Emerging Challenges in Primary Care: 2017

GLP-1 Receptor Agonists: New Insights and New Strategies for Successful Long-Term Diabetes Management
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Disclosures

- **Richard S. Beaser, MD** has no financial relationships to disclose.

- **Robert S. Busch, MD, FACE** serves as a speaker for Astra Zeneca, Eli Lilly, Boehringer Ingelheim, Novo Nordisk, and Shire. Dr. Busch also serves as a researcher for Astra Zeneca, Novo Nordisk, Janssen, and Amgen.

- **Mark Stolar, MD** serves as a speaker/advisory board member for Astra Zeneca.

- **Richard Pratley, MD** serves as a speaker/consultant for AstraZeneca. Dr. Pratley also serves as a consultant for Boehringer-Ingelheim, GlaxoSmithKline, Hanmi Pharmaceutical Co., Ltd., Janssen Pharmaceuticals, Inc., and Ligand Pharmaceuticals, Inc. Additionally, Dr. Pratley performs research under contract for Lexicon Pharmaceuticals, Sanofi-Aventis US, LLC, Lilly, Merck, and Takeda. Dr. Pratley performs research, is a speaker and consultant for Novo Nordisk. All honoraria and fees are directed to a non-profit. Dr. Pratley does not receive any direct compensation for these activities.

- **Jeff Unger, MD, ABFM, FACE** serves on the advisory board for Abbott, Novo Nordisk, Janssen, and Intarcia.
Learning Objectives

- Discuss the role of postprandial hyperglycemia in the pathogenesis of diabetic complications.

- Incorporate GLP-1 RA therapy into practice to reduce post-prandial hyperglycemia and decrease glycemic variability.

- Compare GLP-1 RAs for glycemic efficacy and differential impact on postprandial glycemic control.

- Discuss various GLP-1 RA combination strategies with, or as a possible alternative to, basal insulin in the diabetic patient not at glycemic target.
PRE-TEST QUESTIONS
Pre-test ARS Question 1

At about what level of A1C does postprandial glucose account for >50% of total A1C?

1. ~7%
2. ~8%
3. ~9%
4. ~10%
Pre-test ARS Question 2

Comparing the differences between shorter and longer-acting GLP-1 receptor agonists, which of the following statements is true?

1. Longer-acting have a greater impact on reducing postprandial glucose
2. Longer-acting have a greater impact on fasting glucose
3. Shorter acting have a greater impact on increasing fasting insulin secretion
4. Shorter acting have a greater impact on fasting glucose
Pre-test ARS Question 3

The advantages of combining GLP-1 receptor agonists with basal insulin include all of the following, EXCEPT:

1. Less risk for weight gain compared to insulin alone
2. Reductions in both fasting and postprandial glucose levels
3. Significantly lower incidence of hypoglycemia compared to insulin alone
4. Potential for reduced doses of basal insulin when GLP-1 RA added to insulin therapy
Pre-test ARS Question 4

A 49-year-old man with 10-year history of T2DM and NSTEMI 2 years ago works on a farm and has long active days. His A1C is 7.8%, FBG 70-120 mg/dL and PPG 180-220 mg/dL. Meds include metformin 1000 mg bid and basal insulin 38 U qam. Which of the following might be appropriate to manage hyperglycemia and cardiovascular risk?

1. Add sulfonylurea
2. Add rapid-acting insulin before each meal
3. Discontinue basal insulin and start GLP-1RA
4. Add GLP-1RA and reduce dose of basal insulin
Pre-test ARS Question 5

When adjusting therapy in patients with type 2 diabetes, how often do you consider using GLP-1 receptor agonists in combination with basal insulin:

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always
Pre-test ARS Question 6

Please rate your confidence in your ability to utilize GLP-1RAs in clinical practice:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident
ADA 2016: Standards of medical care in diabetes

Healthy eating, weight control, increased physical activity

**Initial mono-therapy**
- Metformin

**Two-drugs combined**
- SU
- TZD
- DPP-4i
- SGLT2i
- GLP-1 RA
- Insulin

**Three-drugs combined**
- TZD DPP-4i SGLT2i GLP-1 RA Insulin
- SU DPP-4i SGLT2i GLP-1 RA Insulin
- SU TZD SGLT2i Insulin
- SU TZD DPP-4i Insulin
- SU TZD Insulin
- SU TZD DPP-4i SGLT2i GLP-1 RA

