Incretin Hormones: Evolving Treatment Strategies For Type 2 Diabetes
Session 3: What Every Practitioner Should Know About Incretin Hormones: Evolving Treatment Strategies for Type 2 Diabetes

Learning Objectives

- Discuss the pathophysiology and management of type 2 diabetes, including updates on incretin hormones and combination therapies.
- Identify 2 newer approaches to achieve long-term glycemic control and A1c targeted goals in patients with type 2 diabetes.

Faculty

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

Dr Lawrence Blonde is director of the Ochsner Diabetes Clinical Research Unit in the Department of Endocrinology, Diabetes and Metabolism, and associate internal medicine residency program director at the Ochsner Medical Center in New Orleans. 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.”

Dr Blonde’s clinical and research activities have focused on patients with diabetes mellitus and investigations of new therapies and health care delivery systems for them. He has also published and presented information about the use of computers to enhance medical education and patient care.

Dr Blonde is a member of the board of directors of both the American Association of Clinical Endocrinologists (AACE) and the Council for the Advancement of Diabetes Research and Education (CADRE), as well as a member of the National Quality Forum Adult Diabetes Care Consensus Maintenance Committee. He was chair of the American Diabetes Association (ADA) Doing Better Committee and a former member of the ADA board of directors. Dr Blonde is a current member and former chair of the ADA Professional Practice Committee, which develops practice guidelines for the care of people with diabetes.

Dr Blonde has served on the Microsoft Health Care Users Group Board of Directors and as a member of the Residency Review Committee for Internal Medicine and the Transitional Review Committee of the Accreditation Council for Graduate Medical Education. He has also been a member of the Council of the Association of Program Directors in Internal Medicine, the Council of the Association of Subspecialty Professors, and the American College of Physicians (ACP) Medical Informatics Subcommittee, for which he served as chair.

Laurence Kennedy, MD
Chief, Division of Endocrinology
Department of Medicine, University of Florida
Gainesville, Florida

Dr Laurence Kennedy is chief of the Endocrine Division in the Department of Medicine at the University of Florida. He received his medical degrees (MB and MD) at Queen’s University, Belfast, Northern Ireland; completed a residency program at Royal Victoria Hospital, Belfast; and underwent postgraduate training in endocrinology at Royal Victoria Hospital and the University of Florida. A general endocrinologist of considerable experience, Dr Kennedy holds clinics specializing in diabetes mellitus and pituitary disorders, as well as general endocrinology.

In the diabetes field, Dr Kennedy’s research interests have included the significance of glycation of proteins and hemoglobin, and how this may be utilized clinically. He has conducted significant clinical research in diabetes, covering development of diabetes complications and treatment of type 2 diabetes by diet, and was an investigator in the United Kingdom Prospective Diabetes Study. His clinical research, conducted with colleagues in Belfast, in patients with Cushing’s syndrome has given him extensive insight into the management of this uncommon and clinically challenging condition. Dr Kennedy continues to be involved in clinical trials of new therapies for type 2 diabetes; the management of pituitary disorders; and the potential of salivary cortisol in various clinical settings.
Dr Kennedy has been published in various scientific journals, including *Diabetes*, *Diabetes Care*, *Diabetologia*, the *Journal of Clinical Endocrinology and Metabolism*, the *British Medical Journal*, and the *Lancet*. Dr Kennedy is a member of the Endocrine Society and the American Diabetes Association (ADA) and chairs the clinical section of the ADA Grant Review Committee.

**Faculty Financial Disclosure Statements**

The presenting faculty report the following:

Dr Blonde is an investigator for Amylin Pharmaceuticals; AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Eli Lilly and Company; MannKind Corporation; Merck & Co., Inc.; Novo Nordisk Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; Pfizer Inc.; and sanofi-aventis U.S.; and is a speaker and consultant for Abbott; Amylin Pharmaceuticals, Inc.; Eli Lilly and Company; GlaxoSmithKline; LifeScan; Merck & Co., Inc.; Novartis Pharmaceuticals Corporation; Novo Nordisk Pharmaceuticals, Inc.; Pfizer Inc.; and sanofi-aventis U.S.

Dr Kennedy receives non-CME lecture honoraria from Merck & Co., Inc.

**Education Partner Financial Disclosure Statement**

The content collaborators at Vindico Medical Education have nothing to disclose.

