Pro et contra of incretin therapy in type 2 diabetes

Dario Rahelić

Department of Endocrinology, Diabetes and Metabolic Disorders
Dubrava University Hospital
Zagreb, Croatia

14th EFLM Continuing Postgraduate Course in Clinical Chemistry and Laboratory Medicine, Dubrovnik, Croatia, October 26th 2014
590 000 000
241990
United Nations Resolution 61/225: World Diabetes Day

On 20 December 2006, the United Nations General Assembly passed Resolution 61/225. This landmark Resolution recognizes diabetes as a chronic, debilitating and costly disease associated with major complications that pose severe risks for families, countries and the entire world. It designates 14 November, the current World Diabetes Day, as a United Nations Day to be observed every year beginning in 2007.

December 20, 2006
This United Nations resolution recognized that tackling diabetes is likely to be one of the most important challenges for the global public health community in the 21st century.
President Obama proclaims November 2010 as National Diabetes Month to support diabetics

November 3, 2010 — President Barack Obama recently proclaimed November 2010 to be National Diabetes Month, during which he urged Americans to learn the risk factors and warning signs that are associated with type 1 and type 2 diabetes.

Approximately 24 million diabetics live with this diagnosis in the U.S. today. Type 1 diabetes - commonly known as juvenile onset diabetes - is most often diagnosed in young people, while the risk of type 2 diabetes is highest among individuals who are older, overweight, inactive or have a family history of diabetes.
1552 BC- an Egyptian healer Hesy-Ra wrote about a disease with frequent urination as one symptom.
250 BC first time word *Diabetes* was mentioned
1921-Insulin discovery
First patient who received insulin: Leonard Thompson (1908 – 1935)

December 15th 1922

February 15th 1923
How First looks in pictures......

Early advertisements informed the public of the availability of the first commercial insulin in 1923. It was manufactured and marketed by Eli Lilly and Company.

The **first insulin vials** and first U-20 and U-40 formulations were packaged in wooden containers. (1923)

An insulin filling line (up) and finishing line (down), at Eli Lilly and Company, the first company to mass produce insulin, beginning in 1923.

First News paper publication – **Toronto Daily Star**
DIET ADJUSTMENT AND INSULIN THERAPY IN DIABETES MELLITUS

By ERNEST S. du BRAY, M.D., San Francisco
(From the Department of Medicine in the University of California Medical School.)

I. Introduction—In a sub-titude, as expressed be possibl. appear of uncomplica the pancrea that diet diabetic manag

By George Graham, M.D., F.R.C.P.Lond., Assistant Physician, St. Bartholomew's Hospital; Physician, Royal Northern Hospital.

In opening a discussion on the present position of the treatment of diabetes with insulin it is unnecessary to speak about some aspects which had to be considered a nd rather discuss the principles which will agree that while

NOTES, COMMENTS, AND ABSTRACTS.

THE PRESENT POSITION OF INSULIN THERAPY.

By George Graham, M.D., F.R.C.P.Lond., Assistant Physician, St. Bartholomew's Hospital; Physician, Royal Northern Hospital.

In opening a discussion on the present position of the treatment of diabetes with insulin it is unnecessary to speak about some aspects which had to be considered and rather discuss the principles which will agree that while

Indications for Insulin Therapy.

When insulin was first introduced it was said that if patients could take a reasonable amount of food, say 50 g. of carbohydrate and an adequate caloric value, without passing sugar, it was unnecessary to give them insulin. This view is still held by some, but I have never accepted it. The improvement which occurs in the clinical condition after a small dose of insulin, 5, 10, or 15 units, is very striking. The patient gains weight and feels capable of doing work, even if no change is made in the diet. This other process besides the sugar acids containing one or more of the basic constituents lysine, arginine, and histidine. The raw material from which the protamines are obtained is the ripe sperm of fish. Investigating the solubility in serum of various protamines Hagedorn and his colleagues finally hit upon a protamine (not hitherto described) from the sperm of Salmo irideus, which formed a compound with insulin having a lower solubility than any they had so far used: the minimum solubility is reached at a pH of 7.3—that is, near the reaction of serum. For a period of more than two years they treated about eighty-five
Notes, Comments, and Abstracts.

