Cardiovascular Pharmacology of Incretins

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Outline

• Introduction to glucagon like peptide-1 (GLP-1)

• GLP-1 receptor (GLP-1R) agonism & cardiovascular risk factors

• GLP-1 receptor (GLP-1R) agonism & cardiovascular outcomes during ischemic heart disease & heart failure

• DPP-4 inhibition & cardiovascular outcomes during ischemic heart disease

• Limitations
Glucagon Like Peptide-1 (GLP-1)

- GLP-1 is a 29 amino acid peptide secreted from the gut in response to nutrient ingestion and potentiates glucose-stimulated insulin secretion.

- Dipeptidyl-peptidase 4 (DPP-4) is the primary enzyme responsible for the metabolism/inactivation of GLP-1.

- GLP-1R agonists and DPP-4 inhibitors represent novel therapies for the treatment of type 2 diabetes, of which a number have recently been FDA approved (exenatide, liraglutide, sitagliptin).
Why Study the Role of Incretins & Cardiovascular Health

- New US FDA guidelines recommend that manufacturers developing novel therapies for T2DM provide evidence that the therapy will not increase the risk for cardiovascular mortality
  - the ideal anti-diabetic therapy should not only improve glycemia, but also improve cardiovascular outcomes
GLP-1 Receptor Agonists Improve Glucose Control Through Multiple Mechanisms

- **Pancreas**
  - ↑ β-cell Proliferation
  - ↓ β-cell Apoptosis
  - ↑ Insulin Secretion
  - ↓ Glucagon Secretion

- **Liver**
  - ↓ Hepatic Glucose Production

- **Intestine**
  - ↓ Gastric Emptying

- **Brain**
  - ↓ Appetite

**Adipose**
- ↓ Adiposity

**GLP-1**

*GLP-1 Receptor Agonists Improve Glucose Control Through Multiple Mechanisms* (Ussher JR and Drucker DJ. *Endocrine Reviews.* 2012.)
GLP-1R Agonism Improves Cardiovascular Risk Factors that may Indirectly Improve Cardiac Function

- GLP-1R agonists are associated with improved plasma lipid profiles
- GLP-1R agonists are associated with reductions in blood pressure
- GLP-1R agonists are associated with reductions in body weight
GLP-1 Receptor Agonist Treatment Improves Lipid Profiles

LEAD-6

Change from baseline (mmol/L)

BID, twice daily; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein; OD, once daily; TC, total cholesterol; TG, triglycerides


LEAD = Liraglutide Effect and Action in Diabetes
DPP-4 Inhibition Reduces Postprandial Total Serum Triglycerides after 4 Weeks of Treatment in Humans

Vildagliptin 100 mg daily*

Placebo**

TG=triglycerides

ITT population (intention-to-treat).


**Study LAF2217. Data on file, Novartis Pharmaceuticals, 2 December 2005, p.36.
GLP-1R Agonism Improves Cardiovascular Risk Factors that may Indirectly Improve Cardiac Function

- GLP-1R agonists are associated with improved plasma lipid profiles
- GLP-1R agonists are associated with reductions in blood pressure
- GLP-1R agonists are associated with reductions in body weight
GLP-1 Receptor Agonists Reduce Blood Pressure

Systolic Blood Pressure: Liraglutide vs. Exenatide  LEAD 6

GLP-1 Receptor Agonists Reduce Blood Pressure

LEAD Program: When Used to Treat T2D, Liraglutide Consistently Reduces SBP

GLP-1R Agonism Improves Cardiovascular Risk
Factors that may Indirectly Improve Cardiac Function

- GLP-1R agonists are associated with improved plasma lipid profiles
- GLP-1R agonists are associated with reductions in blood pressure
- GLP-1R agonists are associated with reductions in body weight
Exenatide and Liraglutide Produce Comparable Weight Loss after 26 weeks in Human Subjects with T2DM

Treatment difference in changes NS

Baseline 93.1 kg

Baseline 93.0 kg

Weight change (kg)

Mean (2SE)

Lead 6 Data on file (Study NN2211-1797)
Liraglutide Reduces Visceral Body Fat: CT Scan in Substudy

**LEAD-2**

**Visceral adipose tissue**

Mean change from baseline (cm$^2$)

- Liraglutide 1.2 mg/day + metformin (1.5–2 g)
- Liraglutide 1.8 mg/day + metformin (1.5–2 g)
- Placebo + metformin (1.5–2 g)
- Glimepiride 8 mg/day + metformin (1.5–2 g)

**Subcutaneous adipose tissue**

Mean change from baseline (cm$^2$)

- Liraglutide 1.2 mg/day + metformin (1.5–2 g)
- Liraglutide 1.8 mg/day + metformin (1.5–2 g)
- Placebo + metformin (1.5–2 g)
- Glimepiride 8 mg/day + metformin (1.5–2 g)

CT, computerized tomography
Data are mean ± SE; *$p<0.05$; **$p<0.01$; ***$p<0.001$ vs. glimepiride + metformin; n=160.

