Incretin-Based Therapies for Type 2 Diabetes: Mechanism-Based Strategies to Achieve Patient-Centered Care

September 19, 2013
Boston Convention & Exhibition Center
Boston, Massachusetts

Education Partner:
Integritas Communications, LLC
Session 1: Incretin-Based Therapies for Type 2 Diabetes: Mechanism-Based Strategies to Achieve Patient-Centered Care

Learning Objectives

1. Discuss the multisystem causes and consequences of type 2 diabetes mellitus (T2DM), including pathologic roles of the incretin pathways and the rationale for early diagnosis.
2. Individualize treatment goals for patients with T2DM based on disease duration, age, relevant comorbidities, and ongoing evaluations of hemoglobin A1C levels and therapeutic responses.
3. Evaluate the mechanisms of action and clinical profiles of incretin-based therapies, including glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors.
4. Develop and tailor personalized multimodal treatment plans for T2DM that include lifestyle interventions and incretin-based therapies alone or in combination with other antihyperglycemic medications.
5. Educate diverse populations of patients with T2DM about lifestyle modifications, benefits and risks of various antihyperglycemic medications, and the importance of treatment adherence.

Faculty

Lawrence Blonde, MD, FACP, FACE
Director, Ochsner Diabetes Clinical Research Unit
Department of Endocrinology
Ochsner Medical Center
New Orleans, Louisiana

Dr Lawrence Blonde is the director of the Ochsner Diabetes Clinical Research Unit at the Ochsner Medical Center in New Orleans, Louisiana. Among his many other professional responsibilities, Dr Blonde is an associate of internal medicine residency program director. Dr Blonde graduated from Albany Medical College in New York, where he also completed his internship, residency, and endocrinology fellowship. On staff at Ochsner since 1974, he is board certified in internal medicine, nuclear medicine, and endocrinology.

Dr Blonde is chair of the steering committee of the National Diabetes Education Program, a partnership of the National Institutes of Health, the Centers for Disease Control and Prevention, and more than 200 public and private organizations working to “change the way diabetes is treated.” He is also a member of the board of directors of the American Association of Clinical Endocrinologists, a member of the National Quality Forum adult diabetes care consensus maintenance committee, and chair of the American Diabetes Association doing better committee, which develops practice guidelines for the care of people with diabetes.

Javier Morales, MD
Vice President
Principal Clinical Trials Investigator
Advanced Internal Medicine Group, PC
New Hyde Park, New York

Dr Morales is in private practice with the Advanced Internal Medicine Group in New Hyde Park, New York. After having graduated from the University of Medicine and Dentistry of New Jersey-New Jersey Medical School, his medical training included residencies at Memorial Sloan-Kettering Cancer Center and North Shore University Hospital, where he served as chief medical resident. He serves on multiple committees at St. Francis Hospital in Roslyn, New York, and in addition to several publications, has served as principal investigator for several different studies and clinical trials. He is active in the educational sector, having presented at many Pri-Med symposia. He also serves as clinical instructor for several nurse practitioner programs, and physician assistant programs, in addition to the internal medicine residency program at North Shore University Hospital and Winthrop University Hospital. In addition to being an avid musician and percussionist, Dr Morales is fluent in Spanish, Italian, and Portuguese. He is a member of the American Medical Association, American College of Physicians, American Society of Clinical Pathologists, National Hispanic Medical Association, Nassau County Medical Society, American Academy of Family Physicians, and American Association of Clinical Endocrinologists, and is a fellow of the Interamerican College of Physicians and Surgeons.
Dr Jack Leahy is a professor of medicine and chief of the division of endocrinology, diabetes and metabolism at The University of Vermont College of Medicine. After earning his medical degree at the Medical College of Virginia in Richmond, Dr Leahy completed an internship, residency, chief residency in medicine, clinical fellowship in endocrinology, and fellowship in research at the same institution. He is board certified in internal medicine and in endocrinology and metabolism.

Dr Leahy's current National Institutes of Health (NIH) research activities focus on the mechanism of beta-cell function. He has authored over 60 publications on various topics important to identifying causes of beta-cell dysfunction in diabetes as well as the clinical impact on patient therapy and patient outcomes. Additionally, he has authored 16 book chapters and has served as editor for several medical books. He is currently the editor-in-chief for *Insulin Therapy and Your Practice: Strategies for Improving Patient Outcomes* and co-editor for *Diabetes, Year Book of Endocrinology*.

A member of the American Diabetes Association, the American Association for the Advancement of Science, the American Federation of Clinical Research, the European Association for the Study of Diabetes, and the Endocrine Society, Dr Leahy has served on various committees for these professional societies. He has also served on committees for the NIH and the Juvenile Diabetes Research Foundation. Dr Leahy has received numerous awards for his research and teaching activities.

**Faculty Financial Disclosure Statements**
The presenting faculty reports the following:

Lawrence Blonde MD, FACP, FACE, is a member of the speakers bureaus and a consultant for Amylin Pharmaceuticals, LLC, Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Sanofi-Aventis U.S., LLC, and Santarus, Inc.; is a member of the speakers bureaus for AstraZeneca/Bristol-Myers Squibb Company and Johnson & Johnson Diabetes Institute; is a consultant for Eisai Inc., GlaxoSmithKline, Pfizer Inc., and Vivus, Inc.; and receives research support from Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis U.S., LLC.