**Combined injectable therapy**
- Basal insulin + Mealtime insulin or GLP-1 RA

**Escalate therapy at 3 months if target not achieved**

DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; TZD, thiazolidinedione ADA. Diabetes Care. 2016;39(Suppl. 1):S1–S2.
Likelihood of Monotherapy Failure in ADOPT

Cumulative Incidence of Fasting Glucose Greater than 180 mg/dl

- Rosiglitazone
- Metformin
- Glyburide

Likelihood of Monotherapy Failure in ADOPT

N = 3652

N Eng J Med 2006;355:2427-43
Ominous Octet

Islet beta cell
Impaired insulin secretion
Decreased incretin effect
Increased lipolysis

Islet alpha cell
Increased glucagon secretion
Increased glucose reabsorption

Hyperglycemia

- Increased hepatic glucose production
- Neurotransmitter dysfunction
- Decreased glucose uptake

Progressive β-Cell Dysfunction Is a Key Driver of Progressive Dysglycemia in T2D

By the time of diabetes onset, up to 80% of β-cell function may be lost\(^1,2\)

Deteriorating β-cell function is partially driven by the incretin defect

Fasting vs Postprandial Glucose Contribution to HbA1c

Contribution

Postprandial Plasma Glucose  Fasting Plasma Glucose

HbA1c Range (%)  <7.3  7.3-8.4  8.5-9.2  9.3-10.2  >10.2

%  70%  50%  45%  40%  30%

GLP-1 RAs Mimic and Extend Actions of Endogenous GLP-1

<table>
<thead>
<tr>
<th>Endogenous GLP-1 RA</th>
<th>GLP-1 RAs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inactivation</strong></td>
<td></td>
</tr>
<tr>
<td>Rapid</td>
<td>Delayed</td>
</tr>
<tr>
<td>• Cleavage by DPP-4</td>
<td>• Resistance to DPP-4</td>
</tr>
<tr>
<td>• Renal elimination</td>
<td>• Resistance to renal filtration</td>
</tr>
<tr>
<td>• Physiologic</td>
<td>• Pharmacologic</td>
</tr>
<tr>
<td><strong>Concentration</strong></td>
<td></td>
</tr>
<tr>
<td>• Prandial/early postprandial</td>
<td>• Prandial/early postprandial</td>
</tr>
<tr>
<td><strong>Timing of effects</strong></td>
<td></td>
</tr>
</tbody>
</table>

GLP-1 RA

- **Exenatide**
  - 5-10 mcg **twice daily** (Byetta® 2005)
  - 2 mg **once weekly** (Bydureon® 2012)

- **Liraglutide**
  - 1.2-1.8 mg daily (Victoza® 2010)
  - 3 mg daily (weight loss indication, Saxenda® 2014)

- **Albiglutide**
  - 30-50 mg once weekly (Tanzeum® 2014)

- **Dulaglutide**
  - 0.75-1.5 mg once weekly (Trulicity® 2014)

- **Lixisenatide** 10-20mcg daily (Adlyxin 2017)
### GLP-1 RA

<table>
<thead>
<tr>
<th>Exenatide, Exenatide LAR, Liraglutide, Albiglutide, Dulaglutide, Lixisenatide</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mechanism</strong></td>
</tr>
</tbody>
</table>
| **Primary physiological action(s)** | • ↑glucose-dependent insulin secretion  
• ↓glucose-dependent glucagon secretion  
• ↑Satiety  
• Slows gastric emptying |
| **Advantages** | • ↓Postprandial glucose excursions  
• ↓Weight |
| **Limitations** | • Patient training requirements (injectable therapy)  
• Gastrointestinal side effects (nausea, vomiting [less with longer-acting agents])  
• Hypoglycemia possible when used with insulin, if insulin doses are not reduced |
| **Cost** | High (relative to other generic agents, ie metformin) |

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Case 1: Meet Cherise

- Cherise is a 38 year old African American female with a 5 yr history of type 2 diabetes on maximum SFU and metformin.

- She could not tolerate TZDs due to edema and refused to start insulin.

