Update on DPP-4 Inhibition in T2DM: Implications from Recent and Ongoing Trials

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Disclosures

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- Research Support: Lilly, Merck, Novo Nordisk, Sanofi, Takeda

All honoraria directed toward a non-profit which supports education and research
Outline

- Rationale for incretin therapy in T2DM
- Pharmacology of DPP-4 inhibitors
- Efficacy of DPP-4 inhibitors
- DPP-4 inhibitor use in special populations
  - Elderly
  - CKD
Multiple Metabolic Defects Contribute to Hyperglycemia in T2DM

- Increased Glucose Reabsorption
- Increased Lipolysis
- Increased Glucagon Secretion
- Impaired Insulin Secretion
- Decreased Incretin Effect
- Decreased Glucose Uptake
- Increased HGP
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

DeFronzo, Diabetes. 2009
The Incretin Effect Is Diminished in Type 2 Diabetes

Normal Glucose Tolerance

Type 2 Diabetes

*P≤.05
GLP-1 and GIP Augment Insulin Secretion by the β-Cell in a Glucose-Dependent Manner

**Glucose entry**
- GLUT2
- Glucokinase

**Glucose metabolism**
- ADP/ATP
- ATP → cAMP → PKA

**GLP-1/GIP**

**EPAC**

**Insulin secretory granules**
- ADP/ATP
- Ca²⁺ opens

**Insulin secretion**
- Ca²⁺
- K⁺

**Potassium (K$_{\text{ATP}}$) channel**
- Kir 6.2
- SUR 1

K$_{\text{ATP}}$ channel subunits:
- SUR 1=regulatory subunit;
- Kir 6.2=inward rectifying channel
No Significant Reduction in GLP-1 Secretion in Patients with Type 2 Diabetes


*P < 0.05 compared with control.

*Integrate GLP-1 (% of Control)

Individual Studies of Patients with Type 2 Diabetes and Weight-Matched, Non-Diabetic Controls
GLP-1 but not GIP Enhances Insulin Secretion in Patients with T2DM

GIP = glucose-dependent insulinotropic peptide; GLP-1 = glucagon-like peptide-1; T2DM = type 2 diabetes mellitus

Hyperglycemia Downregulates Incretin Receptor Expression

Insulin Response to Physiologic Levels of GLP-1 Is Impaired in Type 2 Diabetes

**Glucose Dependent Effects of GLP-1 in T2DM**

*P*<0.05.

GLP-1 = glucagon-like peptide–1.

Adapted from Nauck et al. Diabetologia. 1993;36:741-44.
GLP-1 Addresses Multiple Metabolic Defects in T2DM

- Impaired Insulin Secretion
- Increased Glucagon Secretion
- Increased HGP
- Decreased Incretin Effect
- Increased Lipolysis
- Increased Glucose Reabsorption
- Decreased Glucose Uptake
- Neurotransmitter Dysfunction

DeFronzo. Diabetes. 2009
The Incretin Defect in T2DM

- Substantial impairment – 40% of normal response
- Not due to impaired secretion of GLP-1 or GIP
- Absent insulinotropic response to GIP
  - Beta-cell GIP receptor down-regulation
- Decreased response to GLP-1
  - Can be overcome by achieving higher than physiologic GLP-1 levels
- GLP-1 infusions that achieve higher levels effective at enhancing insulin secretion and suppressing glucagon in a glucose-dependent manner

Rationale for Using Incretin Therapies in the Treatment of Type 2 Diabetes

- Incretins play a key and early role in maintaining glucose homeostasis
- Incretin effects are diminished in patients with type 2 diabetes
- Incretin-based therapies
  - Target multiple defects of type 2 diabetes, including those not addressed by traditional medications
  - Do not cause hypoglycemia
  - Have favorable effects on weight
ADA/EASD Position Statement: Managing Hyperglycemia in Type 2 Diabetes

Monotherapy

- **METFORMIN**
  - Efficacy (↓ A1C): High
  - Hypoglycemia: Low
  - Weight: Neutral/loss
  - Side effects: GI/lactic acidosis
  - Costs: Low
  - Proceed after 3 mo. if needed