Javier Morales, MD, is a member of the speakers bureaus and advisory boards of Boehringer Ingelheim, Novo Nordisk, Sanofi-Aventis U.S., LLC, and Warner Chilcott.

Jack Leahy, MD, is on the advisory boards of Janssen Pharmaceuticals, Inc., Novo Nordisk, and Sanofi-Aventis U.S., LLC.

**Education Partner Financial Disclosure Statement**
The content collaborators at Integritas Communications report the following:

James Kappler, PhD, has no financial relationships to disclose.

**Suggested Reading List**


Incretin-Based Therapies for Type 2 Diabetes: Mechanism-Based Strategies to Achieve Patient-Centered Care

Speakers
Jack Leahy, MD (Virtual Presenter)
Lawrence Blonde, MD, FACP, FACE
Javier Morales, MD

Session 1
8–9:30 am

Presenter Disclosure Information

The following relationships exist related to this presentation:

► Lawrence Blonde MD, FACP, FACE, is a member of the speakers bureaus and a consultant for Amylin Pharmaceuticals, LLC., Janssen Pharmaceuticals, Inc., Merck & Co., Inc., Novo Nordisk, Sanofi-Aventis U.S., LLC, and Santarus, Inc.; is a member of the speakers bureaus for AstraZeneca/Bristol-Myers Squibb Company and Johnson & Johnson Diabetes Institute; is a consultant for Eisai Inc., GlaxoSmithKline, Pfizer Inc., and Wyco, Inc.; and receives research support from Eli Lilly and Company, Novo Nordisk, and Sanofi-Aventis U.S., LLC.

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► Jack Leahy, MD, is on the advisory boards of Janssen Pharmaceuticals, Inc., Novo Nordisk, and Sanofi-Aventis U.S., LLC.

Scientific Insights Into INCRETIN SIGNALING AND TYPE 2 DIABETES

Jack L. Leahy, MD
Professor of Medicine
Chief, Division of Endocrinology, Diabetes, and Metabolism
University of Vermont College of Medicine
Burlington, Vermont

Medications Discussed in Program For pmICME (Not for Use in the Program)

• Medication classes
  - GLP-1 receptor agonists
  - DPP-4 inhibitors
  - Statins
  - ACE inhibitors
  - Insulin
  - Amylin mimetics
  - Thiazolidinediones
  - Meglitinides
  - SGLT-2 inhibitors
  - α-glucosidase inhibitors
  - Biguanides
  - Antidiabetic drugs
  - Thienopyridine antiplatelet agents
  - D2 dopamine-receptor agonists
  - Bile acid sequestrants
  - Thiazide diuretics

• Specific medications
  - Glipizide
  - Sitagliptin
  - Ramipril
  - Metformin
  - Sulfonylurea insulin
  - Basal insulin
  - Insulin glargine
  - Insulin detemir
  - Liraglutide
  - Basal insulin
  - Lispro insulin
  - Liraglutide
  - Saxagliptin
  - Alogliptin
  - Alogliptin
  - Alitracarbitil
  - Sitagliptin
  - Linagliptin
  - Alogliptin
  - saxagliptin

Incretin Effect

IV, intravenous.

N=8 metabolically healthy control subjects.
Glucose Homeostasis
Gastrointestinally Mediated Glucose Disposal

\[
\text{GIGD (\%) = } \frac{100 \times (\text{Glucose Oral} - \text{Glucose IV})}{\text{Glucose Oral}}
\]

GIGD in Healthy Individuals = 60\% (Range, 20\%–80\%)

GIGD, gastrointestinally mediated glucose disposal.

Scientific Insights Into Incretin Signaling and T2DM
Key Points

- **Incretin effect**: more insulin secreted in response to oral glucose compared with IV glucose\(^1\)
- Two peptide hormones stimulate insulin release in response to food ingestion\(^2\)
  - GLP-1 and GIP
- Reduced incretin effect is an early sign of T2DM\(^3\)
- Patients with T2DM do not respond to GIP, and GLP-1 and GIP are rapidly degraded by DPP-4\(^2\)
  - Research has focused on DPP-4 inhibitors and alternative GLP-1 RAs

DPP-4, dipeptidyl peptidase-4; RA, receptor agonist.

Terrance Visit

**PCP Visit**

- 67-year-old Caucasian man
- Retired plumber lives with wife
- BMI, 28.6 kg/m\(^2\) (overweight)
- Has become much less active over last year
- Family history
  - Father treated for T2DM

**Medical history**
- Hypertension
  - Blood pressure
  - BP, 138/85 mm Hg
  - Lipids
    - LDL-C, 72 mg/dL
    - HDL-C, 39 mg/dL
    - TG, 155 mg/dL
    - TC/HDL-C, 3.5
    - ApoB, 83 mg/dL

**ACR, 2.4 mg/mmol**
**BP, 138/85 mm Hg**

Despite no overt symptoms of hyperglycemia, should Terrance be screened for T2DM?

