DPP-4 inhibitors
Beyond Glycemic Control in Diabetes Treatment

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What is wrong with the pancreas?

Oh TJ et al, ICDM 2012
Insulin and glucagon responses during OGTTs

N = 14 for NGT, N = 16 for T2DM. All participants were Koreans.

Abstract No: OP3-1
Oh TJ et al, ICDM 2012
Mechanisms of Glycemic Lowering Action of the DPP-4i

- Increases glucose utilisation by muscle and adipose
- Decreases hepatic glucose release
- Improving overall glucose control

Adapted from Drucker DJ. Expert Opin Invest Drugs. 2003;12(1):87–100
What is there beyond glycemic control?
Figure 5. DPP-4 substrates that directly or indirectly regulate cardiovascular function. Multiple DPP-4 substrates have been identified that act on multiple peripheral tissues that influence the cardiovascular system. For a summary of these direct effects on target tissues, refer to Table 1. SP, Substance P.
GLP-1 receptors are primarily expressed in pancreatic beta cells.
GLP-1 receptors are also expressed in various extrapancreatic tissues

- Heart
- Lung
- Kidney
- CNS
- Enteric/pph nervous system
- GI tract
- Vascular endothelial cells
- Etc.

• GLP-1-Receptor; green
• Vascular/cardiac smooth muscle; red
• Nuclei: blue

Cho YM and Kieffer TJ. Pharmacol Ther 2012
Ban et al. Circulation 2008
What is there beyond glycemic control?

CV protection

Neuroprotection

Renoprotection

Extrapancreatic effects
What is there beyond glycemic control?

- CV protection
- Neuroprotection
- Renoprotection

Extrapancreatic effects
DPP-4 inhibition reduces infarct size and improves cardiac function after ischaemia/reperfusion injury in rodents.

**Ex vivo rat hearts**
(2 weeks treatment *in vivo*)

- Control
- Vilda
- Sita
- Vilda + ex9-39
- Sita + ex9-39

+/- exendin 9-39

**Isolated heart from normoglycaemic mice**
(acute pretreatment *in vivo*)

- Perfusion
- Ischaemia
- Reperfusion

LV developed pressure (mmHg)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Control</th>
<th>Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
<td>40</td>
</tr>
<tr>
<td>40</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>60</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>80</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>100</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>120</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*p<0.05

Sitagliptin improved functional recovery after ischemia/reperfusion injury ex vivo in normoglycemic mice.

Vilda = vildagliptin
Sita = sitagliptin
Exendin 9-39 = a GLP-1 receptor antagonist

Hausenloy et al, Heart (2010), abstract FC1

Sauvé et al; Diabetes 2010
Linagliptin or GLP-1 receptor activation reduces infarct size in an acute myocardial infarction model in rats

1. Hocher B et al., Int J Cardiol 2012 Jan 2 [Epub ahead of print]

**Treated with Linagliptin and its backup compound (BI 14361)**

- **Area at risk**
- **Infarct size**
- **Infarct size / Area at risk**

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>BI14361</th>
<th>Vehicle</th>
<th>Linagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>7 days</strong></td>
<td>0</td>
<td>1</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td><strong>8 weeks</strong></td>
<td>0</td>
<td>1</td>
<td>*</td>
<td>**</td>
</tr>
</tbody>
</table>

Data are means ± SD. n = 8–12 per group for the 7-day follow-up and n = 16–8 for the 8-week follow-up. *p < 0.05, **p < 0.001 vs respective vehicle group

**Treated with Exendin-4**

- **Control**
- **Exendin-4 (0.03 nM)**

Infarcted tissue (grey)  Surviving muscle (red)

Ischaemia/reperfusion protocol
Postconditioning protocol - exendin-4 given at end of ischaemic period
DPP-4 inhibition or GLP-1 receptor activation improves CV risk factors.

- Blood pressure
- Postprandial lipemia
- Endothelial function
Reduction in blood pressure with GLP-1 analogue

All subjects. ***p≤0.0001, **p≤0.001, *p<0.05 vs. comparator

### Vital sign change: GLP-1 analogue vs. DPP4 inhibitor

<table>
<thead>
<tr>
<th>Vital signs</th>
<th>Mean change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>100 mg sitagliptin (n=219)</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>−0.94 (−2.69 to 0.81)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>−1.78&lt;sup&gt;a&lt;/sup&gt; (−2.95 to −0.61)</td>
</tr>
<tr>
<td>Heart rate (beats per min)</td>
<td>−0.64&lt;sup&gt;a&lt;/sup&gt; (−1.79 to 0.52)</td>
</tr>
</tbody>
</table>

Pratley et al. Lancet 2010;375:1447–56

Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial.
DPP4 inhibitors improve postprandial lipid and lipoprotein metabolism

Sitagliptin reduced intima-media ratio in the carotid artery of OLETF rats with balloon injury in a dose-dependent manner.