2-drug combinations

- **METFORMIN +**
  - SU: High
  - Moderate risk
  - Gain
  - Hypoglycemia: Low
  - Order does not indicate preference
  - Proceed after 3 mo. if needed

- **METFORMIN +**
  - TZD: High
  - Low risk
  - Gain
  - Edema, HF, Fx: High
  - Intermediate
  - Proceed after 3 mo. if needed

- **METFORMIN +**
  - DPP4-I: Intermediate
  - Low risk
  - Neutral
  - Rare
  - High
  - Proceed after 3 mo. if needed

- **METFORMIN +**
  - GLP-1-RA: High
  - Low risk
  - Loss
  - GI: High
  - Rare
  - Proceed after 3 mo. if needed

- **METFORMIN +**
  - Insulin: Highest
  - High risk
  - Loss
  - Hypoglycemia: Variable
  - Edema, HF, Fx: High
  - Order does not indicate preference
  - Proceed after 3 mo. if needed

3-drug combinations

- **SU +**
  - TZD
  - DPP4-I
  - GLP-1-RA
  - Insulin: Order does not indicate preference
  - Proceed after 3-6 mo. if needed

- **TZD +**
  - SU
  - DPP4-I
  - GLP-1-RA
  - Insulin: Order does not indicate preference
  - Proceed after 3-6 mo. if needed

- **DPP4-I +**
  - SU
  - TZD
  - GLP-1-RA
  - Insulin: Order does not indicate preference
  - Proceed after 3-6 mo. if needed

- **GLP-1-RA +**
  - SU
  - TZD
  - DPP4-I
  - GLP-1-RA
  - Insulin: Order does not indicate preference
  - Proceed after 3-6 mo. if needed

- **Insulin +**
  - SU
  - TZD
  - DPP4-I
  - GLP-1-RA
  - Insulin: Order does not indicate preference
  - Proceed after 3-6 mo. if needed

More complex insulin strategies

- Insulin usually in combination with 1-2 noninsulin agents
- (multiple daily doses)


Best of the Cardiometabolic Health Congress Regional Conference Series
Outline

- Rationale for incretin therapy in T2DM
- Pharmacology of DPP-4 inhibitors
- Efficacy of DPP-4 inhibitors
- DPP-4 inhibitor use in special populations
  - Elderly
  - CKD
# DPP-4 Inhibitors Differ in Molecular Structures and Pharmacologic Properties

<table>
<thead>
<tr>
<th>Chemical Class</th>
<th>β-Phenethylamines&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Cyanopyrrolidines</th>
<th>Aminopiperidine&lt;sup&gt;8&lt;/sup&gt;</th>
<th>Xanthine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generic Name</td>
<td>Sitagliptin&lt;sup&gt;2,3&lt;/sup&gt;</td>
<td>Vildagliptin&lt;sup&gt;2,4,5&lt;/sup&gt;</td>
<td>Saxagliptin&lt;sup&gt;2,6,7&lt;/sup&gt;</td>
<td>Alogliptin&lt;sup&gt;9,10&lt;/sup&gt;</td>
</tr>
<tr>
<td>Molecular Structure</td>
<td><img src="image1.png" alt="Molecule" /></td>
<td><img src="image2.png" alt="Molecule" /></td>
<td><img src="image3.png" alt="Molecule" /></td>
<td><img src="image4.png" alt="Molecule" /></td>
</tr>
<tr>
<td>DPP-4 Inhibitory Activity (IC&lt;sub&gt;50&lt;/sub&gt;)</td>
<td>9.96 ± 1.03 nM</td>
<td>5.28 ± 1.04 nM</td>
<td>3.37 ± 0.90 nM</td>
<td>6.9 ± 1.5 nM</td>
</tr>
<tr>
<td>Half-life</td>
<td>12.4 h</td>
<td>~2–3 h</td>
<td>2.5 h (parent) 3.1 h (metabolite)</td>
<td>12.4–21.4 h</td>
</tr>
</tbody>
</table>

DPP-4=dipeptidyl peptidase-4. IC<sub>50</sub>=half maximal inhibitory concentration