**A1c, 8.2%**
**FPG, 192 mg/dL**
  - Second test, 196 mg/dL
**eGFR, 80 mL/min/1.73 m\(^2\)**
**ACR, 2.4 mg/mmol**
**BP, 138/85 mm Hg**

**Lipids**
- LDL-C, 72 mg/dL
- HDL-C, 39 mg/dL
- TG, 155 mg/dL
- TC/HDL-C, 3.5
- ApoB, 83 mg/dL

**What should be considered when setting his glycemic target?**

CCA, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; BP, blood pressure.
AACE 2011/2013 and ADA 2013
Goals for Glycemic Control

Target Treatment Goals  AACE 2011/2013,1,2  ADA 2013,3
A1c  ≤6.5%  <7.0%
Fasting glucose  Fasting and premeal plasma glucose:  <110 mg/dL  70-130 mg/dL
Postprandial glucose  2-hour postprandial plasma glucose  <140 mg/dL  <180 mg/dL

Macrovascular and Microvascular Risk
A1c Levels and Disease Duration

Impact of Intensive Therapy for Diabetes
Summary of Major Clinical Trials

Glycemic Control and Major Cardiovascular Events
Summary of Major Clinical Trials

Glycemic Control and Major Cardiovascular Events
Subgroup Analysis

ADA/EASD Position Statement
Setting Glycemic Goals in T2DM

More Stringent Factors  Less Stringent
Highly motivated, adherent, excellent self-care capacities  Patient attitude and expected treatment efforts  Less motivated, nonadherent, poor self-care capacities
Low  Risks potentially associated with hypoglycemia, other adverse events

Trials Hazard Ratio (95% CI)

Macrovascular Risk
VADT 0.81 (0.62–1.07)
UKPDS 0.92 (0.79–1.07)
VADT 0.83 (0.61–1.13)

Major Cardiovascular Events
ACCORD 1.00 (0.72–1.39)
UKPDS 0.90 (0.78–1.04)
VADT 0.90 (0.70–1.16)

ADRDCE 0.97 (0.81–1.16)
ADVANCE 0.94 (0.84–1.06)

Study Microvascular CVD Mortality

UKPDS1  More stringent  Less stringent

ACCORD 0.90 (0.78–1.04)
VADT 0.90 (0.70–1.16)

B, CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; VADT, Veterans Affairs Diabetes Trial.

Value for Test  P Value for Test of Difference

High A1c  ≤ 7.5%  0.04  (0.75–0.99)
≤ 7.5%–8.5%  0.04  (0.75–0.99)
≤ 8.5%  0.04  (0.75–0.99)

History of macrovascular disease
Present  1.00  (0.95–1.06)
Absent  0.94  (0.87–1.01)

Trials Hazard Ratio (95% CI)
Terrance
Setting Glycemic Targets

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lifestyle Intervention (n=2570)</th>
<th>Support and Education (n=2575)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, 67 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Newly diagnosed BMI</td>
<td>28.6 kg/m²</td>
<td>A1c, 8.2%</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>138/85 mm Hg</td>
<td></td>
</tr>
<tr>
<td>History of myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lipid profile not optimal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not adherent to myocardial infarction therapy</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

What would you set as an A1c target for Terrance? What other clinical goals are required?

Terrance
Initial Treatment

- Target A1c, 7.0%
- PCP begins by discussing lifestyle modifications for Terrance
- Suggests a certified diabetes educator
  - Patient education
  - Detailed dietary and exercise recommendations

What are the likely benefits of these approaches?

LOOK AHEAD Study
Intensive Lifestyle Intervention and Risk Reduction

- Diet modification, exercise, behavioral training
- Group support with in-person and telephone follow-ups

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lifestyle Intervention</th>
<th>Support and Education</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight loss, %</td>
<td>4.5</td>
<td>-0.58*</td>
</tr>
<tr>
<td>Treadmill fitness, % METS</td>
<td>12.74</td>
<td>1.96*</td>
</tr>
<tr>
<td>A1c, %</td>
<td>-0.36</td>
<td>-0.09*</td>
</tr>
<tr>
<td>Systolic pressure, mm Hg</td>
<td>-5.33</td>
<td>-2.97*</td>
</tr>
<tr>
<td>Diastolic pressure, mm Hg</td>
<td>-2.92</td>
<td>-2.48*</td>
</tr>
<tr>
<td>HDL-C, mg/dL</td>
<td>3.67</td>
<td>1.97*</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>-25.56</td>
<td>-19.75*</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.01; ***P<0.001

In patients with T2DM, weight loss and exercise can reduce insulin resistance and hepatic glucose production

Reducing T2DM Complications
Cardiovascular Disease

Comprehensive Diabetes Management

<table>
<thead>
<tr>
<th>BP</th>
<th>A1c</th>
<th>Lipids</th>
<th>BMI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;140/80 mm Hg</td>
<td>&lt;7.0%</td>
<td>LDL-C &lt;100 mg/dL</td>
<td>&lt;25 mg/kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL-C &gt;40 mg/dL</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Triglycerides</td>
<td></td>
</tr>
</tbody>
</table>

Lifestyle Modifications
Healthy Diet; Exercise; Smoking Cessation

Weight Reduction in T2DM

- Behavioral modification
  - Self-monitoring of food intake with daily log
  - Stimulus control
  - Cognitive restructuring
  - Stress management
- Physical activity
  - At least 150 min/week of moderate activity
  - Aerobic, resistance, flexibility training
- Dietary changes
  - Reduce saturated and trans fatty acids, cholesterol, and sodium
  - Calorie restriction
  - Key factor for weight loss
  - Moderate calorie restriction recommended
  - 500–1000 kcal/day fewer than baseline intake

In patients with T2DM, weight loss and exercise can reduce insulin resistance and hepatic glucose production

