Prof. Manfredi Rizzo, MD, PhD

ASSOCIATE PROFESSOR
OF INTERNAL MEDICINE
School of Medicine
University of Palermo, Italy

&

ASSOCIATE PROFESSOR
OF INTERNAL MEDICINE
School of Medicine
University of South Carolina, USA

&

DIRECTOR
Department of Population Health
Euro-Mediterranean Institute of
Science and Technology, Italy

Novel anti-diabetic therapies
Evolution of Diabetes Technology and Treatments: Timeline

- **Urine Tasting**: 1776
- **Urine Test Strips**: early 1900s
- **Insulin Injections**: 1922
- **Glucose Meters**: 1977
- **Insulin Pumps**: 1978
- **Glucose Sensors**
  - **Insulin Analogs**
  - **New Oral agents**
- **New Insulins**
- **Real-Time Monitoring**
- **Incretin-based Therapies**
- **Genetics; Artificial Pancreas**: 2000 - ?
“Everything that can be invented has been invented.”

Charles Duell
Director, United States Patent Office, 1899
What are the incretins?
**Incretin Hormones Have Key Roles in Glucose Homeostasis**

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>GIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>▪ Is released from L cells in ileum and colon(^1,2)</td>
<td>▪ Is released from K cells in duodenum(^1,2)</td>
</tr>
<tr>
<td>▪ Stimulates insulin response from beta cells in a glucose-dependent manner(^1)</td>
<td>▪ Stimulates insulin response from beta cells in a glucose-dependent manner(^1)</td>
</tr>
<tr>
<td>▪ Inhibits glucagon secretion from alpha cells in a glucose-dependent manner(^1)</td>
<td>▪ Does not affect gastric emptying(^2)</td>
</tr>
<tr>
<td>▪ Inhibits gastric emptying(^a,1,2)</td>
<td>▪ Has no significant effects on satiety or body weight(^2)</td>
</tr>
<tr>
<td>▪ Reduces food intake and body weight(^a,2)</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\)Effects occur only with pharmacologic levels of GLP-1.


GIP=glucose-dependent insulino tropic peptide; GLP-1=glucagon-like peptide-1.
Incretin Effect

- Insulin response is greater with oral glucose load, rather then intravenous glucose infusion.

Nauck et al. Diabetologia 1986;29:46–52. *p≤0.05. n=8 healthy volunteers
The Incretin Effect in Non-diabetic and Type 2 Diabetic Subjects

Control Subjects (n=8)

Patients With Type 2 Diabetes (n=14)

The incretin effect is diminished in type 2 diabetes

Incretin Effect

Oral glucose load
Intravenous (IV) glucose infusion

T2DM patients have altered secretion of GLP-1

Adapted from Toft-Nielsen et al. J Clin Endocrinol Metab 2001;86:3717–23
In T2DM, GLP-1 infusion (but not GIP infusion) can restore insulin response

Adapted from Vilsbøll et al. Diabetologia 2002;45:1111–9. Data are means ± SEM.
The glucagon-like peptide-1

[Diagram showing the sequence of amino acids in the glucagon-like peptide-1 (GLP-1) including: His, Ala, Glu, Gly, Thr, Phe, Thr, Ser, Asp, Val, Ser, Lys, Ala, Ala, Gin, Gly, Glu, Leu, Tyr, Ser, Glu, Phe, Ile, Ala, Trp, Leu, Val, Lys, Gly, Arg, Gly]
GLP-1 Effects in T2DM patients

![Graphs showing glucose, insulin, and glucagon levels over time with comparisons between Placebo and GLP-1 groups.](image)

N=10; Media ± SEM; *p<.05.

Endocrine action of GLP-1

Only 10–15% of native GLP-1 secreted reaches the pancreas in the native form.