## Pharmacokinetic Properties of DPP-4 Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin (Merck)(^1)</th>
<th>Vildagliptin (Novartis)(^2)</th>
<th>Saxagliptin (BMS/AZ)(^3)</th>
<th>Alogliptin (Takeda)(^5)</th>
<th>Linagliptin (BI)(^6)–(^8)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Absorption</strong> (t_{\text{max}}) (median)</td>
<td>1–4 h</td>
<td>1.7 h</td>
<td>2 h (4 h for active metabolite)</td>
<td>1–2 h</td>
<td>1.34–1.53 h</td>
</tr>
<tr>
<td><strong>Bioavailability</strong></td>
<td>~87%</td>
<td>85%</td>
<td>~75 %(^4)</td>
<td>N/A</td>
<td>29.5%</td>
</tr>
<tr>
<td><strong>Half-life (t_{1/2}) at clinically relevant dose</strong></td>
<td>12.4 h</td>
<td>~2–3 h</td>
<td>2.5 h (parent)</td>
<td>12.4–21.4 h (25–800 mg)</td>
<td>113–131 h (1–10 mg)</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>38% protein bound</td>
<td>9.3% protein bound</td>
<td>Low protein binding</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td>~16% metabolized</td>
<td>69% metabolized mainly renal (inactive metabolite)</td>
<td>Hepatic (active metabolite) CYP3A4/5</td>
<td>&lt;8% metabolized</td>
<td>~26% metabolized</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Renal 87% (79% unchanged)</td>
<td>Renal 85% (23% unchanged)</td>
<td>Renal 75% (24% as parent; 36% as active metabolite)</td>
<td>Renal (60%–71% unchanged)</td>
<td>Feces 81.5% (74.1% unchanged); Renal 5.4% (3.9% unchanged)</td>
</tr>
</tbody>
</table>

DPP-4=dipeptidyl peptidase-4.

Inhibition of DPP-4 Increases Active GLP-1 and GIP to Lower Glucose

DPP-4 inhibitor

DPP-4

Active GLP-1

Inactive GLP-1

DPP-4

Active GIP

Inactive GIP

Incretin effects
• Augments glucose-induced insulin secretion
• Inhibits glucagon secretion and hepatic glucose production
• Increases glucose disposal
Linagliptin Increases Active GLP-1 and GIP and Suppresses Glucagon
Effect of DPP-4 Inhibition on Insulin Secretion in Drug-naïve Patients

D’Alessio, et al. JCEM 2009

238% increase in AIRg
(P<0.001 vs wk 0, P<0.05 vs PBO)
DPP-4 Inhibition Enhances α-cell Sensitivity to Glucose

Vildagliptin

- Vilda week 0 (50 mg twice daily, n=14)
- Vilda week 12 (50 mg twice daily, n=14)

Placebo

- PBO week 0 (n=14)
- PBO week 12 (n=14)

PBO=placebo; vilda=vildagliptin
*P <0.05 vs week 0.
D’Alessio DA, et al. JCEM 2009
DPP-4 Inhibition Improves Insulin Sensitivity

Mean difference = 0.65 mg/kg/min
95% CI (0.03, 1.26)
\( P = 0.040 \)

*\( P < 0.05 \) or better vs PBO
DPP-4 Inhibition Improves Postprandial Lipid and Lipoprotein Metabolism

Before vilda, week 0 (n=13)
Vilda 50 mg twice daily, week 4 (n=15)

TG=triglycerides; vilda=vildagliptin
Outline

- Rationale for incretin therapy in T2DM
- Pharmacology of DPP-4 inhibitors
- Efficacy of DPP-4 inhibitors
- DPP-4 inhibitor use in special populations
  - Elderly
  - CKD
Efficacy of DPP-4 Inhibitor Therapy Added to Metformin

[Diagram showing BLA1C (%)]

DPP-4 Inhibitors: Glycemic Efficacy When Added as a Third Oral Agent

1. Drugs@FDA.

**Added to PIO + MET**

- **ALO (25 mg)**: -0.80
- **LINA (5 mg)**: -0.7
- **SAXA (5 mg)**: -0.10
- **SITA (100 mg)**: -0.10
- **PBO**: -1.3