LOOK AHEAD Diabetes Remission With Intensive Lifestyle Interventions

Remission Prevalence

<table>
<thead>
<tr>
<th>Year</th>
<th>Intensive lifestyle intervention</th>
<th>Diabetes support and education</th>
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</thead>
<tbody>
<tr>
<td>0</td>
<td>12%</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>15%</td>
<td>8%</td>
</tr>
<tr>
<td>8</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>12</td>
<td>21%</td>
<td>12%</td>
</tr>
<tr>
<td>16</td>
<td>24%</td>
<td>14%</td>
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</table>

Remission Duration

<table>
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<tr>
<th>Year</th>
<th>Intensive lifestyle intervention</th>
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<td>16</td>
<td>24%</td>
<td>14%</td>
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</table>

**Terrance**

**Initial Pharmacotherapy**
- A1c, 8.2%
- FPG, 192 mg/dL
- Second test, 196 mg/dL
- eGFR, 80 mL/min/1.73 m²
- BP, 138/85 mm Hg
- Poor adherence with past daily medications
- Lipids
  - TC, 195 mg/dL
  - HDL-C, 39 mg/dL
  - LDL-C, 72 mg/dL
  - TG, 155 mg/dL
- ApoB, 83 mg/dL

**Symptoms**
- BP, 138/85 mm Hg
- eGFR, 80 mL/min/1.73 m²
- FPG, 192 mg/dL
- A1c, 8.2%

**Ussher JR, Drucker DJ.**

1. Rosenstock J, et al.

**Treatment**
- PBO Sax Met Sax + P

**Baseline**

<table>
<thead>
<tr>
<th>Pancreas</th>
<th>Glucagon Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Hepatic Glucose Production</td>
</tr>
<tr>
<td>Brain</td>
<td>Satiety</td>
</tr>
<tr>
<td>Intestine</td>
<td>Improved Glycemia</td>
</tr>
</tbody>
</table>

**Incretin-Based Therapies**

**Reducing Hyperglycemia**

- GLP-1 RA
- DPP-4 inhibitor
- AG inhibitor
- SGLT-2 inhibitor
- TZD
- SU/GlN

**GLP-1 RAs produce greater effects on hyperglycemia, whereas DPP-4 inhibitors are generally more tolerable**

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**AACE/ACE Algorithm for Glycemic Control**

**Lifestyle Modification**

<table>
<thead>
<tr>
<th>Entry A1c &lt; 7.5%</th>
<th>Entry A1c &gt; 7.5%</th>
<th>Entry A1c &gt; 9.0%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
<td><strong>Dual Therapy</strong></td>
<td><strong>Insulin + Other Agents</strong></td>
</tr>
<tr>
<td>Metformin</td>
<td>GLP-1 RA</td>
<td>No Symptoms</td>
</tr>
<tr>
<td>GLP-1 RA</td>
<td>DPP-4 inhibitor</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>DPP-4 inhibitor</td>
<td>AG inhibitor</td>
<td>Symptomatic</td>
</tr>
<tr>
<td>AG inhibitor</td>
<td>SGLT-2 inhibitor</td>
<td>Additional</td>
</tr>
<tr>
<td>SGLT-2 inhibitor</td>
<td>Basal Insulin</td>
<td>Diabetic</td>
</tr>
<tr>
<td>Basal Insulin</td>
<td>Colesevelam</td>
<td>ваться</td>
</tr>
<tr>
<td>Colesevelam</td>
<td>Bromocriptine QR</td>
<td>Add-on to</td>
</tr>
<tr>
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<td>GLP-1 RA</td>
<td>corexen</td>
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**If A1c > 6.5% in 3 months, add second drug (Dual Therapy)**

**If not at goal in 3 months, proceed to triple therapy**

**Possible benefits in few adverse events**

- Use with caution

**Note of medications listed as a target**

- GLP-1 agonists: GLP-1 receptor agonists: SGLT-2, sodium-glucose cotransporter-2; DPP-4, dipeptidyl peptidase-4.

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**Glucose Control With Sitagliptin**

**Monotherapy and Combination Therapy**

**T2D**

<table>
<thead>
<tr>
<th>N</th>
<th>ADD-on to Metformin vs Placebo 24 Weeks³</th>
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<th>ADD-on to Placebo vs Sitagliptin 24 Weeks³</th>
<th>ADD-on to Placebo vs Metformin 54 Weeks³</th>
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**N**: Number of patients

**ADD-on to Metformin vs Placebo**

**ADD-on to Placebo vs Metformin**

**ADD-on to Placebo vs Sitagliptin**

**ADD-on to Placebo vs Metformin**

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**Glucose Control With Saxagliptin**

**Monotherapy and Combination Therapy**

**T2D**

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**ADD-on to Placebo vs Metformin**

**ADD-on to Placebo vs Sitagliptin**

**ADD-on to Placebo vs Metformin**

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**Glucose Control With Linagliptin**

**Monotherapy and Combination Therapy**

**T2D**

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<td>0.9</td>
</tr>
</tbody>
</table>

**N**: Number of patients

**ADD-on to Metformin vs Placebo**

**ADD-on to Placebo vs Metformin**

**ADD-on to Placebo vs Sitagliptin**

**ADD-on to Placebo vs Metformin**

---

**AG inhibitor**

**DPP-4 inhibitor**

**SU/GLN**

**TZD**

**DPP-4 inhibitor**

---

**Garber AJ, et al.**

6. See Drugs@FDA (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/021995s023lbl.pdf).
In an 82-week exenatide completer cohort, weight loss was similar across:

