Management of Blood Glucose with non-Insulin therapies in DM type 2

Jorge De Jesus MD FACE
Disclosures

• Dr Jorge De Jesús has received honorariums as speaker for the following pharmaceutical companies: Merck; Janssen; Sanofi -Aventis

• Dr Jorge De Jesús has no conflicts of interests with any entity for the information included in this presentation
Objectives
During this **30 minutes** presentation the audience will be able to:

- Recognize that DM 2 is a multifactorial disease
- DM is a progressive disease and eventually many patients will need insulin in their therapies
- Oral therapies included in the presentation:
  - Metformin; DPP4 inhibitors; SGLT2 inhibitors
- Parenteral, non insulin therapies: GLP-1 RA
- Some non FDA approved therapies will be discussed

The organizers of the activity have been authorized to distribute handouts of this presentation
Pre- Test

• Treatment of Diabetes Mellitus should be centered in the patient and individualized.

• Due to the multifactorial nature of the disease combination therapy is needed early in the treatment of this condition

• Efforts should be made to prevent DM in high risk individuals.
Diabetes type 2 is a polygenic and multifactorial disease

The Ominous Octet

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

Islet β-cell

Islet α-cell

Hyperglycemia
US Trends in Type 2 Diabetes Treatment, 1997-2012: Medication Classes

Steady increase in type 2 diabetes treatment visits between 1997 and 2007, peaking at 35.3 million visits in 2007, and declining to 31.2 million visits in 2012.

Total visits, millions

<table>
<thead>
<tr>
<th>Year</th>
<th>1997</th>
<th>2007</th>
<th>2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visits, millions</td>
<td>23.6</td>
<td>35.3</td>
<td>31.2</td>
</tr>
</tbody>
</table>

% of visits by medication class

- Sulfonylureas: 61% (1997), 22% (2012)
- Glitazones*: 6% (1997), 16% (2012)
- Biguanide (metformin): 53% (2012)
- DPP-4 inhibitors†: 21% (2012)
- GLP-1 agonists†: 4% (2012)

*~96% of visits involved pioglitazone products in 2012; †Not FDA approved in 1997

Percentages shown are % of treatment visits where medication classes were prescribed.

US Trends in Type 2 Diabetes Treatment, 1997-2012: Insulin Use

Stable insulin use seen from 1997 to 2012

However, when visits examined by insulin type:

- Regular: 2% of visits since 1997
- NPH: 3% of visits since 1997
- Short-acting: doubled in use from 1997 to 2012
- Long-acting: <1% of visits in 1997 to ~18% in 2012

Percentages shown are % of treatment visits where medication classes were prescribed

US Trends in Type 2 Diabetes Treatment, 1997-2012: Number of Treatments

Visit with single treatment
Visit with single compound
Visit with 2+ treatments

Percentages shown are % of treatment visits where medication classes were prescribed
*Including fixed-dose combination therapy

INDIVIDUALIZE GOALS

A1C ≤ 6.5%
For patients without concurrent serious illness and at low hypoglycemic risk

A1C > 6.5%
For patients with concurrent serious illness and at risk for hypoglycemia
Algorithm for Adding/Intensifying Insulin

**Start Basal (Long-Acting Insulin)**
- **A1C < 8%**
  - TDD 0.1–0.2 U/kg
- **A1C > 8%**
  - TDD 0.2–0.3 U/kg

Insulin titration every 2–3 days to reach glycemic goal:
- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - FBG > 180 mg/dL: add 20% of TDD
  - FBG 140–180 mg/dL: add 10% of TDD
  - FBG 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - BG < 70 mg/dL: 10% – 20%
  - BG < 40 mg/dL: 20% – 40%

Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)

**Glycemic Goal:**
- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**Intensify (Prandial Control)**
- **Add GLP-1 RA**
  - Or SGLT-2i Or DPP-4i
- **Add Prandial Insulin**
  - **Basal Plus 1, Plus 2, Plus 3**
    - Begin prandial insulin before largest meal
    - If not at goal, progress to injections before 2 or 3 meals
    - Start: 10% of basal dose or 5 units
  - **Basal Bolus**
    - Begin prandial insulin before each meal
    - 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
    - Start: 50% of TDD in three doses before meals

