linagliptin and 2675 to placebo. In this placebo cohort, from which one active comparator trial was removed, there were fewer primary and secondary outcome events. Linagliptin did not affect the primary outcome compared with placebo (HR, 1.09; 95% CI, 0.68 to 1.75).

Hospitalization for congestive heart failure was assessed in 8 of the trials, which occurred in 12 of 1834 patients (0.7%) in the linagliptin group and 9 of 1175 patients (0.8%) in the comparator groups. The incidence rate per 1000 years at risk was 9.5% and 8.8%, respectively. Linagliptin did not reduce hospitalization for heart failure (HR, 1.04; 95% CI, 0.43 to 2.47).

Thus, in a representative cohort of patients with T2DM, with a diverse background from low to high CV risk and concomitant treatments from treatment-naïve to insulin, linagliptin was not associated with an increased risk for CV events. Based on the limited number of congestive heart failure cases leading to hospitalization, no increased risk with linagliptin was observed.

ENDURE: Alogliptin Effective and Safe Through 2 Years

Written by **Mary Mosley**

The Efficacy and Safety of Alogliptin Plus Metformin Compared to Glipizide Plus Metformin in Subjects With Type 2 Diabetes Mellitus (T2DM) study [ENDURE; NCT00856284] showed that there were greater reductions in the primary endpoint of least square mean change from baseline in HbA1C at 104 weeks with two doses of the DPP-4 inhibitor alogliptin compared with the sulfonylurea glipizide. Stefano Del Prato, MD, UOC Malattie Metaboliche e Diabetologia, Pisa, Italy, presented the results.

In this multicenter, double-blind, active-controlled study, patients whose T2DM was not controlled on a stable dose of metformin were randomized to one of three study arms: alogliptin 12.5 mg QD plus metformin 1500 to 3000 mg QD (ALO 12.5; n=880); alogliptin 25 mg QD plus metformin 1500 to 3000 mg QD (ALO 25; n=885); or glipizide 5 mg QD, titrated to 20 mg maximum, plus metformin 1500 to 3000 mg QD (GLIP; n=874) [Del Prato S et al. EASD 2013 (abstr 113)].

Most (62.3%) of the patients were white, 50.3% were women, and their mean age was 55.4 years. Body mass index was 31 kg/m^2, baseline HbA1C was 7.6%, and diabetes duration was 5.5 years. The changes achieved in the three treatment arms are shown in Table 1.

Table 1. Changes in Metabolic Parameters by Treatment Arm in ENDURE

	ALO 12.5	ALO 25	GLIP
HbA1C reduction (%)	–0.68	–0.72	–0.59
HbA1C ≤7.0% (%)	45.6*	48.5*	42.8
Fasting plasma glucose (mg/dL)	–0.9**	–3.2**	–5.4
Mean weight change (kg)	–0.68**	–0.89**	0.95
Hypoglycemia (≥1 event; %)	2.5	1.4	23.2
Severe hypoglycemia (n)	1	0	6

*p=0.004 ALO 25 vs. GLIP; ALO 12.5 vs GLIP nonsignificant; **p<0.001 for both ALO groups vs. GLIP.

Safety was similar in the three treatment arms, with a similar number of adverse events (AEs), serious AEs, or AEs resulting in discontinuing treatment. Upper respiratory tract infection, nasopharyngitis, diarrhea, hypertension, headache, and back pain were the most common AEs overall and in each treatment group. One patient in the ALO 25 and 3 in the GLIP arms had pancreatitis. A total of 11 patients died (3 in ALO 12.5; 3 in ALO 25; 5 in GLIP).

ENDURE demonstrated the sustained efficacy of alogliptin through 104 weeks of treatment, with significantly more patients taking the 25-mg dose achieving an HbA1C ≤7%, plus a lower rate of hypoglycemia with both doses compared with glipizide.

Trough DPP-4 Inhibition Differs Between the Approved DPP-4 Inhibitors

Written by **Wayne Kuznar**

A pharmacodynamics study in patients with type 2 diabetes mellitus (T2DM) reveals that sitagliptin QD provides greater inhibition of dipeptidyl peptidase-4 (DPP-4) through the dosing interval (ie, measured at trough, 24 hours following the last morning dose) than either saxagliptin 5 mg QD or vildagliptin 50 mg QD and similar DPP-4 inhibition to vildagliptin 50 mg BID. The findings come from a randomized, placebo-controlled, open-label, crossover study presented by Harvey L. Katzeff, MD, Merck/MSD, Whitehouse Station, New Jersey, USA.

Because the soluble form of DPP-4 is shed into the circulation, measurement of DPP-4 activity in blood is possible. Inhibitors of DPP-4 are heterogeneous in structure and have different pharmacokinetic, pharmacodynamic, and DPP-4-binding characteristics. No direct comparison of DPP-4 inhibition among these agents using a single inhibition assay in the same cohort had been conducted prior to this study. An assay that minimized *ex vivo* plasma dilution was used to