Session 10: Drugs

GLP-1 receptor agonists

Dr. Manel Mata

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Grup DAP_Cat, Barcelona Research Support Unit. IDIAP-Jordi Gol. CIBERDEM. RedGDPS (Spanish Network of Primary Care Groups for the Study of Diabetes)
Session 10: Drugs

GLP-1 receptor agonists

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Conflict of interest disclosure:

Honoraria from AstraZeneca, GlaxoSmithKline, Eli Lilly, Novo Nordisk and Sanofi for the participation in advisory boards and lectures about the treatment of diabetes.
Session 10: Drugs
GLP-1 receptor agonists

Agenda

- Mechanism of action and benefits
- GLP-1ra in the algorithms
- GLP-1ra as alternative to basal insulin
- GLP-1ra as alternative to prandial insulin added to basal insulin
- Adverse Effects. Cardiovascular and pancreatic safety
- Key factors when choosing a GLP-1ra
- Messages to take home
The ‘ideal’ drug for type 2 diabetes

- Safe
- Efficacious
- Durable control
- Well-tolerated
- Low risk of hypoglycaemia
- Weight neutral or weight loss
- Reduction of long term complications

Metformin is the recommended first line agent
GLP-1ra are a good option in the second and third steps
GLP-1 is released by the small intestine after meal ingestion and enhances glucose-stimulated insulin secretion (*incretin action*.)

Kerr Saraiva F & Sposito AC. Cardiovasc Diabetol. 2014;13(142)
Pleiotropic effects of GLP-1 and GLP-1ra

Kerr Saraiva F & Sposito AC. Cardiovasc Diabetol. 2014;13(142)
GLP-1ra different effects based on the duration of their action in the receptor

Exenatide BID
Lixisenatide

Dulaglutide
Exenatide LAR
Albiglutide
Liraglutide

Madsbad S. Diabetes Obes Metab. 2016;18(4):317-32
### GLP-1 receptor agonists

<table>
<thead>
<tr>
<th>Brand Name</th>
<th>Injection Frequency</th>
<th>Usual Dose</th>
<th>Clinical Trial Program</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>Byetta®</td>
<td>Twice daily</td>
<td>10 μg</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Lyxumia®</td>
<td>Once daily</td>
<td>20 mg</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Victoza®</td>
<td>Once daily</td>
<td>1.2-1.8 mg</td>
</tr>
<tr>
<td>Exenatide LAR</td>
<td>Bydureon®</td>
<td>Once weekly</td>
<td>2 mg</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Eperzan®</td>
<td>Once weekly</td>
<td>50 mg</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Trulicity®</td>
<td>Once weekly</td>
<td>1.5 mg</td>
</tr>
</tbody>
</table>

### Favorable effects

- ↓↓ HbA1c
- ↓↓ Weight
- ↑ Satiety
- ↓ Blood Pressure
- No Hypoglycaemia
- Neutral or ↓ CVD

### Adverse effects

- ↑↑↑ Nausea
- ↑ Diarrhea
- ↑ Vomiting
- ↑ Heart Rate
- ↑ Pancreatitis
- Pancreas cancer (?)
GLP-1ra in the algorithm of T2DM treatment
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dci14-2441
Need for personalized care: the benefits versus risks of diabetes therapy must be assessed for each patient.
ADA/EASD Position Statement
A patient-centered approach

Based on:

Preferences, needs and values of the patient
Shared decisions
Resources and support
Patients’ preferences related to the effects of T2DM treatment
Monthly willingness to pay in Denmark

N=270

WTP for Beneficial Attributes

WTP to avoid detrimental attributes

45-50% of T2DM patients are obese

50-75% of T2DM patients have metabolic syndrome
Weight and antidiabetic drugs

- GLP-1ra
- SGLT-2i
- Metformin
- AGi
- DPP-4i
- Glitazones
- Glinides
- Sulfonylureas
- Insulin
The consequences of hypoglycaemia

- Coma
- Hospitalisation costs
- Cardiovascular complications
- Death
- Increased risk of dementia
- Reduced quality of life
- Increased risk of car accident
- Increased risk of seizures
- Weight gain due to defensive eating
- Loss of consciousness