- Baseline -42.0 (-47.8, -36.1)
- 6-7 -34.6 (-38.4, -30.9)
- 7-8 -33.9 (-44.4, -23.4)
- 9-10 -33.3 (-37.5, -29.2)

**Incretin-Based Therapies**

Cardiovascular Effects

- Direct effects of GLP-1 in humans
  - Improved endothelial function
  - Reduced fasting and postprandial plasma free fatty acid levels
  - Reduced postprandial levels of TG and ApoB
  - Reduced levels of cardiovascular risk biomarkers (eg, PAI-1, BNP)
- DPP-4 targets multiple peptide substrates that positively affect cardiovascular function
- Indirect effects of incretins on cardiovascular function
  - Insulin-induced increases in glucose utilization and decreases in fatty acid metabolism in myocardial tissue
  - Reduced visceral body fat and body weight

BNP: B-type natriuretic peptide; PAI-1: plasminogen activator inhibitor-1.
**GLP-1 RAs in T2DM**

**Improved Lipid Profiles**

<table>
<thead>
<tr>
<th>Drug</th>
<th>TC</th>
<th>LDL-C</th>
<th>HDL-C</th>
<th>TG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide BID</td>
<td>720</td>
<td>24</td>
<td>540</td>
<td>0</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>720</td>
<td>24</td>
<td>540</td>
<td>0</td>
</tr>
<tr>
<td>Exenatide QW</td>
<td>720</td>
<td>24</td>
<td>540</td>
<td>0</td>
</tr>
</tbody>
</table>

**Results**

- **Exenatide BID**
  - TC: 720 mg/dL
  - LDL-C: 24 mg/dL
  - HDL-C: 540 mg/dL
  - TG: 0 mg/dL

- **Liraglutide**
  - TC: 720 mg/dL
  - LDL-C: 24 mg/dL
  - HDL-C: 540 mg/dL
  - TG: 0 mg/dL

- **Exenatide QW**
  - TC: 720 mg/dL
  - LDL-C: 24 mg/dL
  - HDL-C: 540 mg/dL
  - TG: 0 mg/dL

**Notes**

- Indicates non-significant difference.
- Significant difference.

**References**


---

**DPP-4 Inhibitors for T2DM**

**Cardiovascular Events**

<table>
<thead>
<tr>
<th>Agent</th>
<th>MACE</th>
<th>P value</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitagliptin</td>
<td>0.86</td>
<td>&gt;0.001</td>
<td>0.40</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>0.87</td>
<td>&gt;0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>0.87</td>
<td>&lt;0.01</td>
<td>0.05</td>
</tr>
</tbody>
</table>

**Cardiovascular mortality**

<table>
<thead>
<tr>
<th>Agent</th>
<th>0.60</th>
<th>&lt;0.01</th>
</tr>
</thead>
</table>

**Not approved in US.**

**References**


**Blood Pressure and Lipid Changes With GLP-1 RAs**

**Meta-Analysis of RCTs**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>−3.57 mm Hg</td>
<td>−5.49 to −1.66</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>−1.38 mm Hg</td>
<td>−2.02 to −0.73</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>−3.9 mg/dL</td>
<td>(&lt;0.1 mmol/L) to −6.19 to −1.55</td>
</tr>
</tbody>
</table>

**References**


---

**SAVOR-TIMI 53**

**Primary and Secondary End Points**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Primary End Point</th>
<th>Secondary End Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saxagliptin</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Placebo</td>
<td>12%</td>
<td>14%</td>
</tr>
</tbody>
</table>

**Hazard ratio, 0.96 (upper boundary of the one-sided repeated CI, 1.16)**

**References**


---

**EXAMINE**

**Alogliptin after ACS in T2DM**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cumulative Incidence of Primary End Point Event %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alogliptin</td>
<td>12%</td>
</tr>
<tr>
<td>Placebo</td>
<td>14%</td>
</tr>
</tbody>
</table>

**Hazard ratio, 0.95 (upper boundary of the one-sided repeated CI, 1.16)**

**References**


---

**Incretin-Based Therapies**

**Cardiovascular Outcome Trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Agent</th>
<th>Patients (N)</th>
<th>Duration (y)</th>
<th>Patient-Years</th>
<th>Estimated Completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>TEOS (NCT01144338)</td>
<td>Liraglutide</td>
<td>9341</td>
<td>5</td>
<td>46200</td>
<td>2018</td>
</tr>
<tr>
<td>SAVOR TIMI-53 (NCT00968708)</td>
<td>Alogliptin</td>
<td>5400</td>
<td>4.75</td>
<td>25650</td>
<td>2013</td>
</tr>
<tr>
<td>CAROLINA (NCT01243424)</td>
<td>Linagliptin</td>
<td>6000</td>
<td>7.7</td>
<td>46200</td>
<td>2018</td>
</tr>
<tr>
<td>LEADER (NCT01179048)</td>
<td>Saxagliptin</td>
<td>9341</td>
<td>5</td>
<td>46705</td>
<td>2016</td>
</tr>
<tr>
<td>EXSCEL (NCT01144338)</td>
<td>Exenatide QW</td>
<td>9500</td>
<td>5.5</td>
<td>52250</td>
<td>2017</td>
</tr>
</tbody>
</table>

