GLP-1 receptor agonists: The cardiovascular benefits beyond glucose control

Filip K. Knop, MD PhD
Professor of endocrinology, Consultant endocrinologist
University of Copenhagen
Copenhagen, Denmark
**Faculty Disclosure**

**Declaration of financial interests**

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<tr>
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<th>I have received a research grant(s)/ in kind support</th>
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<td>A</td>
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<td>B</td>
<td>Not related to presentation</td>
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Introduction to GLP-1

Role in physiology and type 2 diabetes pathophysiology
Glucose-dependent pancreatic effects (implications for risk of hypo)
Effects beyond glycaemic control
Practical considerations
Plasma glucose during 25 g oral glucose in healthy subjects

- Small-intestinal glucose absorption → plasma glucose rises
- Elevated plasma glucose → insulin secretion
- Insulin facilitates glucose uptake → plasma glucose drops

Adapted from: Nauck et al. J Clin Endocrinol Metab 1986;63:492–498
Plasma glucose during 25 g oral glucose,

Adapted from: Nauck et al. J Clin Endocrinol Metab 1986;63:492–498
Plasma glucose during 25 g oral glucose, 50 g glucose and 100 g glucose

Adapted from: Nauck et al. J Clin Endocrinol Metab 1986;63:492–498
Plasma glucose during 25 g oral glucose, 50 g glucose and 100 g glucose

“Elevated plasma glucose → insulin secretion”

(2) Not completely true!

Adapted from: Nauck et al. J Clin Endocrinol Metab 1986;63:492–498
The incretin hormones
Glucose-dependent insulinotrophic polypeptide (GIP)
Glucagon-like peptide-1 (GLP-1)

GLP-1 receptors in pancreatic islets

GLP-1 receptor expression in the human pancreas
OGTT and IIGI in 10 healthy subjects – exposing the incretin effect

\[
\text{Incretin effect (\%)} = \frac{\int \beta \text{SR}_{\text{OGTT}} - \int \beta \text{SR}_{\text{IIGI}}}{\int \beta \text{SR}_{\text{OGTT}}} \times 100\%
\]

GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; OGTT, oral glucose tolerance test; IIGI, isoglycaemic intravenous glucose infusion; \(\int \beta \text{SR}\), beta-cell secretory response
Healthy subjects are able to increase their incretin effect in response to increasing oral glucose loads…thereby preventing exaggerated glucose excursions.

Adapted from: Nauck et al. J Clin Endocrinol Metab 1986;63:492–498
OGTT and IIGI in 10 patients with T2DM and 10 healthy controls

CTRL, healthy controls; OGTT, oral glucose tolerance test; IIGI, isoglycaemic intravenous glucose infusion; T2DM, type 2 diabetes mellitus

Alpha- and beta-cell effects of GLP-1 are glucose dependent – also in patients with type 2 diabetes

Effects on insulin and glucagon cease alongside the occurrence of normoglycaemia

GLP-1, glucagon-like peptide 1; T2DM, type 2 diabetes mellitus
## Liraglutide: Hypoglycaemia reported in LEADER

<table>
<thead>
<tr>
<th>Hypoglycaemia Type</th>
<th>Rate ratio (95% CI)</th>
<th>p-value</th>
<th>Liraglutide N</th>
<th>Liraglutide %</th>
<th>Placebo N</th>
<th>Placebo %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed hypoglycaemia</td>
<td>0.80 (0.74; 0.88)</td>
<td>&lt;0.001</td>
<td>2039</td>
<td>43.7</td>
<td>2130</td>
<td>45.6</td>
</tr>
<tr>
<td>Severe hypoglycaemia</td>
<td>0.69 (0.51; 0.93)</td>
<td>0.016</td>
<td>114</td>
<td>2.4</td>
<td>153</td>
<td>3.3</td>
</tr>
</tbody>
</table>

Confirmed hypoglycaemia was defined as plasma glucose level of less than 56 mg per decilitre (3.1 mmol per litre) or a severe event. Severe hypoglycaemia was defined as hypoglycaemia for which the patient required assistance from a third party. Analysed using a negative binomial regression model.

%: percentage of group; CI: confidence interval; N: number of patients

Effect of iv GLP-1 infusion in type 2 diabetes

GLP-1, glucagon-like peptide 1; iv, intravenous; T2DM, type 2 diabetes mellitus
GLP-1: Beyond glucose metabolism

Liver
- Glycogen storage

Brain
- Neuroprotection
- Neurogenesis
- Memory

Heart
- Myocardial contractility
- Heart rate
- Myocardial glucose uptake
- Ischaemia-induced myocardial damage

Kidney
- Natriuresis

GI tract
- Motility

Fat cells
- Glucose uptake
- Lipolysis

Blood vessel
- Endothelium-dependent vasodilation

Pancreas
- New β-cell formation
- β-cell apoptosis
- Insulin biosynthesis

Skeletal muscle
- Glucose uptake

DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1
Adapted from Meier JJ et al. Nat Rev Endocrinol 2012;8:728–742
In the rodent and monkey brain, GLP-1R is abundantly expressed in many regions.