**Drug List**

<table>
<thead>
<tr>
<th>Generic</th>
<th>Trade</th>
<th>Generic</th>
<th>Trade</th>
</tr>
</thead>
<tbody>
<tr>
<td>exenatide</td>
<td>Byetta</td>
<td>rosiglitazone</td>
<td>Avandia</td>
</tr>
<tr>
<td>glimepiride</td>
<td>Amaryl</td>
<td>sitagliptin</td>
<td>Januvia</td>
</tr>
<tr>
<td>glipizide</td>
<td>Glucotrol</td>
<td>sitagliptin + metformin</td>
<td>Janumet</td>
</tr>
<tr>
<td>glyburide</td>
<td>DiaBeta/Micronase/Glynase</td>
<td>vildagliptin</td>
<td>Galvus</td>
</tr>
<tr>
<td>metformin</td>
<td>Glucophage/Glucophage XR</td>
<td>Investigational</td>
<td></td>
</tr>
<tr>
<td>nateglinide</td>
<td>Starlix</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pioglitazone</td>
<td>Actos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pramlintide</td>
<td>Symlin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>repaglinide</td>
<td>Prandin</td>
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</tbody>
</table>

**Suggested Reading List**


What Every Practitioner Should Know About Incretin Hormones: Evolving Treatment Strategies for Type 2 Diabetes

Speakers:
Lawrence Blonde, MD, FACP, FACE
Laurence Kennedy, MD

What are incretins?

1. Pituitary factors that control glucagon secretion
2. Gastrointestinal hormones that affect insulin secretion
3. Pancreatic factors that influence GI motility
4. Plant-derived sterols that influence appetite
5. Animal-derived venoms

Incretins have been shown to:

1. Increase gastric emptying
2. Delay first-phase insulin secretion
3. Reduce postprandial hyperglucagonemia
4. Increase beta cell mass in patients with type 2 diabetes
5. Improve erectile dysfunction

Which incretin-based therapies do you currently use in your practice?

1. Sitagliptin
2. Exenatide
3. Both sitagliptin and exenatide
4. I do not use incretin-based therapies
Approved combination therapies include:

1. Sitagliptin + exenatide
2. Sitagliptin + insulin
3. Sitagliptin + metformin
4. Exenatide + insulin
5. Glitazones + pramlintide

73 million Americans with or at risk for diabetes


YOUR treatment goals for patients with T2DM are:

1. A1C < 6%
2. A1C ≤ 6.5%
3. A1C < 7%
4. A1C < 8%

What percentage of YOUR patients have achieved the ADA recommended minimal target of A1C < 7%?

1. < 25%
2. 25 to 50%
3. 50 to 75%
4. > 75%

ADA Recommended Goals for Type 2 Diabetes

<table>
<thead>
<tr>
<th>Measurements</th>
<th>Goals</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1C*</td>
<td>&lt;7%</td>
</tr>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>70-130 mg/dL</td>
</tr>
<tr>
<td>Peak postprandial plasma glucose</td>
<td>&lt;180 mg/dL</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/80 mm Hg</td>
</tr>
<tr>
<td>Lipids</td>
<td></td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>&lt;100 mg/dL (&lt;70 mg/dL)†</td>
</tr>
<tr>
<td>HDL cholesterol (♂)</td>
<td>&lt;110 mg/dL</td>
</tr>
<tr>
<td>HDL cholesterol (♀)</td>
<td>&gt;40 mg/dL</td>
</tr>
</tbody>
</table>

* Therefore, the A1C goal for selected individual patients is as close to normal (< 6%) as possible without significant hypoglycemia.
† A reduction in LDL to a goal of 70 mg/dL is an option in very high-risk patients with overt CVD

ADA Goals

A1C ≥7% should serve as a call to action to initiate or change therapy with the goal of achieving an A1C level as close to the non-diabetic range as possible or, at a minimum, decreasing the A1C <7%. 1

Therefore, the A1C goal for selected individual patients is as close to normal (<6%) as possible without significant hypoglycemia. 2

Type 2 Diabetes

ADA/EASD Consensus Guidelines Treatment Algorithm

ADA/EASD Global Treatment Strategy

Case 1

How would you manage her increasing A1C?

This is the Problem

Bewildering treatment options due to the complex pathophysiology
**Disadvantages**

3. **Insulin** (glitazones), Thiazolidinediones, Sulfonylureas, and Metformin 1

- **Step Exenatide 0.5**
- **Glucosidase inhibitors 0.5**

"Severe hypoglycemia is relatively infrequent with sulfonylurea therapy. The longer-acting agents (e.g., chlorpropamide and glibenclamide glyburide) are more likely to cause hypoglycemia than glipizide, extended-release glipizide, glimepiride, or gliclazide. †Pioglitazone. ‡Rosiglitazone. §Repaglinide is more effective at..."
Case 1: Review

- 37-year-old Hispanic female, high school teacher presents with a 3-year history of type 2 diabetes treated with metformin 1000 mg b.i.d.
- HbA1C initially improved to 6.2% from 8.5% at initial presentation
- HbA1C has been increasing, and at most recent visit was 7.4%
- Lipid and blood pressure values are consistent with guidelines and maintained with a statin and an ACE inhibitor
- BMI 31 kg/m²

How would you NOW manage her increasing A1C?