DPP-4 Inhibition Does Not Seem to be Associated with Increased Risk for Major Cardiovascular Events

<table>
<thead>
<tr>
<th>DPP-4 inhibitor better</th>
<th>Comparator better</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linagliptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.15 0.34 0.74</td>
<td></td>
<td>5,239</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.41 0.68 1.12</td>
<td></td>
<td>10,246</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.62 0.84 1.14</td>
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<td>10,988</td>
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<tr>
<td>Saxagliptin</td>
<td></td>
<td></td>
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<tr>
<td>0.23 0.42 0.80</td>
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<td>4,607</td>
</tr>
<tr>
<td>Alogliptin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.21 0.63 1.19</td>
<td></td>
<td>3,489</td>
</tr>
</tbody>
</table>

Risk ratio for major CV events

2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial

Figure 2: Timecourse of adjusted $^*$ mean HbA$_1c$ values over 2 years in the completers cohort†

2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial

Figure 3: Relative risk of cardiovascular events, independently adjudicated by a clinical event committee in the treated set of patients

Summary – Cardiovascular Effects

- DPP-4 inhibition (and GLP-1 agonists) show benefits in some cardiovascular variables:
  - Improves myocardial survival in ischemic heart disease
  - Improves functional recovery after ischemia/reperfusion injury
  - Improves endothelial dysfunction (not shown here)
  - Improves lipids and blood pressure: small but significant benefits reported
  - Exhibits anti-atherosclerotic effects (rodent)
  - Exhibits weight loss (with GLP-1 analogues) or weight neutrality (with DPP-4i): secondary effect
What is there beyond glycemic control?

- CV protection
- Neuroprotection
- Renoprotection

Extrapancreatic effects
Gut derived GLP-1 may enter the brain via leaks in the blood brain barrier such as area postrema and subfornical organs.

* Sivertsen J et al. *Nature Reviews Cardiology* 9, 209-222
Potential Neuroprotective Effects of GLP-1 Receptor Agonists - Acute Stroke Model

Data from a mouse model of transient focal cerebral ischemia-reperfusion injury
10 µg exenatide administered IV at 0 h after reperfusion (mean ± SEM; n = 5)

Infarct volume

<table>
<thead>
<tr>
<th>Time after reperfusion</th>
<th>Vehicle</th>
<th>Exenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 h</td>
<td>30 ± 2</td>
<td>15 ± 2</td>
</tr>
<tr>
<td>72 h</td>
<td>40 ± 3</td>
<td>20 ± 3</td>
</tr>
<tr>
<td>7 d</td>
<td>45 ± 4</td>
<td>30 ± 4</td>
</tr>
</tbody>
</table>

* *p < 0.05; **p < 0.01 vs vehicle

Typical infarct area

Neurological deficit

<table>
<thead>
<tr>
<th>Time after reperfusion</th>
<th>Neurological deficit score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post</td>
<td>3.0</td>
</tr>
<tr>
<td>24 h</td>
<td>2.5</td>
</tr>
<tr>
<td>72 h</td>
<td>2.0</td>
</tr>
<tr>
<td>7 d</td>
<td>1.5</td>
</tr>
</tbody>
</table>

* *p < 0.05 vs vehicle

GLP-1 Receptor Agonists Have Neurotrophic Actions - *in vivo* Alzheimer’s Disease Model

- Liraglutide injected i.p. once daily for 8 weeks in 7-month-old mice (Alzheimer’s model; APPswe/PS1E9)
- Liraglutide improved histological hallmarks of Alzheimer’s Disease

Effects of long-term inhibition of DPP-4 in Alzheimer-prone mice

Freezing time after an electric shock

Brain GLP-1 level

D'Amico M et al. Experimental Gerontology 2010
Summary: Neuroprotective effect

- An increasing amount of evidence points toward a neuroprotective and neurotrophic effect of GLP-1.
- Several studies have shown a positive effect of GLP-1 agonist treatment on cognitive function, memory and learning.
- These findings lead to a growing interest in exploring possible roles of DPP4 inhibitors (or GLP-1) treatment in a number of neurodegenerative diseases.
What is there beyond glycemic control?

- CV protection
- Neuroprotection
- Renoprotection

Extrapancreatic effects
The GLP-1 Receptor is Present in the Kidney and decreases albuminuria in diabetic mice.

Immunostaining

Effect of a GLP-1R agonist on albuminuria

Western blot

Mima A,...., King GL. Diabetes 61:2967–2979, 2012
DPP-4 enzymatic activity is very high in the kidney.