- Her HbA1c for the past 2 years has been between 7.9% and 8.8%. Most recent: 9.0%

- PMH sig. for dyslipidemia, hypertension and central obesity (BMI 43). Her weight is not a concern for her.

- Strong family history of type 2 diabetes as her mother and grandmother are both on dialysis and a maternal aunt recently died of a CVA
ARS Question

Which of the following might help Cherise improve her glycemic control?

1. Recommend GLP-1RA and show her an injection pen
2. Tell her that she will need insulin if she does not lose significant weight
3. Add DPP-4 inhibitor and consider SGLT-2 inhibitor if response insufficient
4. Recommend full basal-bolus regimen and remind her of her family history of kidney disease
Case 1: Helping Cherise Succeed
(Current rx metformin 2000 max SU)

- Her PCP was concerned about the high HbA1C and recommended insulin, but she refused to start insulin as it made her “too anxious” and wanted to work harder on fitness and a medication that will help with weight loss.

- She agreed to start dulaglutide once weekly. She developed nausea for the first 3 weeks post injection and stopped the medication. She admits giving an injection was not a big deal, but stated taking insulin just made her nervous.

- Over the next two months she tried her best to diet and exercise but follow up HbA1c was still 8.6%.

- How can you now effectively transition Cherise to accepting insulin therapy or restarting her GLP-1 RA?
Barriers to Injectables: The CLINICIAN Side of the Equation

- **Misperceptions**
  - The need to advance Rx is never-ending (therapeutic fatigue)
  - Insulin: most appropriate for end-stage Rx
  - Patients don’t want to use injectables

- **Reality-based Concerns**
  - Time demands of instructing patients about injections
  - Unfamiliarity with the variety of devices (e.g., various pens)

- **Misplaced Blame**
  - If only the patient would exercise and lose weight, they wouldn’t need insulin

- **Knowledge gaps**
  - Role of glucotoxicity in disease progression and therapeutic failure
  - Typical weight changes (gain): insulin
  - Typical weight changes (loss): GLP-1 RA
  - Familiarity with ADA/EASD and AACE Guidelines
Suggestions for Overcoming Fear of Injections

“Dry run” injection
(Insert needle without injecting drug)

Reinforce that injection is relatively painless
• Injection is into fatty tissue versus muscle

Reinforce that injection is easy
• Injection devices are quick and easy-to-use
• Have pen available for demonstration
Patient-level meta-analysis: HbA1c reduction across baseline categories

HbA1c, glycosylated haemoglobin
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001 vs. liraglutide 1.8 mg
Henry et al. Endocr Pract 2011;17:906–913
HbA1c and Weight Change with Sitagliptin vs. Dulaglutide Once Weekly added to Metformin after 52 weeks (AWARD-5)

HbA1c Reductions (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Change in HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide 0.75 mg</td>
<td>-0.87</td>
</tr>
<tr>
<td>Dulaglutide 1.5 mg</td>
<td>-1.1</td>
</tr>
<tr>
<td>Sitagliptin 100 mg</td>
<td>-0.39</td>
</tr>
</tbody>
</table>

Weight Loss (kg)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Change in Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dulaglutide 0.75 mg</td>
<td>-3.03</td>
</tr>
<tr>
<td>Dulaglutide 1.5 mg</td>
<td>-2.6</td>
</tr>
<tr>
<td>Sitagliptin 100 mg</td>
<td>-1.53</td>
</tr>
</tbody>
</table>

P < .001

GLP-1 RA Pharmacologic Activity Is Higher With GLP-1 RAs Than With DPP-4 Inhibitors


N=61 metformin-treated, evaluable patients.
Comparing GLP-1 RAs
Shorter-Acting vs Longer-Acting Formulations

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Shorter Acting</th>
<th>Longer Acting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exenatide BID, lixisenatide</td>
<td>Albiglutide, dulaglutide, exenatide QW, liraglutide, semaglutidea</td>
</tr>
<tr>
<td>Half-life</td>
<td>2-5 hours</td>
<td>12 hours to several days</td>
</tr>
<tr>
<td>Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FPG reduction</td>
<td>Modest</td>
<td>Strong</td>
</tr>
<tr>
<td>Postprandial hyperglycemia reduction</td>
<td>Strong</td>
<td>Modest</td>
</tr>
<tr>
<td>Fasting insulin secretion stimulation</td>
<td>Modest</td>
<td>Strong</td>
</tr>
<tr>
<td>Glucagon secretion</td>
<td>Reduction</td>
<td>Reduction</td>
</tr>
<tr>
<td>Weight reduction</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Potential for nausea</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Clinical Pearl:
Select GLP-1 RAs for T2DM based on the patient’s hyperglycemia profile and preferences.