P ≤ .01 vs PIO + MET

**Added to MET + SU**

- **ALO (25 mg)**: -0.80
- **LINA (5 mg)**: -0.7
- **SAXA (5 mg)**: -0.10
- **SITA (100 mg)**: -0.10
- **PBO**: -1.3

P ≤ .05 vs PBO

**Added to MET + OAD**

- **SAXA (5 mg)**: -1.2
- **SITA (100 mg)**: -1.07
- **PBO**: -1.3

P < .0001 vs PBO

P ≤ .01 vs BL

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**Notes:**

- **ALO**: 26-wk trial; PIO, 15 mg.
- **LINA**: 24-wk trial, BL A1C 8.1-8.2%.
- **SAXA**: 24-wk trial, BL A1C 8.2-8.4%.
- **SITA/SAXA**: 24-wk trial, BL A1C 8.5-8.9%; OAD: GLIM, AGI, or PIO.
DPP-4 Inhibitors Offer Improved Glycemic Efficacy When Added to Insulin Regimens

- **ALO (25 mg)**: 26-wk trial, BL A1C 9.3%, 55 units insulin median TDD at BL.
- **LINA (5 mg)**: 24-wk trial, BL A1C 8.3%. 40–42 units insulin mean TDD at BL.
- **SAXA (5 mg)**: 24-wk trial, BL A1C 8.7%, 53–55 units insulin mean TDD at BL. intermediate, long-acting, or premixed INS only.
- **SITA (100 mg)**: 24-wk trial, BL A1C 8.6–8.7%. 42–45 units insulin median TDD at BL, intermediate, long-acting, or premixed INS only.

**Δ A1C From BL, %**

- **ALO**: 0.0
- **LINA**: -0.6
- **SAXA**: -0.3
- **SITA**: -0.6

**P values**:
- **P < .01 vs PBO**
- **P < .05 vs PBO**
- **P < .001 vs PBO**

**Drugs@FDA.**

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*ALO*: 26-wk trial, BL A1C 9.3%, 55 units insulin median TDD at BL.

*LINA*: 24-wk trial, BL A1C 8.3%. 40-42 units insulin mean TDD at BL.

*SAXA*: 24-wk trial, BL A1C 8.7%, 53-55 units insulin mean TDD at BL. intermediate, long-acting, or premixed INS only.

*SITA*: 24-wk trial, BL A1C 8.6-8.7%. 42-45 units insulin median TDD at BL, intermediate, long-acting, or premixed INS only.

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1. Drugs@FDA.
Glycemic Control With DPP-4 Inhibitors in a Head-to-Head Clinical Trial

A1C Change from Baseline (%), SE

<table>
<thead>
<tr>
<th></th>
<th>Study design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>18-week study</td>
<td>Noninferior glycemic control for SAXA vs SITA</td>
</tr>
<tr>
<td></td>
<td>N = 677</td>
<td>No differences in weight loss (0.4 kg) or AE occurrences</td>
</tr>
<tr>
<td></td>
<td>BL A1C = 7.7%</td>
<td></td>
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<tr>
<td></td>
<td>Add-on to MET</td>
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</tr>
</tbody>
</table>