What are the Direct Actions of GLP-1 on the Heart?

GLP-1

Brain

Intestine

Stomach

Pancreas

Liver

Adipose tissue

Muscle

- Cardioprotection
- Cardiac function

- Glucose production
- Glucose uptake and storage

- Insulin sensitivity
- Insulin secretion
- Glucagon secretion
- Insulin biosynthesis
- β-cell proliferation
- β-cell apoptosis

- Neuroprotection
- Appetite
- Gastric emptying
The GLP-1 Receptor Is Expressed in Cardiomyocytes and Endothelial Cells in the Murine Heart


Figure 1. GLP-1R expression in mouse cardiac and vascular tissues. Staining of pancreatic islets by the polyclonal anti–GLP-1R antibody (A) was eliminated by preadsorption with a GLP-1R–specific peptide (B). Labeling of mesenteric arteries with anti–smooth muscle α-actin (red), anti–GLP-1R (green), and Hoechst nuclear stain (blue) revealed GLP-1R expression on medial SMCs (arrows in C). Hearts labeled with anti–sarcomeric α-actin (red), anti–GLP-1R (green), and Hoechst nuclear stain (blue) revealed GLP-1R expression on cardiomyocytes (F), endocardium (arrowheads in G), vascular endothelium, and SMCs (arrowheads and arrows, respectively, in H).
A 72 hr Infusion of GLP-1 Following Successful Angioplasty Improves Global LV Function & Regional Wall Motion Recovery in Humans

GLP-1 Protects Against AMI in the Rat Heart

- GLP-1 was infused (via the right jugular) throughout *in vivo* ischemia (35 min) and reperfusion (2 hr) in the rat.

Bose AK et al. Diabetes. 2005
GLP-1 Protects Against Reperfusion Injury in the Isolated Mouse Heart

- Treatment of the isolated mouse heart with GLP-1 improves the recovery of LV developed pressure following a 30 min global ischemic insult.

- Of interest, protection was still observed in GLP1 receptor knock out mice.
Exenatide Reduces Infarct Size in Pigs Following In Vivo Ischemia/Reperfusion Injury

- Pigs were subjected to 75 min occlusion of the left circumflex artery followed by 72 hrs of reperfusion (exenatide treatment 5 min prior to reperfusion)

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Infarct Size (% of AAR)

p = 0.031

Placebo  Exenatide
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Exenatide Reduces Infarct Size in Pigs Following In Vivo Ischemia/Reperfusion Injury

- The reduction in infarct size following exenatide treatment was associated with an improvement in LV function.

Albiglutide Reduces Infarct Size in Rats Following In Vivo Ischemia/Reperfusion Injury

- Rats were treated with albiglutide (subcutaneous injection) for 3 days prior to 30 min occlusion of the LAD coronary artery followed by 24 hrs of reperfusion.

Exenatide infusion 15 min prior to primary percutaneous intervention for a 6 hr duration improves the myocardial salvage index in patients with ST-segment myocardial infarction.

Table 2: Outcomes evaluated with cardiac magnetic resonance

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Exenatide</th>
<th>n</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall study population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage index</td>
<td>54</td>
<td>0.71 ± 0.13</td>
<td>51</td>
<td>0.62 ± 0.16</td>
<td>0.003</td>
</tr>
<tr>
<td>Infarct size (g)/area at risk (g)</td>
<td>54</td>
<td>0.30 ± 0.15</td>
<td>51</td>
<td>0.39 ± 0.15</td>
<td>0.003</td>
</tr>
<tr>
<td>Area at risk (g)</td>
<td>54</td>
<td>42 ± 21</td>
<td>51</td>
<td>39 ± 14</td>
<td>0.43</td>
</tr>
<tr>
<td>Final infarct size (g)</td>
<td>60</td>
<td>13 ± 9</td>
<td>57</td>
<td>17 ± 14</td>
<td>0.11</td>
</tr>
<tr>
<td>Final infarct size (%LV)</td>
<td>60</td>
<td>11 ± 7</td>
<td>57</td>
<td>12 ± 6</td>
<td>0.33</td>
</tr>
<tr>
<td>LVEF 3 months (%)</td>
<td>60</td>
<td>55 ± 9</td>
<td>57</td>
<td>55 ± 11</td>
<td>0.82</td>
</tr>
</tbody>
</table>

GLP-1 is not Universally Protective Against AMI & Reperfusion Injury

Pigs *in vivo* were subjected to 1 hr ischemia (left anterior descending coronary artery occlusion) followed by 2 hrs of reperfusion. GLP-1 infused throughout or only during reperfusion.