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aNot approved by the FDA for use in the United States.
Effects of Exenatide BID vs Exenatide QW on PPG

Data presented are means ± SE
PPG taken from SMBG profile
Head-to-Head Trials Comparing Efficacy of GLP-1 RAs


\[ \Delta A1C, \% \]

- **LEAD-6**
  - Added to MET ± SU
  - EXP BID 10 mcg: -0.8
  - LIRA 1.8 mg: -1.1
  - EXP QW 2.0 mg: -1.6
  - ALBI 50 mg: -1.0
  - DULA 1.5 mg: -1.5
  - \( a \)

- **DURATION-5**
  - Added to Drug-naïve or MET ± SU ± TZD
  - EXP BID 10 mcg: -0.9
  - LIRA 1.8 mg: -1.5
  - EXP QW 2.0 mg: -1.3
  - ALBI 50 mg: -0.8
  - DULA 1.5 mg: -1.0
  - \( a,b \)

- **DURATION-6**
  - Added to Drug-naïve or MET ± SU ± TZD
  - EXP BID 10 mcg: -1.5
  - LIRA 1.8 mg: -1.0
  - EXP QW 2.0 mg: -1.3
  - ALBI 50 mg: -1.5
  - DULA 1.5 mg: -1.0
  - \( a \)

- **HARMONY-7**
  - Added to MET ± SU ± TZD
  - EXP BID 10 mcg: -0.8
  - LIRA 1.8 mg: -1.0
  - EXP QW 2.0 mg: -1.0
  - ALBI 50 mg: -1.4
  - DULA 1.5 mg: -1.4
  - \( c \)

- **AWARD-1**
  - Added to MET ± TZD
  - EXP BID 10 mcg: -1.0
  - LIRA 1.8 mg: -1.5
  - EXP QW 2.0 mg: -1.5
  - ALBI 50 mg: -1.0
  - DULA 1.5 mg: -1.4
  - \( a \)

- **AWARD-6**
  - Added to MET
  - EXP BID 10 mcg: -1.1
  - LIRA 1.8 mg: -1.4
  - EXP QW 2.0 mg: -1.4
  - ALBI 50 mg: -1.4
  - DULA 1.5 mg: -1.4
  - \( c \)

\( a P < .05 \) between groups.

\( b \) Noninferiority vs LIRA not met.

\( c \) DULA noninferior to LIRA, \( P < .0001 \).
Patient Education Talking Points for GLP-1 RA

- Instruct on good injection technique
- GI disturbances
- May cause hypoglycemia when used with sulfonylureas or insulin
- Exenatide twice daily or liraglutide: Prime or set up pen device only once when medication is first started
- Store refrigerated until pen is in use, then keep at room temperature
- Discuss signs and symptoms of pancreatitis when initiating therapy

ARS Question

Which of the following can help minimize gastrointestinal side effects when initiating GLP-1RA?

1. Eat smaller meals and more slowly
2. Use short-term antiemetic therapy for select patients
3. Increase dose slowly, especially shorter-acting agents
4. All of the above
# Nausea and Vomiting

## Pooled Results From Placebo-Controlled Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Nausea Incidence, %</th>
<th>Vomiting Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albiglutide&lt;sup&gt;1&lt;/sup&gt;</td>
<td>11</td>
<td>4</td>
</tr>
<tr>
<td>Dulaglutide&lt;sup&gt;2&lt;/sup&gt;</td>
<td>12-21</td>
<td>6-13</td>
</tr>
<tr>
<td>Exenatide twice daily&lt;sup&gt;3&lt;/sup&gt;</td>
<td>8-44</td>
<td>4-18</td>
</tr>
<tr>
<td>Exenatide once weekly&lt;sup&gt;4&lt;/sup&gt;</td>
<td>11-27</td>
<td>11</td>
</tr>
<tr>
<td>Liraglutide&lt;sup&gt;5&lt;/sup&gt;</td>
<td>8-35</td>
<td>6-17</td>
</tr>
<tr>
<td>Lixisenatide&lt;sup&gt;6&lt;/sup&gt;</td>
<td>25%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Potential approaches to reduce risks for nausea and vomiting<sup>3,6</sup>