ARH, arcuate nucleus; AP, area postrema; LS, septal nucleus; ME, median eminence; NTS, nucleus tractus solitarius

Targeting of discrete regions in the mouse brain following peripheral administration of acylated GLP-1R agonists

Peripheral (s.c.) once-daily injection of *liraglutide* to mice for 4 days

GLP-1R, glucagon-like peptide-1 receptor; s.c., subcutaneous
GLP-1: Beyond glucose metabolism

- **Brain**
  - Neuroprotection
  - Neurogenesis
  - Memory

- **Heart**
  - Myocardial contractility
  - Heart rate
  - Myocardial glucose uptake
  - Ischaemia-induced myocardial damage

- **Kidney**
  - Natriuresis

- **Liver**
  - Glycogen storage

- **GI tract**
  - Motility

- **Fat cells**
  - Glucose uptake
  - Lipolysis

- **Kidney**
  - Natriuresis

- **Blood vessel**
  - Endothelium-dependent vasodilation

- **Skeletal muscle**
  - Glucose uptake

DPP-4, dipeptidyl peptidase-4; GI, gastrointestinal; GLP-1, glucagon-like peptide-1
Adapted from Meier JJ et al. Nat Rev Endocrinol 2012;8:728–742
Liraglutide inhibits progression of early, low-burden atherosclerotic lesion development in mice

*\( p < 0.05 \) vs vehicle by one-way ANOVA; data are mean ± SEM; performed in ApoE\(^{-/-}\) mice with early, low-burden atherosclerotic lesions

ApoE\(^{-/-}\), apolipoprotein E knockout; ANOVA, analysis of variance; Ex-9, exendin-9; IMR, intima:media ratio; Lira, liraglutide; SEM, standard error of the mean

Semaglutide significantly attenuates aortic plaque lesions in LDLr⁻/⁻ mice in a dose-independent manner.

* *p<0.05; **p<0.001, vs vehicle.

Rakipovski G et al. Abstract submitted for the American Diabetes Association 77th Scientific Sessions; Jun 9–13, 2017; San Diego, USA
Liraglutide reduces atherosclerotic lesion formation via modulation of macrophage cell fate in ApoE⁻/⁻ mice

- Analysis of macrophages for МΦ1 (pro-atherogenic) and МΦ2 (pro-resolving) macrophage markers, showed that liraglutide modulates macrophage cell fate towards МΦ2 pro-resolving macrophages
- This coincided with decreased atherosclerotic lesion formation

Completed and ongoing CVOTs with GLP-1RAs

- **ELIXA** (Lixisenatide vs Pbo)
  - n=6,000; duration 2.1 yrs
  - Q1 2015 – RESULTS

- **LEADER** (Liraglutide vs Pbo)
  - n=9,340; duration 3.8 yrs
  - Q4 2015 – RESULTS

- **FREEDOM-CVO** (ITCA 650 Exenatide vs Pbo)
  - n=4,000; duration ~2 yrs
  - Q2 2016 – TOPLINE

- **SUSTAIN 6** (Semaglutide vs Pbo)
  - n=3,297; duration ~2.8 yrs
  - Q1 2016 – RESULTS

- **EXSCEL** (Exenatide QW vs Pbo)
  - n=14,000; duration ~7.5 yrs
  - Q2 2017 – RESULTS

- **PIONEER 6** (Oral semaglutide OD vs Pbo)
  - n=3,176; duration ~2 yrs
  - completion Q3 2018

- **REWIND** (Dulaglutide QW vs Pbo)
  - n=9,622; duration ~6.5 yrs
  - completion Q3 2018

- **HARMONY OUTCOME** (Albiglutide QW vs Pbo)
  - n~5,000; duration ~4 yrs
  - completion Q2 2019

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CVOT, cardiovascular outcome trial; Exe, exenatide GLP-1RA; glucagon-like peptide-1 receptor agonist; OD, once daily; Pbo, placebo; QW, once weekly; yrs, years.
CV outcomes with GLP-1 RA

**ELIXA\(^1\)**
Lixisenatide vs Pbo

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
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<tbody>
<tr>
<td>Primary composite MACE</td>
<td>0.87 (0.78–0.97)</td>
</tr>
<tr>
<td>CV death</td>
<td>0.78 (0.66–0.93)</td>
</tr>
<tr>
<td>Nonfatal MI</td>
<td></td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>0.85 (0.74–0.97)</td>
</tr>
<tr>
<td>Hosp. for HF</td>
<td></td>
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**LEADER\(^2\)**
Liraglutide vs Pbo

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.74 (0.58–0.95)</td>
</tr>
</tbody>
</table>

**SUSTAIN 6\(^3\)**
Semaglutide vs Pbo

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.61 (0.38–0.99)</td>
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</table>

**EXSCEL\(^4\)**
Exenatide OW vs Pbo

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>0.86 (0.77–0.97)</td>
</tr>
</tbody>
</table>

**FREEDOM-CVO (ITCA 650 vs Pbo)**

<table>
<thead>
<tr>
<th>Event</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>upper bound 95% CI (1.0–1.8) non-inferior</td>
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When you prescribe a GLP-1RA in your high-risk type 2 diabetes patients, remember to / that…

• Use a GLP-1RA with proven CVD benefits (liraglutide / semaglutide / exenatide)
• GLP-1 lowers blood glucose via pleiotropic mechanisms including strictly glucose-dependent effects on pancreatic glucagon and insulin secretion (no hypo risk!)
• GLP-1 acts in the brain lowering appetite and food intake (body weight loss!)
• GLP-1RAs reduce systolic blood pressure (most likely via a natriuretic effect in the kidneys) – and increase heart rate by 2-6 bpm (most likely via GLP-1Rs in the sinoatrial node)
• Most frequent are mild to moderate gastrointestinal side effects (e.g. nausea, vomiting) which typically cease after 1-3 months of treatment
• Most GLP-1RAs can be used in patients with chronic kidney disease (eGFR down to 30)
• GLP-1RA treatment has few interactions and can be combined with other glucose-lowering drugs (e.g. SGLT2is)
• Few contraindications: Type 1 diabetes, ketoacidosis, (CHF NYHA class IV)