LEADER: Liraglutide VICTOZA CV Outcomes Trial Summary

Liraglutide: Cardiovascular (CV) Outcomes and Mortality in Patients with Type 2 Diabetes (T2DM)

In patients with T2DM and at high risk of CV events, does liraglutide reduce CV risk compared to placebo when added to standard care?

**BOTTOM LINE**

- Liraglutide is the first drug of its class (GLP1-A) to demonstrate positive CV outcomes in a RCT.
- Compared to standard care, for every 100 patients with T2DM and high CV disease risk, treatment with liraglutide for ~4 years will result in 2 less CV events (composite endpoint of: CV death (significant), nonfatal stroke (NS), nonfatal MI (NS)), 2 less cases of nephropathy, but 1 extra case of acute gallbladder disease, and 2 extra cases of discontinuation due to adverse events such as nausea, vomiting and diarrhea.
- Liraglutide resulted in an additional ~2.3kg weight loss over the placebo group, and also affected BP [SBP≤11.2 mmHg, DBP<0.6 mmHg] and heart rate (↑3 BPM).
- Areas of caution: Previous trials with similar drugs, designs and endpoints had only neutral results.

**BACKGROUND**

- Liraglutide (VICTOZA x 3000-5750/100days) is a glucagon-like peptide-1 agonist (GLP1-A) approved in 2010 for use in patients with T2DM as add-on to metformin alone, metformin+SU, metformin+basal insulin.2
- Non-inferior outcome trial mandated by the FDA to ensure CV safety in the “post-rosiglitazone era”.3

**TRIAL BACKGROUND**


**INTERVENTION**: Liraglutide 1.8mg subcut daily vs. placebo, added to existing therapy.
- Patients were randomized to liraglutide 0.6 mg subcut daily and titrated after 2 weeks to a maximum of 1.8mg based on tolerance (median dose 1.78mg).
- If patient did not reach recommended target for glycemic control (HbA1c ≤7% or individualized target at investigator’s discretion), addition of antihyperglycemics (except GLP1-A DPP4-I, and pramlintide) including insulin, were permitted.

**INCLUSION**: T2DM, HbA1c ≥7.0%, ≥50 years old with ≥1 CV condition (CHD, cerebrovascular disease CKD ≥stage 3, HF NYHA class II-III, PVD) or ≥60 years old with ≥1 CV risk factor (microalbuminuria, proteinuria, HTN+LVH, LV dysfunction, ABI <0.9).

**EXCLUSION**: T1DM; use of: GLP1-A, DPP4-I, pramlintide, rapid acting insulin; familial/personal history of multiple endocrine neoplasia type 2 or medullary thyroid cancer, acute ≤14 days coronary or cerebrovascular event or planned revascularization.

**POPULATION**: Randomized: n=9340 ~64%, 77% Caucasian, age 64.3±7.2 yrs, duration of diabetes ≥12.8±8 yrs, HbA1c 8.7%±1.6, BMI 32.5±6.3 kg/m2, SBP 135.9±17.8 mmHg, DBP 77.1±10.2 mmHg

- **CV comorbidity/risk factors**: MI ≥30.7%, stroke or TIA ≥16.1%, revascularization ≥39%, >50% stenosis (coronary, carotid, lower extremity arteries) 25.4%, HF NYHA class II-III ≥14%, CKD (eGFR <60 mL/min/1.73m2) ≥24.7%, microalbuminuria or proteinuria ≥11.3%, HTN+LVH ≥5.3%, LVH ≥4.2%, ABI <9.2 4.2%.
- **Medications**: 92.3% on antihypertensives (55.4% BB, 51% ACEI, 31.8% ARBs, 32% CCB [some patients were on multiple agents]), 72% on statins, 62.9% on ASA, 15.7% on other antiplatelet agent, 76.4% on metformin, 50.5% on SU, 6.2% on TZD, and 44.5% on insulin.