THE PRESENT POSITION OF INSULIN THERAPY.*

BY GEORGE GRAHAM, M.D., F.R.C.P.LOND.,
ASSISTANT PHYSICIAN, ST. BARTHOLOMEW'S HOSPITAL;
PHYSICIAN, ROYAL NORTHERN HOSPITAL.

In opening a discussion on the present position of the treatment of diabetes with insulin it is unnecessary to speak in detail about some aspects which had to be considered a year ago, and I would rather discuss the principles which are controlling its use. Everyone will agree that while insulin is invaluable in the treatment of diabetes it cannot be called a cure. The points which I would like to consider are these:—(1) The aims of treatment with insulin. (2) The type of case which should be treated with insulin. (3) The best type of diet. (4) The value of insulin in the treatment of other infections and minor complications.

The Aims of Treatment.

One of the chief difficulties in deciding these points is the improvement which takes place in the clinical condition of the patients on all varieties of treatment with insulin. The patients nearly always feel so much better that it is difficult to say which is the correct line of treatment, and another five years may have to pass before some of these questions can be answered with certainty. Before the introduction of insulin it was accepted that the patient's diet should be so adjusted that the urine did not contain any sugar, and that the fasting value of the blood-sugar was within the normal limits of 0.08 to 0.12 or 0.13 per cent. In order to achieve this it was necessary in severe cases to give a diet of very low carbohydrate value, and the patients were all much under the normal weight. When insulin was available the natural thought of most workers was that the patient need no longer be undernourished. The carbohydrate was increased so that at some time of the day the blood-sugar was raised above the normal level and sugar was excreted in the urine. Of the eight groups of workers in Canada and the United States who took part in the early study of insulin only two, the Toronto school (Banting, Campbell, and Fletcher) and Allen's school, aimed at keeping the fasting value of the blood-sugar within normal limits; one, Joslin, tried to keep the urine sugar-free; but the other five all thought that it was unnecessary to keep

of the 15 to 20 per cent. which was common before. Further, the weight curve should be the guide to the total caloric value of the diet and should determine whether it should be increased or decreased. In children there should be a slow increase. This is necessary as the children have to grow, but they should never be allowed to become fat, and should always be underweight.

Indications for Insulin Therapy.

When insulin was first introduced it was said that if patients could take a reasonable amount of food, say 50 g. of carbohydrate and an adequate caloric value, without passing sugar, it was unnecessary to give them insulin. This view is still held by some, but I have never accepted it. The improvement which occurs in the clinical condition after a small dose of insulin, 5, 10, or 15 units, is very striking. The patient gains weight and feels capable of doing work, even if no change is made in the diet. This is also Joslin's view, and it would seem as if insulin helped with some other process besides the sugar metabolism, although there is no other proof of this at present.

Insulin has been used in the treatment of the young adult who has had an acute attack of the disease and has come under observation a short while after the onset of symptoms. The sad experience of these cases before the introduction of insulin was that this type of patient responded well to dietetic treatment, but after one to two years began to lose tolerance in spite of all restrictions. The average duration of life of this type of patient for the age-period 20 to 40 was only 5.3 years (Joslin). It therefore seemed justifiable to treat these patients with insulin early in the disease in order to try to prevent the fall in sugar tolerance and perhaps cause a definite rise in sugar tolerance. If small amounts of carbohydrate are given together with sufficient insulin to deal with this sugar the work of the beta cells will be reduced to a minimum. I have been watching six patients and testing the sugar tolerance at intervals by means of a dose of sugar. The actual amount of carbohydrate varies, as four patients are taking 16 to 20 g., one 30 g., and one 60 g. The dose of insulin also varied from 8 to 15 units. It is usually given in one dose, but two patients take it in two doses.

