No Increased Cardiovascular Risk for Lixisenatide in ELIXA

First Cardiovascular Safety Trial to Provide Data on a GLP-1 Receptor Agonist

The investigational GLP-1 receptor agonist, lixisenatide, neither reduced nor increased cardiovascular events compared with placebo in ELIXA.

There was no increased risk for the primary endpoint, a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, and hospitalization for unstable angina, among subjects with type 2 diabetes and recent acute coronary syndrome who took lixisenatide vs placebo: 13.4% vs 13.2% (HR=1.02; 95% CI: 0.89-1.17).

ELIXA was a randomized, double-blind, placebo-controlled trial that enrolled 6,068 subjects with type 2 diabetes and a recent acute coronary syndrome (ACS) event. Subjects were randomized to lixisenatide 10 mcg/d (up- or down-titrated to max 20 mcg/d; n=3,034) or placebo (n=3,034).

Secondary endpoints included the primary endpoint plus heart failure hospitalization, heart failure hospitalization, and all-cause death.

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The secondary composite outcome, a composite of CV death, nonfatal MI, or nonfatal stroke, occurred among 10.2% of sitagliptin- and placebo-treated subjects (HR=0.99; 95% CI: 0.89-1.10; P=0.84).

No significant between-group differences were seen for heart failure hospitalization and other secondary outcomes, including all-cause mortality. The rate of hospitalization for heart failure was the same at 3.2% in the sitagliptin and placebo groups (HR=1.00; 95% CI: 0.83-1.20; P=0.98). There were also no differences in the rate of the composite outcome of hospitalization for heart failure or cardiovascular death, or for all-cause mortality, between the two groups.

**Findings consistent with previous DPP-4 inhibitors outcomes trials**

The conclusion that sitagliptin is not associated with a change in long-term cardiovascular event rates is consistent with findings from other DPP-4 outcomes trials, including SAVOR-TIMI 53 and EXAMINE. Both trials showed that saxagliptin and alogliptin, respectively, neither increased nor decreased major cardiovascular events. An excess rate of heart failure hospitalization was noted in the saxagliptin group in SAVOR-TIMI 5, however; and in EXAMINE, a nonsignificant numerical imbalance in heart failure hospitalization among subjects treated with alogliptin that was not seen in a post-hoc analysis of the composite of heart failure hospitalization or cardiovascular death.

**Adverse Events**

There was no significant difference with respect to adverse events in the two groups. Acute pancreatitis was uncommon overall, although numerically more frequent in the sitagliptin group, occurring in 23 subjects (0.3%) vs 12 subjects (0.2%) in the placebo group (HR=1.93; 95% CI: 0.96-3.88; P=0.07). Confirmed cases of pancreatic cancer were also uncommon, occurring numerically less frequently in the sitagliptin group: 9 subjects (0.1%) vs 14 subjects (0.2%) taking placebo (HR=0.66; 95% CI: 0.28-1.51; P=0.32).

Rates of severe hypoglycemia were comparable in the two groups. Subjects who had at least one episode of severe hypoglycemia had longer diabetes duration and were more often on insulin therapy. Those who had two or more episodes of severe hypoglycemia during the trial were required to discontinue sitagliptin.

**Glucose lowering**

At 4 months, mean A1C was 0.4% lower for sitagliptin compared with placebo: the least-squares mean difference was -0.29% for (95% CI: -0.32 to -0.27). The difference narrowed over the remainder of the study period.

Subjects taking sitagliptin took fewer additional antihyperglycemic agents and were less likely to need long-term insulin therapy (P<0.001 vs placebo for both).

**About the study**

TECOS was a randomized, double-blind, placebo-controlled, event-driven trial that enrolled 14,671 subjects with type 2 diabetes and established CVD. Subjects were randomized to sitagliptin 100 mg/d (or 50 mg/d if baseline eGFR ≥40 and <50 ml/min/1.73 m²) or placebo on top of usual care: stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin).


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**Rate of the primary composite endpoint**

<table>
<thead>
<tr>
<th>Group</th>
<th>% Subjects</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>11.4%</td>
<td>0.98 (0.88-1.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo</td>
<td>11.6%</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

(95,072) subjects were enrolled: 7,332 in each group.

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Combination Insulin Degludec/Liraglutide Tops Insulin Glargine in DUAL V

The novel once-daily combination of insulin degludec/liraglutide (IDegLira) more effectively lowered A1C, weight, and hypoglycemia risk than insulin glargine in the DUAL V study.