**RESULTS**

**Follow-up: 3.8 yrs (median)**

<table>
<thead>
<tr>
<th>TABLE 1: EFFICACY &amp; SAFETY – PRIMARY &amp; SECONDARY ENDPOINTS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLINICAL ENDPOINTS ITT ANALYSIS</strong></td>
</tr>
<tr>
<td><strong>PRIMARY ENDPOINT</strong></td>
</tr>
</tbody>
</table>
| First occurrence of death from cardiovascular causes, nonfatal MI or stroke | 13% (n=608) | 14.9% (n=694) | 0.87 (0.78-0.97) | 0.01 (superiority) | <0.001 (non-inferiority) | 1.9% | 53 | Composite endpoint primarily driven by CV in CV death (other components were NS).
| EXPANDED ENDPOINTS | | | | | | | |
| Death from CV causes | 4.7% (n=219) | 6.0% (n=278) | 0.78 (0.66-0.93) | 0.007 | 1.3% | 77 | Analysis at 36 months shows a mean difference of -0.40% in the liraglutide vs placebo group (95% CI, -0.45 to -0.34) for HbA1c.
| Death from any cause | 8.2% (n=381) | 9.6% (n=447) | 0.85 (0.74-0.97) | 0.02 | 1.4% | 72 | |
| Non-fatal MI | 6.0% (n=281) | 6.8% (n=317) | 0.88 (0.75-1.03) | 0.11 | 0.8% | - | |
| Non-fatal stroke | 3.4% (n=159) | 3.8% (n=177) | 0.89 (0.72-1.11) | 0.30 | 0.4% | - | |
| Hospitalization for HF | 4.7% (n=218) | 5.3% (n=248) | 0.87 (0.73-1.05) | 0.14 | 0.6% | - | |
| MICROVASCULAR ENDPOINTS | | | | | | | |
| Nephropathy | 5.7% (n=268) | 7.2% (n=337) | 0.78 (0.67-0.92) | 0.003 | 1.5% | 67 | Nephropathy = new onset of macroalbuminuria or doubling of SCr and eGFR <45mL/min/1.73m2 or need for continuous RRT. |
| Retinopathy | 2.3% (n=106) | 2.0% (n=92) | 1.15 (0.87-1.52) | =0.33 | 0.3% | - | |
### Table 2 – Adverse Events (AE)

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>LiRagLudite 1.8MG Subcut Daily</th>
<th>Placebo</th>
<th>P Value</th>
<th>ARR/AIR</th>
<th>NNT/NNH</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Gallstone Disease</td>
<td>3.1% (n=145)</td>
<td>1.9% (n=90)</td>
<td>&lt;0.001</td>
<td>1.2%</td>
<td>84</td>
<td>- Pancreatic neoplasms and pancreatitis are of particular interest for GLP1-A. Despite no definitive evidence at this time, other outcome trials have raised concerns (Schuppan). This study was not powered to evaluate these risks.</td>
</tr>
<tr>
<td>Any AE leading to discontinuation from trial</td>
<td>9.5% (n=444)</td>
<td>7.3% (n=339)</td>
<td>&lt;0.001</td>
<td>2.2%</td>
<td>46</td>
<td>- Placebo group, compared to the liRagLudite group, received more insulin (43.2% vs 28.6%, respectively) and SU (10% vs 7.6%, respectively), which may possibly explain ↑ hypoglycemia in placebo group.</td>
</tr>
<tr>
<td>Severe Hyperglycemia</td>
<td>2.4% (n=114)</td>
<td>3.3% (n=153)</td>
<td>0.02</td>
<td>0.9%</td>
<td>111</td>
<td>-</td>
</tr>
<tr>
<td>Severe Adverse Events</td>
<td>32.2% (n=1502)</td>
<td>32.8% (n=1533)</td>
<td>0.51</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Any Major Neutropenia</td>
<td>6.3% (n=296)</td>
<td>6.0% (n=279)</td>
<td>0.46</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Pancreatic Carcinoma</td>
<td>0.3% (n=13)</td>
<td>0.1% (n=5)</td>
<td>0.06</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6% (n=77)</td>
<td>0.4% (n=18)</td>
<td>&lt;0.001</td>
<td>1.2%</td>
<td>84</td>
<td>-</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.7% (n=31)</td>
<td>&lt;0.1% (n=2)</td>
<td>&lt;0.001</td>
<td>0.6%</td>
<td>166</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.6% (n=27)</td>
<td>0.1% (n=5)</td>
<td>&lt;0.001</td>
<td>0.5%</td>
<td>200</td>
<td>-</td>
</tr>
<tr>
<td>Increase Lipase Levels</td>
<td>0.3% (n=15)</td>
<td>0.2% (n=11)</td>
<td>0.43</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Acute Pancreatitis</td>
<td>0.4% (n=18)</td>
<td>0.5% (n=23)</td>
<td>0.44</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.9% (n=44)</td>
<td>0.7% (n=33)</td>
<td>0.21</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Strengths, Limitations, & Uncertainties

