Case 1: Eric

- 47 yr. old, centrally obese (BMI 32) male with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several times

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>166 - 231 mg/dL</td>
<td>(~182 mg/dL)</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>133 - 138 mg/dL</td>
<td>(~140 mg/dL)</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>112 - 273 mg/dL</td>
<td>(~211 mg/dL)</td>
</tr>
<tr>
<td>Bedtime</td>
<td>159 - 231 mg/dL</td>
<td>(~194 mg/dL)</td>
</tr>
</tbody>
</table>

He tests 2-4 times a week

Which of the following would you recommend for Eric if he were your patient?

A: Initiate basal insulin
B: Initiate a GLP-1 receptor agonist
C: Initiate a basal bolus insulin regimen
D: Initiate a fixed combination of a basal insulin and a GLP-1 receptor agonist

This exact question will be repeated at the end of the lecture
**Natural History of Type 2 Diabetes**

- Prediabetes
- Type 2 Diabetes

**Macrovascular complications**

**Microvascular complications**

- Prediabetes and Early Type 2 Diabetes: Generally Asymptomatic

**Insulin resistance**

- Postprandial glucose
- Fasting glucose

**Progression of Dysglycemia**

- Prediabetes and Early Type 2 Diabetes: Generally Asymptomatic

**Diagnosis of Type 2 Diabetes**

- Typically Delayed Years to Decades

Adapted from Ramlo - Halsted BA, Edelman SV. *Prim Care.* 1999;26:771-789

**ADA Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations**

- Injectable Options After Oral Agents
- Basal Insulin and/or Mealtime Insulin or GLP-1 Receptor Agonist

**Generic and Trade Names: Insulin**

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-Acting Insulin</td>
<td></td>
</tr>
<tr>
<td>Regular U-500 Regular</td>
<td>Humulin R, Novolin R</td>
</tr>
<tr>
<td>Aspart</td>
<td>Humulin R-U-500</td>
</tr>
<tr>
<td>Glulisine</td>
<td>Novolog</td>
</tr>
<tr>
<td>Lispro (U-100 and U-200)</td>
<td>Apidra</td>
</tr>
<tr>
<td>Inhaled insulin</td>
<td>Afrezza</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermediate-Acting: MGI</td>
<td>Humulin N Novolin MGI</td>
</tr>
<tr>
<td>Long-Acting: Detemir</td>
<td>Levemir</td>
</tr>
<tr>
<td>Glargine (U-100)</td>
<td>Lantus</td>
</tr>
<tr>
<td>Glargine (U-300)</td>
<td>Toujeo</td>
</tr>
<tr>
<td>Degludec (U-100/200)</td>
<td>Treloba</td>
</tr>
</tbody>
</table>

**Follow-On Biologic: Basaglar**

- Basaglar
**Time Action Profiles: Traditional Insulins**

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Onset</th>
<th>Peak</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Regular</td>
<td>10-15 mins</td>
<td>60-90 mins</td>
<td>4-5 hr</td>
</tr>
<tr>
<td>NPH</td>
<td>1-3 hr</td>
<td>5-8 hours</td>
<td>12-18 hr</td>
</tr>
<tr>
<td>Detemir</td>
<td>90 mins</td>
<td>Relatively peakless</td>
<td>12-24 hr</td>
</tr>
<tr>
<td>Glargine</td>
<td>90 mins</td>
<td>Relatively peakless</td>
<td>24 hr</td>
</tr>
</tbody>
</table>

**Inhaled insulin:** peak by 10-15 min, duration of 2-3 hrs.

---

**Shortcomings of Basal Insulins Include:**

- Hypoglycemia resulting in:
  - Insulin under-dosing
  - Insufficient glycemic control
- Weight gain
  - Inconsistent insulin action...leading to inconsistent blood glucose levels
- Not enough flexibility with timing of injections
- Insufficient duration of action...therefore, requiring a minimum of 1 and, sometimes, 2 injections/day
- Large volume injections required for some patients

---

**Two New Basal Insulins Recently Added To Our List Of Options**

1. U-300 glargine a long-acting basal insulin
2. U-100 and U-200 degludec a long-acting basal insulin

---

GLP-1/Basal Insulin
**PK/PD Profile with Glar U300 vs Glar U100**

Glar U300 glargine has a more even and prolonged PK/PD profile. May need 13 to 17% more than previous dose of glargine U-100.