1. Reinforce lifestyle modification
2. Increase metformin to 3 g
3. Add a sulfonylurea
4. Add nateglinide or repaglinide
5. Add a glitazone (TZD)
6. Add sitagliptin
7. Add exenatide
8. Add basal insulin
9. Add alpha glucosidase inhibitor
10. Do nothing

Classification of Incretin-Related Therapies

- GLP-1 Mimetics (injectable)
  - Exenatide
  - Exenatide LAR*
- GLP-1 Analogs (injectable)
  - Liraglutide*
- Incretin enhancers (DPP-4 inhibitors) (oral)
  - Sitagliptin
  - Vildagliptin*
  - Saxagliptin*
  - Alogliptin*

* Not currently approved

Change in A1C in Exenatide Phase 3 Clinical Trials

Baseline A1C 8.5 8.5 8.5
8.2 8.3 8.2
8.7 8.5 8.6

MET 0.9*
SU 0.5
MET + SU 0.5

Change in A1C (%)
–0.9*
–1.0
–0.5
0
0.5
0

MET=metformin; SU=sulfonylurea.

Exenatide LAR 30-Week Study Vs. Exenatide B.I.D.

A1C Change From Baseline* (%) % Patients Reaching A1C Goal (≤7%)
Exenatide LAR (2 mg q.w.) –1.3 P = 0.002 77
Exenatide LAR twice daily (10 µg b.i.d.) –1.6 P = 0.004 61

-39% of exenatide LAR patients with baseline A1C ≥ 9.0% achieved A1C ≤ 6.5% at endpoint
-Both groups were associated with ~4 kg weight loss
-Neuropathy was mild and transient, and occurred less frequently with exenatide LAR


Once-Daily Liraglutide Decreases A1C Over 14 Weeks

<table>
<thead>
<tr>
<th>Δ A1C vs Pb (%)</th>
<th>A1C ≤ 7% (%)</th>
<th>Δ FPG vs Pb (mM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 0.65 mg</td>
<td>–1.3*</td>
<td>38*</td>
</tr>
<tr>
<td>Liraglutide 1.25 mg</td>
<td>–1.7*</td>
<td>48*</td>
</tr>
<tr>
<td>Liraglutide 1.90 mg</td>
<td>–1.8*</td>
<td>46*</td>
</tr>
<tr>
<td>Placebo</td>
<td>–</td>
<td>5</td>
</tr>
</tbody>
</table>

Δ = 0.05 vs Pb.

Classification of Incretin-Related Therapies

- GLP-1 Mimetics (injectable)
  - Exenatide
  - Exenatide LAR*

- GLP-1 Analogs (injectable)
  - Liraglutide*

- Incretin enhancers (DPP-4 inhibitors) (oral)
  - Sitagliptin
  - Vildagliptin*
  - Saxagliptin*
  - Alogliptin*

* Not currently approved

Incretin Secretion and DPP-4-Mediated Inactivation

Mixed Meal
Intestinal GLP-1 Release
GLP-1 (1-37) Active
GLP-1 (7-36) Active
DPP-4
GLP-1 (9-36) Inactive at the GLP-1R

Increased insulin secretion
Enhanced beta-cell proliferation
Reduced beta-cell apoptosis
Reduced glucagon secretion (GLP-1)

\[ t_{1/2} = 1 \text{ to } 2 \text{ min} \]

t1/2 = 1 to 2 min

Alogliptin Monotherapy Improves Low-Dose OHA Monotherapy or Using OHA or Patients Not

Goldstein a


N = 329

A1C (%)

Time (weeks)

Placebo

Alogliptin 12.5 mg

Alogliptin 25 mg

Initial Combination With Sitagliptin Plus Metformin Study Design

Patients Not Using Antihyperglycemic; Adding Sitagliptin
Low-Dose OHAs Combination

- Screening Period
- Diet and Exercise Run-in Period
- For UGMA, Placebo; for Period

Week 1
Day 1

Week 24

Plac"o

Sitagliptin 100 mg qd

Metformin 500 mg bid

Metformin 1,000 mg bid

Sitagliptin 50 mg

Metformin 500 mg bid

Sitagliptin 100 mg

Metformin 1,000 mg bid

Initial Combination Therapy With Sitagliptin Plus Metformin Compared to Monotherapy