Native GLP-1 is rapidly degraded by DPP-IV

Human L cells (GLP-1)

Enzyme (DPP-IV: Di-Peptidyl Peptidase-IV)

DPP-IV (red); GLP-1 (green)

Adapted from: Hansen et al. Endocrinology 1999; 140:5356–63
A Brief History of Incretins

1932 – First definition of incretins³
1964 – First demonstration of DPP-4⁶
1966 – First description of DPP-4⁶
1986 – Incretin effect shown to be reduced in patients with type 2 diabetes⁷
1995 – DPP-4 identified as an enzyme that inactivates GIP and GLP-1⁹,¹⁰

1902 – First observation of intestinal effect on pancreatic secretion¹,²
1964 – Demonstration of the incretin effect¹,⁴,⁵
1973 – GIP identified as a human incretin¹
1987 – GLP-1 identified as a human incretin⁸

DPP-4=dipeptidyl peptidase-4; GIP=glucose-dependent insulinotropic peptide; GLP-1=glucagon-like peptide-1.
Incretin-Based Therapies:

1. DPP4-inhibitors
2. GLP-1 analogues
Incretin-based therapies available in Italy

**DPP-4 inhibitors:**
- Sitagliptin
- Vildagliptin
- Saxagliptin
- Linagliptin
- Alogliptin

**Human GLP-1 analogues:**
- Exenatide
- Liraglutide
- Lixisenatide
- Dulaglutide
### GLP-1R Agonists vs DPP-4 Inhibitors

<table>
<thead>
<tr>
<th>GLP-1R Agonists</th>
<th>DPP-4 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Orally Available</td>
</tr>
<tr>
<td></td>
<td>Physiological</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
</tbody>
</table>

In preclinical studies, GLP-1R agonists and DP-4 inhibitors are both effective.

GLP-1R agonists are orally available and have a physiological mechanism. DPP-4 inhibitors are also orally available and have a physiological mechanism.

GLP-1R agonists and DPP-4 inhibitors both cause weight loss and increase insulin secretion. GLP-1R agonists do not cause nausea and vomiting, while DPP-4 inhibitors do.

GLP-1R agonists and DPP-4 inhibitors both have the potential for immunogenicity, but DPP-4 inhibitors are more likely to cause nausea and vomiting.
Incretin-based therapies and CV risk markers
Incretins and Cardio-Metabolic Risk

- Glucose Metabolism
- Renal Disease
- Blood Pressure
- Endothelium
- Atherosclerosis
- Weight

INCRETIN-BASED THERAPIES

Drucker DJ. Cell Metab. 2006; 3 (3):153-165.
GLP-1 receptor is expressed in cardiac and vascular tissues

Miocardiocytes

Endocardium

Endothelium + VSMC

Ban K, Circulation 2008, 117:2340
GLP-1 improves left ventricular function in post-AMI patients who underwent revascularization

**LVEF (%)**

- **Baseline**
  - Control
  - Native GLP-1

- **Post i.v. GLP-1**
  - Control
  - Native GLP-1

*p < 0.01

GLP-1 improves endothelial function in T2DM patients, even in those with T2DM and CHD

Data are mean ± SEM.
FMD = Flow-Mediated Dilation (endothelial-dependent vasodilation)

Liraglutide improves CV risk markers in T2DM patients

LEAD-1–6: meta-analysis

Change from baseline to week 26 with liraglutide 1.8 mg once daily

- BNP: -11.9%
- hsCRP: -23.1%
- PAI-1: -7.6%

P<0.001

Plutzky et al. Diabetologia 52 (Suppl. 1): S299, 2009
Plutzky et al. Circulation 120:S397, 2009
Exenatide improves Blood Pressure in T2DM patients

Treatment for 3,5 yrs with exenatide 10 μg BID

Systolic BP Change by 3.5-years
Weight Change Quartiles

Diastolic BP Change by 3.5-years
Weight Change Quartiles
Plasma Lipid changes by Sitagliptin

Plasma Lipid changes by Exenatide

Incretin-based therapies and plasma lipids

*Variazioni dal basale (mmol/L)*

**Variazioni dal baseline (mg/dL)**

**Total Cholesterol**

- Liraglutide 1.8 mg
- Rosiglitazone
- Glimepiride
- Insulin glargine
- Exenatide
- Placebo

**LDL-Cholesterol**

- Liraglutide 1.8 mg
- Rosiglitazone
- Glimepiride
- Insulin glargine
- Exenatide
- Placebo

* p<0.05; ** p<0.01; *** p<0.0001 vs. liraglutide. Dati espressi come valori medi ± 95% CI; LEAD 1–6: meta-analisi

