Cardiac mechanisms of GLP-1 receptor agonists

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Faculty Disclosure
Declaration of financial interests
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Disclosures

Professor Filip K. Knop, MD PhD, of Gentofte Hospital, University of Copenhagen, Denmark has served on scientific advisory panels and/or been part of speaker’s bureaus for, served as a consultant to and/or received research support from:

• Amgen
• AstraZeneca
• Boehringer Ingelheim
• Carmot Therapeutics
• Eli Lilly
• Gubra
• MedImmune

• MSD/Merck
• Munidpharma
• Norgine
• Novo Nordisk
• Sanofi
• Zealand Pharma
Contemporary CVOTs in diabetes and obesity

Trials with filled boxes are completed. Trials with a white background are ongoing.

AGI, alpha-glucosidase inhibitor; CVOT, cardiovascular outcomes trial; DPP-4i, dipeptidyl peptidase-4 inhibitor; ER, extended release; GLP-1RA, glucagon-like peptide-1 receptor agonist; ITCA 650, continuous subcutaneous delivery of exenatide; PPAR-αγ, peroxisome proliferator-activated receptors-α and γ; OW, once weekly; SGLT-2i, sodium–glucose co-transporter 2 inhibitor; SU, sulphonylurea; TZD, thiazolidinedione.

ClinicalTrials.gov.

*Estimated enrolment; †Stopped early after a median follow-up of 57.4 months following futility analysis.

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ClinicalTrials.gov.
Recent CVOTs with antidiabetic agents

Primary composite endpoint: MACE

*MACE+


* MACE+
Introduction to the incretin hormone GLP-1
The incretin hormones

Glucose-dependent insulinotropic polypeptide (GIP)

Glucagon-like peptide-1 (GLP-1)

Potential modes of action for GLP-1 receptor activation to impact CV and/or renal disease.

GLP-1 receptors are widely distributed in the human body.
Mechanism for CV/CKD risk reduction is likely to be multifactorial\textsuperscript{1–3}

- Glycaemia
- Body weight
- Blood pressure
- Blood lipids

CV, cardiovascular; CKD, chronic kidney disease

GLP-1R expression

GLP-1R identified in 50+ regions

GLP-1R, glucagon-like peptide-1 receptor
Jensen et al. Endocrinology 2018;159:665–75
Significant difference between treatments analysed in individual brain regions using a false discovery rate value of 5% to correct for multiple comparisons.

AP, area postrema; ARH, arcuate hypothalamic nucleus; DMH, dorsomedial nucleus of the hypothalamus; GLP-1R, glucagon-like peptide-1 receptor; i.v., intravenous; ME, median eminence; OV, vascular organ of the lamina terminalis; NTS, nucleus of the solitary tract; PVH, paraventricular hypothalamic nucleus; PVp, periventricular hypothalamic nucleus, posterior part; SF, septofimbrial nucleus; SFO, subfornical organ; SO, supraoptic nucleus; TU, tuberal nucleus; VT750, VivoTag-S750 radiolabelled

Salinas et al. Sci Rep 2018:8:10310

i.v. injection of 0.1 mg/kg liraglutide\textsuperscript{VT750} in mice, n=6

Many untargeted GLP-1Rs

GLP-1R targeting in cerebral nuclei, hypothalamus and hindbrain

*Significant difference between treatments analysed in individual brain regions using a false discovery rate value of 5% to correct for multiple comparisons.
Significant difference between treatments analysed in individual brain regions using a false discovery rate value of 20% to correct for multiple comparisons

AP, area postrema; ARH, arcuate hypothalamic nucleus; BLA, basolateral amygdalar nucleus; BST, bed nuclei of the stria terminals; CeA, central amygdalar nucleus; LC, locus ceruleus; MTN, midline group of the dorsal thalamus; NTS, nucleus of the solitary tract; PB, parabrachial nucleus; PSTN, parasubthalamic nucleus

Salinas et al. Sci Rep 2018; 8: 10310

Potential direct activation in:
- ARH (hypothalamus)
- AP and NTS (medulla)

Secondary activation in regions associated with control of food intake

*Significant difference between treatments analysed in individual brain regions using a false discovery rate value of 20% to correct for multiple comparisons

s.c. injection of 0.4 mg/kg liraglutide in mice, n=6
Change in body weight (%)  
Baseline to week 52: J2R-MI data (phase 2)

All randomised, effectiveness estimand. Graph is estimated mean data ± min/max
J2R-MI, jump-to-reference – multiple imputation; s.c., subcutaneous

Semaglutide is not indicated for the treatment of overweight / obesity
Mechanism for CV risk reduction is likely to be multifactorial\(^1\)–\(^3\)

- Glycaemia
- Body weight
- Blood pressure
- Blood lipids

CV, cardiovascular
Renal mode of action of GLP-1 therapy

GLP-1R expression in cells of the juxtaglomerular apparatus and in the wall of afferent arterioles in kidney (non-human primate)

-> vasodilatation of afferent arteriole

GLP-1 suppresses the activity of the sodium-hydrogen exchanger NHE3 – contributing to natriuresis