**References**

Incretin-Based Therapies Safety

- GLP-1 RAs
  - Most prominent adverse effects are gastrointestinal (nausea)\(^1\)
  - Minimizes nausea through gradual dose escalation and mealtime administration of GLP-1 RAs
- DPP-4 inhibitors
  - Most common adverse effects nasopharyngitis, headache, nausea, hypersensitivity, and skin reactions\(^1\)
  - Generally well-tolerated\(^1\)
    - One study found adherence to DPP-4 inhibitor ( saxagliptin) higher than to GLP-1 RA, sitagliptin, or linagliptin\(^2\)
- Long-term safety analysis requires postmarketing monitoring studies\(^2\)
  - Case reports of pancreatitis\(^2\)
  - Healthcare database analyses have not confirmed increased pancreatitis rate with incretin-based therapies
  - Pancreatic cancer\(^4\)
    - AACE: "Insufficient evidence exists to support a definitive link between antisympathetic medications and cancer development"

EMA Assessment Report for GLP-1 Based Therapies

- "Pancreatitis...no new data has emerged that implies that this risk is higher compared to what has previously been concluded"
- Pancreatic cancer... currently no support from clinical trials that GLP-1 based therapies increase risk
  - numbers of spontaneous reports limited and... confounding factors and/or short-term exposure common
  - However, long-term consequences... largely unknown
- Still some uncertainties... (re) long-term pancreatic safety associated with these products and updates to the risk management plans (including planned and ongoing studies) and harmonization of warnings in product information should be taken forward
- Additional information will be captured in the ongoing cardiovascular outcome studies

Recommendations for Incretin Therapies Potential Pancreatitis Risk

GLP-1 RAs
- Precautions
  - Cases have been reported
  - Patients with pancreatitis history
  - Avoid exenatide BID or QW
  - Consider treatment other than GLP-1 RA
- Recommendations
  - Ask about pancreatitis history
  - Educate patients, monitor for signs/symptoms
  - Discontinue promptly if pancreatitis symptoms occur
  - If acute pancreatitis is confirmed, do not report GLP-1 RA
  - Report cases of pancreatitis to www.fda.gov/safety

DPP-4 Inhibitors
- Precautions
  - Cases have been reported
  - Unknown if pancreatitis history increases risk with DPP-4 inhibitor use
- Recommendations
  - Observe for signs/symptoms at initiation
  - If pancreatitis is suspected
    - Promptly discontinue use
    - Initiate appropriate management

Recommendations for GLP-1 RA Use Possible Thyroid and Endocrine Risk

Prescribing Information

<table>
<thead>
<tr>
<th>Contraindications</th>
<th>Exenatide BID</th>
<th>Exenatide QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Do not use if history of MTC or MEN2</td>
<td>X</td>
<td>X</td>
</tr>
</tbody>
</table>

Recommendations

- Liraglutide and EXN QW are contraindicated in patients with MEN2 or a personal or family history of MTC\(^1\)
- Counsels patients regarding MTC risk and symptoms of thyroid tumors\(^1\)
- Value of routine calcitonin and/or ultrasound monitoring is uncertain; such monitoring may lead to unnecessary procedures\(^1\)
- Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist\(^1\)
- To monitor potential associations, report MTC to state cancer registry, regardless of treatment

EMA, European Medicine Agency

Recommendations for Incretin Therapies Possible Renal Impairment Risk

Prescribing Information

<table>
<thead>
<tr>
<th>Precautions</th>
<th>Exenatide BID</th>
<th>Liraglutide</th>
<th>Exenatide QW</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal impairment</td>
<td>Use with caution if (CrCl &lt;30 mL/min) or ESRD</td>
<td>Use with caution if (CrCl &lt;30 mL/min) or ESRD</td>
<td></td>
</tr>
</tbody>
</table>

Recommendations

- Use with caution in patients with renal impairment or renal transplantation, especially when initiating or escalating doses
- Hypovolemia due to nausea/vomiting may worsen renal function
- Do not use exenatide BID or exenatide QW in patients with severe renal impairment or ESRD

Terrance Initial Pharmacotherapy

- Terrance’s PCP suggests that Terrance may benefit from metformin in combination with a DPP-4 inhibitor
- Current treatments
  - Aspirin therapy
  - Simvastatin 40 mg daily
  - Ramipril 5 mg twice daily

Would you initiate these medications sequentially, concurrently, or as a combination? What dosing considerations are required with the various DPP-4 inhibitors? Would you change or add any other medications?
Terrance
**Key Points**

- Individualize goals and treatment intensity for T2DM
  - Disease duration and life expectancy
  - Risks of hypoglycemia
  - Comorbidities
  - Psychosocial factors
- Ensure lifestyle modifications are the foundation of any treatment regimen for T2DM
- Monitor multiple metabolic targets for comprehensive management and reduction of cardiovascular risk
  - A1c, lipids, BP
- Consider incretin-based therapies
  - Clinically relevant reductions in A1c
  - Potential benefits for cardiovascular outcomes

Mary
**Background**

- 50-year-old African American attorney
  - Divorced
  - Mother of 2 teenaged boys
  - Nonsmoker
  - Occasional glass of wine before bed
- Does not adhere to exercise or dietary recommendations

- Family history
  - Mother has cardiovascular disease
  - Both sisters are “big ladies”
- 10-year history of T2DM
  - Target A1c, 6.5%
  - Metformin 1000 mg twice daily
  - Insulin glargine
    - 3 weeks ago, titrated to 60 units at night
    - Rapid-acting insulin
      - 18 units before dinner
- 5-year history of dyslipidemia
  - Atorvastatin 10 mg