Plutzky et al. Diabetologia 2009; 52 (Suppl. 1):S299
Liraglutide decreases carotid intima-media thickness in patients with type 2 diabetes: 8-month prospective pilot study

Manfredi Rizzo\textsuperscript{1,2,3}, Manisha Chandalia\textsuperscript{4}, Angelo Maria Patti\textsuperscript{1}, Vittoria Di Bartolo\textsuperscript{1}, Ali A Rizvi\textsuperscript{3}, Giuseppe Montalto\textsuperscript{1} and Nicola Abate\textsuperscript{4*}
Rizzo et al. Cardiovascular Diabetology 2014, 13:49
http://www.cardiab.com/content/13/1/49

$p = 0.0010$

baseline
after 4 months
after 8 months

carotid intima-media thickness (mm)
Effect of Liraglutide on oxidative stress

\[ p = 0.0283 \]
Before Liraglutide

After Liraglutide

Rizzo Montalto Lab - ITALY
Incretin-Based Therapies and CV Outcome
FDA Now Requires CV data With New Submissions

- Owing to the potential for CV risk with drugs for T2DM, in December 2008, the FDA issued new guidance for all diabetes drugs in development: **Manufacturers of diabetes drugs and biologics need to provide evidence that therapy will not increase the risk of CV events**

More robust and adequate design and data collection are required for Phase 2/3 clinical trials:
- New diabetes therapies should not increase CV risk compared with current therapies, especially when used by older patients and in those with advanced diabetes or renal impairment
- Trials should include patients at higher risk of CV events
- CV events occurring during clinical trials should be analyzed by independent committees
- This includes major events (CV mortality, MI, and stroke) and can also include hospitalization for ACS, urgent revascularization procedures, and other end points

Numerous Studies Assessing CV Outcomes in T2DM Drugs Are Either Recently Completed or Ongoing

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Drug</th>
<th>Enrollment</th>
<th>Timing</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DPP-4 Inhibitors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVOR</td>
<td>Saxagliptin</td>
<td>N=16,492</td>
<td>Began 2010; Complete</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin</td>
<td>N=5384</td>
<td>Began 2009; Complete</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin</td>
<td>N=14,000</td>
<td>Began 2008; Ending 2014</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin</td>
<td>N=6000</td>
<td>Began 2010; Ending 2018</td>
</tr>
<tr>
<td>CARMELINA</td>
<td>Linagliptin</td>
<td>N=8300</td>
<td>Began 2013; Ending 2018</td>
</tr>
<tr>
<td><strong>GLP-1 Agonists</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELIXA</td>
<td>Lixisenatide</td>
<td>N=6000</td>
<td>Began 2010; Ending 2014</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide</td>
<td>N=9500</td>
<td>Began 2010; Ending 2017</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide</td>
<td>N=9340</td>
<td>Began 2010; Ending 2016</td>
</tr>
<tr>
<td>REWIND</td>
<td>Dulaglutide</td>
<td>N=9622</td>
<td>Began 2011; Ending 2019</td>
</tr>
<tr>
<td>SUSTAIN 6</td>
<td>Semaglutide</td>
<td>N=3260</td>
<td>Began 2013; Ending 2016</td>
</tr>
</tbody>
</table>

*Trial ending dates are anticipated based on publicly available information.
Risk Profile of patients at Baseline in Incretin CV Outcome Trials

- Risk Factors
- Stable CAD-CVD-PAD
- ACS patients

SAVOR-Timi-Saxa
EXAMINE-Alogliptin
Tecos-Sitagliptin
CAROLINA-Linagliptin
LEADER-Liraglutide
ELIXA- Lixisenatide
EXSCEL-Exenatide LAR (population not yet defined)
REWIND-Dulaglutide

Results
- Q2-3 2013
- Dec 2013
- Dec 2014
- Sep 2018
- May 2014
- Jan 2016
- Mar 2017
- Apr 2019

Adapted from CT.gov Nov 19th 2012
Where do the Incretin Based Therapies fit in the pharmacologic therapy of T2DM?
**T2DM Anti-hyperglycemic Therapy: General Recommendations**