### Long-term Studies of DPP-4 Inhibitors vs. Sulfonylureas

<table>
<thead>
<tr>
<th>Study duration</th>
<th>Linagliptin 5mg⁴</th>
<th>Alogliptin 25mg¹</th>
<th>Sitagliptin 100mg²</th>
<th>Saxagliptin 5mg³</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>104-week</td>
<td>104-week</td>
<td>104-week</td>
<td>52-week extension of 52-week study</td>
</tr>
<tr>
<td>Add-on to</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
<td>Metformin</td>
</tr>
<tr>
<td>Comparator</td>
<td>Glimepiride</td>
<td>Glipizide</td>
<td>Glipizide</td>
<td>Glipizide</td>
</tr>
<tr>
<td>Average SU dose</td>
<td>3.0mg</td>
<td>5.2mg</td>
<td>9.2mg</td>
<td>15mg</td>
</tr>
<tr>
<td>Baseline HbA1c (%)</td>
<td>7.43–7.53</td>
<td>7.59–7.61</td>
<td>7.30–7.31</td>
<td>7.65</td>
</tr>
<tr>
<td>HbA1c reduction: DPP-4i SU</td>
<td>-0.35</td>
<td>-0.72</td>
<td>-0.54</td>
<td>-0.41</td>
</tr>
<tr>
<td></td>
<td>-0.53 Non-inferior</td>
<td>1.4%</td>
<td>1.4%</td>
<td>0.89</td>
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<tr>
<td></td>
<td></td>
<td>-0.51 Non-inferior</td>
<td>-1.6</td>
<td>-0.35</td>
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<tr>
<td>HbA1c reduction: SU</td>
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<td></td>
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<tr>
<td>Body weight (kg) DPP-4i SU</td>
<td>-1.4 +1.3</td>
<td>-0.95 +0.89</td>
<td>-1.6 +0.7</td>
<td>-1.5 +1.3</td>
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</tr>
<tr>
<td>hypoglycaemia DPP-4i SU</td>
<td>7% 36%</td>
<td>1.4% 23.2%</td>
<td>5.3% 34.1%</td>
<td>3.5% 38.4%</td>
</tr>
</tbody>
</table>

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Comparison of HbA1c Change in Long-Term Studies of DPP-4 Inhibitors

Linagliptin + metformin vs glimepiride\(^4\)
104 weeks (PPS)

Sitagliptin + metformin vs glipizide\(^2\)
104 weeks (PPS)

Saxagliptin + metformin vs glipizide\(^3\)
52-week extension of 52-week study (FAS)

Alogliptin + metformin vs glipizide\(^1\)
104 weeks (PPS)

PPS=per protocol set; FAS=full analysis set
Initial Combination Therapy With Linagliptin and Metformin in Patients with T2DM

Initial Combination Therapy with Empagliflozin and Linagliptin in T2DM

N=674 individuals with T2DM who had not received diabetes therapy for ≥12 weeks (week 24 data).

Change From Baseline in A1c, %
Mean Baseline
- 7.99% (n=134)
- 8.04% (n=135)
- 7.99% (n=133)
- 8.05% (n=132)
- 8.05% (n=133)

Empagliflozin 25 mg/Linagliptin 5 mg
- Change: -0.14 (-0.33, 0.06) P=0.179
Empagliflozin 10 mg/Linagliptin 5 mg
- Change: -0.41 (-0.61, -0.21) P<0.001
Empagliflozin 25 mg
- Change: -0.57 (-0.76, -0.21) P<0.001
Empagliflozin 10 mg
- Change: -0.41 (-0.61, -0.21) P<0.001
Linagliptin 5 mg
- Change: 0.1 (-0.9, 1.1) P=0.801

Change From Baseline in Body Weight, kg
Mean Baseline
- 87.9 (n=134)
- 87.3 (n=135)
- 86.7 (n=133)
- 87.8 (n=132)
- 89.5 (n=133)

Empagliflozin 25 mg/Linagliptin 5 mg
- Change: 0.1 (-0.9, 1.1) P=0.801
Empagliflozin 10 mg/Linagliptin 5 mg
- Change: -0.5 (-1.5, 0.5) P=0.362
Empagliflozin 25 mg
- Change: -2.0 (-3.0, -1.0) P<0.001
Empagliflozin 10 mg
- Change: -1.2 (-2.2, -0.2) P=0.018
Linagliptin 5 mg
Outline

- Rationale for incretin therapy in T2DM
- Pharmacology of DPP-4 inhibitors
- Efficacy of DPP-4 inhibitors
- DPP-4 inhibitor use in special populations
  - Elderly
  - CKD
Other adverse reactions reported in clinical studies with treatment of linagliptin were hypersensitivity (eg, urticaria, angioedema, localized skin exfoliation, or bronchial hyperreactivity) and myalgia.

The overall incidence of adverse events with linagliptin was similar to placebo.
Hypoglycemia May be a Barrier to Glycemic Control in Patients With Type 2 Diabetes

- Hypoglycemia is an important limiting factor in glycemic management.
- It may be a significant barrier in terms of treatment adherence and achievement of a lifelong goal of attaining normal glycemic levels.
- Fear of hypoglycemia is an additional barrier to control.