Insulin titration every 2–3 days to reach glycemic goal:
- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% – 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% – 40%

*Glycemic Goal*

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### Profiles of Antidiabetic Medications

<table>
<thead>
<tr>
<th>3A=45-59; 3B=30-44</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th></th>
<th>MET</th>
<th>GLP-1 RA</th>
<th>SGLT-2i</th>
<th>DPP-4i</th>
<th>AGi</th>
<th>TZD (moderate dose)</th>
<th>SU GLN</th>
<th>COLSVE</th>
<th>BCR-QR</th>
<th>INSULIN</th>
<th>PRAML</th>
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<tbody>
<tr>
<td>HYPO</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate/Severe</td>
<td>Mild</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate to Severe</td>
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<tr>
<td>WEIGHT</td>
<td>Slight Loss</td>
<td>Loss</td>
<td>Loss</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
<td>Gain</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Gain</td>
</tr>
<tr>
<td>RENAL/GU</td>
<td>Contraindicated CKD Stage 3B,4,5</td>
<td>Exenatide Not Indicated CrCl &lt; 30 Genital Mycotic Infections</td>
<td>Not Effective with eGFR &lt; 45 Dose Adjustment Necessary (Except Linagliptin)</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>More Hypo Risk</td>
<td>Neutral</td>
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<tr>
<td>GI Sx</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Mild</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Moderate</td>
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<tr>
<td>CHF</td>
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<td>Neutral</td>
<td>Neutral</td>
<td>Moderate</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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<tr>
<td>ASCVD</td>
<td>Benefit</td>
<td>Possible Benefit</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Safe</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
</tr>
<tr>
<td>BONE</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Moderate Fracture Risk</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
<td>Neutral</td>
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</tbody>
</table>

**Legend:**
- Few adverse events or possible benefits
- Use with caution
- Likelihood of adverse effects
- Uncertain effect

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TOP MEDICAL NEWS FROM ACROSS MEDSCAPE

FDA: Metformin Safe for Some Patients With Renal Problems

Changing its course in response to mounting evidence, the agency said the diabetes drug can be used safely in patients with mild and, in some cases, moderate kidney impairment.

News Alerts, April 08, 2016 | 13 comments

contraindicated GFR< 30 ml/min
DPP-4 Inhibitors: Benefits and Risks

**Benefits**

- Lower HbA$_{1c}$ by $\sim 0.5\%$ to $0.9\%$
- Low risk of hypoglycemia as monotherapy or when used with metformin
- Weight neutral

**Risks and Adverse Events**

- Hypoglycemia risk when given with SUs or insulin$^a$
- Pancreatitis: new safety data available but patients should still be monitored for signs and symptoms$^{b,c}$

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## DPP-4 Inhibitors: Large-Scale CV Safety Studies

<table>
<thead>
<tr>
<th>Trial</th>
<th>DPP-4 Inhibitor</th>
<th>Study Findings Released/Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-hoc analyses</td>
<td>All</td>
<td>February 2013&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
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</tr>
<tr>
<td>SAVOR-TIMI</td>
<td>Saxagliptin</td>
<td>September 2013&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>September 2013&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>2014&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>2018&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

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TECOS: No Increased CV Risk With Sitagliptin Vs Placebo in High-Risk Subjects With Type 2 Diabetes

Primary composite endpoint: CV death, nonfatal MI, nonfatal stroke, hospitalization for UA

- **Sitagliptin (n=7,332):** 11.4%
- **Placebo (n=7,339):** 11.6%

HR=0.98 (95% CI, 0.88-1.09) \( P<0.001 \)

