In type 1 diabetes, adding liraglutide to insulin increased hypoglycemia and hyperglycemia with ketosis

Question

In patients with type 1 diabetes mellitus, does adding liraglutide to treat-to-target insulin treatment improve glycemic control?
Methods

- **Patients**: 1398 patients 18 to 75 years of age (mean age 44 y, 52 % women) who had type 1 diabetes for ≥ 12 months treated with basal bolus or continuous subcutaneous insulin infusion for ≥ 6 months, stable insulin treatment for the past 3 months, body mass index ≥ 20 kg/m², and hemoglobin (Hb) A₁c levels 7.0% to 10%

- **Exclusion criteria**: treatments that affect glycemic control, acute or chronic pancreatitis, estimated glomerular filtration rate < 30 mL/min/1.73 m², calcitonin level > 50 ng/L at baseline, personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type2, or severe neuropathy
Design: Randomized placebo-controlled trial (ADJUNCT ONE Treat-To-TargetRandomizedTrial)

Setting: 177 centers in 17 countries.

Outcomes: Primary efficacy outcomes included HbA$_{1c}$ levels, body weight, and insulin dose reduction. Safety outcomes included symptomatic hypoglycemia (hypoglycemic symptoms plus plasma glucose < 3.1 mmol/L [56 mg/dL]) and hyperglycemia with ketosis (plasma ketone level > 1.5 mmol/L).
Main results

The main results are in the Table. Insulin dose was reduced with liraglutide 1.8 mg and 1.2 mg compared with placebo ($P < 0.05$). Symptomatic hypoglycemia increased with liraglutide 1.8 mg and 1.2 mg ($P < 0.05$) and hyperglycemia with ketosis increased with 1.8 mg ($P = 0.02$).
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Dose</th>
<th>Mean change from baseline</th>
<th>Mean difference (95% CI) at 1 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Liraglutide</td>
<td>Placebo</td>
</tr>
<tr>
<td>HbA1c</td>
<td>1.8 mg</td>
<td>−0.54%</td>
<td>−0.34%</td>
</tr>
<tr>
<td></td>
<td>1.2 mg</td>
<td>−0.49%</td>
<td>−0.34%</td>
</tr>
<tr>
<td></td>
<td>0.6 mg</td>
<td>−0.43%</td>
<td>−0.34%</td>
</tr>
<tr>
<td>Body weight</td>
<td>1.8 mg</td>
<td>−4.0</td>
<td>0.9</td>
</tr>
<tr>
<td>(kg)</td>
<td>1.2 mg</td>
<td>−2.7</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td>0.6 mg</td>
<td>−1.3</td>
<td>0.9</td>
</tr>
</tbody>
</table>

†Hb = hemoglobin; other abbreviations defined in Glossary.
Conclusion

In patients with type 1 diabetes, liraglutide 1.8 and 1.2 mg added to treat-to-target insulin treatment reduced hemoglobin A$_{1c}$ levels, body weight, and insulin dose but increased risk for hypoglycemia and hyperglycemia with ketosis (1.8 mg), compared with placebo.
Commentary

❖ Is there a medication other than insulin that can benefit patients with type 1 diabetes?
❖ The ADJUNCT ONE trial by Mathieu and colleagues randomized 1398 patients with type 1 diabetes and suboptimal glycemic control to insulin plus placebo or 3 different doses of subcutaneous liraglutide. At 1 year, liraglutide 1.8 mg and 1.2 mg reduced HbA$_1c$ levels, insulin dose, and weight compared with placebo.
However, the trial found an increase in symptomatic hypoglycemia and 8 cases of diabetic ketoacidosis in the liraglutide groups compared with 0 in the placebo group. These results differ from the reduction in hypoglycemia found in the LEADER trial and led the manufacturer, Novo Nordisk, to announce in August 2015 that it would not apply for approval of liraglutide (Victoza) for use in patients with type 1 diabetes.
The strong tendency of insulin to cause hypoglycemia complicates the addition of a second therapeutic agent. Liraglutide, a seemingly hypoglycemia-proof GLP-1RA whose action depends on the presence of glucose, exacerbates hypoglycemic events in patients with type 1 diabetes.