The blood-sugar curves after a dose of 50 g. show that the change in tolerance which has taken place has been very slight, but what change there is, is in favour of an improvement. It is too early to say much about these patients as it will be another four years before they reach the average of their class. Still it may prove a hopeful line of research.
Only around one-third of patients* in developing countries achieve HbA$_{1c}$ <7%:

The International Diabetes Management Practice Study (IDMPS)

<table>
<thead>
<tr>
<th>Region</th>
<th>Patients with HbA$_{1c}$ &lt;7% (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asia</td>
<td>37.3</td>
</tr>
<tr>
<td>Eastern Europe</td>
<td>36.0</td>
</tr>
<tr>
<td>Latin America</td>
<td>36.0</td>
</tr>
<tr>
<td>All</td>
<td>36.4</td>
</tr>
</tbody>
</table>

*n = 6,346

*Patients with HbA$_{1c}$ test (36% of overall population)

PPG has a major impact on the 24-hour glucose profile in patients with type 2 diabetes.

Landmark trials in type 1 diabetes

DCCT: A1C and Microvascular Complications


DCCT/EDIC: Incidence of Nonfatal MI, Stroke, or Death

MI = myocardial infarction.
DCCT = Diabetes Control and Complications Trial.
EDIC = Epidemiology of Diabetes Interventions and Complications.

Lessons from UKPDS: better glucose control means fewer complications

EVERY 1% reduction in HbA$_{1c}$

Deaths from diabetes

Heart attacks

Microvascular complications

Peripheral vascular disorders

REDUCED RISK*

-21%

-14%

-37%

-43%

*p<0.0001

Stratton et al. UKPDS 35. BMJ. 2000;321:405–12
# Landmark trials in type 2 diabetes

<table>
<thead>
<tr>
<th>Lesson</th>
<th>Trial</th>
<th>Outcome</th>
<th>Detail</th>
<th>Therapy</th>
<th>Intervention group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Hyperglycemia is a treatable and reducible risk</td>
<td>Better glycemic control improves outcome (microvascular and diabetes-related endpoints)</td>
<td>$\text{HbA}_{1C}$ 7.0% (6.2%-8.2%) in the intensive group compared with 7.9% (6.9%-8.8%)</td>
<td>Sulfonylurea</td>
<td>From diagnosis or insulin</td>
</tr>
<tr>
<td>2</td>
<td>Metformin is an effective first-line treatment</td>
<td>Better glycemic control improves outcome (microvascular and macrovascular)</td>
<td>7.4% in the metformin group compared with 8.0% in the conventional group. Effects shown in diabetes-related endpoints, all-cause mortality, and MI</td>
<td>Metformin</td>
<td>In the overweight (&gt;120% ideal body weight)</td>
</tr>
<tr>
<td>3</td>
<td>Treatment needs to focus on early glycemic control</td>
<td>Early glycemic control has a legacy effect</td>
<td>Effects in the first ten years persist despite no later difference in control</td>
<td>Sulfonylurea, insulin, and metformin</td>
<td>In newly diagnosed patients studied for a median of 20 years</td>
</tr>
<tr>
<td>4</td>
<td>Aggressive treatment in those with established pathology is counterproductive</td>
<td></td>
<td></td>
<td></td>
<td>Median duration of type 2 diabetes 10 years, and who had either established cardiovascular disease or additional cardiovascular risk factors</td>
</tr>
<tr>
<td>5</td>
<td>Progressive incremental therapy towards target late in diabetes reduces complications</td>
<td>Relative risk reduction, 14%; 95% CI, 3% to 23%; $P=0.015$</td>
<td>$\text{HbA}_{1C}$ 7.3% and 6.5% at the end of the trial</td>
<td>Mainly gliclazide modified release (91%) and metformin (74%)</td>
<td>Median duration of diabetes 8 years</td>
</tr>
</tbody>
</table>

* Excluding gliclazide

**Table II.** Lessons learnt from trials of glycemia in diabetes.

Abbreviations: ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular disease; Prospective Evaluation; $\text{HbA}_{1C}$, glycated hemoglobin; MI, myocardial infarction; UKPDS, United Kingdom Prospective Diabetes Study; UKPDS-PTM, United Kingdom Prospective Diabetes Study Post-Trial Monitoring.
3. ANTI-HYPERGLYCEMIC THERAPY

• Therapeutic options: **Lifestyle**
  - Weight optimization
  - Healthy diet
  - Increased activity level
3. ANTI-HYPERGLYCEMIC THERAPY

- **Therapeutic options:**
  
  *Oral agents & non-insulin injectables*

  - Meglitinides
    - α-glucosidase inhibitors
    - Bile acid sequestrants
    - Dopamine-2 agonists
  - Metformin
    - Sulfonylureas
    - Thiazolidinediones
    - DPP-4 inhibitors
  - GLP-1 receptor agonists