About TECOS

Cardiovascular safety study of the DPP-4 inhibitor, sitagliptin

Randomized, double-blind, placebo-controlled, event-driven trial

N=14,671 subjects with type 2 diabetes and CVD

Randomization + usual care*:
- Sitagliptin 100 mg/d†
- Placebo

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TECOS=Trial Evaluating Cardiovascular Outcomes with Sitagliptin
HR=hazard ratio; UA=unstable angina
*Or 50 mg/d if baseline eGFR ≥30 and <50 ml/min/1.73 m²; †Stable doses of one or two oral antihyperglycemic agents (metformin, pioglitazone, or sulfonylurea) or insulin (with or without metformin)

SAVOR-TIMI 53: No Increase in CV Events with Saxagliptin in Patients With or At Risk for CVD

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal ischemic stroke

HR, 1.0 (95% CI, 0.89-1.12);
P = 0.99 for superiority
P < 0.001 for noninferiority

% patients with primary endpoint

<table>
<thead>
<tr>
<th></th>
<th>Saxagliptin (n=8,280)</th>
<th>Placebo (n=8,212)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>7.3% (n=613)</td>
<td>7.2% (n=609)</td>
</tr>
</tbody>
</table>

Saxagliptin is not FDA approved for cardiovascular risk reduction.
SAVOR-TIMI 53 = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus—Thrombolysis in Myocardial Infarction 53; CV = cardiovascular; MI = myocardial infarction

SAVOR-TIMI 53: Saxagliptin Increased Hospitalization for Heart Failure

HR, 1.27 (95% CI, 1.07-1.51); P=0.007

Hospitalization for heart failure, %

3.5% (n=289) for Saxagliptin (n=8,280)
2.8% (n=228) for Placebo (n=8,212)

Saxagliptin is not FDA approved for cardiovascular risk reduction.
SAVOR-TIMI 53=Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus–Thrombolysis in Myocardial Infarction 53

EXAMINE: No Increase in CV Events with Alogliptin

Primary Endpoint

Primary endpoint: composite of CV death, nonfatal MI, or nonfatal stroke

HR, 0.96 (95% CI, ≤1.16*);
P = 0.32 for superiority
P < 0.001 for noninferiority

% patients with primary endpoint

Alogliptin (n=2,701) Placebo (n=2,679)

11.3% 11.8%

*Upper boundary of one-sided repeated CI
Median follow-up: 18 months
Alogliptin is not FDA approved for cardiovascular risk reduction.
EXAMINE = Examination of Cardiovascular Outcomes with Alogliptin versus Standard of Care
CV = cardiovascular; MI = myocardial infarction
FDA Drug Safety Communication: FDA adds warnings about heart failure risk to labels of type 2 diabetes medicines containing saxagliptin and alogliptin
Severe Joint Pain from Diabetes Meds
Renal Handling of Glucose

(180 L/day) (900 mg/L) = 162 g/day

SGLT1

SGLT2

S1

S3

90%

10%

Glucose

No Glucose
Rationale for SGLT2 Inhibitors

- Inhibit glucose reabsorption in the renal proximal tubule
- Resultant glucosuria leads to a decline in plasma glucose and reversal of glucotoxicity
- This therapy is simple and nonspecific
- Even patients with refractory type 2 diabetes are likely to respond
SGLT-2 Inhibitors: Benefits

- Lower HbA$_{1c}$ by $\sim0.4\%$ to $0.9\%$\textsuperscript{a}
- Reduce weight by $\sim3$ to $4$ kg\textsuperscript{a-c}
- Reduce systolic BP by $\sim5$ to $6$ mm Hg\textsuperscript{d,e}
- Low risk of hypoglycemia\textsuperscript{d,e}
- No increased cardiovascular risk; studies ongoing\textsuperscript{f-h}

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SGLT-2 Inhibitors: Risks & Adverse Effects

- Main adverse effects
  - Genitourinary tract infections, mainly genital
  - Increased LDL-C with canagliflozin

- Safety concerns
  - Volume depletion/orthostatic hypertension

- Less HbA$_{1c}$ reduction in patients with stage 3 CKD; not recommended for those with stage 4-5 CKD