References:
Benefits
HbA1c reduction
Reduced complications

Safety
Hypoglycaemia
Weight gain
Specific adverse effects
Long-term side effects

Cost

T2DM treatment choice
Risks vs Benefits
Annual cost of antidiabetic drugs in Spain

- ArGLP-1
- ISGLT-2
- IDPP-4
- Pioglitazone
- Inh. α-Glucosidases
- Repaglinida
- Sulfonylureas
- Metformina
Evolution of new antidiabetic drugs in Catalunya (Spain) from 2007 to 2013

-% patients

2007 2008 2009 2010 2011 2012 2013

DPP4i
Glinides
Glitazones
GLP1ra
GLP-1ra in the 2015 Nice guideline

Second Intensification of drug treatment (triple therapy)

1.6.28 If triple therapy with metformin and 2 other oral drugs (see recommendation 1.6.27) is not effective, not tolerated or contraindicated, consider combination therapy with metformin, a sulfonylurea and a glucagon-like peptide-1 (GLP-1) mimetic for adults with type 2 diabetes who:

- have a BMI of 35 kg/m² or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) and specific psychological or other medical problems associated with obesity or

- have a BMI lower than 35 kg/m² and:
  - for whom insulin therapy would have significant occupational implications or
  - weight loss would benefit other significant obesity-related comorbidities. [new 2015]
GLP-1ra in the 2015 Nice guideline

Stop if no efficacy (HbA1c+weight loss)

1.6.29 Only continue GLP-1 mimetic therapy if the person with type 2 diabetes has had a beneficial metabolic response (a reduction of at least 11 mmol/mol [1.0%] in HbA1c and a weight loss of at least 3% of initial body weight in 6 months). [2015]

1.6.31 In adults with type 2 diabetes, only offer a GLP-1 mimetic in combination with insulin with specialist care advice and ongoing support from a consultant-led multidisciplinary team[^]. [new 2015]
GLP1ra vs oral antidiabetic drugs
GLP-1ra vs DPP4i in patients treated with Metformin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Δ mean HbA1c from baseline (%)</th>
<th>Exe 1/w</th>
<th>Sita 1/d</th>
<th>Liraglutide vs Sitagliptin</th>
<th>Dula 1.5 1/w</th>
<th>Sita 1/d</th>
<th>Albiglutide vs Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide LAR vs Sitagliptin¹</td>
<td>-1.5</td>
<td>-0.9</td>
<td>-1.5</td>
<td>-1.5</td>
<td>-1.1</td>
<td>-0.4</td>
<td>-0.6</td>
</tr>
<tr>
<td>Dulaglutide vs Sitagliptin²</td>
<td>-0.9</td>
<td>-0.9</td>
<td>-1.1</td>
<td></td>
<td></td>
<td>-0.4</td>
<td>-0.3</td>
</tr>
<tr>
<td>Liraglutide vs Sitagliptin³</td>
<td>-1.2</td>
<td></td>
<td>4.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albiglutide vs Sitagliptin⁴</td>
<td>-0.3</td>
<td></td>
<td>1.7</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Weight (kg): -2.3 -0.8 -3.0 -1.2 -3.0 -1.5 -1.2 -0.9
Hypos (%): 2.0 1.5 5.0 5.0 10.2 4.8 3 1.7

GLP1ra vs basal insulin
GLP-1ra vs basal insulin in patients treated with Met ± SU

Daily Liraglutide

LEAD 5

Lira Glargine

-1.3

Weekly Exenatide

DURATION 3

Exe Glargine

-1.2

-1.0

Weekly Albiglutide

HARMONY 4

Albi Glargine

-0.7

-0.8

Weekly Dulaglutide

AWARD 2

Dula Glargine

-0.9

-0.6

Δ mean HbA1c from baseline (%)

Weight (kg):

-1.8 +1.6

-2.1 +2.4

-1.1 +2.6

-1.9 +1.4

Hypos (%):

27 29

36 56

17 27

54 69

DURATION-3:
79% of patients treated with Once Weekly Exenatide lost weight and reduced HbA1c vs 31% with Glargine

Modified ITT population, N=448.
GLP1ra vs prandial insulin in patients on basal insulin
Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes

Diabetes Care 2015;38:140–149 | DOI: 10.2337/dc14-2441

**Basal insulin**
(usually with metformin +/- other noninsulin agent)

- **Start:** 10 U/day or 0.1–0.2 U/kg/day
- **Adjust:** 10–15% or 2–4 U once/twice weekly to reach FBG target.
- **For hypo:** Determine and address cause;↓ dose by 4 U or 10–20%.