- Educate patients on meal size, eating pace, and dose timing relative to meals
- Use incremental dosing, particularly with shorter-acting agents
- Prescribe short-term antiemetic therapy for select patients

**Clinical Pearl:**

Recommend that patients eat smaller meals and more slowly when initiating treatment with a GLP-1 RA.

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Weight Loss With GLP-1 RAs Not Driven by Gastrointestinal Adverse Events

In a 82-week exenatide completer cohort, weight loss was 1) similar across degrees of nausea, 2) progressive despite stable nausea incidence, and 3) unlikely to be driven by nausea.

NVD, nausea, vomiting, diarrhea; PBO, placebo. \(^aP<0.05\) vs baseline; \(^bP<0.05\) vs placebo.

GLP-1 RAs Added to Multiple Oral Agents: Comparisons With Basal Insulin

* ≈ 70% on MET monotherapy background
† ≈ 70% on MET + SU background

GLP-1 RAs vs Basal Insulin

Patient Quartiles Based on Baseline HbA1c

- Exenatide QW
- Glargine
- Liraglutide
- Glargine

LEAD-5, Liraglutide Effect and Action in Diabetes.
Intensifying Treatment with Combination Injectable Therapy

When added to oral antihyperglycemic therapy, basal insulin alone may not be sufficient for reaching HbA1c goals, especially as fasting plasma glucose approaches normal levels.

Basal insulin

Essential component of the treatment strategy when HbA1c target is not achieved despite intensive therapy with 3 antihyperglycemic agents.

Combination injectable therapy

Options for intensified therapy

- Basal-bolus insulin
- Basal insulin + GLP-1 RA

Not at Goal: Intensifying Therapy Beyond OAD + Basal:
Meet Dave – 52 y/o Irish American Construction Foreman

- Type 2 diabetes for 8 years.
- Meds: metformin 1000 mg bid, glipizide 10mg bid and levemir 80 units bid.
- FBS 160 -180 mg/dl.
- Sometimes misses evening insulin dose when falling asleep on the couch watching TV. Morning glucose seems no different when he misses his second dose.
- He doesn’t check his blood sugar often in the evening because it was over 240 on the few times he checked.
More about Dave:

- Dave works 5-10 hour shifts during season and has to drive an hour each way to work. On his days off he helps his brother remodel a house. He has no other defined exercise as his arthritis of both knees is becoming quite symptomatic.

- His BMI is 36.8. His mother and sisters are all obese and all have type 2 diabetes, but only 2 of 5 are on insulin.

- He is hypertensive, hypercholesterolemic, and is an ex smoker having quit 5 years ago when his grandchildren were born.
Laboratory Assessment

- HbA1c 8.9%
- FBS 165 mg/dl
- Creatinine 1.5 mg/dl
- Microalbumin 75 mg/g creat N <30
- Tc 190 mg/dl HDL 35mg/dl TG 190mg/dl LDL 117mg/dl
ARS: Which of the following statements about Dave is correct?

1. Given his high CV risk, a GLP-1 RA or SGLT-2 inhibitor is recommended as part of his therapy

2. His beta cell function is gone since he is not responding to glipizide

3. Bolus insulin would control postprandial glucose in this patient more effectively than a GLP-1 RA

4. Addition of an SGLT-2 inhibitor could get this patient close to target
ARS: What is the next best step for Dave to get him to goal?