- Cardiovascular safety studies show no increased cardiovascular risk

Conclusion Summary

Following recent reports of cases of diabetic ketoacidosis (DKA) in patients treated with sodium glucose cotransporter 2 (SGLT2) inhibitors, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) convened a public conference in which experts from Europe and the United States evaluated each case and case series. Upon review of the available material, together with a thorough discussion of the impact of SGLT2 inhibitors on human metabolism, the experts concluded that the prevalence of DKA is infrequent and the risk-benefit ratio overwhelmingly favors continued use of SGLT2 inhibitors with no changes in current recommendations.
DKA: Canagliflozin Clinical Program

17,596 patients with type 2 diabetes from randomized controlled trials

12 patients with DKA

6 patients had LADA or were GAD-positive

Euglycemic DKA: Case Studies

13 episodes of euglycemic DKA

9 patients from clinical practices across the United States on SGLT2 inhibitors

2 had type 2 diabetes; DKA occurred postsurgical procedure

7 had type 1 diabetes

Euglycemic DKA
Predictable and Detectable

Contributors to DKA

- Undertreatment due to inadequate insulin therapy or noncompliance
- Physiologic stressors
- Intercurrent illness
- Infection
- Certain medications

SGLT2 Inhibitor-Induced Euglycemic DKA

• Misdiagnosis? Type 2 diabetes vs latent autoimmune diabetes (LADA)

• Patients with type 2 diabetes can be susceptible to DKA under stressful conditions

• SGLT2-induced glycosuria lowers plasma glucose levels, predisposing to increased ketogenesis

DKA Prevention

- Euglycemic DKA is detectable, and therefore, preventable
- Patients can test their blood ketone at home
- Ketouria and ketonemia can be monitored
- Clinicians and patients need to be educated on the unique presentation of euglycemic DKA

2015 AACE/ACE Expert Recommendations: DKA

- Unclear if DKA occurs more often in patients with type 2 diabetes than prior to the use of SGLT2 inhibitors
- DKA mostly occurs in situations of insulin deficiency
- At this time, no changes in prescribing guidance have been mandated for SGLT2 inhibitors
2015 AACE/ACE Expert Recommendations: DKA (cont)

- Patients and healthcare professionals need to be aware of the signs of DKA and promptly seek treatment to properly manage the acidosis, if present.
- Urinary ketones and low bicarbonate may be inaccurate measures of DKA.
- Beta hydroxybutyrate and arterial pH recommended for diagnostic confirmation.
Invokana and Invokamet (canagliflozin): Drug Safety Communication - New Information on Bone Fracture Risk and Decreased Bone Mineral Density

Class effect??
Canagliflozin: Changes to Adverse Reactions Section: Risk for Bone Fractures

“The occurrence of bone fractures was evaluated in a pool of 9 clinical trials with a mean duration of exposure to canagliflozin of 85 weeks. The incidence rates of adjudicated bone fractures were 1.1, 1.4, and 1.5 per 100 patient-years of exposure in the comparator, canagliflozin 100 mg, and canagliflozin 300 mg groups, respectively. Fractures were observed as early as 12 weeks after treatment initiation and were more likely to be low trauma (e.g., fall from no more than standing height), and affect the upper extremities.”
EMP A-REG OUTCOME TRIAL

Bone Fractures

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%) Rate*</td>
<td>N (%) Rate*</td>
<td>N (%) Rate*</td>
<td></td>
</tr>
<tr>
<td>Bone fractures</td>
<td>91 (3.9) 1.6</td>
<td>92 (3.9) 1.6</td>
<td>87 (3.7) 1.5</td>
</tr>
</tbody>
</table>

*Rate = per 100 patient-years. Patients treated with ≥ 1 dose of study drug.

