Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes

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Drug Overview

- MOA: Long acting glucagon-like peptide 1 receptor agonist
  - Increases glucose dependent insulin secretion
  - Decreases inappropriate glucagon secretion
  - Increases β-cell growth and replication
  - Increases satiety
- A1c reduction: ~1%
Advantages and Disadvantages

• **Advantages**
  - No hypoglycemia
  - Decreases weight
  - Decreases post prandial glucose excursions
  - Decreases some CV risk factors

• **Disadvantages**
  - GI side effects (nausea, vomiting, diarrhea)
  - Increases HR
  - Can possibly cause acute pancreatitis
  - C-cell hyperplasia/medullary thyroid tumors in animals
  - Injectable
  - Training requirements
Recommended Place in Therapy

• Alternative monotherapy agents such as thiazolidinediones (TZDs), alpha-glucosidase inhibitors (AGIs), meglitinides, dipeptidyl peptidase-4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) agonists should be reserved for patients who have contraindications to or are unable to tolerate metformin or Sulfonylureas (SFU).

• If noninsulin monotherapy, at the maximum tolerated dose, does not achieve or maintain the A1C target over 3 months, then add a second oral agent, a GLP-1 agonist, or basal insulin.
Healthy eating, weight control, increased physical activity, and diabetes education

Metformin

If A1C target not achieved after ~3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin + Metformin + Metformin + Metformin + Metformin + Metformin +
Sulfonylurea high low risk neutral / loss GI / lactic acidosis
Thiazolidinedione high low risk neutral / loss GI / lactic acidosis
DPP-4 inhibitor intermediate low risk neutral / loss GI / lactic acidosis
SGLT2 inhibitor intermediate low risk neutral / loss GI / lactic acidosis
GLP-1 receptor agonist high low risk neutral / loss GI / lactic acidosis
Insulin (basal) highest high risk neutral / loss GI / lactic acidosis

If A1C target not achieved after ~3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference—choice dependent on a variety of patient- and disease-specific factors):

Metformin + Metformin + Metformin + Metformin + Metformin + Metformin +
Sulfonylurea + Thiazolidinedione + DPP-4 inhibitor + SGLT2 inhibitor + GLP-1 receptor agonist +
TZD SU SU TAZD SU TAZD
or DPP-4-i or SGLT2-i or GLP-1-RA or Insulin^5 or TAZD or DPP-4-i
or SGLT2-i or GLP-1-RA or Insulin^5 or TAZD or DPP-4-i
or SGLT2-i or GLP-1-RA or Insulin^5

If A1C target not achieved after ~3 months of triple therapy and patient (1) on oral combination, move to injectables; (2) on GLP-1-RA, add basal insulin; or (3) on optimally titrated basal insulin, add GLP-1-RA or mealtime insulin. In refractory patients consider adding TAZD or SGLT2-i:

Metformin +
Basal insulin + Mealtime insulin or GLP-1-RA

VA/DoD Criteria for Use

Exclusion Criteria
- Type 1 diabetes
- History of hypersensitivity to GLP-1 agonist or excipients
- ESRD or CrCl <30ml/min (for exenitide)
- Personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2
- Severe gastrointestinal disease
- History of pancreatitis

Inclusion criteria
- Type 2 diabetes
- Inadequate glycemic control on two oral medications, one of which should be metformin
- OR
- Inadequate glycemic control on basal insulin + metformin (or another agent if unable to use metformin)

**Study Design**

- Multi-center, randomized, double blind, placebo controlled trial
  - 2 week placebo run-in
  - 30 day safety follow-up
- 9,340 patients
  - A1c >7%
  - High risk of cardiovascular disease

## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide (N=4,668)</th>
<th>Placebo (N=4,672)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Male sex</strong></td>
<td>3011 (64.5)</td>
<td>2992 (64.0)</td>
</tr>
<tr>
<td><strong>Age, years</strong></td>
<td>64.2 ± 7.2</td>
<td>64.4 ± 7.2</td>
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<tr>
<td><strong>Diabetes duration, years</strong></td>
<td>12.8 ± 8.0</td>
<td>12.9 ± 8.1</td>
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<tr>
<td><strong>Geographic region</strong></td>
<td></td>
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<tr>
<td>Europe</td>
<td>1639 (35.1)</td>
<td>1657 (35.5)</td>
</tr>
<tr>
<td>North America</td>
<td>1401 (30.0)</td>
<td>1446 (31.0)</td>
</tr>
<tr>
<td>Asia</td>
<td>360 (7.7)</td>
<td>351 (7.5)</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>1268 (27.2)</td>
<td>1218 (26.1)</td>
</tr>
<tr>
<td><strong>Glycated hemoglobin, %</strong></td>
<td>8.7 ± 1.6</td>
<td>8.7 ± 1.5</td>
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<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>32.5 ± 6.3</td>
<td>32.5 ± 6.3</td>
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<tr>
<td><strong>Body weight, kg</strong></td>
<td>91.9 ± 21.2</td>
<td>91.6 ± 20.8</td>
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<tr>
<td><strong>Systolic blood pressure, mmHg</strong></td>
<td>135.9 ± 17.8</td>
<td>135.9 ± 17.7</td>
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<tr>
<td><strong>Diastolic blood pressure, mmHg</strong></td>
<td>77.2 ± 10.3</td>
<td>77.0 ± 10.1</td>
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<tr>
<td><strong>Heart failure</strong></td>
<td>835 (17.9)</td>
<td>832 (17.8)</td>
</tr>
<tr>
<td><strong>Established CVD (age ≥ 50)</strong></td>
<td>3831 (82.1)</td>
<td>3767 (80.6)</td>
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<tr>
<td>Prior myocardial infarction</td>
<td>1464 (31.4)</td>
<td>1400 (30.0)</td>
</tr>
<tr>
<td>Prior stroke or transient ischemic attack</td>
<td>730 (15.6)</td>
<td>777 (16.6)</td>
</tr>
<tr>
<td>Prior revascularization</td>
<td>1835 (39.3)</td>
<td>1191 (25.5)</td>
</tr>
<tr>
<td>&gt;50% stenosis of coronary, carotid, or lower extremity arteries</td>
<td>1188 (26.4)</td>
<td>1191 (25.5)</td>
</tr>
<tr>
<td>Documented symptomatic CHD</td>
<td>412 (8.8)</td>
<td>406 (8.7)</td>
</tr>
<tr>
<td>Documented asymptomatic cardiac ischemia</td>
<td>1241 (26.6)</td>
<td>1231 (26.3)</td>
</tr>
<tr>
<td>Heart failure NYHA II-III</td>
<td>653 (14.0)</td>
<td>652 (14.0)</td>
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<tr>
<td>Chronic kidney disease</td>
<td>1185 (25.4)</td>
<td>1122 (24.0)</td>
</tr>
<tr>
<td><strong>CVD risk factors (age ≥ 60)</strong></td>
<td>837 (17.9)</td>
<td>905 (19.4)</td>
</tr>
<tr>
<td><strong>Microalbuminuria or proteinuria</strong></td>
<td>501 (10.7)</td>
<td>558 (11.9)</td>
</tr>
<tr>
<td>Hypertension and left ventricular hypertrophy</td>
<td>248 (5.3)</td>
<td>251 (5.4)</td>
</tr>
<tr>
<td>Left ventricular systolic or diastolic dysfunction</td>
<td>203 (4.3)</td>
<td>191 (4.1)</td>
</tr>
<tr>
<td>Ankle-brachial Index &lt;0.9</td>
<td>110 (2.4)</td>
<td>116 (2.5)</td>
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<tr>
<td><strong>Renal function</strong></td>
<td></td>
<td></td>
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<tr>
<td>Normal (eGFR ≥ 90)</td>
<td>1620 (34.7)</td>
<td>1655 (35.4)</td>
</tr>
<tr>
<td>Mild Impairment (eGFR 60-89)</td>
<td>1932 (41.4)</td>
<td>1975 (42.3)</td>
</tr>
<tr>
<td>Moderate Impairment (eGFR 30-59)</td>
<td>999 (21.4)</td>
<td>935 (20.0)</td>
</tr>
<tr>
<td>Severe Impairment (eGFR &lt; 30)</td>
<td>117 (2.5)</td>
<td>107 (2.3)</td>
</tr>
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</table>
End Points

• Primary:
  • Time from randomization to first occurrence of a composite CV outcome (CV death, non-fatal MI, or non-fatal stroke)

• Exploratory:
  • Time from randomization to first occurrence of an expanded composite CV outcome
  • Time from randomization to all cause death
  • Time from randomization to each individual component of the expanded composite CV outcome
  • Microvascular outcome