Pigs *in vivo* were subjected to 40 min ischemia (left anterior descending coronary artery occlusion) followed by 2.5 hrs of reperfusion.


Kristensen J *et al.* *BMC Cardiovascular Disorders*. 2009.
GLP-1 Infusion Improves Cardiac Function of the Failing Heart

- Heart failure was induced in dogs via 28 days of rapid pacing of the right ventricle, following which GLP-1 (1.5 pmol/kg/min) was infused for 48 hours and cardiac function monitored.
GLP-1 Infusion Enhances Survival and Improves Cardiac Function in the Spontaneously Hypertensive and Heart Failure Prone rat


Table 3. In Vivo Hemodynamic Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline Treatment</th>
<th>GLP-1 Treatment</th>
<th>P*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, months</td>
<td>9 months, n=10</td>
<td>12 months, n=11</td>
<td>0.826</td>
<td></td>
</tr>
<tr>
<td>Mean arterial pressure, mmHg</td>
<td>133±16</td>
<td>127±21</td>
<td>0.527</td>
<td>0.497</td>
</tr>
<tr>
<td>Heart rate, min⁻¹</td>
<td>376±28</td>
<td>401±27*</td>
<td>0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Stroke volume, mL</td>
<td>1.5±0.1</td>
<td>1.0±0.1*</td>
<td>0.295</td>
<td>0.001</td>
</tr>
<tr>
<td>Cardiac output, mL/min</td>
<td>564±38</td>
<td>402±43*</td>
<td>0.357</td>
<td>0.944</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>9.61±0.2</td>
<td>9.80±0.1</td>
<td>0.0004</td>
<td>0.582</td>
</tr>
<tr>
<td>LVESD, mm</td>
<td>1.73±0.23</td>
<td>2.94±0.18*</td>
<td>0.033</td>
<td>0.016</td>
</tr>
<tr>
<td>LV ejection, %</td>
<td>82±4</td>
<td>70±4</td>
<td>0.776</td>
<td>0.903</td>
</tr>
</tbody>
</table>
Liraglutide Improves Survival and Reduces Infarct Size in a Mouse Model of Myocardial Injury

Mice were treated twice daily with liraglutide (70 μg/kg BW) before permanent occlusion of the LAD coronary artery.

Effects are independent of weight loss.

Liraglutide Directly Increases Cyclic AMP and Enhances Survival in Murine Cardiomyocytes

GLP-1 Treatment Decreases Apoptosis in HL-1 Atrial Cardiac Myocytes
GLP-1 Infusion has Favourable Effects in Heart Failure Patients

12 patients with New York Heart Association Class III/IV heart failure were infused with GLP-1 for 5 weeks (2.5 pmol/kg/min) and compared to 9 patients on standard therapy.
What About DPP-4 Inhibition & Cardiovascular Outcomes

It remains to be determined whether the beneficial effects on cardiovascular function following DPP-4 inhibition are due to elevations in plasma GLP-1 levels.


Ussher JR and Drucker DJ. *Endocrine Reviews*. 2012

SDF-1α (1-68) → GLP-1 (7-36) → BNP (1-32) → SP(1-11) → NPY (1-36) → PYY (1-36) → GLP-2 (1-33) → GIP (1-42)

Progenitor Cell → Blood Vessel → Kidney → Heart → Brain → Adipose Tissue

B

BNP (3-32) → GLP-1 (9-36) → NPY (3-36) → PYY (3-36) → DPP-4

Ussher JR and Drucker DJ. *Endocrine Reviews*. 2012
DPP-4 Inhibition Enhances Granulocyte Colony Stimulating Factor-Induced Myocardial Regeneration in a SDF-1α Dependent Manner

Are there Potential Limitations with GLP-1 Based Therapy & Cardiovascular Outcomes?
Heart rate (67±/−2 bpm vs. 65 ±/− 2 bpm; p=0.016) and DBP (71±/−2 mmHg vs. 68 ±/− 2 mmHg; p=0.008) increased during GLP-1 treatment.