Clinical Relevance

Use of SGLT2 Inhibitors in Older Individuals

- In patients at high risk for falls, consider discontinuing the diuretic if starting an SGLT2 inhibitor

- Consider lowering the recommended dose of the SGLT2 inhibitor in high-risk patients (off-label)

- Physical therapy for balance and strength training can be helpful
Canagliflozin
Change in BMD

- Postmarketing study evaluated changes in BMD over 2 years in 714 older adults (mean age, 64 y)
- Placebo-corrected decreases in BMD at the total hip (0.9% and 1.2% with 100 mg and 300 mg canagliflozin, respectively) and lower spine (0.3% and 0.7% with 100 mg and 300 mg canagliflozin, respectively)
- Placebo-adjusted BMD declines of 0.1% seen at the femoral neck for both canagliflozin doses, and of 0.4% at the distal forearm for patients taking the 300-mg canagliflozin dose

Invokana® PI 2015.
## Risk Factors for Recurrent Falls

### Major Risk Factors for Recurrent Falls

<table>
<thead>
<tr>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Female gender</td>
</tr>
<tr>
<td>History of previous falls</td>
</tr>
<tr>
<td>Mobility impairment</td>
</tr>
<tr>
<td>Low level of activity</td>
</tr>
<tr>
<td>Arthritis</td>
</tr>
<tr>
<td>Cognitive impairment</td>
</tr>
<tr>
<td>Fall-risk-increasing drugs</td>
</tr>
</tbody>
</table>

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## EMPA-REG OUTCOME TRIAL

### DKA

<table>
<thead>
<tr>
<th>Adverse Effect</th>
<th>Placebo (n = 2333)</th>
<th>Empagliflozin 10 mg (n = 2345)</th>
<th>Empagliflozin 25 mg (n = 2342)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>Rate*</td>
<td>N (%)</td>
</tr>
<tr>
<td>DKA</td>
<td>1 (&lt; 0.1)</td>
<td>0.02</td>
<td>3 (0.1)</td>
</tr>
</tbody>
</table>

*Rate = per 100 patient-years. Patients treated with ≥ 1 dose of study drug.

Lower All-Cause & CV Mortality With Empagliflozin Vs Placebo in High-Risk Patients

EMPA-REG OUTCOME

Placebo (n=2,333) vs Empagliflozin (n=4,687)

Death from any cause

RRR=32%

% Subjects

Death from CV causes

RRR=38%

% Subjects

HR=0.68 (0.57-0.82)
P<0.001

HR=0.62 (0.49-0.77)
P<0.001

39 patients would need to be treated over 3 years to prevent 1 death

CV=cardiovascular; MI=myocardial infarction; RRR=relative risk reduction

Many patients with type 2 diabetes continue to have poor control and would benefit from insulin therapy. However, resistance to the introduction of insulin therapy can be high on both the part of the healthcare provider and the patient.

A number of new, long acting basal insulins are in development that provide good metabolic control, with lower a risk of hypoglycemia, than the currently available insulins. Providing greater flexibility in dosing time from day to day.

These attributes may address some of the current barriers to insulin initiation and intensification that currently limit the effectiveness of diabetes care.
Diabetes type 2 is a polygenic and multifactorial disease

The Ominous Octet

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

Islet β-cell

Islet α-cell

Hyperglycemia
THE HISTORY OF INCRETINS

• In 1902, Bayliss and Starling proposed that intestinal mucosa contains a hormone, which stimulates the exocrine secretion of the pancreas ("Secretin"). However, oral administration of extracts of intestinal mucosa failed to help several patients with type 1 diabetes.

• In 1932 La Barre proposed the name ‘incretin’ for a hormone extracted from the upper gut mucosa, which caused hypoglycaemia and proposed a possible therapeutic role in diabetes.

• In 1939–1940, based on their studies, Leow et al. concluded the existence of incretins was “questionable.” No further research in this area was performed for about thirty years until 1970. However, as molecular biology advanced this hypothesis was re-visited with the subsequent development of a therapeutic strategy that would revolutionise the treatment of type 2 diabetes.
The Potential for GLP-1 Agonists and Other Gut Hormones

- Limitations of native or mimetic GLP-1 as therapy
  - Rapidly degraded by DPP-4 in minutes
  - Requires continuous subcutaneous injection

- Alternative approaches
  - Modification of molecule to prolong time of action
    - Exenatide; Liraglutide
  - Agents to limit DPP-4 activity
    - DPP-4 Inhibitors: Sitagliptin, Vildagliptin, Saxagliptin, denagliptin