---

**Add 1 rapid insulin** injection before largest meal

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose. If HbA1c<8%, consider basal by same amount.
- **Adjust:** ↑ dose by 1–2 U or 10–15% once/twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause;↓ corresponding dose by 2–4 U or 10–20%.

---

**Consider GLP1 ra**

**Add ≥2 rapid insulin** injections before meals (**basal–bolus**)

- **Start:** 4 U, 0.1 U/kg, or 10% basal dose/meal.
  - If HbA1c<8%, consider basal by same amount

---

**Change to premixed insulin** twice daily

- **Start:** Divide current basal dose into 2/3 AM, 1/3 PM or 1/2 AM, 1/2 PM,
- **Adjust:** ↑ dose by 1–2 U or 10–15% once/twice weekly until SMBG target reached.
- **For hypo:** Determine and address cause;↓ corresponding dose by 2–4 U or 10–20%.

---

If not controlled, consider basal-bolus.
GLP-1ra vs prandial insulin in patients on basal insulin

<table>
<thead>
<tr>
<th>Treatment Comparison</th>
<th>∆ mean HbA1c from baseline (%)</th>
<th>Weight (kg)</th>
<th>Major hypos</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily Exenatide vs Lispro¹</td>
<td>EXE 2/d</td>
<td>Lispro 3/d</td>
<td>-1.13</td>
</tr>
<tr>
<td>Albiglutide vs Lispro²</td>
<td>ALBI 1/sem</td>
<td>Lispro 3/d</td>
<td>-0.82</td>
</tr>
<tr>
<td>Liraglutide vs Aspart³</td>
<td>LIRA 1/d</td>
<td>Aspart 1/d</td>
<td>-0.74</td>
</tr>
<tr>
<td>Lixisenatide vs Glulisine⁴</td>
<td>LIXI 1/d</td>
<td>Glulisine 3/d</td>
<td>-0.6</td>
</tr>
</tbody>
</table>

4. Rosenstock J et al. Poster ADA 2015; Boston, USA
GLP-1ra

Gastrointestinal Adverse Effects
Pancreatitis and pancreas cancer
Cardiovascular Safety
## GLP1ra Adverse Effects

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Albiglutide</th>
<th>Placebo</th>
<th>Dulaglutide 1.5</th>
<th>Placebo</th>
<th>Liraglutide 1.8</th>
<th>Placebo</th>
<th>Exenatide LAR</th>
<th>Placebo</th>
<th>Lixisenatide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13.1</td>
<td>10.5</td>
<td>12.6</td>
<td>6.7</td>
<td>17.1</td>
<td>3</td>
<td>13</td>
<td>0</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Nausea</td>
<td>11.1</td>
<td>9.6</td>
<td>21.1</td>
<td>5.3</td>
<td>28.4</td>
<td>5.3</td>
<td>27</td>
<td>15</td>
<td>23</td>
<td>4</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4.2</td>
<td>2.6</td>
<td>12.7</td>
<td>2.3</td>
<td>11</td>
<td>2.3</td>
<td>0</td>
<td>0</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Injection-site reactions</td>
<td>10.5</td>
<td>2.1</td>
<td>0.5</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>10.5</td>
<td>0</td>
<td>4.6</td>
<td>0</td>
</tr>
<tr>
<td>Heart rate increase (bpm)</td>
<td>+1-2</td>
<td>Ref</td>
<td>+2-3</td>
<td>Ref</td>
<td>+1-2</td>
<td>Ref</td>
<td>0</td>
<td>Ref</td>
<td>0</td>
<td>Ref</td>
</tr>
</tbody>
</table>

No increase in hypoglycaemias
Small increase in pancreatitis
Risk of pancreas cancer (?)
Conclusions
The available evidence suggests that the incidence of pancreatitis among patients using incretins is low and that the drugs do not increase the risk of pancreatitis.

