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].

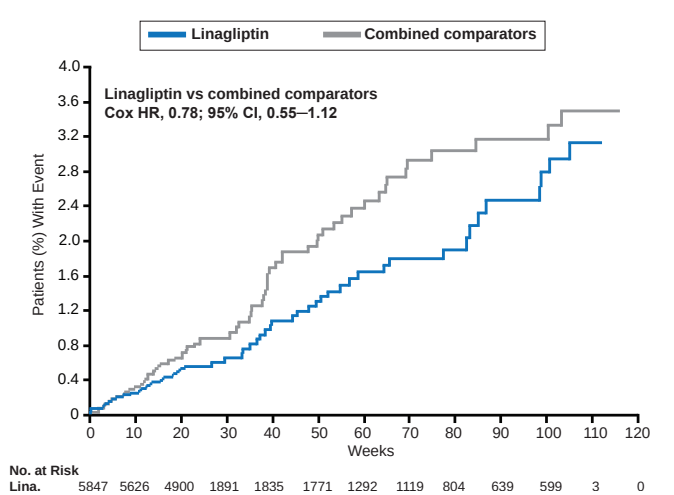
Diabetes almost doubles the risk of a number of vascular diseases including coronary artery disease, myocardial infarction (MI), ischemic stroke, and hemorrhagic stroke. The risk of stroke for individuals with diabetes is similar to those with a history of coronary heart disease [Grundy SM et al. *Circulation* 2004].

Dr. Johansen reported on the comparison of the incidence of CV events and CV mortality in 9459 T2DM patients who had been treated with linagliptin (n=5847; 5687 treated with 5 mg, 160 treated with 10 mg) with a comparator group of patients who did not receive the drug (n=3612; placebo 2675, glimepiride 775, voglibose 162). The data were derived from 19 double-blind randomized controlled trials that each lasted a minimum of 12 weeks. Adverse CV events were identified using the Standard Medical Dictionary for Regulatory Activities and the identified trigger events and accompanying data were prospectively adjudicated by a blinded independent expert committee.

The primary endpoint was a composite of CV death, nonfatal stroke, nonfatal MI, and hospitalization for unstable angina pectoris. Secondary CV endpoints included CV death, fatal stroke, and fatal MI. The cumulative exposure (person-years) was 4421.3 for patients receiving linagliptin and 3254.7 for the comparator patients.

The frequency of primary outcome events was similar in the linagliptin-treated patients (n=60; 1.0%) and the comparator group (n=62; placebo 36, active comparators 26; 1.7%). Incidence rates of the primary endpoint per 1000 years at risk were lower for patients treated with linagliptin (13.4) than for the comparator patients (18.9), as was the hazard ratio (0.78; 95% CI, 0.55 to 1.12; Figure 1 and Table 1). Tertiary endpoints were similar in both groups.

Figure 1. Primary Composite Endpoint of CV Death, Nonfatal MI, Stroke, and HUA Over Time



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Dr. Johansen and colleagues concluded that the pooled data obtained from a large number of T2DM patients with a spectrum of CV risk and a varied treatment history ranging from none to insulin dependence bolsters the view that linagliptin does not increase the risk of adverse CV events. This retrospective assurance now paves the way for prospective studies [CAROLINA, NCT01243424 and CARMELINA, NCT01897532] designed to assess the therapeutic benefit of linagliptin in T2DM.

Table 1. Drug Exposure and Incident/Incidence Rates of CV Endpoints and Mortality

	Linagliptin (n=5847)		Total Comparators (n=3612)	
Median exposure (range), days	175 (1776)		182 (1804)	
Cumulative drug exposure, patient-years	4421.3		3254.7	
	Incidence n (%)	**Incidence Rate (per 1000 Years)**	**Incidence n (%)**	**Incidence Rate (per 1000 Years)**
Primary Endpoints				
CV death, stroke, MI, or UAP with hospitalization	60 (1.0)*	13.4	62 (1.7)*	18.9
Secondary Endpoints				
CV death, stroke, or MI	42 (1.6)*	21.5	46 (2.6)*	29.1
All adj.CV events	0.96 (0.7)	8.7	95 (1.3)	13.7
FDA-custom MACE	0 39 (0.7)	9.3	45 (1.3)	14.0
Tertiary Endpoints				
CV death	11 (0.2)	2.4	8 (0.2)	2.4
Nonfatal MI	23 (0.4)	5.1	20 (0.6)	6.1
Nonfatal stroke	9 (0.2)	2.0	19 (0.5)	5.8
TIA	1 (0.02)	0.2	8 (0.2)	2.4
UAP with hospitalization	22 (0.4)	4.9	16 (0.4)	4.8
Total mortality	18 (0.3)	4.0	16 (0.4)	4.8

*Total: 4P-MACE, 122; 3P-MACE, 88

CV=cardiovascular; MI=myocardial infarction; UAP=unstable angina pectoris; TIA=transient ischemic stroke.

DURATION-3 Trial Results

Written by **Brian Hoyle**

Three-year data from the Efficacy of Exenatide Once Weekly and Once-Daily Insulin Glargine in Patients With Metformin Alone or in Combination With Sulfonylurea trial [DURATION-3; NCT00641056] have confirmed previously reported 26- and 84-week results demonstrating the superiority of the exenatide regimen for glycemic and weight control, and lowered risk of hypoglycemia [Diamant M et al. *Lancet* 2010; Diamant M et al. *Diabetes Care* 2012].