GLP-1 Effects

- Vomiting
- Diarrhea
- Nausea
- Abdominal pain

- Appetite↓
- Food intake↓
- = Weight loss

- Gastric emptying↓

- Insulin secretion↑
- Glucagon secretion↓
- Plasma glucose↓

GLP-1 levels achieved with incretin mimetics

GLP-1 levels achieved with incretin enhancers
## Differentiation of GLP-1-RAs

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Source&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Human-based OR exendin-4-based</td>
</tr>
<tr>
<td>Dose frequency&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Twice-daily OR once-daily OR once-weekly</td>
</tr>
<tr>
<td>Pharmacokinetics&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Short-acting OR long-acting</td>
</tr>
<tr>
<td>Receptor agonism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Transitory OR continuous</td>
</tr>
<tr>
<td>Main glycemic target&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>Prandial OR fasting</td>
</tr>
</tbody>
</table>

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## Short-Acting vs Long-Acting GLP-1 RAs: Pharmacokinetic Differences

<table>
<thead>
<tr>
<th>Category</th>
<th>Agent</th>
<th>Half-life</th>
<th>$T_{\text{max}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short-acting GLP-1 RAs</td>
<td>Exenatide bid$^a$</td>
<td>2.4 hours</td>
<td>2 h</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide$^a$</td>
<td>2.7-4.3 hours</td>
<td>1.25-2.25 hours</td>
</tr>
<tr>
<td>Long-acting GLP-1 RAs</td>
<td>Liraglutide$^a$</td>
<td>13 hours</td>
<td>8-12 hours</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide$^b$</td>
<td>90 hours</td>
<td>24-48 hours</td>
</tr>
<tr>
<td></td>
<td>Albiglutide$^a$</td>
<td>5 days</td>
<td>3-5 days</td>
</tr>
<tr>
<td></td>
<td>Semaglutide$^a$</td>
<td>~7 days</td>
<td>1-1.5 days</td>
</tr>
<tr>
<td></td>
<td>Exenatide qw$^g$</td>
<td>7-14 days</td>
<td>6-7 weeks</td>
</tr>
</tbody>
</table>

---

**Glp-1 receptor agonists**

**Short acting**
- Exenatide (twice a day)
- Liraglutide (once daily)
- Lixisenatide* (once daily)

**Long acting (one a week)**
- Exenatide QW (Bydureon)
- Albiglutide (Tanzeum)
- Dilaglutide (Trulicity)
- *Semaglutide
- *ITCA 650 pump (exenatide continuous)

*not yet approved by FDA
Potential of Once-Weekly GLP-1 Receptor Agonists: Exenatide QW

- HbA$_{1c}$ lowering = -1.6%
- Fewer gastrointestinal adverse effects than shorter-acting GLP-1 RAs
  - Incidence varies among once-weekly GLP-1 RAs
- Average weight loss = -4.3 kg
- Durability of response

Exenatide once-weekly
Albiglutide once-weekly
Dulaglutide*


[12]
Glycemic Control With GLP-1 RAs: Head-to-Head Studies

**LEAD-6**
- SU or MET ± SU
  - BL HbA1c: 8.2% 8.1%
  - Change in HbA1c (%)
    - Liraglutide 1.8 mg qd: -1.1
    - Exenatide 10 μg bid: 0.8
- *P* < 0.0001

**DURATION-6**
- MET ± SU/SU/MET+PIO
  - BL HbA1c: 8.4% 8.5%
  - Change in HbA1c (%)
    - Liraglutide 1.8 mg qd: -1.5
    - Exenatide 2 mg: -1.3
- *P* = 0.02

**HARMONY-7**
- MET ± TZD ± SU
  - BL HbA1c: 8.2% 8.2%
  - Change in HbA1c (%)
    - Liraglutide 1.8 mg qd: -1.0
    - Albiglutide 50 mg qw: -0.8
- *P* = 0.0846 for noninferiority

**AWARD-6**
- MET
  - BL HbA1c: 8.1% 8.1%
  - Change in HbA1c (%)
    - Liraglutide 1.8 mg qd: -1.4
    - Dulaglutide 1.5 mg qw: -1.4
- *P* < 0.001 for noninferiority

