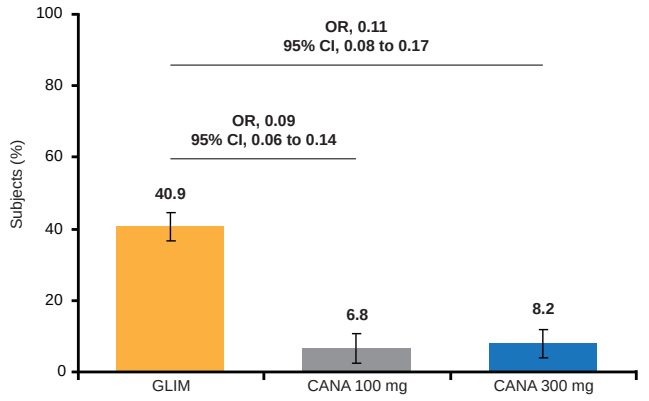
stable from Week 26 to Week 104. Increases in LDL-C and HDL-C were smaller in patients randomized to glimepiride relative to canagliflozin, and these increases were also stable from Week 26.

Fewer subjects had hypoglycemic events with either dose of canagliflozin than with glimepiride (Figure 1).

Figure 1. Documented Hypoglycemic Episodes*



*Includes episodes that were biochemically documented (≤3.9 mmol/L) or severe (ie, requiring the assistance of another individual or resulting in seizure or loss of consciousness).

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The incidences of adverse events were 73.3%, 77.9%, and 78.4% with canagliflozin 100 mg and 300 mg and glimepiride, respectively. The incidences of serious adverse events were 9.7%, 9.7%, and 14.3% in the three groups, respectively. The rates of genital mycotic infection rates were higher in the canagliflozin groups than in the glimepiride group (Table 1). Higher rates of osmotic diuresis-related adverse events and urinary tract infections were observed with canagliflozin compared with glimepiride.

Table 1. Incidence of Selected Adverse Events

	Subjects, n (%)		
	GLIM (n=482)	CANA 100 mg (n=483)	CANA 300 mg (n=485)
Urniary tract infection	33 (6.8)	51 (10.6)	42 (8.7)
Genital mycotic infection			
Male	5 (1.9)	24 (9.5)	22 (9.1)
Female	6 (2.7)	32 (13.9)	38 (15.6)
Osmotic diuresis-related AEs*	10 (2.1)	28 (5.8)	32 (6.6)
Volume-related AEs†	11 (2.3)	8 (1.7)	12 (2.5)

*Includes dry mouth, micturition urgency, nocturia, pollakiuria (increased urine frequency), polydipsia, polyuria (increased urine volume), thirst, and urine output increased; †Includes blood pressure decreased, dehydration, dizziness postural, hypotension, orthostatic hypotension, presyncope, and syncope; AE=adverse event.

A larger decrease in estimated glomerular filtration rate was observed with glimepiride (6.2 mL/min/1.73 m^2) than with canagliflozin 100 and 300 mg (2.0 and 3.8 mL/min/1.73 m^2, respectively) at Week 104.

New Insulin Glargine Formulation Associated With Less Nocturnal Hypoglycemia

Written by Wayne Kuznar

A long-acting basal insulin glargine formulation, 300 U/mL (Gla-300), controlled glycemia as well as insulin glargine 100 U/mL (Gla-100) in patients with type 2 diabetes mellitus (T2DM) but with less nocturnal hypoglycemia. Matthew C. Riddle, MD, Oregon Health & Science University, Portland, Oregon, USA, presented findings from a Phase 3 multicenter, open-label study comparing the two insulin glargine formulations in patients with T2DM who were using basal plus mealtime insulin.

Gla-100 is a widely used basal insulin with no pronounced peak of action and a duration of action of ~24 hours; it causes less hypoglycemia than human neutral protamine Hagedorn (NPH) insulin [Riddle MC et al. *Diabetes Care* 2003]. The investigational insulin glargine (Gla-300) contains the same molecule as Gla-100 but in a lower volume. It has a flatter and more prolonged pharmacokinetic and pharmacodynamics profile than Gla-100 [Jax T et al. EASD 2013 (abstr 1029)]. Whether or not the differences in pharmacokinetics between Gla-100 and Gla-300 translate into a clinical benefit is being tested in a worldwide series of Phase 3 studies in several populations of patients with type 1 diabetes mellitus and T2DM. The data presented here from the Comparison of a New Formulation of Insulin Glargine With Lantus in Patients With Type 2 Diabetes Mellitus on Basal Plus Mealtime Insulin [EDITION I; NCT01499082] were the first from this series of Phase 3 trials.

Adults (n=807) with T2DM on a basal-bolus insulin regimen that included at least 42 U/day of basal glargine or NPH insulin were randomized to 6 months of open-label treatment with either Gla-300 or Gla-100 once daily in the evening while continuing mealtime insulin. The basal insulin was titrated weekly to achieve a fasting plasma glucose of 80 to 100 mg/dL. Mealtime insulin dosage was not systematically titrated, with adjustments made at investigators' discretion only for safety reasons.

Subjects' mean age was 60 years, their mean duration of diabetes was 15.8 years, and their mean body mass index was 36.6 kg/m^2. More than half of the patients were using metformin. On entry, the mean basal insulin dose was 0.67 U/kg/day and the mean total insulin dose was 1kg/day. The mean baseline HbA1C level was 8.16%.

The primary endpoint, the change in HbA1C from baseline to Month 6, was –0.83% in both the Gla-100 and Gla-300 groups, the 0.0% difference met the criterion for noninferiority of Gla-300. There were no differences

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.