# LEADER: Liraglutide VICTOZA CV Outcomes Trial Summary[1]

## Liraglutide: Cardiovascular (CV) Outcomes and Mortality in Patients with in 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↓1.2 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.[ELIXA] Liraglutide is rather new; too early to be certain of long term effects (e.g., pancreatic and thyroid carcinoma).**
- **Cost may be prohibitive to some patients (~$690 ✗⊗ for 100days and currently not covered on SK or NIHB formularies).**

## BACKGROUND

- Liraglutide (VICTOZA ✗⊗ ~$750/100days) 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[1,4-6]

**DESIGN**: Randomized, double-blind, placebo-controlled, international (32 countries) multi-centre (410 sites) trial with a 2 week run-in phase. Non-inferiority analysis for primary efficacy outcome followed by superiority analysis (ITT population). Funding: Novo Nordisk (VICTOZA manufactuer) & National Institutes of Health. Enrollment/Follow-up period: 2010- 2015.

**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 (HgA1c ≤ 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 of <0.9).

**EXCLUSION:** T1DM; use of: GLP1-A, DPP4-I, pramlinitide, 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, HgA1c 8.7%±1.6, BMI 32.5±6.3 kg/m$^2$, 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/1.73m$^2$) ~24.7%, microalbuminuria or proteinuria ~11.3%, HTN+LVH ~5.3%, LVH ~4.2%, ABI <0.9 2.4%.

**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 1: EFFICACY & SAFETY - PRIMARY & SECONDARY ENDPOINTS**

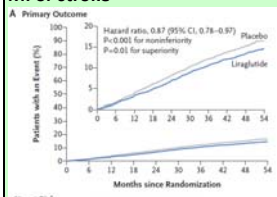
| CLINICAL ENDPOINTS ITT ANALYSIS | LIRAGLUTIDE 1.8MG SUBCUT DAILY n=4668 | PLACEBO n=4672 | HR 95% CI | P VALUE | ARR/ARI | NNT/NNH /3.8YRS | COMMENTS |
|---|---|---|---|---|---|---|---|
| **PRIMARY ENDPOINT** | | | | | | | |
| **First occurrence of death from cardiovascular causes, nonfatal MI or stroke**   | 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 ↓ 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/1.73m$^2$ 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)**

| CLINICAL ENDPOINTS | | LIRAGLUTIDE 1.8MG SUBCUT DAILY n=4666 | PLACEBO n=4672 | P VALUE | ARR/ARI | NNT/NNH /3.8YRS | COMMENTS |
|---|---|---|---|---|---|---|---|
| SAE | ACUTE GALLSTONE DISEASE | 3.1% (n=145) | 1.9% (n=90) | <0.001 | 1.2% | 84 | -**Pancreatic neoplasms** and **pancreatitis** are of particular interest for GLP1-A. Despite no definitive evidence at this time, other outcome trials have raised concerns (Sitagliptin).[3] This study was not powered to evaluate these risks.<br><br>-**Placebo group, compared to the liraglutide group, received more insulin** (43.2% vs 28.6%, respectively) **and SU** (10.8% vs 7.6%, respectively), which may possibly explain ↑ hypoglycemia in placebo group. |
| | ANY AE LEADING TO DISCONTINUATION FROM TRIAL | 9.5% (n =444) | 7.3% (n=339) | <0.001 | 2.2% | 46 | |
| | SEVERE HYPOGLYCEMIA | 2.4% (n=114) | 3.3% (n=153) | 0.02 | 0.9% | 111 | |
| | SEVERE ADVERSE EVENTS | 32.2% (n=1502) | 32.8% (n=1533) | 0.51 | - | - | |
| | ANY MALIGNANT NEOPLASM | 6.3% (n=296) | 6.0% (n=279) | 0.46 | - | - | |
| | PANCREATIC CARCINOMA | 0.3% (n =13) | 0.1% (n =5) | 0.06 | - | - | |
| OTHER AE | NAUSEA | 1.6% (n=77) | 0.4% (n=18) | <0.001 | 1.2% | 84 | |
| | VOMITING | 0.7% (n =31) | <0.1% (n=2) | <0.001 | 0.6% | 166 | |
| | DIARRHEA | 0.6% (n=27) | 0.1% (n=5) | <0.001 | 0.5% | 200 | |
| | INCREASE LIPASE LEVELS | 0.3% (n=15) | 0.2% (n=11) | 0.43 | - | - | |
| | ACUTE PANCREATITIS | 0.4% (n=18) | 0.5% (n=23) | 0.44 | - | - | |
| | HYPOTHYROIDISM | 0.9% (n=44) | 0.7% (n=33) | 0.21 | - | - | |

## 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 liraglutide 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 study,[7] **ELIXA** 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]).