The ideal use of combination therapy—the standard of care in type 2 diabetes—remains to be determined for type 1 diabetes.
in metformin-treated type 2 diabetes, weekly dulaglutide was noninferior to daily liraglutide for HbA$_{1c}$ levels

In patients with uncontrolled type 2 diabetes who are receiving metformin therapy, is weekly dulaglutide noninferior to daily liraglutide for reducing hemoglobin (Hb) A₁c levels?
Methods

**Patients:**
599 patients ≥ 18 years of age (mean age 57 y, 52% women) who had type 2 diabetes (HbA1c level 7% to 10% [53 to 86 mmol/mol]); had body mass index ≤ 45 kg/m²; and were using metformin, ≥ 1500 mg/d, at a stable dose for ≥ 3 months

**Exclusion criteria:**
previous pancreatitis, recent CV event, serum calcitonin level ≥ 5.79 pmol/L (≥ 20 pg/mL), serum creatinine level ≥ 132.6 μmol/L (≥ 1.5 mg/dL) in men and ≥ 123.8 μmol/L (≥ 1.4 mg/dL) in women, creatinine clearance < 60 mL/min, or use of other antihyperglycemic drugs.
❖ **Design:**
Randomized controlled trial (Assessment of Weekly Administration of LY2189265 [dulaglutide] in Diabetes-6 [AWARD-6] study). ClinicalTrials.gov NCT01624259

❖ **Setting:**
62 centers in the Czech Republic, Germany, Hungary, Mexico, Poland, Romania, Spain, Slovakia, and the USA.

❖ **Outcomes:**
Primary outcome was change in HbA$_{1c}$ level at 26 weeks. Other outcomes included proportion of patients achieving target HbA$_{1c}$ level (< 7.0% [< 53 mmol/mol]); weight; and adverse events (AEs), including pancreatitis and pancreatic enzyme levels, CV events, and hypoglycemia (plasma glucose level ≤ 3.9 mmol/L).
Main results

Dulaglutide was noninferior to liraglutide for change in HbA$_{1c}$ levels. At 26 weeks, the liraglutide group had greater weight loss than the dulaglutide group; dulaglutide and liraglutide did not differ for the proportion of patients with HbA$_{1c}$ level < 7% (68% in both groups, $P = 0.93$), serious AEs (2% vs 4%, $P = 0.13$), hypoglycemia (9% vs 6%, $P = 0.15$), or treatment emergent abnormal changes in pancreatic enzyme levels (25% vs 33%, $P = 0.052$). 1 patient in the liraglutide group had a CV event, and no patients had adjudicated pancreatitis.
### Weekly dulaglutide vs daily liraglutide in type 2 diabetes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Change from baseline</th>
<th>At 26 wk</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dulaglutide</td>
<td>Liraglutide</td>
<td>Mean difference (95% CI)</td>
</tr>
<tr>
<td>HbA₁c level</td>
<td>−1.42%</td>
<td>−1.36%</td>
<td>−0.06% (−0.19 to 0.07)§</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>−2.90</td>
<td>−3.61</td>
<td>0.71 (0.17 to 1.26)</td>
</tr>
</tbody>
</table>

‡Hb = hemoglobin; CI defined in Glossary.
§P < 0.001 for noninferiority (margin for difference in HbA₁c level ≤ 0.40%).
Conclusion

In patients with type 2 diabetes treated with metformin, weekly dulaglutide was noninferior to daily liraglutide for reducing HbA$_{1c}$ levels at 26 weeks
Results from AWARD-6 suggest that once-weekly dulaglutide can achieve similar glycemic control and clinically similar but statistically less weight loss compared with daily liraglutide.

The side effect profile of the 2 GLP-1 analogues is comparable after 6 months of treatment. Both drugs had similar effects on quality of life, although these were not reported in detail.
What is the clinical relevance of these findings? We still don’t know. Further studies are needed to clarify if the ease of administration of once-weekly dulaglutide, which reduces the treatment burden on patients, translates into improved adherence and reduced risk for long-term complications in type 2 diabetes.
In patients with type 2 diabetes and high CV risk, liraglutide reduced a composite CV outcome at a median 3.8 years.

