creatinine, urinary ratio of albumin to creatinine, use of angiotensin receptor blockers, educational status, presence of integrated health plan, and presence of certified diabetes educator on staff at randomization. Model 2 added assignment to blood pressure or lipid trial, treatment assignment within these, severe hypoglycemia, and weight change. Model 3 added the updated average HbA1C, and Model 4 added the glycemic treatment arm assignment. Results from all 4 models by total, basal, and bolus insulin are presented in Table 1.

Table 1. HRs for CV Mortality of Insulin Dose (per 1 unit/kg) From Cox Proportional Hazards Model

Insulin Categories	Unadjusted HR (95% CI)*	Model 1*	Model 2*	Model 3*	Model 4*
Total insulin	1.83 (1.45–2.31) p<0.0001	1.21 (0.92–1.6) p=0.1726	1.21 (0.91–1.61) p=0.1912	1.12 (0.84–1.49) p=0.4540	0.99 (0.74–1.34) p=0.9693
Basal insulin	2.29 (1.62–3.23) p<0.0001	1.3 (0.87–1.94) p=0.2073	1.29 (0.85–1.95) p=0.2272	1.13 (0.74–1.72) p=0.5636	0.94 (0.61–1.46) p=0.7955
Bolus insulin	3.36 (2.0–5.66) p<0.0001	1.65 (0.88–3.11) p=0.1172	1.63 (0.85–3.12) p=0.1399	1.48 (0.77–2.84) p=0.2365	1.23 (0.63–2.4) p=0.5478

*For the unadjusted model, and Models 1 to 4, only a single insulin exposure was entered into the model at a time. Thus, each cell represents the results for that insulin variable being the only one within the model.

Based on the unadjusted HRs, a daily insulin dose increase by 1 unit/kg of body weight was associated with a 1.83- (total insulin), 2.29- (basal insulin) and 3.36-fold increase in risk of CV mortality (all p<0.0001). However, results from the four models did not confirm these findings. After adjustment for baseline covariates in Model 1, the HRs became nonsignificant indicating no association of insulin dose with CV mortality. Additionally, no association between insulin dose and CV mortality emerged after adjustments were made for on-treatment factors.

Dr. Siraj concluded that these results do not support the idea that insulin dose is an independent risk factor for CV mortality in the ACCORD population.

Canagliflozin Reduces HbA1C in Patients With Stage 3 CKD, With the Change Greater in Patients With Higher eGFR

Written by **Wayne Kuznar**

The sodium glucose cotransporter-2 inhibitor canagliflozin reduces HbA1C level in patients with type 2 diabetes mellitus (T2DM) and stage 3 chronic kidney disease (CKD), an effect that is more pronounced with higher levels of estimated glomerular filtration rate (eGFR), according to the results of a pooled analysis. Gary Meininger, MD, Janssen Research and Development LLC, Raritan, New Jersey, USA, presented the results of this pooled analysis of four randomized, double-blind, placebo-controlled Phase 3 trials that compared canagliflozin with placebo in patients with inadequately controlled T2DM and stage 3 CKD.

Options for glycemic control in patients with T2DM and impaired renal function are limited, said Dr. Meininger. Canagliflozin has been approved in the United States as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. However, its approved dosage is limited to 100 mg QD in patients with moderate renal impairment with an eGFR ≥45 and <60 mL/min/1.73 m^2, and it is not indicated in patients with an eGFR <45 mL/min/1.73 m^2.

The present pooled analysis included 1085 patients with T2DM and stage 3 CKD (eGFR ≥30 and <60 mL/min/1.73 m^2) who were randomized to canagliflozin 100 or 300 mg, or placebo for 18 to 26 weeks.

In the overall study population, the mean change from baseline to efficacy assessment in HbA1C was –0.52% in the canagliflozin 100-mg group; –0.62% in the canagliflozin 300-mg group; and –0.14% in the placebo group (p<0.001 for both canagliflozin groups vs placebo). When assessed by baseline eGFR, a greater reduction in HbA1C with canagliflozin was observed in patients with eGFR ≥45 mL/min/1.73 m^2 and <60 mL/min/1.73 m^2 than in those with eGFR ≥30 and <45 mL/min/1.73 m^2.

In the 88.2% of all participants who were on background insulin or a sulfonylurea, the rates of documented episodes of hypoglycemia were greater with canagliflozin 100 mg and 300 mg (41.9% and 43.8%, respectively) than with placebo (29.2%).

Weight loss was also greater in the canagliflozin groups than in the placebo groups, and the effect was greater in patients with eGFR ≥45 mL/min/1.73 m^2 than in those with eGFR ≥30 and <45 mL/min/1.73 m^2.

Systolic blood pressure decreased more in the overall study population in the canagliflozin groups versus the placebo group. In the subgroup with eGFR ≥30 and <45 mL/min/1.73 m^2, systolic blood pressure increased by 0.8 mm Hg in each canagliflozin group and by 5.7 mm Hg in the placebo group.