DUAL V randomized 557 adults with uncontrolled type 2 diabetes to 20 U to 50 U of insulin glargine to IDegLira (n=278) or continued insulin glargine uptitration (n=279). All subjects were also taking metformin. IDegLira doses were 16 U of insulin degludec plus liraglutide 0.6 mg with a maximum of 50 dose steps. Mean pre-trial insulin glargine dose was 32 U (no max). The primary endpoint was A1C change over 26 weeks.

**Significant A1C reduction with IDegLira**

IDegLira reduced A1C from 8.4% at baseline to 6.6% at Week 26, a significant 1.8% decrease compared with a 1.1% reduction (8.2% at baseline, 7.1% at Week 26) with insulin glargine (P<0.001).

Significantly more subjects in the IDegLira group achieved A1C <7% vs the glargine group: 72% vs 47% (P<0.001). The percentage of subjects who achieved A1C <7.0% without experiencing hypoglycemia was 54% for IDegLira and 29% for glargine.

Each group experienced an approximate 30% mean reduction in fasting plasma glucose from baseline to Week 26. FPG decreased from 160 mg/dL to 110 mg/dL (mean).

**Weight reduction with IDegLira and increase with glargine**

Mean weight decreased from 88.3 kg at baseline to 86.9 kg at Week 26 in the IDegLira group. Insulin glargine increased weight from 87.3 kg at baseline to 89.1 kg at Week 26.

**Less hypoglycemia with IDegLira**

While overall adverse events were similar in both groups, there were fewer cases of hypoglycemia with IDegLira than with glargine: 79 vs 137. Instances of nocturnal hypoglycemia were also fewer with IDegLira: 17 vs 68 with glargine. More patients withdrew from IDegLira treatment than for glargine treatment (completion rate: 90% vs 95%, respectively).

**More stable insulin dose in IDegLira arm**

Daily insulin titration occurred rapidly in both treatment arms for the first 8 to 10 weeks of the study. Beyond that time, the insulin dose was more stable for IDegLira at 41 U compared with 66 U with glargine.

Baseline characteristics were similar across the two groups. Mean A1C was 8.4% and 8.2% in the IDegLira and glargine arms, respectively. Diabetes duration was 11 years, BMI approximately 32 kg/m², and age 60 years in both groups.

IDegLira is an investigational compound; it is not yet FDA approved in the United States for the treatment of type 2 diabetes or overweight/obesity. Insulin degludec and insulin glargine are not FDA approved in the United States for the treatment of overweight/obesity.

ELIXA  Continued from page 1

Hazard ratios for select secondary outcomes:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome plus heart failure hospitalization</td>
<td>0.97</td>
<td>(0.85, 1.10)</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>0.96</td>
<td>(0.75, 1.23)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>0.94</td>
<td>(0.78, 1.13)</td>
</tr>
</tbody>
</table>

Glycemic control was slightly better with lixisenatide: mean post-baseline difference, -0.27% (95% CI: -0.32 to -0.22). Lixisenatide also showed small but significant benefits for urinary albumin to creatinine ratio (24% vs 24% from baseline to month 24), weight loss (-0.7 kg), and blood pressure (-0.8 mm Hg) vs placebo.

There was no increased risk for hypoglycemia in the lixisenatide group; nausea, vomiting, and heart rate were, however, higher for lixisenatide-treated patients.

There were no increases in pancreatitis or pancreatic cancer noted.

Baseline characteristics were similar in the lixisenatide and placebo groups.

<table>
<thead>
<tr>
<th></th>
<th>Lixisenatide (n=3,034)</th>
<th>Placebo (n=3,034)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean diabetes duration</td>
<td>9.4 yrs</td>
<td>9.2 yrs</td>
</tr>
<tr>
<td>Mean FPG</td>
<td>148 mg/dL</td>
<td>149 mg/dL</td>
</tr>
<tr>
<td>Mean A1C</td>
<td>7.6%</td>
<td>7.7%</td>
</tr>
<tr>
<td>BMI</td>
<td>30 kg/m2</td>
<td>30 kg/m2</td>
</tr>
<tr>
<td>Avg age</td>
<td>60 yrs</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td>22%</td>
<td></td>
</tr>
<tr>
<td>History of stroke</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>22%</td>
<td></td>
</tr>
</tbody>
</table>

In 2008, the FDA mandated cardiovascular safety trials for all new type 2 diabetes drugs. ELIXA is the first events-driven cardiovascular outcomes study to provide data for a GLP-1 receptor agonist.