*ADA-EASD Position Statement: Management of Hyperglycemia in T2DM*

*Diabetes Care, Diabetologia. 19 April 2012 [Epub ahead of print]*
GLP-1 analogs
- Improve pancreatic islet glucose sensing
- Slow gastric emptying
- Improve satiety

Biguanides
- Increase glucose uptake
- Decrease hepatic glucose production

Sulfonylureas
- Increase insulin secretion from pancreatic β-cells

Glinides
- Increase insulin secretion from pancreatic β-cells

DPP-4 inhibitors
- Prolong GLP-1 action leading to improved pancreatic islet glucose sensing
- Increase glucose uptake

Thiazolidinediones
- Decrease lipolysis in adipose tissue
- Increase glucose uptake in skeletal muscle
- Decrease glucose production in liver

SGLT-2 inhibitors
- Inhibit glucose reabsorption from renal tubules
- Promote urinary glucose excretion

α-glucosidase inhibitors
- Delay intestinal carbohydrate absorption

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon like peptide-1; SGLT-2, sodium-glucose co-transporter
Cheng AY et al. CMAJ. 2005;172:213-26
Metformin
Stepwise approach?

INSULIN

OH

OH

OH

OH

OH

OH

OH

diet
PPG is the first recognized alteration in people with type 2 diabetes on the 24-hour glucose profile

INSULIN AND SULPHONYLUREA PROMOTE WEIGHT GAIN

Up to 5 kg is already gained within just 3 years with a sulphonylurea or insulin

<table>
<thead>
<tr>
<th>Change in weight (kg)</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet initially then sulphonylureas, insulin and/or metformin if FPG&gt;15 mmol/L</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Conventiona
* Glibenclamide
* Insulin
* Metformin


FPG - fasting plasma glucose
General approach to the management of T2DM

1. Diet and exercise
2. Oral monotherapy
3. Oral combination
4. Oral + insulin
5. Insulin

Adapted from Riddle MC. Endocrinol Metab Clin North Am. 2005;34:77–98
Pancreatic islet function deteriorates over time, causing disease progression

Diagnosis

Glucose

Postprandial glucose
Fasting glucose

Insulin

Insulin resistance
Insulin secretion

Inadequate β-cell function
Decreasing β-cell function

NGT
Prediabetes (IFG/IGT)
Diabetes

IFG=impaired fasting glucose ; NGT = normal glucose tolerance ; IGT = impaired glucose tolerance

Adapted from Rickheim P, Flader J, Carstensen AK. Type 2 Diabetes BASICS. International Diabetes Center; 2000
GUT AS ENDOCRINE ORGAN

- **Cholecystokinin**
  - Gall bladder contraction
  - Gastrointestinal motility
  - Pancreatic exocrine secretion

- **Secretin**
  - Pancreatic exocrine secretion
  - **GIP**
    - Incretin activity
  - **Motilin**
    - Gastrointestinal motility

- **Ghrelin**
  - Hunger
  - Growth hormone release

- **Gastrin**
  - Acid secretion

- **Insulin and glucagon**
  - Glucose homeostasis

- **Pancreatic polypeptide**
  - Gastric motility
  - Satiation

- **Amylin**
  - Glucose homeostasis
  - Gastric motility

- **GLP-1**
  - Incretin activity
  - Satiation

- **GLP-2**
  - Gastrointestinal motility and growth

- **Oxyntomodulin**
  - Satiation
  - Acid secretion

- **PYY**
  - Satiation
INCRETINS

• gut hormones that are secreted from enteroendocrine cells into the blood within minutes after eating

• stimulate a decrease in blood glucose levels

Incretin

Intestine Secretion

Insulin

Creutzfeldt; 1985
| **GLP-1**  
| Glucagon-like peptide-1 | **GIP**  
| Glucose-dependent insulinotropic polypeptide |
| --- | --- |
| • 30-amino acid peptide secreted in response to the oral ingestion of nutrients by L cells, primarily in the ileum and colon | • 42- amino acid peptide secreted by the K cells of the proximal duodenum and proximal jejunum |
| • Receptors present in islet α- and β-cells and in peripheral tissues including the central and peripheral nervous systems, heart, kidneys, lungs and GI tract | • Receptors present predominantly in islet β-cells, and in adipose tissue and the central nervous system |