• Safety and Adverse Events

Major Inclusion Criteria

• Type 2 diabetes
• Anti-diabetic drug naïve or treated with one or more oral anti-diabetic drugs or treated with human NPH insulin or long-acting insulin analogue or premixed insulin, alone or in combination with oral anti-diabetic drugs
• Glycated hemoglobin ≥7.0%
• Age ≥ 50 years and established CV disease or chronic renal failure

OR

• Age ≥ 60 years and risk factors for CV disease

Major Exclusion Criteria

- Type 1 diabetes
- Use of a GLP-1 receptor agonist, pramlintide, any DPP-4 inhibitor or rapid acting insulin
- Acute decompensation of glycemic control
- Acute coronary or cerebrovascular event in the previous 14 days
- Family or personal history of multiple endocrine neoplasia type 2 or familial medullary thyroid carcinoma

Primary Hypothesis
- Liraglutide would be non-inferior to placebo with regards to the primary outcome, with a margin of 1.30 for the upper boundary of the 95% CI of the hazard ratio.

Time to event analysis was based on the Cox proportional hazard model.

Non-inferiority was established for the primary outcome if the upper limit of the two-sided 95% confidence interval of the hazard ratio was <1.30.

Superiority was established for the primary outcome if the upper limit of the two-sided 95% confidence interval of the hazard ratio was <1.00.

Primary and Exploratory Outcomes

<table>
<thead>
<tr>
<th>Table 1. Primary and Secondary Outcomes.</th>
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<tbody>
<tr>
<td><strong>Outcome</strong></td>
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<td></td>
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<tr>
<td>Primary composite outcome‡</td>
</tr>
<tr>
<td>Expanded composite outcome‡</td>
</tr>
<tr>
<td>Death from any cause</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
</tr>
<tr>
<td>Death from noncardiovascular causes</td>
</tr>
<tr>
<td>Myocardial infarction§</td>
</tr>
<tr>
<td>Fatal§</td>
</tr>
<tr>
<td>Nonfatal§</td>
</tr>
<tr>
<td>Silent§</td>
</tr>
<tr>
<td>Stroke§</td>
</tr>
<tr>
<td>Fatal§</td>
</tr>
<tr>
<td>Nonfatal§</td>
</tr>
<tr>
<td>Transient ischemic attack§</td>
</tr>
<tr>
<td>Coronary revascularization</td>
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<tr>
<td>Hospitalization for unstable angina pectoris</td>
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<tr>
<td>Hospitalization for heart failure</td>
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<tr>
<td>Microvascular event</td>
</tr>
<tr>
<td>Retinopathy</td>
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<tr>
<td>Nephropathy</td>
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</tbody>
</table>

* Hazard ratios and P values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
† The primary composite outcome in the time-to-event analysis consisted of the first occurrence of death from cardiovascular causes (181 patients in the liraglutide group vs. 227 in the placebo group), nonfatal (including silent) myocardial infarction (275 vs. 304), or nonfatal stroke (152 vs. 163). The P value is for superiority.
§ The expanded composite outcome included death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or hospitalization for unstable angina pectoris or heart failure.
¶ This analysis was not prespecified.
Primary and Exploratory Outcomes

Glycemic Control and Cardiovascular Risk Factors

A HbA1c

B Body Weight

C Systolic and Diastolic Blood Pressure

D Heart Rate

Selected Adverse Events Reported During the Trial

- Liraglutide had a lower incidence of severe hypoglycemia and confirmed hypoglycemia.
- Liraglutide had a higher incidence of acute gallstone disease, injection site reaction, and GI side effects.
- Liraglutide had a lower incidence of pancreatitis.
- Liraglutide had a higher incidence of benign and malignant neoplasms, and pancreatic carcinoma.

Discussion

• Comparison of Liraglutide to other anti-diabetic agents
  • DPP-4 inhibitors and risk of hospitalization for heart failure
  • Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
  • Lixisenatide in Acute Coronary Syndrome
Discussion

• Limitations
  • Patients followed for 3.5-5 years
  • Patients enrolled were at high risk of CV events and A1c at baseline was >7%
  • Sponsored by Novo Nordisk
Conclusion

• The addition of Liraglutide to a standard regimen in patients with type 2 diabetes and high risk of cardiovascular events, may lower the patient’s risk of cardiovascular events and death from any cause
References

• Uptodate


• Lane W., SWeinrib S., Rappaport J., Hale C. The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial. Diabetes, obesity, and Metabolism 16: 827–832, 2014.