1. Add an SGLT-2 inhibitor
2. Add pioglitazone
3. Discontinue glipizide and add bolus insulin
4. Discontinue glipizide and add a GLP-1 RA
5. 2 and 4
6. 1 and 4
Combining GLP-1 RA and Basal Insulin

- **Basal insulin analogs**
  - Simple to initiate
  - Control nocturnal hyperglycemia and FPG
  - Lower hypoglycemia risk than NPH
  - Can cause weight gain
  - Achieve HbA1c target in ~50%<sup>a</sup>

- **GLP-1 RAs**
  - Simple to initiate
  - Can control FPG and PPG
  - Do not impair α-cell response to hypoglycemia (reduce risks of severe hypoglycemia)
  - Weight-lowering
  - Achieve HbA1c target in ~60%<sup>a</sup>

**Complementary actions**

**Additive effects**

**Potential for better overall HbA1c control**

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<sup>a</sup>Percentage achieving <7% across baseline HbA1c quartiles for liraglutide and exenatide once weekly vs insulin glargine.

After Basal Insulin, Once-Weekly GLP-1 RA vs. Three Times Daily Prandial Insulin

After Basal Insulin, Once-Weekly GLP-1 RA vs. Three Times Daily Prandial Insulin


-1.5 (95% CI: −2.1, −1.0)
Bolus Insulin vs GLP-1 RA in Combination with Optimized Basal Insulin + Metformin

Change in Key Endpoints*

- Exenatide BID
- Lispro TID

*P < .001 for all key endpoints

Safety:
- Minor Hypoglycemia
- Nocturnal Hypoglycemia
- Serious AEs

Percent of Patients
GLP-1 RAs and Basal Insulin in T2DM Management: Complementary and Additive Features

<table>
<thead>
<tr>
<th>Basal insulin</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary effects</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Fasting glucose</td>
<td>↓ Postprandial glucose excursions</td>
</tr>
<tr>
<td>↓ Interprandial glucose</td>
<td>↓ Fasting glucose</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td></td>
</tr>
<tr>
<td>↓ Hepatic glucose production</td>
<td>↑ Glucose-dependent insulin secretion</td>
</tr>
<tr>
<td>↑ Non-glucose dependent endogenous insulin</td>
<td>↓ Glucagon secretion</td>
</tr>
<tr>
<td>↓ Glucagon secretion</td>
<td>↓ Hepatic glucose production</td>
</tr>
<tr>
<td>↑ Insulin concentration</td>
<td>↓ Gastric emptying</td>
</tr>
<tr>
<td><strong>Effect on weight</strong></td>
<td></td>
</tr>
<tr>
<td>↑ Body weight</td>
<td>↓ Body weight</td>
</tr>
</tbody>
</table>

Step-wise Process for Implementing GLP-1 RA and Basal Insulin Combination Therapy

Identify patient who is not at HbA1c target despite oral antihyperglycemic medications and basal insulin >0.5-0.7 units/kg or appropriately titrated to morning glucose control*

Discuss with patient the most common potential side effects. Consider reducing basal insulin dose by 20 % if HbA1c is < 8 % to minimize hypoglycemia risk

Encourage patient to regularly self-monitor blood glucose and log the results. Report any hypoglycemia (< 80 mg/dL) events for adjustment of insulin

Teach the patient proper injection technique and dosing based on specific device

Arrange a follow-up visit in approximately 1 month to evaluate treatment efficacy and to assess the patient for possible side effects

*Chance of success may be maximized if HbA1c is within 1–1.5 percentage points of target. Rhinehart AS. Clin Diabetes. 2015; 33(2):73-75.
Dave and his PCP agreed that more insulin was not likely to be effective and he admitted that sometimes he took less insulin as he was afraid of such high doses.

Liraglutide once daily was initiated and glipizide discontinued.

At his six week follow-up, he was tolerating the medication well and HbA1c had already decreased from 8.9% to 8.2%. The dose was increased to 1.8 mg.

At his three month recheck, HbA1c was down to 7.6% and Dave had lost six lbs.