**Healthy**

**Physiological levels**
- Enhancement of glucose-dependent pancreatic insulin secretion
- Inhibition of glucose-dependent pancreatic glucagon secretion

**Pharmacological levels**
- Slowing of gastric emptying
- Appetite reduction

**DM type 2**
- Incretin effect may be reduced due to defective secretory response of incretin hormones at mealtimes or diminished hormonal effect despite near-normal secretion
- Insulinotropic actions are diminished in association with loss of first phase of insulin secretion

**Healthy**

- Augments glucose-dependent insulin secretion

**DM type 2**
- GIP levels are normal or modestly elevated
- Insulinotropic actions of the peptide are diminished

Figure 3. GLP-1 receptor signal transduction pathways in the pancreatic \( \beta \) cell

GLP-1 receptor activation leads to insulin release via stimulation of exocytotic pathways and recruits signaling mechanisms leading to promotion of cell proliferation and survival.
The Incretin Defect in Type 2 Diabetes

Incretin effect accounts for up to 70% of the insulin response to oral glucose intake

1921 Toronto: insulin discovery

1992 Bronx: discovery of exenatide

1996 San Francisco: ADA meeting
Islet Dysfunction Contributes to Both Acute and Chronic Aspects of Type 2 Diabetes

Acute
- Inappropriately high glucagon secretion from α-cells
- Blunted insulin secretion by β-cells

Chronic
- β-cell mass declines over time

Hyperglycemia
Disease Progression
Incretin Hormones Improve Acute and Chronic Aspects of Pancreatic Islet Function

Islet Function

Acute Effects
- Suppression of glucagon secretion (α-cell)
- Improved insulin secretion (β-cell)

Chronic Effects
- Rejuvenation of pancreas
  - ↑ β-cell proliferation
  - ↓ β-cell death
DPP-4 inhibitors
Prevent the degradation of the natural GLP-1 by DPP-4 enzyme

GLP-1 RA
Incretin mimetic
(imitating the effect of natural GLP-1)

DPP-4=dipeptidyl peptidase-4, GLP-1=glucagon-like peptide-1, RA=receptor agonists
DPP-4 inhibitors

SITAGLIPTIN (Januvia)
VILDAGLIPTIN (Galvus)
SAXAGLIPTIN (Onglyza)
LINAGLIPTIN (Trajenta)
ALOGLIPTIN (Vipidia)

Anagliptin approved 2012 in Japan
Teneligliptin approved 2012 in Japan

Gemigliptin (Zemiglo, LG Life sci; phase III)
GLP-1 agonists

Exenatide - byetta
Exenatide LAT - Bydureon
Liraglutide - Victoza
Lixisenatide - Lyxsumia

Albiglutide
Dulaglutide
GUP-NT = Glikemija u plazmi na tašte  GUP-PP= glikemija u plazmi postprandijalno

Meier JJ. Nat Rev Endocrinol 2012; 8: 728–42.
<table>
<thead>
<tr>
<th>Parameters</th>
<th>Short-acting GLP-1 receptor agonists</th>
<th>Long-acting GLP-1 receptor agonists</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compounds</td>
<td>Exenatide</td>
<td>Albigrutide</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide</td>
<td>Dulaglutide</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Exenatide-LAR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liraglutide</td>
</tr>
<tr>
<td>Half-life</td>
<td>2–5 h</td>
<td>12 h–several days</td>
</tr>
<tr>
<td>Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting blood glucose levels</td>
<td>Modest reduction</td>
<td>Strong reduction</td>
</tr>
<tr>
<td>Postprandial hyperglycaemia</td>
<td>Strong reduction</td>
<td>Modest reduction</td>
</tr>
<tr>
<td>Fasting insulin secretion</td>
<td>Modest stimulation</td>
<td>Strong stimulation</td>
</tr>
<tr>
<td>Postprandial insulin secretion</td>
<td>Reduction</td>
<td>Modest stimulation</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Gastric emptying rate</td>
<td>Deceleration</td>
<td>No effect</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Heart rate</td>
<td>No effect or small increase (0–2 bpm)</td>
<td>Moderate increase (2–5 bpm)</td>
</tr>
<tr>
<td>Body weight reduction</td>
<td>1–5 kg</td>
<td>2–5 kg</td>
</tr>
<tr>
<td>Induction of nausea</td>
<td>20–50%, attenuates slowly (weeks to many months)</td>
<td>20–40%, attenuates quickly (~4–8 weeks)</td>
</tr>
</tbody>
</table>