GLP-1, glucagon-like peptide 1; GLP-1R, glucagon-like peptide 1 receptor
Renal mode of action of GLP-1 therapy - natriuresis

3-hour **GLP-1 infusion** (1.5 pmol/kg/min) increased natriuresis in lean, healthy males during ECFV expansion with isotonic NaCl (750 ml/h)

...without affecting renal haemodynamics (as assessed by $^{51}$Cr-EDTA clearance; catheterization of the renal vein and the radial artery)

GLP-1, glucagon-like peptide 1
Asmar A et al. JCEM. 2019 Jul 1;104(7):2509-2519.
Renal mode of action of GLP-1 therapy - natriuresis

GLP-1 infusion had no effect on circulating levels of natriuretic peptides (proANP, ANP and BNP)

…renin or aldosterone

but suppressed circulating ANG II levels
GLP-1RA reduce systolic blood pressure by ~4 mmHg

*Only significant p-values are included. All legend colours depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose)

To aid comparisons in this review, only the highest doses of the GLP-1RA in any given dosing schedule in this trial were included. Results from distinct trials

BID, twice daily; GLP-1RA, glucagon-like peptide-1 receptor agonist; NR, not reported; O2W, every second week; OD, once daily; OW, once weekly; SBP, systolic blood pressure

Dalsgaard et al. Diabetes Obes Metab 2018;20:508–19

Albiglutide was withdrawn from the worldwide market in July 2018
Mechanism for CV risk reduction is likely to be multifactorial\textsuperscript{1–3}

\begin{itemize}
\item Glycaemia
\item Body weight
\item Blood pressure
\item Blood lipids
\end{itemize}

CV, cardiovascular

GLP-1RAs reduce lipids (total cholesterol, fasted)

Only significant p-values are included. Results from distinct trials. All legend colors depict the final dose in the treatment groups (some trials included up-titration to reach this maximum dose).

*To aid comparisons in this review, only the highest doses of the GLP-1RA in any given dosing schedule in this trial were included.†Cholesterol was reported in mg/dL in the publication and so was converted to mmol/L for this figure (conversion factor: 0.0259).

Durations: 1, 5, 6

*Dalsgaard et al. Diabetes Obes Metab 2018;20:508–519

†Miyagawa et al.*

Baseline total cholesterol (mmol/L)

0.0

0.3

0.6

0.9

1.2

P<0.01

4.5 4.7

NR NR

4.7 5.1 4.6

NR NR NR

4.5 NR NR NR

4.6 4.8 5.1

5.3 5.2

Exenatide 2 mg OW

Exenatide 10 µg BID

Liraglutide 0.9 mg OD

Liraglutide 1.8 mg OD

Albiglutide 30 mg OW

Albiglutide 50 mg OW

Albiglutide 50 mg O2W

Dulaglutide 0.75 mg OW

Dulaglutide 1.5 mg OW

Albiglutide was withdrawn from the worldwide market in July 2018.
GLP-1RA (semaglutide) lowers postprandial lipid profiles
Obese individuals at fat-rich breakfast

Hjerpsted et al. Diabetes Obes Metab 2018;20(3):610-619
Mechanism for CV risk reduction is likely to be multifactorial¹⁻³

Other potential mechanisms:
Reduced atherosclerotic burden?

↓ Glycaemia
↓ Body weight
↓ Blood pressure
↓ Blood lipids

Semaglutide attenuated plaque lesion area, partly independent of body weight in LDLr−/− mice

ANOVA: p<0.05; *p<0.05; ***p<0.001
ANOVA, analysis of variance; LDLr−/−, low-density lipoprotein receptor knockout; WD, Western diet
Rakipovski et al. JACC Basic Transl Sci 2018;3:844–57; Rakipovski et al. Abstract 244-OR presented at the American Diabetes Association 77th Scientific Sessions; 9–13 June, 2017; San Diego, USA
Liraglutide reduces atherosclerotic lesion formation via modulation of macrophage cell fate in ApoE-/- mice

- Analysis of macrophages for MΦ1 (pro-atherogenic) and MΦ2 (pro-resolving) macrophage markers, showed that liraglutide modulates macrophage cell fate towards MΦ2 pro-resolving macrophages
- This coincided with decreased atherosclerotic lesion formation

Bruen et al. Cardiovasc Diabetol 2017;16:143
Potential cardiovascular and renal modes of action - summary

- The gut-derived incretin hormone GLP-1 has potent and glucose-dependent insulinotropic and glucagonostatic effects
  -> **GLP-1RA treatment improves glycaemic control without risk of hypoglycaemia**

- GLP-1Rs are found in several areas of the brain; especially in appetite-regulating centres
  -> **GLP-1RA treatment reduces body weight and is associated with GI side effects (e.g. nausea)**

- GLP-1 increases natriuresis (independently of net renal haemodynamics and circulating concentrations of renin, aldosterone and natriuretic peptides; perhaps via suppression of ANG II)
  -> **GLP-1RA treatment reduces systolic blood pressure and reduces risk of macroalbuminuria**

- GLP-1RA treatment is associated with small reductions in circulating lipids

- In mouse models of atherosclerosis, GLP-1RA treatment reduces atherosclerotic plaque development