What now is more important? Further glycemic lowering or reducing CV risk further?
CVD is the Leading Cause of Death in People With T2DM

Years of life lost in people with diabetes compared with peers without diabetes\(^1,\text{a}\)

- **Men**
  - Nonvascular deaths
  - Vascular deaths

- **Women**

Mortality risk associated with diabetes (N=820,900)\(^1\)

- CV death
- All-cause mortality

\(^a\)Information on diabetes type (ie, type 1 or 2) was generally not available, although participants’ ages suggest that a large majority with diabetes would have T2DM (in high-income countries, up to 91% of adults with diabetes have T2DM).\(^2\)

Potential Cardio protective MoA of GLP-1RA

BP, blood pressure; GLP-1, glucagon-like peptide-1; GLP-1RA, glucagon-like peptide-1 receptor agonist; MoA, mode of action
ELIXA
Lixisenatide in Patients With T2DM After ACS

No significant between-group differences in the rates of hospitalization or death

*Primary outcome: CV death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for UA.
N=6068 patients with T2DM who had a myocardial infarction or had been hospitalized for UA within the previous 180 days.
LEADER
Liraglutide in T2DM With High CV Risk

**Primary Outcome**

- HR, 0.87 (95% CI: 0.78, 0.97)
- *P*<0.001 for noninferiority
- *P*=0.01 for superiority

**CV-Related Death**

- HR, 0.78 (95% CI: 0.66, 0.93)
- *P*=0.007

**Death From Any Cause**

- HR, 0.85 (95% CI: 0.74, 0.97)
- *P*=0.02

---

**Table:**

<table>
<thead>
<tr>
<th>Months Since Randomization</th>
<th>Patients With Event, %</th>
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<tbody>
<tr>
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<td>54</td>
<td>50</td>
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</tbody>
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*Composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.
N=9340 patients with T2DM and high CV risk.
SUSTAIN-6
Semaglutide in T2DM With High CV Risk

**Primary Outcome**

- **Hazard ratio, 0.74** (95% CI, 0.58–0.95)
- *P*<0.001 for noninferiority
- *P*=0.02 for superiority

**Nonfatal Stroke**

- **Hazard ratio, 0.61** (95% CI, 0.38–0.99)
- *P*=0.04

**Death From CV Causes**

- **Hazard ratio, 0.98** (95% CI, 0.65–1.48)
- *P*=0.92

---

*Composite of death from CV causes, nonfatal myocardial infarction, or nonfatal stroke.
N=3297 patients with T2DM (A1c ≥7.0%) who were ≥50 years old with established CV disease or chronic kidney disease (Stage 3 or worse) OR were ≥60 years old with ≥1 CV risk factor were randomized to placebo or semaglutide 0.5 mg or 1.0 mg once weekly.
The combination of a GLP-1 RA and insulin may be highly effective for optimal glucose control, ameliorating the adverse effects often associated with insulin.

Data from clinical studies support the therapeutic potential of GLP-1 RA-insulin combination therapy, typically showing beneficial effects on:

- glycemic control
- body weight
- low incidence of hypoglycemia
- in established insulin therapy, facilitating reductions in insulin dose
GLP-1 RA/Basal Insulin Fixed-Ratio Combination

A1c, %

Baseline A1c Category, %

Total Trial Population

n= 833 413 414

≥7.5–≤8.5

>8.5–≤9.0

>9.0

6.0 6.4 6.2 6.6

7.2 7.1 7.1 7.0

8.0 8.0 8.0 8.0

6.4 6.4 6.4 6.4

5.5 5.5 5.5 5.5

8.3 8.3 8.3 8.3

GLP-1 RA/Basal Insulin Fixed-Ratio Combination

A1c, %

Baseline A1c Category, %

Total Trial Population

n= 833 413 414

≥7.5–≤8.5

>8.5–≤9.0

>9.0

6.0 6.4 6.2 6.6

7.2 7.1 7.1 7.0

8.0 8.0 8.0 8.0

6.4 6.4 6.4 6.4

5.5 5.5 5.5 5.5

8.3 8.3 8.3 8.3

P<0.01.

N=1660 insulin-naive adults with T2DM (mean A1c, 8.3%; mean BMI, 31.2 kg/m²) uncontrolled on oral agents assigned to IDegLira, insulin degludec, or liraglutide 1.8 mg daily (DUAL I Extension).

**Fixed-Ratio IGLarLixi vs Glargine/GlarLixi**

*Add-on to Metformin in T2DM*

- \( P = 0.013; \) \( P < 0.0001 \) vs glargine;
- IGLarLixi formulation: insulin glargine 2 U/lixisenatide 1 µg.
- LOCF, last observation carried forward; LS, least squares.