Abbreviations: GLP-1, glucagon-like peptide 1; LAR, long-acting release.
Effect on HbA$_1$c across the LEAD trials

<table>
<thead>
<tr>
<th>Baseline HbA$_1$c (%)</th>
<th>Monotherapy LEAD-3</th>
<th>Metformin combination LEAD-2</th>
<th>SU combination LEAD-1</th>
<th>Met + TZD combination LEAD-4</th>
<th>Met + SU combination LEAD-5</th>
<th>Met ± SU combination LEAD-6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.4</td>
<td>8.6</td>
<td>8.6</td>
<td>8.5</td>
<td>8.6</td>
<td>8.4</td>
</tr>
<tr>
<td>#Change in HbA$_1$c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.2 mg</td>
<td>-1.2*</td>
<td>-0.9</td>
<td>-1.1</td>
<td>-1.5*</td>
<td>-1.5*</td>
<td>-1.5*</td>
</tr>
<tr>
<td>Liraglutide 1.8 mg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glimepiride</td>
<td>-1.3</td>
<td>-1.3</td>
<td>-1.1</td>
<td>-1.5*</td>
<td>-1.5*</td>
<td>-1.5*</td>
</tr>
<tr>
<td>Rosiglitazone</td>
<td></td>
<td></td>
<td></td>
<td>-0.8</td>
<td>-0.5</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-0.5</td>
<td>-0.8</td>
</tr>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.1</td>
</tr>
<tr>
<td>Exenatide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-1.1*</td>
</tr>
</tbody>
</table>

Weight effects across LEAD trials

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Met combination</th>
<th>SU combination</th>
<th>Met + TZD combination</th>
<th>Met + SU combination</th>
<th>Met ± SU combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-3&lt;sup&gt;3&lt;/sup&gt;</td>
<td>LEAD-2&lt;sup&gt;2&lt;/sup&gt;</td>
<td>LEAD-1&lt;sup&gt;3&lt;/sup&gt;</td>
<td>LEAD-4&lt;sup&gt;4&lt;/sup&gt;</td>
<td>LEAD-5&lt;sup&gt;5&lt;/sup&gt;</td>
<td>LEAD-6&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Change in body weight (kg)

- Liraglutide 1.2 mg
- Liraglutide 1.8 mg
- Glimepiride
- Rosiglitazone
- Glargine
- Exenatide
- Placebo

*<sup>p</sup>≤0.0001 vs active comparator; †<sup>p</sup>≤0.01, †††<sup>p</sup>≤0.0001 vs placebo (active comparators vs placebo not shown)

Data from core trials

MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione.

### GLP-1RA comparative studies: Hypoglycaemia

<table>
<thead>
<tr>
<th>Hypoglycaemia</th>
<th>LEAD-6&lt;sup&gt;1&lt;/sup&gt;</th>
<th>DURATION-6&lt;sup&gt;2&lt;/sup&gt;</th>
<th>HARMONY-7&lt;sup&gt;3&lt;/sup&gt;</th>
<th>Kapitza et al.&lt;sup&gt;48&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lira 1.8 mg OD n=233</td>
<td>Exe 10 μg BID n=231</td>
<td>Lira 1.8 mg OD n=450</td>
<td>Albi 50 mg OW n=404</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lira 1.8 mg OD n=461</td>
<td>Lira 1.8 mg OD n=408</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lira 1.8 mg OD n=41</td>
<td>Lixi 20 μg OD n=77</td>
</tr>
<tr>
<td>Proportion of subjects experiencing</td>
<td>NR</td>
<td>NR</td>
<td>4.0</td>
<td>0†</td>
</tr>
<tr>
<td>hypoglycaemia* (%)</td>
<td></td>
<td></td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>16.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0†</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0†</td>
<td></td>
</tr>
<tr>
<td>Hypoglycaemia* rate/patient year</td>
<td>1.9</td>
<td>2.6</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Major hypoglycaemia† (%)</td>
<td>0</td>
<td>0.2</td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*Minor hypoglycaemia (signs or symptoms associated with hypoglycaemia and fingerstick blood glucose level 3 mmol/L that were either self-treated or resolved on their own)
†Requiring medical assistance
‡4-week study
§Event with clinical symptoms with either plasma glucose <3.3 mmol/L or prompt recovery after oral carbohydrate administration if no plasma glucose measurement available