---

Potential Clinical Advantages of GLP-1 Receptor Agonists

- Weight reduction
- Low to no risk for hypoglycemia when used as monotherapy

Physiologic Effects of GLP-1 Receptor Agonists

• Increased GLP-1 activity
  – Decreased glucagon production\(^a\)
  – Increased insulin synthesis and secretion\(^a\)

• Glycemic control
  – Decreased HbA\(_{1c}\)\(^{b,c}\)
  – Decreased FPG\(^{a-c}\)
  – Decreased PPG\(^a\)

• Weight effects
  – Decreased gastric emptying\(^a\)
  – Decreased caloric intake\(^a\)
  – Weight loss\(^{a-c}\)

Potential for GLP-1 RAs as First-Line Therapy

- Metformin will likely remain first-line therapy
- Increasing clinical research into clinical effects of GLP-1 RAs but no current evidence that these agents improve insulin sensitivity
- Can we identify early responders to treatment?
- Cost of GLP-1 RAs currently high; may be a barrier for some

Choosing Between Agents With Low Rates of Hypoglycemia

<table>
<thead>
<tr>
<th>Antihyperglycemic Agent</th>
<th>Effect on Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1 RAs</td>
<td></td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td></td>
</tr>
<tr>
<td>SGLT-2 inhibitors</td>
<td></td>
</tr>
</tbody>
</table>
Potential Clinical Disadvantages of GLP-1 Receptor Agonists

- Compliance
- Injectable
- Gastrointestinal adverse effects
- Training requirements
- High cost

Pharmacologic Treatment Options for Type 2 Diabetes (2 of 4)

Lifestyle interventions—diet, exercise, and education—are the foundation of any type 2 diabetes treatment program.

<table>
<thead>
<tr>
<th>Class/Agent(s)</th>
<th>Cost</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine-2 agonists</td>
<td>High</td>
<td>No hypoglycemia</td>
<td>Modest A1C efficacy</td>
</tr>
<tr>
<td>• Bromocriptine (quick release)</td>
<td></td>
<td>CVD events</td>
<td>Dizziness/syncope, Nausea, Fatigue, Rhinitis</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>High</td>
<td>No hypoglycemia</td>
<td>Urticaria, angioedema, Acute pancreatitis, Heart failure hospitalization</td>
</tr>
<tr>
<td>• Linagliptin</td>
<td></td>
<td>Well tolerated</td>
<td></td>
</tr>
<tr>
<td>• Sitagliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Alogliptin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Vilagliptin†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>High</td>
<td>No hypoglycemia</td>
<td>GI side effects (nausea, vomiting, diarrhea), Acute pancreatitis</td>
</tr>
<tr>
<td>• Exenatide (regular, XR)</td>
<td></td>
<td>Weight reduction</td>
<td>C-cell hyperplasia/medullary thyroid tumors, Heart rate</td>
</tr>
<tr>
<td>• Liraglutide</td>
<td></td>
<td>Decreases PPG excursions</td>
<td>Injectable, Training requirements</td>
</tr>
<tr>
<td>• Albiglutide</td>
<td></td>
<td>Decreases some CVD risk factors</td>
<td></td>
</tr>
<tr>
<td>• Dulaglutide</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lixisenatide†</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 receptor agonists
—Exenatide (regular, XR)
—Liraglutide
—Albiglutide
—Dulaglutide
—Lixisenatide†

<table>
<thead>
<tr>
<th>Cost</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>No hypoglycemia</td>
<td>GI side effects</td>
</tr>
<tr>
<td></td>
<td>Weight reduction</td>
<td>May cause acute pancreatitis</td>
</tr>
<tr>
<td></td>
<td>Decreases PPG excursions</td>
<td>C-cell hyperplasia/medullary thyroid tumors</td>
</tr>
<tr>
<td></td>
<td>Decreases some CVD risk factors</td>
<td>Heart rate, Injectable, Training requirements</td>
</tr>
</tbody>
</table>