ELIXA=Evaluation of Cardiovascular Outcomes in Patients With Type 2 Diabetes After Acute Coronary Syndrome During Treatment With Lixisenatide

Lixisenatide is an investigational agent; it is not yet FDA approved in the United States for the treatment of type 2 diabetes.


For more on lixisenatide, see Glycemic Control, No Hypoglycemia With Insulin Glargine/Lixisenatide on page 4

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SAVOR-TIMI 53 at 2 Years: No Cancer Signal With Saxagliptin

The DPP-4 inhibitor, saxagliptin, was not associated with an increase in cancer incidence or cancer-related death during 2 years of follow-up in subjects with type 2 diabetes who were at high risk for cardiovascular disease in a post-hoc analysis of SAVOR TIMI-53.

For the present report, researchers analyzed data from SAVOR-TIMI 53, which randomized more than 16,000 high-risk type 2 diabetics to saxagliptin 5 mg/d (or 2.5 mg/d with renal impairment) (n=8,250) or placebo (n=8,173). The primary endpoint was cardiovascular death, myocardial infarction, or ischemic stroke.

At 2.1 years, 47% of saxagliptin-treated subjects (326) had at least one cancer compared with 53% of placebo recipients (366): HR=0.89; P=0.13. The number of cancer-associated deaths was similar in both groups.

Cancer incidence increased with age. Diabetes duration did not predict cancer development.

In SAVOR-TIMI 53, cancer rates were similar between groups. There was no excess pancreatic cancer incidence with saxagliptin, and numerically more pancreatic cancers were seen in placebo-treated subjects (12 cases vs 5 cases for saxagliptin; P=0.095).


Glycemic Control, No Hypoglycemia With Insulin Glargine/Lixisenatide

The investigational combination of insulin glargine/lixisenatide (LixiLan) improved glucose control without increasing hypoglycemia risk at any level of A1C reduction when added to metformin among subjects with type 2 diabetes.

Rosenstock and colleagues randomized 323 insulin-naïve subjects to LixiLan plus metformin (n=161) or insulin glargine plus metformin (n=162). LixiLan reduced A1C from 8.1% at baseline to 6.3%. A total of 85% of subjects taking LixiLan achieved A1C <7.0%:

- 68% of LixiLan subjects achieved A1C <7.0% without experiencing hypoglycemia
- 56% of LixiLan subjects achieved A1C <7.0% without experiencing weight gain
- 46% of LixiLan subjects achieved A1C <7.0% without experiencing hypoglycemia or weight gain

A post-hoc analysis of the data, in which subjects were stratified based on A1C achievement of <6.0%, 6.0% to <6.5%, 6.5% to <7.0%, and ≥7.0% revealed no statistically significant relationship between hypoglycemia rates and A1C reduction from baseline.

Mean A1C at baseline was 8.0%. Mean diabetes duration was 6.7 years, and mean age was 56.7 years.

LixiLan is an investigational compound; it is not yet FDA approved in the United States for the treatment of type 2 diabetes or overweight/obesity. Insulin glargine is not FDA approved in the United States for the treatment of overweight/obesity.

SGLT2 inhibitors have been shown in clinical studies to reduce weight among overweight or obese individuals with type 2 diabetes. Weight amelioration in these individuals is associated with improvements in quality of life and glycemic control, and potentially measures of cardiovascular disease (CVD). Two abstracts assessed the efficacy of the SGLT2 inhibitor, dapagliflozin, on these outcomes.

Johnsson and colleagues\(^1\) found that subjects with type 2 diabetes who experienced significant weight loss after 1 year of treatment with dapagliflozin maintained weight loss at 4 years, according to a new analysis.

They retrospectively analyzed data from a double-blind, randomized, controlled phase 3 study that compared the A1C-lowering efficacy of dapagliflozin (≤10 mg/d; n=406) with glipizide (≤20 mg/d; n=408) in subjects with uncontrolled type 2 diabetes despite treatment with stable doses of metformin. The present study assessed body weight in the two treatment groups at 1, 2, 3, and 4 years.

Mean body weight loss in the dapagliflozin group was 3.55 kg after 1 year (adjusted mean change from baseline -3.6 kg), which was maintained up to 4 years. A total of 46% of dapagliflozin weight loss responders at year 1 maintained ≥80% weight loss at 2 years, 35% maintained ≥80% weight loss at 3 years, and 30% maintained ≥80% weight loss at 4 years, regardless of baseline BMI.

