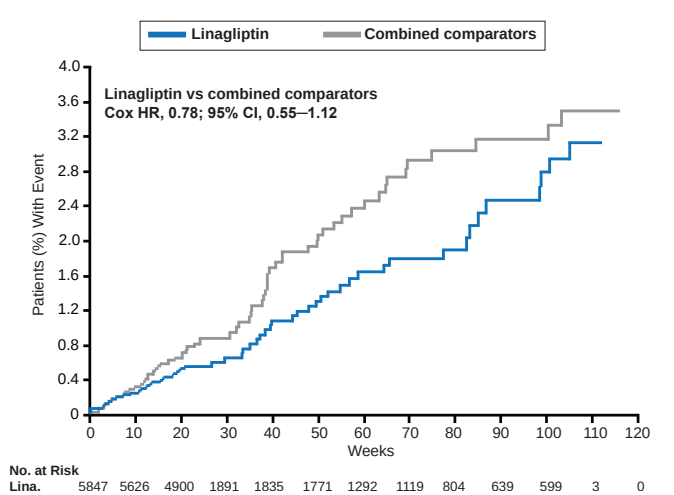
Diabetes almost doubles the risk of a number of vascular diseases including coronary artery disease, myocardial infarction (MI), ischemic stroke, and hemorrhagic stroke. The risk of stroke for individuals with diabetes is similar to those with a history of coronary heart disease [Grundy SM et al. *Circulation*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

DURATION-3 was an open-label, randomized, controlled study of patients with type 2 diabetes mellitus comparing once-weekly injection of exenatide, a glucagon-like peptide-1 receptor agonist, to titrated insulin glargine. Michael Trautmann, MD, Diabetologist and Consultant, Hamburg, Germany, reported the 3-year results, noting that this study was unique in that it compared the two injectable therapies over 3 years in patients who had not achieved an HbA1C level of <7% during treatment with metformin alone or in combination with sulfonylurea.

The 456 enrolled patients were randomized to exenatide 2 mg QW (n=233) or titrated insulin glargine QD (n=223). All patients received metformin with or without sulfonylurea. The study consisted of a 26-week core study period followed by a 130-week controlled extension period. A substantial proportion of participants completed the 156-week regimen (60% in the exenatide arm and 66% in the insulin glargine arm). The baseline characteristics of the intention-to-treat (ITT) subjects and the completers were similar, notably concerning HbA1C level (~8.3%) and duration of diabetes (~8 years).

Dr. Trautmann reported that in the ITT population, mean HbA1C levels at 3 years were significantly lower with exenatide (7.3±0.07%) versus insulin glargine (7.5±0.07%; p=0.033; Figure 1). Similarly, in the completer population, mean HbA1C levels at 3 years were significantly lower with exenatide (7.1±0.08%) versus insulin glargine (7.4±0.08%; p=0.022). The similarity of the findings in the ITT and completer populations emphasizes the representative nature of the 3-year data. Furthermore, significantly more patients in the exenatide arm achieved HbA1C targets of ≤6.5% at 3 years (24% vs 15%; p=0.02 [ITT population]; 28% vs 18% [completer population]).

Patients in the exenatide group gained body weight (mean, −2.49±0.28 kg) while those receiving insulin glargine lost body weight (mean, +2.01±0.28 kg). There was a significant difference between the groups for the change in body weight from baseline to 3 years (mean difference, −4.51±0.37 kg; p<0.001).

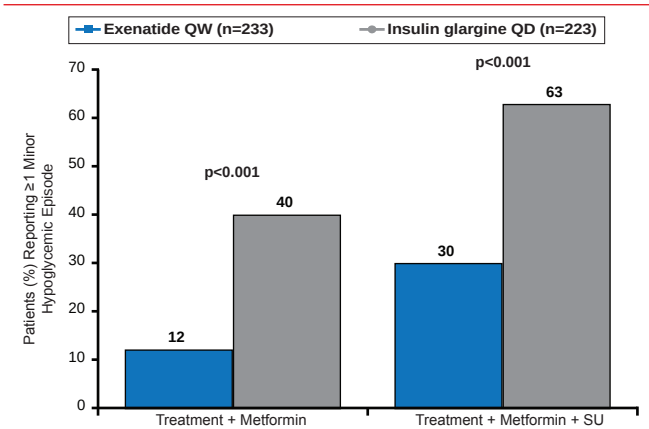
Sixty-eight percent of patients in the exenatide arm displayed both reduced HbA1C and body weight at 3 years compared with only 34% in the insulin glargine arm. Fasting serum glucose was also significantly decreased in patients receiving exenatide (mean, −31.16 mg/dL) versus those receiving insulin glargine (mean, −47.74 mg/dL; p<0.001).

The safety profile of both drugs at 3 years echoed the previous 26- and 84-week results. While subjects receiving exenatide were more prone to gastrointestinal maladies including nausea, vomiting, and diarrhea than those receiving insulin glargine (16% vs 2%; 6% vs 3%; 14% vs 7%, respectively), most adverse events occurred in the first 26 weeks in the exenatide group. Consistent with the better longer-term tolerance of exenatide, the positive rate for anti-exenatide antibodies decreased from 56% at 26 weeks to 19% at 3 years.

Exenatide was associated with significantly fewer incidents of hypoglycemia than insulin glargine when used in combination with metformin alone (p<0.001) or with metformin plus sulfonylurea (p<0.001; Figure 1).

Dr. Trautmann concluded that exenatide is superior to insulin glargine in terms of sustained glycemic control and weight loss, and in lessening the risk of hypoglycemia.

Figure 1. Incidence of Minor Hypoglycemia at 3 Years



QD=once daily; QW=once weekly; SU=sulfonylurea.

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Empagliflozin Improves Glycemic Parameters and Cardiovascular Risk Factors in Patients With Type 2 Diabetes Mellitus

Written by Wayne Kuznar

Patients with type 2 diabetes mellitus (T2DM) who are treated with empagliflozin, a sodium glucose cotransporter 2 inhibitor, as monotherapy or add-on antihyperglycemic therapy experience clinically meaningful improvements in glycemic parameters and several cardiovascular risk factors, according to Thomas Hach, MD, Boehringer Ingelheim Pharma GmbH & Company KG, Ingelheim, Germany. Prof. Hach presented the results of a pooled analysis of four randomized, placebo-controlled Phase 3 trials in which the effects of 24 weeks of empagliflozin were evaluated in 2477 T2DM patients.

In the four trials, patients with HbA1C values ranging from 7% to 10% at screening were randomized to empagliflozin 10 mg (n=831) or 25 mg (n=821) QD or placebo (n=825) for 24 weeks as either monotherapy, add-on to metformin, add-on to metformin plus a sulfonylurea, or add-on to pioglitazone with or without metformin. The