**UNCERTAINITIES:**

- 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 liraglutide 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 liraglutide 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).[8]
- Mechanism behind ↓ CV death and ↓ all cause death not clear, considering liraglutide does not cause a statistically significant change in rates of nonfatal MI or stroke.
  - Similar to other positive CV outcome study,[9] **EMPA-REG** results of primary composite endpoint were primarily driven by a reduction in CV death, as other components were not significantly different.

## HOW DOES THIS TRIAL COMPARE TO PREVIOUS OUTCOME TRIAL(S)?

-**EMPA-REG**[9] examined empagliflozin, a SGLT-2 inhibitor, which significantly decreased primary composite endpoint (CV death, nonfatal stroke and MI) in patients with T2DM and high cardiovascular risk (ARR 1.6%). Hospitalization for HF and all-cause mortality were also significantly decreased. However, the time to benefit occurred quicker in EMPA-REG than LEADER, resulting in the authors speculating that empaglifozin's benefits may be related to hemodynamic changes rather than modifying the progression of atherosclerotic disease.
-**ELIXA**[7] evaluated lixisenatide,[Europe only] which like liraglutide, 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.
-**TECOS**[10] examined sitagliptin, a DPP4-I, 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.
**- Trials recently completed for GLP1-A: SUSTAIN6**[(semaglutide); results not published] and **ongoing: EXSCEL**[(exenatide)](2018), **REWIND**[(dulaglutide)](2018), **HARMONY**[(albiglutide)](2019)

**Unclear where liraglutide 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]).[11]

**RxFILES RELATED LINKS**

- **RxFiles Diabetes Agents Outcomes Table:** http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcomes-Comparison-Summary-Table.pdf
- **RxFiles Diabetes – Landmark Trials and Links**: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf
- **RxFiles Diabetes – ELIXA Trial Summary** http://www.rxfiles.ca/rxfiles/uploads/documents/Lixisenatide-ELIXA%20Trial%20Summary.pdf
- **RxFiles Diabetes – TECOS Trial Summary** http://www.rxfiles.ca/rxfiles/uploads/documents/TECOS-Trial-Summary.pdf
- **RxFiles Diabetes – EMPA-REG Trial Summary** http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf

***X*** =non-formulary in SK ⊗=not covered by NIHB (Non-Insured Health Benefits) ♂=male **ABI**=ankle-brachial index **AE**=adverse event **BMI=** body mass index **BP=**blood pressure **CAD=**coronary artery disease **CKD =**chronic kidney disease **CV**= cardiovascular **CVD**=cardiovascular disease **DBP=**diastolic blood **DPP4-I** =dipeptidyl peptidase-4 inhibitor **eGFR**= estimated glomerular filtration rate **FDA**= Food and Drug Administration **GLP1-A**=glucagon-like peptide-1 agonist **HbA1c**= hemoglobin A1c **HF=**heart failure **HTN**=hypertension **LV**= left ventricular **LVH**=left ventricular hypertrophy **MI**=myocardial infarction **NYHA**= New York Heart Association **NS=**Non-significant **PVD**=peripheral vascular disease **RCT**= randomized controlled trial **RRT**=renal replacement therapy **SAE**=severe adverse event **SBP=**systolic blood pressure **SCr=**Serum creatinine level **SGLT-2**=sodium glucose co-transporter-2 **SU**=sulfonylurea **subcut**= subcutaneous **T1DM**=type 1 diabetes mellitus **T2DM**=type 2 diabetes mellitus **TIA**=transient ischemic attack **TZD**=thiazolidinediones

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