---

Mary
**PCP Visit**

- BMI, 33.2 kg/m²
  - Increased from 31.1 kg/m² over last year
  - A1c, 7.9%
    - Originally 9.9%
  - FPG, 182 mg/dL
  - PPG, 249 mg/dL
- Reports not using preprandial insulin when she is working late at the office
- Reports 2 episodes of symptomatic nocturnal hypoglycemia since last increase in basal insulin dose

**How would you tailor Mary’s treatment regimen?**

---

### Rates of Severe Hypoglycemia

**Intensive vs Standard Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypoglycemia Rate, %</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS1</td>
<td>7.9%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>ADVANCE2</td>
<td>1.8% (1.42-2.44)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACCORD3</td>
<td>1.6%</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>VADT4</td>
<td>3.8%</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

---

**Severe Hypoglycemia vs Adverse End Points**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypoglycemia Rate, %</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE2</td>
<td>1.8% (1.42-2.44)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACCORD3</td>
<td>1.6%</td>
<td>0.001</td>
<td>0.01</td>
</tr>
</tbody>
</table>

---

**Hypoglycemia vs Mortality**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypoglycemia Rate, %</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD1</td>
<td>1.0%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>ADVANCE2</td>
<td>1.0%</td>
<td>1.00</td>
<td>1.00</td>
</tr>
</tbody>
</table>

---

**Severe Hypoglycemia Rates**

<table>
<thead>
<tr>
<th>Study</th>
<th>Hypoglycemia Rate, %</th>
<th>HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADVANCE2</td>
<td>1.8% (1.42-2.44)</td>
<td>0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACCORD3</td>
<td>1.6%</td>
<td>0.001</td>
<td>0.01</td>
</tr>
<tr>
<td>VADT4</td>
<td>3.8%</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

---

**Severe Hypoglycemia vs Adverse End Points**

- Severe Hypoglycemia (n=225)
- No Severe Hypoglycemia (n=10,009)

---

**Severe Hypoglycemia vs Mortality**

- No Hypo
- 1st Hypo

---

**Severe Hypoglycemia Rates**

- No Hypo
- 1st Hypo
Unreported Asymptomatic Episodes of Hypoglycemia

- >45% of patients with T2DM had asymptomatic (unrecognized) hypoglycemia, identified via continuous glucose monitoring
- Similar findings in other studies

ADA/EASD Recommendations
Managing Hyperglycemia in T2DM

- Initial Drug Monotherapy
  - Metformin
    - Efficacy (A1c)
      - High
    - Weight
      - Loss
    - Side Effects
      - GI/Lactic acidosis
    - Costs
      - Low
  - Sulfonylureas
    - Efficacy (A1c)
      - High
    - Weight
      - Gain
    - Side Effects
      - GI/Lactic acidosis, Mycotic infection, OH
    - Costs
      - High
  - GLP-1 RA
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - DPP-4 inhibitor
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - Basal Insulin
    - Efficacy (A1c)
      - Low risk
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Low

Adapted ADA/EASD Recommendations
Avoiding Hypoglycemia

- Initial Drug Monotherapy
  - Metformin
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral/Loss
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - Sulfonylureas
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - GLP-1 RA
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - DPP-4 inhibitor
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - Basal Insulin
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss

Adapted ADA/EASD Recommendations
Avoiding Weight Gain AND Hypoglycemia

- Initial Drug Monotherapy
  - Metformin
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral/Loss
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - Sulfonylureas
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - DPP-4 inhibitor
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss
  - Basal Insulin
    - Efficacy (A1c)
      - High
    - Weight
      - Neutral
    - Side Effects
      - GI
    - Costs
      - Neutral/Loss

Mary's Diagnosis

- The PCP suggests adding a GLP-1 RA to Mary’s treatment regimen
  - Efficacy in achieving A1c, FPG, and PPG targets
  - Reduced risk of hypoglycemia
  - Durability of drug
  - Safety profile
  - Anticipated weight loss

Would you adjust Mary’s insulin regimen (basal or premeal) before initiating a GLP-1 RA?
Combination Therapy
Incretin-Based Agents and Basal Insulin

- Incretin-based therapies
  - Do not impair α-cell response to hypoglycemia and may reduce risk of severe hypoglycemia
  - Improve PPG levels without need for carbohydrate counting or frequent blood glucose monitoring
  - Complement the effects of metformin
  - Medications are weight-neutral (DPP-4 inhibitors) or weight-reducing (GLP-1 receptor agonists)

- Basal insulin affects FPG primarily
- Incretin agents improve both FPG and PPG
- Potential for better overall A1c control


Adding GLP-1 Receptor Agonist to Insulin

- Adding insulin to incretin-based agent
  - Avoids complexity of down-titrating insulin
  - May allow potential nausea associated with GLP-1 receptor agonists to subside before insulin initiation

- Adding incretin-based agent to insulin therapy
  - May benefit patients showing suboptimal glycemic control with insulin or struggles with body weight


Mary
Key Points

- Adverse effects of hypoglycemic events demand patient and caregiver education on risks and health consequences
- Consider incretin-based therapies
  - Low risks of hypoglycemia
  - Beneficial (or no effect) on body weight

Build-a-Case

Jack L. Leahy, MD
Professor of Medicine
Chief, Division of Endocrinology, Diabetes, and Metabolism
University of Vermont College of Medicine
Burlington, Vermont
Build-a-Case