Li L et al. BMJ. BMJ 2014;348:g2366 doi: 10.1136/bmj.g2366 (Published 14 April 2014)
Both agencies 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.

Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs until more data are available; both agencies continue to investigate this safety signal.

Egan AG et al. NEJM 2014; 370(9) Pub Online 27 February 2014
ELIXA: Lixisenatide vs placebo in 6,060 T2DM with a recent coronary event*, mean follow-up 2 years.

**Primary endpoint**

HR (95% CI): 1.017 (0.886, 1.168)

*AMI or Unstable Angina in the previous 180 days*
4/3/16: Novo Nordisk announces that Liraglutide reduces CVD

CardioBrief: Big Victoza Trial Confirms Cardiovascular Benefit
— Drug cut CV deaths, heart attacks, strokes in LEADER, says manufacturer

29/4/16: Novo Nordisk announces that Semaglutide reduces CVD

Medscape Medical News
Now Novo Says Semaglutide Cuts CV Risk: SUSTAIN-6 Top-line Data
Lisa Nainggolan
April 29, 2016

Just over a month after Novo Nordisk announced positive top-line results for liraglutide (Victoza, Novo Nordisk), showing that it significantly reduced the risk of major adverse cardiovascular events in the LEADER Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results—A Long Term Evaluation (LEADER) trial, the company has announced...
GLP1ra choice based on:
- Head to Head studies?
- Efficacy
- Tolerability
- Patient convenience?
- Frequency of injection
- Device
Review of head-to-head comparisons of GLP-1ra Effects on HbA1c

HbA1c reduction

Liraglutide  ****
Dulaglutide  *****
Exenatide OW  ***
Exenatide BID  **
Lixisenatide  **
Albiglutide  **

Madsbad S. Diabetes Obes Metab. 2016;18(4):317-32
Review of head-to-head comparisons of GLP-1ra 
Effects on Weight

<table>
<thead>
<tr>
<th>Baseline weight (kg)</th>
<th>DURATION-1</th>
<th>DURATION-5</th>
<th>Ji et al.</th>
<th>DURATION-6</th>
<th>LEAD-6</th>
<th>GetGoal-X</th>
<th>HARMONY 7</th>
<th>AWARD-6</th>
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<tbody>
<tr>
<td></td>
<td>102</td>
<td>102</td>
<td>97</td>
<td>94</td>
<td>70</td>
<td>70</td>
<td>91</td>
<td>91</td>
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<tr>
<td>Weight reduction</td>
<td>-3.7</td>
<td>-3.6</td>
<td>-1.4</td>
<td>-1.6</td>
<td>-2.5</td>
<td>-2.7</td>
<td>-3.6</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Change from baseline in weight (kg)

- Liraglutide ****
- Dulaglutide ***
- Exenatide OW ***
- Exenatide BID ***
- Lixisenatide ***
- Albiglutide *

Madsbad S. Diabetes Obes Metab. 2016;18(4):317-32
### GLP1ra Adverse effects in Head to Head studies

#### Gastrointestinal AE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Nausea</th>
<th>Vomiting</th>
<th>Diarrhea</th>
<th>Injection-site reactions</th>
<th>Withdrawal due to AEs (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide OW</td>
<td>DURATION-6 [Buse et al. 2013]</td>
<td>43/461</td>
<td>17/461</td>
<td>28/461</td>
<td>73/461</td>
<td>12</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>HARMONY-7 [Pratley et al. 2014]</td>
<td>40/404</td>
<td>20/404</td>
<td>60/404</td>
<td>52/404</td>
<td>31</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>AWARD-1 [Wysham et al. 2014]</td>
<td>78/279</td>
<td>47/279</td>
<td>31/279</td>
<td>1279</td>
<td>8</td>
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<tr>
<td>Exenatide</td>
<td>AWARD-6 [Dungan et al. 2014]</td>
<td>61/299</td>
<td>21/299</td>
<td>36/299</td>
<td>1299</td>
<td>18</td>
</tr>
</tbody>
</table>

*Trujillo JM et al. Ther Adv Endocrinol Metab. 2015 Feb;6(1):19-28*
Daily GLP-1ra

- Exenatide BID, Byetta®
- Liraglutide, Victoza®
- Lixisenatide, Lyxumia®

Weekly GLP-1ra

- Exenatide LAR, Bydureon®
- Albiglutide, Eperzan®
- Dulaglutide, Trulicity®
How to select a GLP-1ra?