**Pharmacodynamics of Insulin Degludec® U-100 and U-200 in Patients with T2DM:**

*Same time course of action*

**Case 2: Jennifer**

- A 56-year-old female diagnosed with type 2 diabetes 6 years ago.
- Currently on maximum doses of 3 oral agents: metformin 1000 mg BID, glipizide 20 mg BID and linagliptin 5 mg QD.
- "Refused" to start insulin for years (afraid of weight gain), but a few months ago did try 10 units of U-300 glargine in the morning. After 3 months on 10 units she felt it "did not work" and she stopped it.
- A1c > 8.5% for the past 2 years.

<table>
<thead>
<tr>
<th>Current SMBG (mg/dl) below:</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>211</td>
<td></td>
<td>185</td>
</tr>
<tr>
<td>Tuesday</td>
<td>247</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Wednesday</td>
<td>181</td>
<td></td>
<td>196</td>
</tr>
<tr>
<td>Thursday</td>
<td>226</td>
<td>179</td>
<td></td>
</tr>
</tbody>
</table>
Which of the following is the single most likely explanation for her failure with basal insulin:

A. Patient fear of insulin  
B. Healthcare provider inertia  
C. Inadequate titration of the U-300 glargine  
D. U-300 glargine should have been given at bedtime

**Initiating Insulin Therapy in Type 2 Diabetes: General Concepts**

Don’t wait forever.  
Address patient concerns/fears.  
Consider combination therapy with oral agents.

Start with basal insulin.  
Titrating the dose is essential (self titration can work well).

Use a fast-acting analog at meal time when indicated. (may only needed to be given with the largest meal).

Self-monitoring of blood glucose (SMBG) is an important tool in motivating patients and in guiding dose adjustments.

**First Goal: Correct Fasting Hyperglycemia**

| Time  | Fasting Glucose (mg/dL) | HbA1c%
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0800</td>
<td>100</td>
<td>7%</td>
</tr>
<tr>
<td>1200</td>
<td>200</td>
<td>7%</td>
</tr>
<tr>
<td>1800</td>
<td>300</td>
<td>7%</td>
</tr>
<tr>
<td>0800</td>
<td>100</td>
<td>9%</td>
</tr>
</tbody>
</table>

Second Goal: Control Postprandial Hyperglycemia if HbA1c Still >7% (or above individual goal)
Combination Therapy:
Adding Basal Insulin to Oral Agents
An Effective Strategy to Initiate Insulin Therapy
- Only 1 injection per day is typically required.
- No need for mixing different types of insulin.
- Convenience (usually given at night or first thing in the morning)
- Slow, safe, and simple titration.
- Low dosage compared to a full insulin regimen.
- Limited weight gain – especially compared to insulin only regimens.
- Effective improvement in glycemic control by suppressing hepatic glucose production.

Case 3: Rick
- 61 yr. old overweight (BMI 30, 220lbs) male
- Type 2 diabetes diagnosed 9 years ago.
- History of CAD s/p MI 2 years ago.
- Treated for 2 years with diet and exercise alone even though his A1c was above 9.5% (“did not want to take medications”).
- Eventually started on metformin, sequentially followed by a sulfonylurea and a DPP-4 inhibitor (100mg sitagliptin), and his A1c fell from 9.9% to 7.9%.
- It took two years (6 clinic visits) to initiate these 3 meds and get his A1c down.

What is this patient’s A1c goal?

Case 3: Rick (continued)
- eGFR 45 ml/min, normal LFTs
- PMH: HTN, dyslipidemia, OSA, CAD, pancreatitis, ED
- Other meds: ACE inhibitor, clopidogrel, atorvastatin, HCTZ and tadalafil, carvedilol, and multiple vitamin supplements.
- Loves to eat at fast food restaurants
- He was asked to test once a day at different times.

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>148 - 229 mg/dL</td>
<td>~175 mg/dL</td>
</tr>
<tr>
<td>Pre-Lunch</td>
<td>131 - 212 mg/dL</td>
<td>~143 mg/dL</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>91 - 155 mg/dL</td>
<td>~119 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>148 - 231 mg/dL</td>
<td>~184 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia.
Which of the following would you suggest for Rick if he were your patient (currently on metformin, DPP-4 inhibitor and a SFU)?