  A study in patients with type 2 diabetes showed increased fear of hypoglycemia as the number of mild/moderate and severe hypoglycemic events increased.

Hypoglycemia With Linagliptin: Mono and Combination Therapy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Monotherapy 24 Weeks¹</th>
<th>Initial Combo w/ Pioglitazone 24 Weeks²</th>
<th>Add-on to Metformin 24 Weeks³</th>
<th>Add-on to Metformin + SU 24 Weeks⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>503</td>
<td>389</td>
<td>700</td>
<td>1055</td>
</tr>
<tr>
<td>Patients Reporting Hypoglycemia (%)</td>
<td>0.6</td>
<td>0</td>
<td>2.3</td>
<td>14.8</td>
</tr>
<tr>
<td>PBO</td>
<td>Lin</td>
<td>Lin + Pio</td>
<td>Met</td>
<td>Lin + Met</td>
</tr>
<tr>
<td>24 Weeks</td>
<td></td>
<td>24 Weeks</td>
<td>24 Weeks</td>
<td>24 Weeks</td>
</tr>
<tr>
<td>14,8</td>
<td>22,7</td>
<td></td>
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</tr>
</tbody>
</table>

Hypoglycemia in Patients with T2DM on Basal Insulin Treated With Linagliptin vs. Placebo
The Problem of Diabetes in Older Adults

- Common – 40% of all patients with diabetes
- Optimal glycemic targets unknown
- Optimal therapeutic approaches unknown
- Clinical heterogeneous population
  - Variable life expectancies
  - Variable comorbidities and functional status
  - Polypharmacy and geriatric syndromes
- Lack of Grade A evidence
  - Exclusion from large RCTs

⇒ Individualize Goals for DM management
Linagliptin Reduced A1C vs Placebo at 24 Weeks in Patients Aged ≥70 Years

Primary Endpoint: Placebo-Adjusted Mean Difference in A1C (%) at 24 Weeks

*P<0.0001. †Placebo corrected.
Baseline A1C: 7.8% for linagliptin-treated group and 7.7% for placebo group; full analysis set; last observation carried forward.

SE=standard error.
Clinical experience with TRADJENTA has not identified differences in response between the elderly and younger patients; however, greater sensitivity of some older individuals cannot be ruled out.

Low Rates of Hypoglycemia With Linagliptin vs. Placebo in Patients Aged ≥70 Years
## DPP-4 Inhibitors: Dosing in Renal Disease

<table>
<thead>
<tr>
<th>Renal Function</th>
<th>Linagliptin(^1)</th>
<th>Sitagliptin(^2)</th>
<th>Saxagliptin(^3)</th>
<th>Alogliptin(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate impairment</strong></td>
<td>No dose adjustment</td>
<td>50 mg once daily</td>
<td>2.5 mg once daily</td>
<td>12.5 mg once daily</td>
</tr>
<tr>
<td>CrCl: 30–50 mL/min or Serum Cr (mg/dL):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &gt;1.7 – ≤3.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women &gt;1.5 – ≤2.5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severe impairment/ESRD</strong></td>
<td>No dose adjustment</td>
<td>25 mg once daily</td>
<td>2.5 mg once daily</td>
<td>6.25 mg once daily</td>
</tr>
<tr>
<td>CrCl &lt;30 mL/min or Serum Cr (mg/dL):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men &gt;3.0</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women &gt;2.5 or dialysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2. Sitagliptin full prescribing information. [http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021995s007lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/021995s007lbl.pdf)
4. Alogliptin full prescribing information. [http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/022271s000lbl.pdf)
Linagliptin Lowers HbA1c Over 52 weeks in Patients with Renal Impairment

Incidence of Renal Adverse Events in T2DM Patients Treated with Linagliptin vs. Control