Use in clinical practice should be customized for individual patients, based on clinical profile and patient preferences

<table>
<thead>
<tr>
<th>GLP-1ra</th>
<th>HbA1c reduction</th>
<th>Weight loss</th>
<th>Postprandial effect</th>
<th>GI effects</th>
<th>Site reactions</th>
<th>Frequency injection</th>
<th>Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>BID</td>
<td>+++</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>++</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>OD</td>
<td>+++</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>+++</td>
<td>+++++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>OD</td>
<td>+++</td>
</tr>
<tr>
<td>Exenatide LAR</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>OW</td>
<td>+</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>OW</td>
<td>++</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>OW</td>
<td>++++</td>
</tr>
</tbody>
</table>
Messages to take home

- GLP-1ra reduce HbA1c, weight, blood pressure and probably cardiovascular events, but are of limited use in primary care mainly because of its high cost.

- GLP-1ra are preferable in the second and third steps of treatment in obese patients as an alternative to basal or prandial insulin with fewer injections, no need of blood glucose monitoring or dose adjustments.

- Adverse gastrointestinal effects (mainly nausea) are frequent but are usually well tolerated and improve spontaneously after several weeks. Don’t use them in patients with history of pancreatitis, gastroparesia or severe renal failure.

- GLP-1ra use in clinical practice should be customized to individual patients, based on their clinical profile and patients preferences.
Thanks for your attention

manelmatacases@gmail.com
CV Outcome trials in Type 2 Diabetes

- **ORIGIN**
  Insulin glargine Sanofi (6/12)

- **SAVOR TIMI 53**
  Saxagliptin AZ/BMS (6/13)

- **EXAMINE**
  Alogliptin Takeda (12/13)

- **TECOS**
  Sitagliptin Merck (12/14)

- **LEADER**
  Liraglutide Novo (1/16)

- **FREEDOM-CVO**
  ItCA650 Servier (7/17)

- **SUSTAIN 6**
  Semaglutide Novo (1/16)

- **EXSCEL**
  Exenatide LAR Amylin (3/17)

- **ELIXA**
  Lixisenatide Sanofi (5/14)

- **EMPA-REG OUTCOME**
  Empagliflozin BI/Lilly (8/15)

- **CANVAS (interim)**
  Canagliflozin J&J 200 events (subm: 1/12)

- **CAROLINA**
  Linagliptin BI/Lilly (9/18)

- **MK-3102-018**
  Omarigliptin Merck (12/20)

- **REWIND**
  Dulaglutide Lilly (4/19)

- **C‐SCADE 8**
  Empagliflozin BI/Lilly (3/18)

- **DECLARE**
  Dapagliflozin BMS/AZ (04/19)

- **--**
  Ertugliflozin MSD (04/20)
Cardiac effects of GLP-1 and GLP-1ra

GLP1ra vs. DPP4i: HbA1c and weight changes

DURATION-2 (26 weeks)

Baseline HbA1c: 8.5%  

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HbA1c (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg OD</td>
<td>-0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exenatide 2 mg OW</td>
<td>-1.5</td>
<td></td>
</tr>
</tbody>
</table>

LIRA-DPP-4 (52 weeks)

Baseline HbA1c: 8.5%

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change in HbA1c (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin 100 mg OD</td>
<td>-0.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg OD</td>
<td>-1.3</td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg OD</td>
<td>-1.5</td>
<td></td>
</tr>
</tbody>
</table>

Weight (kg)

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>DURATION-2</th>
<th>LIRA-DPP-4</th>
</tr>
</thead>
<tbody>
<tr>
<td>-0.8</td>
<td>-2.3</td>
<td>-1.2</td>
</tr>
<tr>
<td>-2.3</td>
<td>-1.2</td>
<td>-2.8</td>
</tr>
<tr>
<td>-1.2</td>
<td>-2.8</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Harmony 8: Albiglutide vs Sitagliptin in Renal Impaired