Weight gain occurred in the glipizide group (adjusted mean change from baseline, 1.4 kg) and was maintained up to 2 years, decreasing after 4 years.

Cefalu and colleagues\(^2\) found that dapagliflozin improved several metabolic risk factors, including blood glucose, systolic blood pressure (SBP), and body weight, without risk for hypoglycemia when taken long term.

They pooled data from two phase 3 studies in which subjects with type 2 diabetes and CVD were assigned dapagliflozin 10 mg/d (n=284) or placebo (n=284). At 104 weeks, subjects taking dapagliflozin demonstrated greater reductions in A1C, body weight, and SBP:

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=284)</th>
<th>Placebo (n=284)</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted mean A1C change from baseline (%)</td>
<td>-0.36 (-0.51, -0.22)</td>
<td>-0.01 (-0.20, 0.18)</td>
<td>-0.35 (-0.59, -0.12)</td>
</tr>
<tr>
<td>Adjusted mean change in body weight (kg)</td>
<td>-3.05 (-3.60, -2.50)</td>
<td>0.11 (-0.45, 0.67)</td>
<td>-3.16 (-3.95, -2.38)</td>
</tr>
<tr>
<td>Adjusted mean SBP change from baseline (mm Hg)</td>
<td>-2.08 (-3.53, -0.64)</td>
<td>-0.05 (-1.53, 1.43)</td>
<td>-2.03 (-4.10, 0.04)</td>
</tr>
</tbody>
</table>

Subjects taking dapagliflozin also demonstrated a better prespecified three-item clinical endpoint for change from baseline in absolute drop in A1C of ≥0.5%, relative drop in body weight of ≥3%, and absolute drop in SBP of ≥3 mm Hg:

- Week 24: 9.5% vs 2.1% for placebo
- Week 52: 10.9% vs 3.5% for placebo
- Week 104: 6.7% vs 1.4% for placebo

No significant differences were found with respect to adverse events, including hypoglycemia, renal impairment, and volume depletion, over 2 years with dapagliflozin or placebo. Hypoglycemia occurred among 106 dapagliflozin-treated subjects (37.3%) and 109 placebo-treated subjects (38.4%). More subjects who were taking dapagliflozin experienced genitourinary tract infections.

Meta-Analysis Shows No Increased Mortality Risk With Sulfonylureas

But Questions Linger Due to Conflicting Earlier Published Reports

Use of sulfonylureas for the treatment of type 2 diabetes did not increase the risk of all-cause or cardiovascular mortality, according to data from a new meta-analysis.¹

Rodas and colleagues pooled data from 47 randomized controlled trials with at least 52 weeks’ duration that analyzed the use of second- or third-generation sulfonylureas for treating type 2 diabetes; the analysis included 37,650 subjects. Sulfonylureas as first- or second-line therapy were not associated with an increased risk of all-cause mortality, cardiovascular mortality, myocardial infarction, or stroke.

<table>
<thead>
<tr>
<th>Total mortality</th>
<th>OR=1.12</th>
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<tbody>
<tr>
<td>(95% CI: 0.96, 1.30)</td>
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<table>
<thead>
<tr>
<th>Cardiovascular mortality</th>
<th>OR=1.12</th>
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<tbody>
<tr>
<td>(95% CI: 0.87, 1.42)</td>
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<table>
<thead>
<tr>
<th>MI</th>
<th>OR=0.92</th>
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<tr>
<td>(95% CI: 0.76, 1.12)</td>
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<table>
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<tr>
<th>Stroke</th>
<th>OR=1.16</th>
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<tr>
<td>(95% CI: 0.81-1.66)</td>
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These new data are in contrast to previous reports suggesting that use of sulfonylureas is associated with increased total and cardiovascular mortality. UKPDS was the first trial to report mortality risk associated with sulfonylurea therapy.² A meta-analysis including 551,912 subjects published in 2013 found that 92% of subjects treated with a sulfonylurea had increased mortality risk compared with those who received a non-sulfonylurea across 13 studies.³ In five studies, treatment with a sulfonylurea alone or combined with other antihyperglycemic agents conferred more than twofold higher risk for cardiovascular mortality (OR=2.72; 95% CI: 1.95, 3.79).

In the present study, glipizide was the only sulfonylurea associated with increased risk for total and cardiovascular mortality.  