Rhonda: Background

• 68-year-old African American woman
• Retired junior high school teacher
• Living with daughter and 3 grandchildren
  – Husband died 5 years ago of liver cancer
• BMI, 34 kg/m²

Build-a-Case

Rhonda: PCP visit

• Initial complaints (appeared 5 months ago)
  – Fatigue, increased thirst
  – Frequent urination, including nocturia
  – Blurry vision
• Medical history
  – Hypertension, hydrochlorothiazide 25 mg daily
  – Current BP, 130/80 mm Hg
• Family history
  – Father: T2DM, hypertension, died after MI
  – Mother: died of pancreatic cancer

Additional Considerations in T2DM

Smoking

• Risk factors for smoking in patients with T2DM¹
  – Younger age, less education, alcohol consumption, lack of physical activity, and depressive symptoms
  – Tobacco control efforts should be intensified in these populations
• Smoking cessation can lead to higher short-term risk for T2DM development²
  – May reflect increased body weight and/or higher leukocyte count
  – Couple smoking cessation with strategies for diabetes prevention/early detection for smokers at risk for diabetes


Additional Considerations in T2DM

History of Abuse

• Nurses Health Study II¹
  – Physical abuse
    • Moderate: 26% higher diabetes risk in adults
    • Severe: 54% higher diabetes risk in adults
  – Forced sexual activity before adulthood
    • 1 occasion: 34% higher diabetes risk in adults
    • >1 occasion: 69% higher diabetes risk in adults
• Consider weight-control interventions designed specifically for survivors of abuse²

². For example, refer to the National Eating Disorders Association for recommended therapists (http://www.nationaleatingdisorders.org/).
How does Rhonda’s reports of increasing memory problems affect your patient work-up?

Additional Considerations in T2DM

**Cognitive Decline**

- ACCORD-MIND cohort
  - Patients 55 to 80 years of age with type 2 diabetes, A1c >7.5%, and high risk of cardiovascular events
  - Randomized to intensive glycemic control (target A1c <6%) or standard therapy (target A1c = 7%-7.9%)
  - In the intensive glycemic control group, rosiglitazone (not insulin) was associated with greater cognitive decline over 40-month period


**Additional Considerations in T2DM**

**Osteoporosis**

- Diabetes is not included in the FRAX 10-year fracture risk calculation
  - FRAX underestimates fracture risk in this population
- One study linked metformin and sulfonylureas to reduced fracture incidence
- Insulin therapy may increase fracture risk, despite little effect on bone density
  - May reflect increased risk of hypoglycemia-related falls
- Exenatide use does not increase fracture risk

FRAX, Fracture Risk Assessment Tool.

**Build-a-Case**

**Rhonda: Primary Care Work-up**

- A1c, 8.5%
- FPG, 197 mg/dL
- Background diabetic retinopathy
- Advised to lose weight
  - Dietary changes and increased exercise
- Support system
  - Rhonda’s daughter promises to help with recommendations

**Rhonda: Initial Treatment and Follow-up**

- Prescribed metformin 500 mg twice daily
  - Titrated to 750 mg twice daily over the next month
- Follow-up appointment 3 months later
  - Reports daily walk and some gardening
  - Changed diet and lost 5 lbs
  - A1c, 8.4%
  - Continued blurry vision
- PCP decides to tailor Rhonda’s treatment plan

FPG, fasting plasma glucose.
How does the presence of comorbid nonalcoholic steatohepatitis affect your treatment recommendations?

Additional Considerations in T2DM
Nonalcoholic Steatohepatitis

• Pioglitazone may be beneficial for patients with mild liver test abnormalities (ALT levels <2.5 times upper limit of normal)
  – Avoid pioglitazone in individuals with active liver disease
• Nonalcoholic steatohepatitis decreases insulin clearance and may increase insulin production from β-cell in response to sulfonylureas
  – May increase risks of hypoglycemia
• GLP-1 RAs have been shown to decrease hepatic fat content with NMR spectroscopy analysis


How does the presence of comorbid urinary incontinence affect your treatment recommendations?

Additional Considerations in T2DM
Urinary Incontinence

• T2DM-related microvascular damage can affect pelvic floor and cause bladder or sphincter muscle dysfunction
• Hyperglycemia-induced diuresis may lead to increased urinary frequency
• T2DM may cause structural changes consistent with detrusor overactivity
  – Larger gaps between myocytes
  – Degenerated nerve fibers
  – Increased density of muscarinic receptors


Build-a-Case
Rhonda: Treatment Tailoring

• Prescribed insulin glargine 10 units at bedtime
  – Insulin dose titrated to 14 units once daily
  – Continues metformin 750 mg twice daily, exercise, and modified diet regimen
• Follow-up appointment 2 months later
  – BMI, 36 kg/m² (previous, 34 kg/m²)
  – A1c, 7.9% (previous, 8.4%)
  – FPG, 182 mg/dL
  – 2-hour PPG, 240 mg/dL
• PCP discusses further adjustments to her treatment regimen

Conclusions

• Comprehensive T2DM management requires diligent monitoring of blood sugars, lipid profile, blood pressure, and body weight
  – Treatment is founded on lifestyle and behavioral modifications
• Significant hypoglycemic episodes are associated with serious adverse outcomes
• GLP-1 RAs and DPP-4 inhibitors augment signaling in the pleotropic incretin hormone system
  – Efficacy in reducing hyperglycemia, with relatively low risks of hypoglycemia and potential for weight loss (or no weight increase)
  – Potential cardiovascular benefits remain an area of active research
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