### Mean Change in HbA1c ± SE, %

<table>
<thead>
<tr>
<th>Weeks</th>
<th>IGLarLixi (n=161)</th>
<th>Glargine (n=162)</th>
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**LS mean difference, -0.17%**

95% CI, -0.312, -0.037

### Mean Change in Body Weight ±SE, kg

<table>
<thead>
<tr>
<th>Visit</th>
<th>IGLarLixi (n=161)</th>
<th>Glargine (n=162)</th>
</tr>
</thead>
<tbody>
<tr>
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**LOCF, last observation carried forward**

**Symptomatic hypoglycemia (≤70 mg/dL):** 22% with IGLarLixi vs 23% with glargine

Incidence of nausea/vomiting was 7.5%/2.5% with IGLarLixi

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Efficacy and Safety of LixiLan, a Titratable Fixed-Ratio Combination of Lixisenatide and Insulin Glargine, Versus Insulin Glargine in Type 2 Diabetes Inadequately Controlled on Metformin Monotherapy: The LixiLan Proof-of-Concept Randomized Trial.

5 severe hypoglycemic episodes reported (3 in 825 IDegLira-treated patients and 2 in 412 insulin degludec-treated patients)

Fewer patients in the IDegLira group than in the liraglutide group reported GI adverse events (nausea, 8.8% vs 19.7%)

GLP-1 RA/Basal Insulin Fixed-Ratio Combination

N=1660 insulin-naive adults with T2DM (A1c, 8.3%; BMI, 31.2 kg/m²) uncontrolled on oral agents.

Intensifying Diabetes Therapy: Utilizing GLP-1 RA Effectively

- The need for insulin providing therapies is intrinsic in a chronic disease that progresses from relative to absolute insulin deficiency over time.

- Postprandial hyperglycemia plays an important and often unmonitored and undertreated role in the progression of diabetes.

- Use of basal insulin at bedtime is an effective means of lowering fasting and diurnal glycemia but does not address postprandial needs.

- The need for basal insulin implies deficiency postprandially as well. GLP-1 RA analogues and short acting insulin both meet that oft unmonitored need but with very different effects on hypoglycemia weight gain and beta cell function.

- GLP-1 RA analogues are a very effective means of providing endogenous insulin and are a very effective entry into injectable therapy as well as adjunct to basal insulin when intensified therapy is needed.
POST-TEST QUESTIONS
Post-test ARS Question 1

At about what level of A1C does postprandial glucose account for >50% of total A1C?

1. ~7%
2. ~8%
3. ~9%
4. ~10%
Comparing the differences between shorter and longer-acting GLP-1 receptor agonists, which of the following statements is true?

1. Longer-acting have a greater impact on reducing postprandial glucose
2. Longer-acting have a greater impact on fasting glucose
3. Shorter acting have a greater impact on increasing fasting insulin secretion
4. Shorter acting have a greater impact on fasting glucose
The advantages of combining GLP-1 receptor agonists with basal insulin include all of the following, EXCEPT:

1. Less risk for weight gain compared to insulin alone
2. Reductions in both fasting and postprandial glucose levels
3. Significantly lower incidence of hypoglycemia compared to insulin alone
4. Potential for reduced doses of basal insulin when GLP-1 RA added to insulin therapy
A 49-year-old man with 10-year history of T2DM and NSTEMI 2 years ago works on a farm and has long active days. His A1C is 7.8%, FBG 70-120 mg/dL and PPG 180-220 mg/dL. Meds include metformin 1000 mg bid and basal insulin 38 U qam. Which of the following might be appropriate to manage hyperglycemia and cardiovascular risk?

1. Add sulfonylurea
2. Add rapid-acting insulin before each meal
3. Discontinue basal insulin and start GLP-1RA
4. Add GLP-1RA and reduce dose of basal insulin
Post-test ARS Question 5

When adjusting therapy in patients with type 2 diabetes, as a result of attending this program, how often will you consider using GLP-1 receptor agonists in combination with basal insulin:

1. Never
2. Rarely
3. Sometimes
4. Often
5. Always
Post-test ARS Question 6

Please rate your confidence in your ability to utilize GLP-1RAs in clinical practice:

1. Not at all confident
2. Slightly confident
3. Moderately confident
4. Pretty much confident
5. Very confident