Model-Adjusted\(^a\) Change From Baseline in HbA\(_{1c}\) At Week 26 by Severity of Renal Impairment (ITT-LOCF)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild 60-89</th>
<th>Moderate 30-59</th>
<th>Severe 15-29, mL/min/1.73 m(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA(_{1c}), %</td>
<td>n = 125</td>
<td>n = 98</td>
<td>n = 19</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>-0.80</td>
<td>-0.83</td>
<td>-1.08</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>-0.67</td>
<td>-0.31</td>
<td>-0.61</td>
</tr>
</tbody>
</table>

\(^a\) Based on analysis of covariance (ANCOVA)

<table>
<thead>
<tr>
<th>HbA(_{1c}), %</th>
<th>Albiglutide</th>
<th>Sitagliptin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model-adjusted LS mean change from baseline</td>
<td>-0.83</td>
<td>-0.52</td>
</tr>
<tr>
<td>Treatment difference (albiglutide vs. sitagliptin) (CI 95%)</td>
<td>-0.32 (-0.49, -0.15)</td>
<td>0.0003</td>
</tr>
</tbody>
</table>

\(^a\)Efficacy data through week 26 in the safety population using an LOCF analysis

Adapted from Leiter LA, et al. Diabetes Care 2014;37:2723-30 [Supplement]
Dulaglutide vs sitagliptin vs placebo

AWARD-5 trial:
1098 T2DM patients on metformin, 52 weeks

<table>
<thead>
<tr>
<th></th>
<th>HbA1c</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>DU 1.5</td>
<td>-1.22</td>
<td>-3.03</td>
</tr>
<tr>
<td>DU 0.75</td>
<td>-1.01</td>
<td>-2.60</td>
</tr>
<tr>
<td>Sita</td>
<td>-0.61</td>
<td>-1.53</td>
</tr>
<tr>
<td>Placebo</td>
<td>+0.03</td>
<td>-1.50</td>
</tr>
</tbody>
</table>

Liraglutide vs insulin glargine and placebo in combination with metformin and sulfonylurea therapy in type 2 diabetes mellitus (LEAD-5 met+SU): a randomised controlled trial

LEAD-5; N=581, 26 weeks

<table>
<thead>
<tr>
<th>AE</th>
<th>Lira</th>
<th>Gla*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any hypo</td>
<td>27.4%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Major hypo</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>10.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>13.9%</td>
<td>1.3%</td>
</tr>
</tbody>
</table>

*Mean daily dose: 24 UI/day

Safety and Efficacy of Once-Weekly Exenatide Compared With Insulin Glargine Titrated to Target in Patients With Type 2 Diabetes Over 84 Weeks

DURATION-3; N=415, 84 weeks

<table>
<thead>
<tr>
<th>AE</th>
<th>ExeW</th>
<th>Gla*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypos**</td>
<td>12%</td>
<td>40%</td>
</tr>
<tr>
<td>Hypos***</td>
<td>36%</td>
<td>56%</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>12%</td>
<td>6%</td>
</tr>
<tr>
<td>Nausea</td>
<td>15%</td>
<td>1%</td>
</tr>
</tbody>
</table>

* Mean daily dose: 35 UI/d
** Symptomatic in patients on Met
*** Symptomatic in patients on SU+Met

HbA1c

- Exe -1.2
- Gla -1.0

Weight

- Exe -2.1
- Gla +2.4

HARMONY 4: randomised clinical trial comparing once-weekly albiglutide and insulin glargine in patients with type 2 diabetes inadequately controlled with metformin with or without sulfonylurea

Weissman PN, et al. Diabetologia 2014;57:2475-84

*Mean daily dose: 30UI
### Dulaglutide vs insulin Glargine (AWARD 2)

add-on to Metformin ± glimepiride, 78 weeks


N=810, 78 weeks  
Glargine, Dulaglutide 0.75 and 150 mg

<table>
<thead>
<tr>
<th></th>
<th>Dulaglutide 1.5 mg</th>
<th>Glargine 0.75 mg</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>-0.59</td>
<td>-0.62</td>
<td>-0.90</td>
</tr>
<tr>
<td>Weight</td>
<td>-1.33</td>
<td>-1.87</td>
<td></td>
</tr>
</tbody>
</table>