A. Work on lifestyle and no medication addition
B. Initiate basal insulin
C. Start a GLP-1 receptor agonist and stop his DPP-4 inhibitor
D. Start a SGLT-2 inhibitor

Case 3: Rick (continued)

- Insulin degludec U-200 was added at night (20 units) and titrated up to 120 units over the next 10 weeks.
- He was asked to test 2x/day (pre-breakfast and bedtime).
- It is important to make sure the patient is not going to bed high.

A1c dropped to 7.1%, no hypoglycemia. Gained 2 lbs in 3 months.
- Oral agents can be continued unless hypoglycemia occurs during the day, in which case the sulfonylurea should be reduced or withdrawn.

Appropriate Self-Titration is Critical to the Success of Insulin Therapy

- An ADA/EASD consensus algorithm for the initiation and adjustment of basal insulin:
  - Start with a long-acting basal insulin.
  - Initiate at 10 units/day or 0.2 units/kg/day.
  - Check fasting glucose and adjust every 3 days.
  - Titrate by 2 units every 3 days until fasting in target range (70 – 130 mg/dL).

ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
**Simple Daily Self-Titration Option**

(much easier to follow by the patient than the 3 day titration)

Increase by **1 to 2 Units** every 1 day until FPG < 120 mg/dL

**EXAMPLE**

- Less than 100: decrease by 2 units
- Between 100 and 150: no change
- Over 150: increase by 2 units

*Once daily may not be recommended for the new longer acting basal insulins (U300 glargine and degludec)*

---

**Second Pitfall In Initiating And Titrating Basal Insulin**

(First one is too slow titration after starting)

Not Paying Attention To Bedtime Glucose Value

1. Ask the patient to do paired testing (test at bedtime and again the next morning).
2. If the bedtime BG is high, it needs to be addressed by either lifestyle modification including reduced caloric consumption and/or post dinner exercise.
3. Other options include prandial insulin or a GLP-1 receptor agonist.

---

**Clinical Pearls:**

**Combination Therapy with Basal Insulin**

1. Start with 10 to 20 units (based on FBS, weight).
2. The key to success is frequent follow up after initiation to avoid "failure" (most patients will need 40 to 70 units/day).
3. Have the patient follow a self-titration regimen and return to clinic or follow-up in some other manner (phone, fax, email, telehealth, etc.) relatively soon.
4. You can usually limit SMBG to only once a day in the morning but check at bedtime once in awhile to make sure the pt. does not need pre dinner fast-acting insulin.

---

*Frequent SMBG is recommended in the initial 4-6 weeks to guide therapy.*

---

GLP-1/Basal Insulin

### Basal Insulin vs GLP-1 RA

<table>
<thead>
<tr>
<th>Basal Insulin</th>
<th>GLP-1 RA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable once or twice a day</td>
<td>Injectable once a day or once weekly</td>
</tr>
<tr>
<td>Need to titrate dose targeting the FBS</td>
<td>No need to titrate dose to BC, but increase dose slowly to avoid GI side effects</td>
</tr>
<tr>
<td>Need to institute home glucose monitoring (SMBG)</td>
<td>No need for SMBG</td>
</tr>
<tr>
<td>Important to have frequent follow up when initiating basal insulin (days to weeks)</td>
<td>Follow up not as crucial</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight loss</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>No hypoglycemia due to the GLP-1 receptor agonist directly</td>
</tr>
</tbody>
</table>

### The Pathogenesis of Type 2 Diabetes: Insulin and Glucagon Responses Are Abnormal

**Healthy Subjects (n = 14)**

**Type 2 Diabetes (n = 12)**

### The Incretin Effect and Its Reduction in Type 2 Diabetes: Insulin secretion after oral versus IV glucose

**Control Subjects**

**Patients With Type 2 Diabetes**

---

*P* ≤ .05 compared with respective value after oral load.