<table>
<thead>
<tr>
<th>Tissue</th>
<th>DPP4 activity (nmol min$^{-1}$ g tissue$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kidney</td>
<td>1460.8 ± 54.9</td>
</tr>
<tr>
<td>Liver</td>
<td>119.7 ± 9.6</td>
</tr>
<tr>
<td>Pancreas</td>
<td>11.2 ± 0.8</td>
</tr>
<tr>
<td>Epididymal fat</td>
<td>19.7 ± 2.8</td>
</tr>
</tbody>
</table>

GLP-1 Reduces Glomerular Hyperfiltration and is Diuretic and Natriuretic in Obese Insulin-Resistant Subjects

Gutzwiller et al, J Clin Endocrinol Metab 2004
Vildagliptin increased active GLP-1 levels, which probably prevented oxidative DNA damage and renal cell apoptosis.
Linagliptin with high tissue penetration property is present not only in glomerulus also in tubules

Microautoradiograms from rat kidney sampled at 3 h after intravenous injection of 7.4 µg/kg [³H] Linagliptin

Presence of Linagliptin is indicated by black area (radioactivity)

Figure 2: The effect of linagliptin and enalapril on UACR in diabetic db/db and healthy control db/m mice

*P<0.05; ***P<0.001 vs. vehicle-treated db/db mice (Mann-Whitney test)
ADA 2012: Renoprotective Effects of the DPP-4 Inhibitor Linagliptin in db/db Mice

**Figure 4:** Quantitative assessment of deposition of extracellular matrix (A) and mesangial expansion (B); and Col1 (C) and α-SMA (D) expression in diabetic db/db and healthy control db/m mice.

*P<0.05; **P<0.01 vs. vehicle-treated db/db mice; †P<0.05 vs. healthy control db/m mice (Mann-Whitney test)
Linagliptin lowered albuminuria in patients with diabetic nephropathy

Adjusted mean change in albuminuria from baseline

**12 weeks treatment**
- Placebo (n=49)
- Linagliptin (n=157)

**24 weeks treatment**
- Placebo (n=55)
- Linagliptin (n=163)

95% of the overall albuminuria lowering effect occurred as early as 12 weeks

*Based on adjusted (log [baseline UACR] and trial effect) geometric mean ratio (Week 12 or 24/baseline). †Relative change was calculated as the ratio of the percentage change in the linagliptin group divided by the percentage change in the placebo group.

Source: Groop PH, et al. ADA 2012 Poster: 953-P
Linagliptin lowers UACR independent of its glucose lowering effect.

There was no correlation between changes in HbA1c and UACR from baseline to Week 24 (Pearson’s r=0.073, n=218)

Adjusted mean change in UACR (%) from baseline at week 24 by quartiles of HbA1c change

Significant change in UACR (%) v. baseline after 24 weeks, Analysis includes all patients from the treated set with a baseline and ≥1 on-treatment value for both HbA1c and UACR

Groop PH, et al. ADA 2012 Poster: 953-P
Linagliptin for Diabetes May Protect Kidney Function

SAN DIEGO, California — Linagliptin appears to have nephroprotective effects when used in the treatment of type 2 diabetes mellitus (T2DM). Maximilian von Eynatten, MD, executive medical director for Boehringer Ingelheim in Ridgefield, Connecticut, reported results of a meta-analysis of 13 phase 3 studies here at Kidney Week 2012, which showed an overall 16% reduction in the risk of reaching a composite renal endpoint.

- The meta-analysis included all completed phase 3, randomized, double-blind, placebo-controlled trials of at least 12 weeks' duration in the linagliptin development program. Drug exposure was a mean of 7 months and ranged from 12 weeks to 2 years.
- All of the trials involved patients with a diagnosis of inadequately controlled T2DM (N = 5466). The linagliptin (n = 3505) and placebo (n = 1961) groups were fairly well matched for demographic, laboratory, and T2DM disease parameters, as well as renal/cardiovascular history and medications.
- The composite primary renal safety endpoint consisted of new-onset microalbuminuria; macroalbuminuria; chronic kidney disease (CKD; first occurrence of serum creatinine of 2.83 mg/dL or greater); worsening of CKD, defined as a loss in estimated glomerular filtration rate (GFR) of more than 50% above baseline; acute renal failure; and all-cause mortality.
- Patients taking linagliptin were 16% less likely to reach the composite renal endpoint compared with patients on placebo (hazard ratio [HR] = 0.84; 95% confidence interval [CI], 0.72 - 0.97; P < .05). The incidence of the renal endpoint was 266.8/1000 patient-years vs 308.9/1000 patient-years on linagliptin vs placebo, respectively.


Medscape Medical News 07 Nov 2012
Summary: renal effect

- GLP-1 reduces glomerular hyperfiltration in obese, insulin-resistant subjects.
- Acute administration of GLP-1 is natriuretic and diuretic in humans.
- DPP-4 inhibition (and GLP-1 agonists) have been suggested to ameliorate diabetic nephropathy independently of glucose control.
- DPP4 inhibitors with high tissue penetration property like linagliptin may distribute into the kidney and exerts anti-albuminuric effect in patients with diabetic nephropathy.
- Further clinical investigations to address the potential renoprotective effects of DPP-4 inhibition is required.