**Strengths:**
- Largest sample size of GLP1-A CV outcome studies and longest duration of all published CV outcome studies to date.
- Well-designed RCT (properly randomized [allocation concealment, balanced baseline demographics]; registered; appropriately powered; all CV outcomes were pre-specified & clinically relevant; blinded, external adjudication of all outcomes, ITT population used for superiority analysis). International, multicentre design helps to reveal potential environmental/geographical confounding factors.
- 97% of the liRagLudite group and 96.6% of the placebo group completed the study; 0.2% loss to follow up for both groups; and vital status not confirmed for <0.05% of all participants.
- Similar to the other GLP1-A CV outcome studies, ELIXA, SUSTAIN-6 hospitalization for HF was neutral.

**Limitations:**
- Funded in part by Novo Nordisk, manufacturer of Victoza. 4/15 steering committee members were employees of Novo Nordisk.
- Subjects who completed or discontinued the trial without having an outcome were censored after their last visit, and events occurring after that visit were not included, meaning key events could have been missed. Study period was only 3.5-5 yrs, so safety and efficacy data for long-term were not observed.
- No adjustments made for multiplicity of exploratory outcomes (risk of false-positive result [type 1 error]).

**Uncertainties:**
- Applicability of observed benefits and risks to groups with lower CV risk.
- Subgroup analysis for geographical region shows no benefit (HR 1.01, 95% CI 0.84-1.22) for North American patients (n=2847) in terms the primary composite outcome.
- Effect of liRagLudite on microvascular outcomes (e.g., retinopathy, neuropathy, nephropathy) as these may take 5-10+ years to develop and median trial follow-up was 3.8 years.
- Unclear why this trial demonstrated positive CV outcome results when many previous outcome trials achieved only neutral results? A neutral effect was also demonstrated in a post hoc analysis of 15 phase 2 and 3 studies of liRagLudite versus control which included approximately 4,000 patients and 39 adjudicated major adverse CV events (incidence ratio 0.73, 95% CI 0.38-1.41). However, the time to benefit occurred quicker in EMRA-REG than LEADER, resulting in the authors speculating that empagliflozin's benefits may be related to hemodynamic changes rather than modifying the progression of atherosclerotic disease.
- EMRA-REG examined liXisenatide, which like liRagLudite, is a GLP1-A, though structurally dissimilar. However, in patients with T2DM and recent acute coronary syndrome, adding liXisenatide to current therapy did not show a definitive CV benefit.
- SUSTAIN-6 evaluated Semaglutide, which like liRagLudite, is a GLP1-A. Semaglutide significantly decreased primary composite endpoint (CV death, nonfatal stroke and MI) in patients with T2DM and high cardiovascular risk (ARR 2.3%); however, in contrast to liRagLudite, the result was driven by a reduction in nonfatal stroke (1.6% vs 2.7%; HR 0.61; 95% CI 0.38-0.99). Hospitalization for HF and all-cause mortality were neutral.
- TECOS examined sitagliptin, a DPP-4i, and its effects on CV outcomes. Like ELIXA, in patients with T2DM and established cardiovascular disease, adding sitagliptin to current therapy did not show a definitive CV benefit.

Unclear where liRagLudite will fit in terms of T2DM management, but remember...
- For vascular protection, CDA 2013 (updated 2016) recommends: lifestyle (nutrition, exercise, smoking cessation); optimal HbA1c control (usually ≤ 7%), BP control (<130/80 mmHg), and cholesterol control (LDL ≤ 2 mmol/L); and lastly CV protective drugs (i.e., ACEI/ARB, statin, ASA [if indicated]).
References:

Prepared By: Rebecca Stan BSP’17, Arbind Gill BSP’17, Caitlin Coons BSP’18. Additional input and review by Loren Regier, Brent Jensen, Lynette Kozar, Brenda Schuster, Marilyn LeBras.

DISCLAIMER: The content of this newsletter represents the research, experience and opinions of the authors and not those of the Board or Management of Saskatoon Health Region (SHR). Neither the authors nor Saskatoon Health Region nor any other party who has been involved in the preparation or publication of this work warrants or represents that the information contained herein is accurate or complete, and they are not responsible for any errors or omissions or for the result obtained from the use of such information. Any use of the newsletter will imply acknowledgment of this disclaimer and release any responsibility of SHR, its employees, servants or agents. Readers are encouraged to confirm the information contained herein with other sources. Additional information and references online at www.RxFiles.ca Copyright 2016 – RxFiles, Saskatoon Health Region (SHR)