**GLP-1 Effects:**
Glucoregulatory Role of Incretins

- GLP-1 secreted upon the ingestion of food
- Promotes satiety and reduces appetite
- Pancreatic beta cells: Enhanced glucose-dependent insulin secretion
- Liver: Reduced hepatic glucose output
- Stomach: Helps regulate gastric emptying


**Glucose-Dependent Effects of GLP-1 on Insulin and Glucagon**

<table>
<thead>
<tr>
<th>Glucose (mg/dL)</th>
<th>Insulin (pmol/L)</th>
<th>Glucagon (pmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>270</td>
<td>200</td>
<td>30</td>
</tr>
<tr>
<td>180</td>
<td>150</td>
<td>20</td>
</tr>
<tr>
<td>90</td>
<td>100</td>
<td>10</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Glucagon (pmol/L)

Time (min)

- Placebo
- Human GLP-1 given via an insulin pump

**Exenatide vs Insulin Studies: A1c and Weight**

<table>
<thead>
<tr>
<th>Exenatide vs Insulin Glargine</th>
<th>Exenatide vs Insulin Glargine + MET or SFU</th>
<th>Exenatide vs Insulin Glargine + MET +/-TZD +/-SFU</th>
<th>Exenatide vs Insulin Aspart 70/30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change in A1c (%):</td>
<td>Change in Weight (lb)</td>
<td>Change in Weight (lb)</td>
<td>Change in Weight (lb)</td>
</tr>
<tr>
<td>ADA GOAL</td>
<td>ADA GOAL</td>
<td>ADA GOAL</td>
<td>ADA GOAL</td>
</tr>
<tr>
<td>n=36</td>
<td>n=33</td>
<td>n=118</td>
<td>n=253</td>
</tr>
<tr>
<td>P=NS for A1c reductions</td>
<td>P&lt;0.05 for weight differences</td>
<td>P&lt;0.05</td>
<td>P&lt;0.05 for weight differences</td>
</tr>
<tr>
<td>1.3%</td>
<td>+4.0 lb</td>
<td>+2.2 lb</td>
<td>+6.6 lb</td>
</tr>
<tr>
<td>1.3%</td>
<td>+5.1 lb</td>
<td>+6.4 lb</td>
<td>+7.8 lb</td>
</tr>
<tr>
<td>0.7%</td>
<td>+4.9 lb</td>
<td>+6.0 lb</td>
<td>+6.4 lb</td>
</tr>
<tr>
<td>1.1%</td>
<td>+5.1 lb</td>
<td>+7.8 lb</td>
<td>+6.8 lb</td>
</tr>
<tr>
<td>1.4%</td>
<td>+6.0 lb</td>
<td>+7.8 lb</td>
<td>+7.8 lb</td>
</tr>
<tr>
<td>1.1%</td>
<td>+7.8 lb</td>
<td>+7.8 lb</td>
<td>+7.8 lb</td>
</tr>
</tbody>
</table>
GLP-1 Receptor Agonists

**Mechanism of Action**
- Mimic the effects of human GLP-1

**Benefits**
- Significant A1c reductions (1.0 to 2.0%)
- Shorter acting GLP-1 RAs have greater effects on PPG
- No hypoglycemia (due to GLP-1 RA directly)
- Once daily and once weekly formulations

**Concerns**
- GI side effects (typically nausea)
- Contraindicated in patients with a personal or family history of MTC or MEN2
- Relative contraindication in patients with a history of pancreatitis (important to know the etiology)

**Clinical Pearls**
- Ideal choice in obese patients with poor control, especially those on large doses of insulin
- No need to initiate or increase glucose testing
- One of the most powerful agents for type 2 diabetes

**Generic and Trade Names: GLP-1 RAs**

<table>
<thead>
<tr>
<th>GLP-1 Receptor Agonists</th>
<th>Generic Name</th>
<th>Trade Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide</td>
<td>Once-weekly</td>
<td>Bydureon</td>
</tr>
<tr>
<td>Twice-daily</td>
<td></td>
<td>Byetta</td>
</tr>
<tr>
<td>Liraglutide</td>
<td>Once-daily</td>
<td>Victoza</td>
</tr>
<tr>
<td>Dulaglutide</td>
<td>Once-weekly</td>
<td>Trulicity</td>
</tr>
<tr>
<td>Albiglutide</td>
<td>Once-weekly</td>
<td>Tanzeum</td>
</tr>
<tr>
<td>Lixisenatide</td>
<td>Once-weekly</td>
<td>Adlyxin</td>
</tr>
<tr>
<td>Semaglutide</td>
<td>Once-weekly</td>
<td>Ozempic</td>
</tr>
<tr>
<td>Basal insulin/GLP-1 Receptor</td>
<td>Glargine/lxisenatide</td>
<td>Soliqua, iGlarLixi</td>
</tr>
<tr>
<td>Agonist Fixed Combination</td>
<td>Degludec/triaplitide</td>
<td>Xalosti, iDegLira</td>
</tr>
</tbody>
</table>