### Initial drug monotherapy
- **Efficacy** (HbA1c)
- **Hypoglycemia**
- **Weight**
- **Side effects**
- **Costs**

If needed to reach individualized HbA1c target after ~3 months, proceed to 2-drug combination (order not meant to denote any specific preference):

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Side effects</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>high</td>
<td>moderate</td>
<td>low</td>
<td>low</td>
<td>low</td>
</tr>
<tr>
<td>Sulfonylurea†</td>
<td>high</td>
<td>moderate</td>
<td>gain</td>
<td>hypoglycemia*</td>
<td>low</td>
</tr>
<tr>
<td>Thiazolidine-dione</td>
<td>high</td>
<td>low</td>
<td>gain</td>
<td>edema, HF, fx's†</td>
<td>high</td>
</tr>
<tr>
<td>DPP-4 Inhibitor</td>
<td>intermediate</td>
<td>low</td>
<td>neutral</td>
<td>low</td>
<td>high</td>
</tr>
<tr>
<td>GLP-1 receptor agonist</td>
<td>high</td>
<td>high risk</td>
<td>loss</td>
<td>hypoglycemia*</td>
<td>variable</td>
</tr>
<tr>
<td>Insulin (usually basal)</td>
<td>highest</td>
<td>high</td>
<td>gain</td>
<td>hypoglycemia*</td>
<td>variable</td>
</tr>
</tbody>
</table>

### Two drug combinations*

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
<th>Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin +</td>
<td>high</td>
<td>low</td>
<td>low</td>
<td></td>
<td>low</td>
</tr>
<tr>
<td>Sulfonylurea†</td>
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<td>gain</td>
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<tr>
<td>Insulin (usually basal)</td>
<td>highest</td>
<td>high</td>
<td>gain</td>
<td>hypoglycemia*</td>
<td>variable</td>
</tr>
</tbody>
</table>

### Three drug combinations

<table>
<thead>
<tr>
<th>Drug Combination</th>
<th>Efficacy (HbA1c)</th>
<th>Hypoglycemia</th>
<th>Weight</th>
<th>Major side effect(s)</th>
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</tr>
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<td>low</td>
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</tr>
</tbody>
</table>

### More complex insulin strategies

**Insulin‡ (multiple daily doses)**

If combination therapy that includes basal insulin has failed to achieve HbA1c target after 3-6 months, proceed to a more complex insulin strategy, usually in combination with 1-2 non-insulin agents.
Future Perspectives...
Dapagliflozin therapy in type-2 diabetes: current knowledge and future perspectives

Manfredi Rizzo, Noor Al-Busaidi & Ali A Rizvi†
†University of South Carolina School of Medicine, Division of Endocrinology, Diabetes and Metabolism, Columbia, SC, USA

Dapagliflozin is a new antidiabetic agent that belongs to the class of sodium glucose transporter 2 (SGLT-2) inhibitors. By decreasing renal glucose absorption, these agents target hyperglycemia independent of insulin secretion or insulin sensitivity. This unique mechanism of action differentiates them from existing antidiabetic agents currently on the market. It has been hypothesized that SGLT-2 inhibitors can be effectively and safely combined with other agents, including insulin, and incretin-based therapies. They can be used either as monotherapy, or in dual- or triple-agent combinations. Dapagliflozin has been shown to be effective and safe in patients with type-2 diabetes, with modest but significant reductions in HbA1c and a number of potentially beneficial and sustained non-glycemic effects, including those on body weight, plasma lipids and systolic blood pressure. In addition, dapagliflozin has been shown to have a generally favorable safety profile and is well tolerated. Ongoing studies may provide definitive answers on the cardiovascular safety and efficacy of SGLT-2 inhibitors in patients with type-2 diabetes.

Keywords: dapagliflozin, glucose, sodium-glucose transporter 2, type-2 diabetes
CONCLUSION

• *Incretin-based therapies are effective and safe therapies for managing T2DM as well as several CV risk markers.*

• *Although the first promising data, the CV Outcome of these therapies remains to be fully elucidated.*

• *Incretin-based therapies may represent effective and safe therapies for managing multiple MetS alterations, including T2DM, as well as the associated CV risk.*