse events causing withdrawal, injection-site reactions, and mortality.

Dr. Riddle concluded that in patients with T2DM who require high-dose basal-bolus insulin therapy, Gla-300 was as effective as Gla-100 in blood glucose control and was associated with a reduction in severe or confirmed nocturnal hypoglycemia.

Initial Triple Therapy Superior to Stepwise Add-On Therapy in Newly Diagnosed Type 2 Diabetes

Written by **Wayne Kuznar**

Newly diagnosed patients with type 2 diabetes mellitus (T2DM) achieve lower HbA1C concentrations with a lower rate of hypoglycemia when started on triple therapy as opposed to stepwise add-on therapy. Results from a randomized open-label study comparing the two strategies were announced by Ralph A. DeFronzo, MD, University of Texas Health Science Center, San Antonio, Texas, USA.

The optimal therapy to achieve HbA1C levels as close to normal as possible while avoiding hypoglycemia, as recommended by the American Diabetes Association and the European Association for the Study of Diabetes, has not been defined, said Dr. DeFronzo. In patients recently diagnosed with T2DM, beginning therapy with drugs that correct known pathophysiologic defects, in theory, should produce a greater, more durable reduction in HbA1C level while avoiding hypoglycemia rather than the currently recommended stepwise approach that can lower plasma glucose but does nothing to correct the underlying pathophysiology.

The efficacy and safety of initiating triple therapy (metformin/pioglitazone/exenatide) was compared with more conventional therapy that focuses on lowering plasma glucose with metformin followed by sequential addition of sulfonylurea and basal insulin to maintain HbA1C ≤6.5% in 169 newly diagnosed patients with T2DM. Patients were drug-naïve, had a mean diabetes duration of 5.1 months and had a mean HbA1C level of 8.6% upon study entry. Medications could be down-titrated when fasting blood glucose levels dropped to <60 mg/dL or the patient had symptoms of hypoglycemia.

At 24 months, HbA1C decreased to 5.9% in patients randomized to triple therapy and to 6.6% in those randomized to conventional therapy (p<0.001). Fasting and postprandial glucose levels were significantly lower in the triple-therapy arm compared with the conventional-therapy arm (p<0.01 for each). Ninety-two percent in the triple-therapy arm achieved an HbA1C <7.0% versus 72% in the conventional therapy arm (p<0.001) and 60% in the triple-therapy arm achieved a final HbA1C <6.0% versus 27% in the conventional arm (p<0.001). The cumulative failure rates (failure to achieve HbA1C ≤6.5%) were 42% in the conventional arm and 17% in the triple-therapy arm (p<0.001).

On multivariate regression analysis, triple therapy and older age were significant predictors of achieving an HbA1C ≤6.5% whereas higher baseline HbA1C and weight gain were significant predictors of treatment failure.

Despite a significantly lower HbA1C level, subjects in the triple-therapy arm had nearly an 8-fold lower rate of hypoglycemia compared with those receiving conventional therapy (0.27 vs 2.1 events per subject per year; p<0.0001).

Subjects in the triple-therapy arm experienced mean weight loss of 1.2 kg compared with mean weight gain of 4.1 kg (p<0.001) in subjects in the conventional-therapy arm.

Dr. DeFronzo concluded that triple therapy that targets the known pathophysiologic defects in new-onset T2DM produces a greater and more durable reduction in HbA1C with less hypoglycemia than conventional therapy with the added benefit of weight loss.