*Limited use in US, †In animals, ‡Not FDA approved in US

Inazuchi SE et al. Diabetes Care, 2015;38(1) 140-149.
Combination of Basal Insulin with a GLP-1 Agonist Has a Scientific Logic

Complementary actions

Basal insulin analogs
- Simple to initiate
- Control nocturnal and FPG
- Lower hypoglycaemia risk vs NPH
- Modest weight increase (1–3 kg)
- Achieve A1C targets in ~50–60%

GLP-1 agonists
- Simple to initiate
- Pronounced PPG control
- No increase in hypoglycaemia
- Weight lowering/neutral effects
- Achieve A1C targets in ~40–60%

Additive effects
## IDegLira* vs Glargine

### Comparison of Efficacy and Safety in DUAL V

Degludec and liraglutide

<table>
<thead>
<tr>
<th>Study Parameter</th>
<th>IDegLira* (N = 278)</th>
<th>Glargine (N = 279)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA$_{1c}$ at randomization, %</td>
<td>8.4</td>
<td>8.2</td>
<td>-</td>
</tr>
<tr>
<td>Mean HbA$_{1c}$ at wk 26, %</td>
<td>6.6</td>
<td>7.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HbA$_{1c}$ change at wk 26, %</td>
<td>-1.8</td>
<td>-1.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HbA$_{1c}$ &lt; 7% at wk 26, %</td>
<td>71.6</td>
<td>47.0</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body weight at baseline, kg</td>
<td>88.3</td>
<td>87.3</td>
<td>-</td>
</tr>
<tr>
<td>Body weight at wk 26, kg</td>
<td>86.9</td>
<td>89.1</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Body weight change at wk 26, kg</td>
<td>-1.4</td>
<td>+1.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Hypoglycemia rate, events/patient year of exposure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Confirmed</td>
<td>2.23</td>
<td>5.05</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Nocturnal</td>
<td>0.22</td>
<td>1.23</td>
<td>&lt; .001</td>
</tr>
</tbody>
</table>

*The US FDA has not approved this medication for use.

# LixiLan* vs Glargine

## Proof-of-Concept Study in Patients With T2D Inadequately Controlled on Metformin

<table>
<thead>
<tr>
<th>Lixenatide GLP-1 RA</th>
<th>LixiLan (N = 161)</th>
<th>Glargine (N = 162)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HbA$_{1c}$, %</td>
<td>8.1</td>
<td>8.0</td>
</tr>
<tr>
<td>Mean HbA$_{1c}$ at week 24, %</td>
<td>6.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Change in HbA$_{1c}$ at week 24, %</td>
<td>-1.8</td>
<td>-1.5</td>
</tr>
<tr>
<td>Proportion achieving HbA$_{1c}$ &lt; 7.0%, %</td>
<td>84.4</td>
<td>78.3</td>
</tr>
<tr>
<td>Body weight at baseline, kg</td>
<td>90.3</td>
<td>91.7</td>
</tr>
<tr>
<td>Body weight at week 24, kg</td>
<td>89.1</td>
<td>92.1</td>
</tr>
<tr>
<td>Change in body weight at week 24, kg</td>
<td>-1.2</td>
<td>+0.4</td>
</tr>
<tr>
<td>Proportion with documented hypoglycemia (≤ 70 mg/dL), %</td>
<td>22</td>
<td>23</td>
</tr>
</tbody>
</table>

*The US FDA has not approved this medication for use.

Rosenstock J, et al. ADA 2014. Abstract 332-OR.\textsuperscript{[14]}

Safety – Patient Education

• “Both [the FDA and EMA] agree that assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer, as expressed recently in the scientific literature and in the media, are inconsistent with the current data.”\textsuperscript{a}

• Educate patients; monitor for signs and symptoms of pancreatitis; ask about medical history of pancreatitis.\textsuperscript{a,b}

• Discontinue the GLP-1 receptor agonist if pancreatitis symptoms occur.\textsuperscript{a,b}

\textsuperscript{b} EMA website.\textsuperscript{[18]}