**Dula 1.5 Glargina**

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Dulaglutide 1.5 mg</th>
<th>Glargine 0.75 mg</th>
<th>Glargine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypos</td>
<td>54.4%</td>
<td>69.1%</td>
<td></td>
</tr>
<tr>
<td>Major Hipos</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>10.6%</td>
<td>5.7%</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>15.4%</td>
<td>1.5%</td>
<td></td>
</tr>
</tbody>
</table>

* Mean daily dose: 29 UI
**Comparativa de guías: Tratamiento de DM tipo 2 (sin insulinaización)**

**AACE 2015**

**MONOTERAPIA:** Iniciar tratamiento con 1ª línea (primera opción MET, ver *tabla*) en pacientes con A1C <7.5% (GR C; NE 3), considerando SU, TZD o glinidas como alternativas (GR C; NE 3)

**TERAPIA DUAL:** (de entrada si HbA1c > 7.5%; GR C; NE 3): MET u otro agente 1ª línea + fármaco de *tabla 2*
- arGLP-1 más útil en terapia dual que en monoterapia
- Recomienda insulina (sola o combinada) si A1C>9% y sintomático (GR A; NE 1)

**TRIPLE TERAPIA:** fármaco de 1ª línea + fármaco 2ª línea + fármaco de *tabla 2* (orden sugerido: arGLP-1, T2D, insulina basal, IDPP-4, α-glucosidasa, SU/glinidas)

**ADA 2016**

**MONOTERAPIA:** MET es 1ª opción (si no es posible, opciones de *tabla 1*). Considerar insulina si síntomas de hiperglicemia, glucemia 300-350 mg/dl o A1C 10-12% (NE E)

**TERAPIA DUAL:** añadir cualquier opción de la *tabla 1* (NE A). Considerar de entrada si A1C is ≥5%
- Enfoque según las características del paciente: efecto, coste, potenciales efectos secundarios, peso, comorbilidades, riesgo de hiperlipidemia y preferencias del paciente (NE E)

**TRIPLE TERAPIA:** MET + (SU o TZD) admite cualquier de *tabla 1*. En triple terapia, la insulina suele ser basal. arGLP-1 solo se combina con MET, SU, TZD o insulina (habitualmente basal), no se considera con IDPP-4 ni ISGLT-2

**NICE 2015**

**MONOTERAPIA:** A1C≥6,5% con cambios de estilo de vida: 1ª opción MET. Si no, considerar: IDPP-4, TZD (pio) o SU

**TERAPIA DUAL:** (si A1C≥7,5%): MET u otro agente (*tabla 1ª intensificación*)
- Opciones sin MET: IDPP-4 + TZD o SU; SU + TZD. ISGLT-2 es otra opción para combinar (MET o los anteriores)

**TRIPLE TERAPIA:** Las opciones con MET en *tabla 2ª intensificación*. En ese escenario también valorar insulinação. Si contraindicación o intolerancia de esos pautas, considerar:
- MET+SU+arGLP-1 (especialmente si IMC≥35), continuando arGLP-1 si reducción A1C1≤9% y ≥3% de peso inicial en 6 meses
- Si la pauta dual no incluye MET, considerar insulinação

**CDA 2015**

**MONOTERAPIA:** MET es 1ª opción si A1C<7 y <8,5 con sobrepeso (GR A; NE 1) o sin sobrepeso (GR D, consenso)
- Si ≥ 8,5 considerar combinación inicial (GR D, consenso). Insulina si síntomas (GR D, consenso)

**TERAPIA COMBINADA:** añadir a MET cualquier opción de diferente clase (*tabla*), individualizando según características del paciente y del fármaco (GR D, consenso)
- No recomendaciones específicas para triple terapia
- Si se combina insulina (prevención de picoglibazona), preferible duración larga a intermedia (GR A; NE 1A)
Review of head-to-head comparisons of GLP-1ra Effects on HbA1c

Trujillo JM et al. Ther Adv Endocrinol Metab 2015; 6(1):19-28
Review of head-to-head comparisons of GLP-1ra
Effects on Weight

Trujillo JM et al. Ther Adv Endocrinol Metab 2015; 6(1):19-28