Question

In patients with type 2 diabetes and high cardiovascular (CV) risk, is liraglutide noninferior to placebo for CV events?
Methods

❖ Patients:

9340 patients (mean age 64 y, 64% men, mean glycated hemoglobin [Hb] level 8.7%) who had type 2 diabetes, glycated Hb level ≥ 7%, and age ≥ 50 years with ≥ 1 CV condition or ≥ 60 years with ≥ 1 CV risk factor

❖ Exclusion criteria:

type 1 diabetes; previous multiple endocrine neoplasia type 2 or medullary thyroid cancer or family history of these conditions; acute coronary or cerebrovascular event in the past 14 days; or use of glucagon like peptide-1 (GLP-1)–receptor agonists, dipeptidyl peptidase-4 inhibitors, pramlintide, or rapid-acting insulin.
**Design:**
Randomized, placebo-controlled, noninferiority trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER] trial). ClinicalTrials.govNCT01179048.

**Setting:** 410 centers in 32 countries

**Outcomes:** Primary outcome was a composite of CV events (CV death, nonfatal myocardial infarction, or nonfatal stroke). Other outcomes included all-cause mortality, an expanded CV composite (primary composite components and coronary revascularization or hospitalization due to heart failure or unstable angina), and a composite microvascular outcome (nephropathy or retinopathy).
Main results

The main results are in the Table
## Liraglutide vs placebo in patients with type 2 diabetes and high CV risk:

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Event rates</th>
<th>At a median 3.8 y</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Liraglutide</td>
<td>Placebo</td>
</tr>
<tr>
<td>Primary CV composite§</td>
<td>13%</td>
<td>15%</td>
</tr>
<tr>
<td>CV death</td>
<td>4.7%</td>
<td>6.0%</td>
</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>6.0%</td>
<td>6.8%</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>3.4%</td>
<td>3.8%</td>
</tr>
<tr>
<td>Expanded CV composite</td>
<td></td>
<td>20%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>8.2%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Composite microvascular outcome†</td>
<td>7.6%</td>
<td>8.9%</td>
</tr>
</tbody>
</table>

---

*CV = cardiovascular; NS = not significant; other abbreviations defined in Glossary. RRR, NNT, and CI calculated from placebo event rates and hazard ratios in article.

§CV death, nonfatal myocardial infarction, or nonfatal stroke.

Primary CV composite components and coronary revascularization (8.7% vs 9.4%, P = 0.18) or hospitalization for either heart failure (4.7% vs 5.3%, P = 0.14) or unstable angina (2.6% vs 2.7%, P = 0.87).

†Retinopathy (2.3% vs 2.0%, P = 0.33) or nephropathy (5.7% vs 7.2%, P = 0.003).
Conclusion

In patients with type 2 diabetes and high cardiovascular risk, liraglutide reduced a composite cardiovascular outcome at a median 3.8 years.
Commentary

- The LEADER trial found that adding liraglutide to standard care improved survival and reduced CV outcomes and microvascular events, namely nephropathy.
Commentary

- Unfortunately, the reasons for such a benefit remain unclear. Was it weight loss, lower incidence of hypoglycemia, lower systolic blood pressure, modestly decreased glycated Hb level, or other reasons on which we can only speculate? Another GLP-1 receptor agonist, lixisenatide, did not show any CV benefit in the ELIXA trial.

- Moreover, safety requires further assessment over a much longer perspective given that patients will probably be prescribed the drug for long-term, if not lifelong, use.
For example, although there was no significant between-group difference in the overall incidence of neoplasia, rates of pancreatic cancer were higher with liraglutide than placebo, whereas the opposite was observed for leukemia and prostate cancer.
Image in clinical medicine
A previously healthy 36-year-old man presented with a 1-month history of fever and pain in both shoulders and knees, which had been preceded by a sore throat 2 weeks before the onset of fever.

- WBC: 13800  neut: 86%  CRP: 26
- ASO: 1478
- Echocardiography: mild aortic regurgitation
- His fever and arthralgias abated after the administration of a NSAID.
- One week later, painless, nonpruritic, red annular macules appeared on the upper limbs and abdomen.
- The rash migrated within hours and then faded over the course of a few days while new lesions appeared.
Acute Rheumatic Fever with Erythema Marginatum
• Erythema marginatum, an evanescent nonpruritic macular rash, is one of the major Jones criteria for the diagnosis of acute rheumatic fever.
• The patient began taking amoxicillin for secondary prophylaxis of rheumatic heart disease. The rash disappeared completely 4 months after presentation, and the antistreptolysin O titer decreased to 246 IU per milliliter 12 months after presentation.