Am J Physiol Heart Circ Physiol. 2010. 298:H1096:

Cardiovascular and metabolic effects of 48-h glucagon-like peptide-1 infusion in compensated chronic patients with heart failure

Mads Halbirk,1,2 Helene Nørrelund,4 Niels Møller,2 Jens Juul Holst,5 Ole Schmitz,2 Roni Nielsen,1,2 Jens Erik Nielsen-Kudsk,1 Søren Steen Nielsen,3 Torsten Toftegaard Nielsen,1 Hans Eiskjær,1 Hans Erik Bøtker,1 and Henrik Wiggers1
GLP-1 Receptor Agonist Treatment is Associated With Increased Heart Rate in Some Studies:

Victoza (Liraglutide) Product Monograph:

Cardiovascular
Increase in Heart Rate: A 24 h time-averaged increase in mean heart rate of 7-8 bpm was reported with VICTOZA® treatment in a clinical trial in healthy volunteers undergoing serial ECG monitoring (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). In patients with diabetes, a 2-4 bpm increase in mean pulse rate was observed in long term clinical trials. Because of limited clinical experience in patients who have cardiac conditions that might be worsened by an increase in heart rate, such as ischemic heart disease and tachyarrhythmia, caution should be observed in these patients (see DRUG INTERACTIONS). The incidence of a composite endpoint for all tachyarrhythmia in pooled clinical trials in diabetic patients was higher for VICTOZA® than for placebo (see ADVERSE REACTIONS, Cardiovascular).
Survival Curves - Rate of All-Cause Mortality According to Time-Varying Persistence or Development of a Heart Rate ≥84 bpm During Follow-Up.

Exenatide-treated patients were less likely to have a CVD event.
### TABLE 2. GLP-1R agonist and DPP-4 inhibitor cardiovascular outcomes trials

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Dose</th>
<th>Primary outcome</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1R agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide</td>
<td>Exenatide Study of Cardiovascular Event Lowering Trial (EXSCEL): a trial to evaluate cardiovascular outcomes after treatment with exenatide once weekly in patients with T2DM</td>
<td>2.0 mg injected sc once weekly</td>
<td>Time to first confirmed cardiovascular event</td>
<td>~9,500</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long-Term Evaluation (LEADER)</td>
<td>Maximum dose 1.8 mg/d injected sc</td>
<td>Time from randomization to first occurrence of nonfatal MI, nonfatal stroke, or cardiovascular death</td>
<td>~8,750</td>
</tr>
<tr>
<td>Lixasenatide</td>
<td>Evaluation of Cardiovascular Outcomes in Patients with Type 2 Diabetes After Acute Coronary Syndrome During Treatment With AVE0010 (Lixisenatide) (ELIXA)</td>
<td>20 μg in 0.2 ml once a day injection 1 h before breakfast</td>
<td>Time to the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or cardiovascular death</td>
<td>~6,000</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Researching Cardiovascular Events with a Weekly Incretin in Diabetes (REWIND)</td>
<td>1.5 mg injected sc once weekly</td>
<td>Time from randomization to first occurrence of nonfatal MI, nonfatal stroke, or cardiovascular death</td>
<td>~9,600</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>Effect of Vildagliptin on Left Ventricular Function in Patients with Type 2 Diabetes and Congestive Heart Failure</td>
<td>50 mg twice daily</td>
<td>LV function as determined via changes in ejection fraction</td>
<td>~490</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Sitagliptin Cardiovascular Outcome Study (0431–082 AM1) (TECOS)</td>
<td>50 or 100 mg/d oral tablet</td>
<td>Time to first confirmed cardiovascular event (nonfatal MI, nonfatal stroke, or hospitalization for unstable angina)</td>
<td>~14,000</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>Cardiovascular Outcomes Study of Alogliptin in Subjects with Type 2 Diabetes and Acute Coronary Syndrome (EXAMINE)</td>
<td>6.25 or 12.5 or 25 mg/d oral tablet</td>
<td>Time from randomization to the first occurrence of a primary major adverse cardiac event (nonfatal MI, nonfatal stroke, or cardiovascular death)</td>
<td>~5,400</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>Does Saxagliptin Reduce the Risk of Cardiovascular Events When Used Alone or Added to Other Diabetes Medications (SAVOR-TIMI 53)</td>
<td>2.5 or 5 mg/d oral tablet</td>
<td>Time to first confirmed cardiovascular event (nonfatal MI, nonfatal ischemic stroke, or cardiovascular death)</td>
<td>~16,500</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>CAROLINA: Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes</td>
<td>5 mg/d oral tablet</td>
<td>Time to the first occurrence of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, or cardiovascular death</td>
<td>~6,000</td>
</tr>
</tbody>
</table>
SUMMARY

- GLP-1R agonists and DPP-4 inhibitors represent a new class of therapeutics for type 2 diabetes

- GLP-1R agonists improve cardiovascular risk factors in humans (reduced plasma lipids, BP, and body weight)

- GLP-1R agonists improve cardiovascular function in ischemic heart disease

- DPP-4 inhibitors also appear to have beneficial cardiovascular effects, whether these effects depend on increased GLP-1 remains to be determined

- Ongoing large-scale, multi-centre cardiovascular outcomes trials will play a key role in determining the role of GLP-1R agonists and DPP-4 inhibitors in the management of type 2 diabetes
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