**ITCA 650—Medical Device To Deliver GLP-1RA Exenatide**

**MEDICINE—EXENATIDE**
- Previously approved GLP-1 therapeutic demonstrated:
  - Glycemic control
  - Weight loss
  - Safety

**TECHNOLOGY**
- Previously approved delivery system
- Small micropump
  - Maintains stability at temps = 37°C
  - Maintains stability for ≥ 12 months

Not yet approved by the FDA
Case 4: Megan

- Megan is a 39 year old female with a 4 year history of type 2 diabetes
- On maximal doses of metformin, SFU, and a DPP-4 inhibitor
- She adamantly does not want to take insulin
- PMH: dyslipidemia, hypertension OSA and overweight (BMI 29)
- eGFR 75 ml/min
- Her A1c for the past 18 months has been ~8.5%

What would you recommend now for Megan?

<table>
<thead>
<tr>
<th>Option</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Start a SGLT-2 inhibitor</td>
</tr>
<tr>
<td>B</td>
<td>Try to convince her to start basal insulin</td>
</tr>
<tr>
<td>C</td>
<td>Start a GLP-1 receptor agonist (discontinue the DPP-4 inhibitor)</td>
</tr>
<tr>
<td>D</td>
<td>Start a fixed combination of a basal insulin and a GLP-receptor agonist (discontinue the DPP-4 inhibitor)</td>
</tr>
</tbody>
</table>

Case 4: Megan (continued)

- She agreed to start a GLP-1 receptor agonist (exenatide, liraglutide, dulaglutide, albiglutide, semaglutide or lixisenatide)
- If prescribing exenatide, it is important to tell the patient that it takes 6 weeks to reach equilibration
- She experienced no nausea or hypoglycemia.
- Over the next three months
- She lost 14 pounds and her A1c fell from 8.6% to 7.3%.

What is this patient’s A1c goal?
Case 5: Amanda
- 36 year old female on maximum oral medications and has been on basal insulin for 12 months (started in May 2014)
- A1c now 7.7%; insulin glargine titrated to 35 units HS (Nov)
- FPG: 81 – 138 mg/dL (November)
- Weight 226lbs (216lbs before starting insulin)
- Strong family history of type 2 diabetes
- Patient was asked to test more frequently than normal for 3 to 4 days before meals and bedtime

<table>
<thead>
<tr>
<th></th>
<th>May 2013</th>
<th>May 2014</th>
<th>November 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1c (%)</td>
<td>7.2</td>
<td>8.6</td>
<td>7.7</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>156</td>
<td>220</td>
<td>81 - 144</td>
</tr>
<tr>
<td>PPG (mg/dL)</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Which of the following would you recommend for Amanda at this point?

- **A** Switch to a premixed insulin before dinner
- **B** Stop the basal insulin and switch to a basal insulin/GLP-1 receptor agonist fixed combination
- **C** Intensify regimen by adding rapid-acting insulin at dinner
- **D** Intensify regimen by adding a GLP-1 receptor agonist

Home glucose monitoring data:

<table>
<thead>
<tr>
<th></th>
<th>Breakfast</th>
<th>Lunch</th>
<th>Dinner</th>
<th>HS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monday</td>
<td>117</td>
<td>184</td>
<td></td>
<td>184</td>
</tr>
<tr>
<td>Tuesday</td>
<td>91</td>
<td></td>
<td>119</td>
<td>210</td>
</tr>
<tr>
<td>Wednesday</td>
<td>111</td>
<td>181</td>
<td>105</td>
<td>239</td>
</tr>
<tr>
<td>Thursday</td>
<td>79</td>
<td></td>
<td>131</td>
<td>221</td>
</tr>
</tbody>
</table>

Fixed Combinations Of Basal Insulin and GLP- Receptor Agonist
- Insulin Degludec/Liraglutide and Insulin Glargine/lixisenatide

1 unit of IDegLira has 0.036 mg of liraglutide (maximum dose is 50 IDeg Long lira)
1 unit of IGlarLixi has 0.33 mcg lixisenatide (maximum dose is 60 IGlar20 mcg lixi)
GLP-1/Basal Insulin
A1c Over Time: A1c 8.3% to 6.4% with Insulin Degludec/Liraglutide