Albi, albiglutide; BID, twice daily; Exe, exenatide; GLP-1RAs, glucagon-like peptide-1 receptor agonists; Lira, liraglutide; NR, not reported; OW, once weekly

The DURATION-4 clinical trial of Bydureon monotherapy versus metformin, sitagliptin, or pioglitazone monotherapy was conducted in adult patients uncontrolled on diet and exercise alone. Bydureon is not indicated as first-line monotherapy in patients uncontrolled on diet and exercise alone.

QD, daily.
In the DURATION clinical trials, Bydureon demonstrated HbA$_{1c}$ reductions of $-1.3\%$ to $-1.9\%$.
Lixisenatid GetGoal Program

Diet
- GetGoal-Mono
  - Add-on to MET

1 OAD
- GetGoal-M
  - Add-on to MET
- GetGoal-F1
  - Add-on to MET
- GetGoal-X
  - Add-on to MET

2 OADs
- GetGoal-S
  - Add on to SU ± MET
- GetGoal-P
  - Add on to pioglitazone ± MET
- GetGoal-M-Asia
  - Add on to MET ± SU

Basal insulin ± OADs
- GetGoal-L
  - Add on to basal insulin ± MET
- GetGoal-L-Asia
  - Add on to basal insulin ± SU
- GetGoal-Duo1
  - Add on to insulin glargine ± MET
GetGoal: change in HbA1C

<table>
<thead>
<tr>
<th>Duration of Diabetes (years)</th>
<th>Baseline A1C (%)</th>
<th>Baseline mean body weight (kg)</th>
<th>Baseline mean BMI (kg/m²)</th>
<th>Background therapy</th>
<th>Study duration (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.4/1.1/1.4</td>
<td>8.0/8.1</td>
<td>89.0/86.5/86.1</td>
<td>32.3/31.6/31.8</td>
<td>None</td>
<td>12</td>
</tr>
<tr>
<td>8.0/9.0</td>
<td>8.0/8.1/8.1</td>
<td>70.8/66.7/90.1</td>
<td>25.2/24.8</td>
<td>None</td>
<td>52 + ext</td>
</tr>
<tr>
<td>6.2/6.2/5.9</td>
<td>8.0/8.1/8.0</td>
<td>90.1/89/90.4</td>
<td>33.3/32.6/33.3</td>
<td>M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>6.0/5.8/6.2</td>
<td>8.1/8.0/8.0</td>
<td>88.1/90.3/87.9</td>
<td>32.1/33.1/32.5</td>
<td>M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>6.8/6.8</td>
<td>8.3/8.2</td>
<td>94.5/96.7/82.6</td>
<td>33.7/33.5</td>
<td>M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>9.1/9.8</td>
<td>8.1/8.1</td>
<td>92.8/97.0/73.6</td>
<td>30.1/30.4</td>
<td>SU ± M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>6.5/6.8</td>
<td>8.1/8.1</td>
<td>73.6/72.9/65.6</td>
<td>33.7/34.4</td>
<td>P ± M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>11/11</td>
<td>8.4/8.4</td>
<td>87.4/89.1/65.9</td>
<td>26.8/27.1</td>
<td>M ± SU</td>
<td>24 + ext</td>
</tr>
<tr>
<td>13.7/14.1</td>
<td>8.5/8.5</td>
<td>65.9/65.6/87.3</td>
<td>31.9/32.6</td>
<td>Bl ± M</td>
<td>24 + ext</td>
</tr>
<tr>
<td>9.6/8.7</td>
<td>7.7/7.7</td>
<td>87.3/86.8/65.7</td>
<td>25.4/25.2</td>
<td>Bl ± SU + IG + M</td>
<td>24 + ext</td>
</tr>
</tbody>
</table>