### Table 3. Safety of linagliptin in T2DM patients with CKD (treated set).

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 1</th>
<th></th>
<th>Study 2</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild RI</td>
<td>Moderate RI</td>
<td>Severe RI</td>
<td></td>
<td></td>
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</tr>
<tr>
<td></td>
<td>Linagliptin</td>
<td>Placebo</td>
<td>Linagliptin</td>
<td>Placebo</td>
<td>Linagliptin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Patients, n</td>
<td>292</td>
<td>283</td>
<td>59</td>
<td>68</td>
<td>54</td>
<td>55</td>
</tr>
<tr>
<td>Any AE, %</td>
<td>78.8</td>
<td>82.7</td>
<td>81.4</td>
<td>88.2</td>
<td>98.1</td>
<td>94.5</td>
</tr>
<tr>
<td>Investigator-reported drug related, AE, %</td>
<td>29.5</td>
<td>28.3</td>
<td>22.0</td>
<td>25.0</td>
<td>48.5</td>
<td>45.0</td>
</tr>
<tr>
<td>AEs leading to discontinuation, %</td>
<td>2.7</td>
<td>4.6</td>
<td>5.1</td>
<td>2.9</td>
<td>14.8</td>
<td>16.4</td>
</tr>
<tr>
<td>Serious AEs, %</td>
<td>14.7</td>
<td>13.8</td>
<td>18.6</td>
<td>20.6</td>
<td>37.0</td>
<td>40.0</td>
</tr>
<tr>
<td>Fatal</td>
<td>1.4</td>
<td>0.4</td>
<td>1.7</td>
<td>2.9</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Immediately life-threatening</td>
<td>1.4</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>3.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.0</td>
<td>0.4</td>
<td>0.0</td>
<td>1.5</td>
<td>0.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Requiring hospitalization</td>
<td>13.4</td>
<td>12.7</td>
<td>16.9</td>
<td>16.2</td>
<td>33.3</td>
<td>36.4</td>
</tr>
<tr>
<td>AEs of special interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal and urinary disorders, %</td>
<td>6.8³</td>
<td>7.4³</td>
<td>8.5⁴</td>
<td>10.3⁴</td>
<td>22.2⁵</td>
<td>25.5⁵</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>5.8</td>
<td>5.3</td>
<td>5.1</td>
<td>13.2</td>
<td>1.9</td>
<td>3.6</td>
</tr>
<tr>
<td>Heart failure, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1.4</td>
<td>0.0</td>
<td>1.7</td>
<td>1.5</td>
<td>3.7</td>
<td>0.0</td>
</tr>
<tr>
<td>Cardiac failure, congestive</td>
<td>0.3</td>
<td>0.4</td>
<td>0.0</td>
<td>1.5</td>
<td>3.7</td>
<td>3.6</td>
</tr>
<tr>
<td>Left ventricular failure</td>
<td>0.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>1.9</td>
<td>0.0</td>
</tr>
</tbody>
</table>
Pancreatitis Risk With DPP-4 Inhibitors

- The available evidence suggests that incretin-based therapies do not themselves increase the risk of pancreatitis in patients with T2DM\(^1\)

- But other factors may increase the risk of pancreatitis with use of DPP-4 inhibitors\(^2\):
  - Obesity
  - Hypertriglyceridemia
  - Gallstones
  - Biliary/pancreatic cancer, or neoplasm
  - Alcohol and/or tobacco use

- **Current prescribing recommendations\(^3\)**
  - Educate patients—ask about pancreatitis history/risk factors
  - Monitor for pancreatitis signs and symptoms—discontinue promptly if they occur

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3. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
Oral therapy, once daily
- Endogenous GLP-1 and GIP levels are increased in response to meals and are transient
- Clinically significant A1c reductions
  - Comparable efficacy to SUs
- Complementary mechanism of action with many drugs
  - Don’t use with GLP-1 receptor agonists
- Very well tolerated
  - No GI sx, no weight gain, low hypoglycemia, no edema
- Adjust dose for CKD: except linagliptin
- Low risk for drug-drug interactions
- Neutral effects on BP, lipids, CVD
Ideal Patient with T2DM for DPP-4 Inhibitor Therapy

- Metformin intolerant
- Combination with metformin
- Weight issues or hypoglycemia risk
- Elderly
- Chronic kidney disease
- Cardiovascular disease
- Convenience of once-daily, well tolerated medication