Mean values (+SEM) based on FAS and LOCF imputed data; EOT = end of trial; p-values are from an ANCOVA ADA/EASD A1c target < 7.0%; AACE A1c target < 6.5%

Body Weight and Hypoglycemia

Hypoglycemia: PG <56 mg/dL and/or requiring assistance, PYE: Patient years exposure; RR: Rate ratio:

Gastrointestinal Side Effects

Post hoc analysis: DUAL II and IV

Subjects experiencing nausea, vomiting or diarrhoea (%)
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide

One dose step = 1 U insulin glargine and 0.33 mcg lixisenatide

Efficacy of Fixed-Ratio Insulin Glargine/Lixisenatide in Insulin Naïve T2DM Patients

Fixed-Ratio Insulin Glargine/Lixisenatide in Insulin Naïve T2DM Patients: Glucose and Weight Effects

Mean weight change:
iGlarLixi - 0.3 kg; Glargine 1.1 kg; Lixi -2.3 kg
iGlarLixi vs Glargine -1.40 kg (p < 0.0001)

With iGlarLixi, nausea that occurred mostly over the first 6-8 weeks was the most common (10%) side effect, which is significantly less than Lixi alone (24%)
Efficacy of Fixed-Ratio Insulin Glargine/Lixisenatide in T2DM Patients Not Controlled on Basal Insulin

T2DM patients not controlled on basal insulin + Met 2nd OAD

Mean A1C (%)

Baseline

Week

iGlarLixi

Glargine

Mean A1C (%)

9.0

7.0

6.5

8.5

8.0

7.5

6.9%

6.1%

7.2%

7.5%

8.1%

8.5%

iGlarLixi

Glargine

Percent Patients (%)

40

10

20

0

60

30

50

55

30

9

% Patients with A1C < 7.0% at Week 30

Mean weight change: iGlarLixi -0.7 kg; Glargine 0.7 kg

iGlarLixi vs Glargine -1.40 kg (p < 0.0001)

Summary: Benefits for Combining GLP-1 Receptor Agonists and Basal Insulin Analogs

- Combined glycemic effects of GLP-1RA and basal insulin provides greater glycemic efficacy than either of its component parts. Dose related adverse effects of each component (nausea and weight gain) are minimized.
- No increased risk of hypoglycemia in the setting of improved glycemic control as compared to basal insulin alone.
- In the setting of inadequate control on basal insulin, adding a GLP-1RA is associated with greater benefits (weight loss and minimal hypo) than adding prandial insulin.
Case 1: Eric

- 47 yr. old, centrally obese (BMI 32) male with a 5 year history of Type 2 diabetes
- Currently on maximum doses of metformin, a SFU, and a DPP4 inhibitor
- History of dyslipidemia, hypertension and ED
- A1c has ranged from 8.1 to 8.5% over the past 2 years
- He and his wife have seen a dietician and CDE several times

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood glucose range</th>
<th>Blood glucose average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Breakfast</td>
<td>156 – 211 mg/dL</td>
<td>~182 mg/dL</td>
</tr>
<tr>
<td>Pre- Lunch</td>
<td>143 – 157 mg/dL</td>
<td>~157 mg/dL</td>
</tr>
<tr>
<td>Pre-Dinner</td>
<td>118 – 224 mg/dL</td>
<td>~211 mg/dL</td>
</tr>
<tr>
<td>Bedtime</td>
<td>152 – 231 mg/dL</td>
<td>~194 mg/dL</td>
</tr>
</tbody>
</table>

No reports of hypoglycemia

He tests 2-4 times a week

Which of the following would you recommend for Eric if he were your patient?

A. Initiate basal insulin
B. Initiate a GLP1-RA
C. Initiate a basal bolus insulin regimen
D. Initiate a fixed combination of a basal insulin and a GLP1-RA

Summary

- GLP-1 agonists represent a tremendous advance in the treatment of type 2 because of glucose lowering in addition to weight loss and reducing the risk of hypoglycemia
- Combination therapy (adding basal insulin to daytime OHAs) is safe, effective and easy to implement
- The fixed combination of basal insulin and a GLP-1 RA has clinical advantages in terms of efficacy, reduced side effects and ease of use
- Communication with the patient to address his/her fears, misperceptions, potential adverse affects, cultural beliefs etc. is crucial.
- Achieving meaningful and sustained HbA1c reductions requires innovative approaches designed with the real world in mind