Note: All lixisenatide dosing is 1-step AM regimen, unless otherwise noted

Source: Previous GetGoal sources

* 24 week data, longer term data was pooled
** 2-step PM dosing
*** 2-step AM dosing

Duration of Diabetes (years): 1.4/1.1/1.4, 8.0/9.0, 6.2/6.2/5.9, 6.0/5.8/6.2, 6.8/6.8, 9.1/9.8, 6.5/6.8, 11/11, 13.7/14.1, 9.6/8.7
Baseline mean body weight (kg): 89.0/86.5/86.1, 70.8/66.7, 90.1/89/90.4, 88.1/90.3/87.9, 94.5/96.7, 82.6/84.5, 92.8/97.0, 73.6/72.9, 87.4/89.1, 65.9/65.6, 87.3/86.8
Baseline mean BMI (kg/m²): 32.3/31.6/31.8, 25.2/24.8, 33.3/32.6/33.3, 32.1/33.1/32.5, 33.7/33.5, 30.1/30.4, 33.7/34.4, 26.8/27.1, 31.9/32.6, 25.4/25.2, 32/31.7
Background therapy: None, None, M, M, M, SU ± M, P ± M, M ± SU, Bl ± M, Bl ± SU, IG + M
Study duration (wks): 12, 52 + ext, 24 + ext, 24 + ext, 24 + ext, 24 + ext, 24 + ext, 24 + ext, 24, 24, 24, 24

**、*** 2-step AM dosing

Note: All lixisenatide dosing is 1-step AM regimen, unless otherwise noted

Source: Previous GetGoal sources
Hypoglycemic Risk of Antihyperglycemic Agents Added to Metformin

Increased risk vs placebo

Meta-analysis: Weight Changes With Antihyperglycemic Agents Added to Metformin

GLP-1 RAs and DPP-4 inhibitors highlighted for avoiding weight gain

In a separate analysis, the SGLT-2 inhibitor canagliflozin was associated with significantly greater weight loss vs sitagliptin over 1 year (−2.3 vs 0.1 kg, respectively; \( P < .001 \)).\(^2\)^\(^a\)

AGI, α-glucosidase inhibitor.
Added to MET + SU.
GLP-1RAs have desirable effects beyond glycaemic control

GLYCAEMIC CONTROL
WEIGHT LOSS
CV FUNCTION

Myocardial function and survival in animal models\textsuperscript{1,2}
Improved biomarkers of cardiovascular risk\textsuperscript{1,2}
Systolic blood pressure\textsuperscript{1}

Delayed gastric emptying\textsuperscript{1,2}
Fullness and satiety\textsuperscript{1,2}
Food intake\textsuperscript{1,2}

Insulin secretion\textsuperscript{1,2}
Insulin biosynthesis\textsuperscript{1,2}
Beta-cell glucose sensitivity\textsuperscript{2}
Glucagon secretion\textsuperscript{2}

CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus
Incretin based therapies: A novel treatment approach for non-alcoholic fatty liver disease

Kristina Blaslov, Tomislav Bulum, Karin Zibar, Lea Duvnjak
Incretin based therapy

CONTRA

Non responders

Thyroid C-cell cancer in animal models

Pancreatitis

Pancreatic neoplasm
Pancreatic Safety of Incretin-based Drugs

“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.”*

*Note that the FDA and EMA have not reached a final conclusion regarding a potential causal association.

Incretin based therapeutic options

- Incretin effect is necessary for normal α- and β- cell function
  - Incretin effect is reduced in people with type 2 diabetes
- Increasing the incretin effect should improve α- and β-cell function and glycemic control
Healthy eating, weight control, increased physical activity

Initial drug monotherapy
- Effectiveness (↓ HbA1c)
- Hypoglycemia
- Weight
- Side effects
- Costs

Two drug combinations
- Effectiveness (↓ HbA1c)
- Hypoglycemia
- Weight
- Major side effect(s)
- Costs

Three drug combinations

More complex insulin strategies