The incidence of overall adverse events (AEs) was higher with canagliflozin (74.0% with 100 mg and 75.3% with 300 mg) than with placebo (70.4%). Intravascular volume-related adverse events were also more common with canagliflozin (5.0% and 8.5% in the 100- and 300-mg groups, respectively) than with placebo (2.6%). The percentage of these events in the canagliflozin groups was greater in patients with eGFR ≥30 and <45 mL/min/1.73 m^2 (6.6% and 11.1% in the 100- and 300-mg groups, respectively) relative to placebo (1.7%) than in those with eGFR ≥45 mL/min/1.73 m^2 (4.2% and 7.1% with 100-mg and 300-mg

canagliflozin, respectively, vs 3.0% with placebo). Renal-related adverse events also occurred more frequently with canagliflozin compared with placebo, and the rates were higher in all three groups with eGFR ≥30 and <45 mL/min/1.73 m^2.

Education Improves Hypoglycemia Awareness Regardless of Technology Used for Insulin Delivery

Written by Brian Hoyle

Education concerning hypoglycemia benefits patients with type 1 diabetes (T1D) with impaired awareness of hypoglycemia, regardless of the system used to deliver insulin and monitor blood glucose, according to Stuart Little, MBBS, Newcastle University, Newcastle, United Kingdom, who reported on the Prevention of Recurrent Severe Hypoglycaemia: A Definitive Randomized Controlled Trial Comparing Optimised MDI and CSII With or Without Adjunctive Real-time Continuous Glucose Monitoring [HypoCOMPaSS; EUCTR2009-015396-27].

Typically, ~25% of patients with T1D have an impaired awareness of hypoglycemia. This lack of knowledge can lead to a markedly higher risk of life-threatening episodes of severe hypoglycemia.

In this study, 96 T1D patients with impaired awareness of hypoglycemia were randomized to either the conventional multiple daily injections of insulin aspart or insulin glargine (n=50) or pump-mediated delivery of insulin aspart (n=46). In both groups, glucose was either episodically or continuously monitored. All participants received a standardized 2-hour information program concerning the recognition of risk factors and symptoms of hypoglycemia, which proved equally effective in reducing episodes of hypoglycemia. The primary endpoint was the difference in awareness of hypoglycemia as determined using the Gold score at 24 weeks. Secondary endpoints were measures of overall glycemic control and patient reported outcomes including fear of hypoglycemia and treatment satisfaction.

The participants had a mean age of 49 years (range, 18 to 74 years), mean duration of diabetes of 29 years, and were C-peptide negative. Their impaired awareness of hypoglycemia was ≥4, as measured using the Gold score, which queries knowledge of the onset of hypoglycemia, with the response ranked on a 7-point scale ranging from 1 ("always aware") to 7 ("never aware") [Gold AE et al. *Diabetes Care* 1994]. Two thirds of the participants were women, two thirds had retinopathy, one quarter had nephropathy, and one quarter had concomitant immune-treated thyroid disease. The mean HbA1C level was 8.2%.

By 4 weeks, biochemical hypoglycemia measured by continuous monitoring was significantly reduced from 53.3 minutes (3.7% of time) to 24.5 minutes (1.7% of time), ~30 minutes less each day (p<0.001 vs baseline). The reduction was sustained over the remaining 20 weeks. At 24 weeks, a statistically significant improvement in the median Gold score from 5 to 4 was evident for all participants regardless of the method of insulin, compared with the baseline score (p<0.001).

The number of episodes of severe hypoglycemia, defined by the American Diabetes Association as hypoglycemia that requires assistance for treatment, was reduced from 9 at baseline to <1 at 24 weeks (p<0.001), with the proportion of patients affected declining from 92% and 77% at 1 year and 6 months prior to the trial, respectively, to just 19% during the trial.

The mean number of insulin doses decreased significantly by about 8 units over the 24-week trial (p<0.001). Both treatment arms displayed similarities in HbA1C values, Gold score, number of episodes of severe hypoglycemia, mean insulin dose, and fear of hypoglycemia. Participants who received insulin via a pump expressed greater satisfaction with treatment.

Prof. Little and his colleagues concluded that impaired awareness of hypoglycemia can be improved and recurrent hypoglycemia can be prevented through strategies targeted at avoiding severe biochemical hypoglycemia in a high-risk population affected by diabetes for almost 30 years. This benefit of education is more influential than the technology of insulin delivery.

Cardiovascular Safety of Linagliptin in Patients With Type 2 Diabetes

Written by Brian Hoyle

Odd Eric Johansen, MD, Global Senior Medical Director, Metabolism (Diabetes), Boehringer Ingelheim, Frankfurt, Germany, reported on the cardiovascular (CV) safety of linagliptin in nearly 9500 patients with type 2 diabetes mellitus (T2DM) with a wide spectrum of CV risk and treatment history, based on an analysis of 19 randomized controlled trials.

Linagliptin is an oral hypoglycemic compound used in the treatment of T2DM. The target of the drug is dipeptidyl peptidase 4, an enzyme that is important in various functions including the metabolism of glucose. Previous studies have provided evidence that linagliptin is not associated with an increased risk of CV events [Graefe-Mody EU et al. *Curr Med Res Opin* 2009; Deacon CF, Holst JJ. *Expert Opin Investig Drugs* 2010; Friedrich C et al. *Eur J Drug Metab Pharmacokinet* 2011; Johansen OE et al. *Cardiovasc Diabetol* 2012].