24-Week Placebo-Adjusted Results

Mean A1C = 8.8%

Monotherapy

Combination

Sitagliptin 100 mg qd

Metformin 500 mg bid

Metformin 1,000 mg bid

Sitagliptin 50 mg + metformin 500 mg bid

Sitagliptin 50 mg + metformin 1,000 mg bid

Sitagliptin 50 mg bid

Sitagliptin 100 mg bid

Sitagliptin 50 mg bid

Metformin 1,000 mg bid

Placebo

Sitagliptin Plus Metformin Study

Change in Body Weight

1234 Change from Baseline, kg

0  2  4  6  8  10

1234 A1C, %

60  70  80  90  100

Sitagliptin 100 mg qd

Metformin 500 mg bid

Metformin 1,000 mg bid

Sitagliptin 50 mg bid

Sitagliptin 100 mg bid

Sitagliptin 50 mg bid

Placebo

A1C, %

60  70  80  90  100

% P<0.001 vs monotherapy.


Glipizide-Controlled Sitagliptin Add-on to Metformin Noninferiority Study Change in A1C and Incidence of Hypoglycemia

Sitagliptin: Homeostasis Model Assessment of Beta-Cell Function and Proinsulin-to-Insulin Ratio

Sitagliptin Lowers A1C Regardless of Patient Age, Gender, or Body Mass Index

Sitagliptin AUC\(_{0-\text{inf}}\) Increases With Decreasing Creatinine Clearance

Do we need to adjust the dose of sitagliptin for patients with impaired renal function?

Case 2

- 55-year-old Caucasian female postal worker, 15-year history of diabetes, on metformin 1000 mg b.i.d. and glyburide 5 mg b.i.d.
  - A1C has increased over the years to 8.2%
  - Evidence of early microvascular complications (nonproliferative diabetic retinopathy)
  - History of coronary artery disease, but no CHF
  - Lipids, blood pressure and weight are well controlled
How would you manage her increasing A1C?

1. Reinforce lifestyle modification
2. Increase glyburide to 10 mg b.i.d.
3. Add a glitazone (TZD)
4. Add sitagliptin
5. Add exenatide
6. Add basal insulin

Shared Decision Making

• Customize therapy based on the following:
  – Risk of hypoglycemia
  – Cardiovascular status
  – Renal status
  – Weight
  – A1C
  – Cost
  – Adherence
  – Route of administration

What are incretins?

1. Pituitary factors that control glucagon secretion
2. Gastrointestinal hormones that affect insulin secretion
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Discussion: How would you manage her increasing A1C?

<table>
<thead>
<tr>
<th>Treatment Option</th>
<th>Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reinforce lifestyle modification</td>
<td>It is never too late to reinforce lifestyle modification. However, it is not likely that this alone would get the patient to goal.</td>
</tr>
<tr>
<td>Increase glyburide to 10 mg b.i.d.</td>
<td>CVD concerns, Fluid retention, Weight gain, Associated with decreased bone density.</td>
</tr>
<tr>
<td>Add a glitazone (TZD);</td>
<td>Well tolerated, Weight neutral, No long term safety data, Reports of hypersensitivity reactions, Expensive.</td>
</tr>
<tr>
<td>Add sitagliptin</td>
<td>Weight loss, Injectable, Initial GI side effects, Pancreatitis, Expensive.</td>
</tr>
<tr>
<td>Add exenatide</td>
<td>Weight loss, Injectable, Initial GI side effects, Pancreatitis, Expensive.</td>
</tr>
<tr>
<td>Add basal insulin</td>
<td>Greatest A1C-lowering potential, Hypoglycemia, Weight gain.</td>
</tr>
</tbody>
</table>

Earlier and More Aggressive Intervention May Improve Patients’ Chances of Reaching Goal

Published Conceptual Approach

What are incretins?

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Incretins have been shown to:

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Approved combination therapies include:

1. Sitagliptin + exenatide
2. Sitagliptin + insulin
3. Sitagliptin + metformin
4. Exenatide + insulin
5. Glitazones + pramlintide

Conclusion

• Type 2 diabetes is a progressive disease characterized by ongoing beta cell failure
• Most patients with type 2 diabetes should be able to achieve an A1C goal of < 7% with the broad range of antihyperglycemic agents available

Conclusion

• Early pharmacological intervention, combination therapy and persistent titration are often required to achieve these goals
• Incretin-based therapy can be used early and as a component of combination therapy
• DPP-4 inhibitors are well tolerated, weight neutral and not associated with hypoglycemia when used alone or in combination with metformin or TZDs

Questions & Answers