

GLP-1 Receptor Agonists and Basal Insulin

A Conversation Over Which One Should Be Initiated First in Patients Failing Oral Agents

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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



Time	Blood glucose range	Blood glucose average
Pre-Breakfast	166 - 231 mg/dL	(~182 mg/dL)
Pre- Lunch	143 - 197 mg/dL	(~177 mg/dL)
Pre- Dinner	112 - 275 mg/dL	(~213 mg/dL)
Bedtime	159 - 231 mg/dL	(~194 mg/dL)

No reports of hypoglycemia

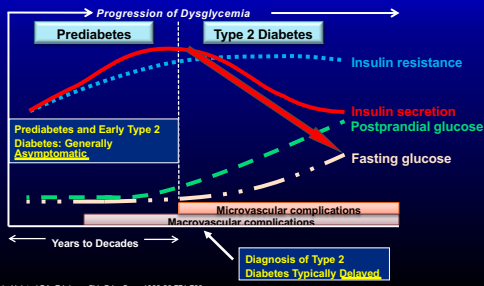
He tests 2- 4 times a week

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

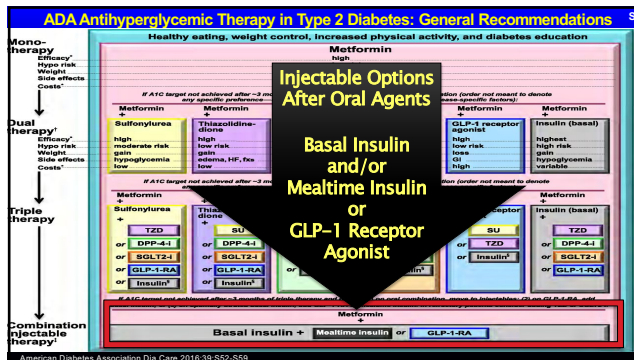
A	Initiate basal insulin
B	Initiate a GLP-1 receptor agonist
C	Initiate a basal bolus insulin regimen
D	Initiate a fixed combination of a basal insulin and a GLP -1receptor agonist

This exact question will be repeated at the end of the lecture

Natural History of Type 2 Diabetes



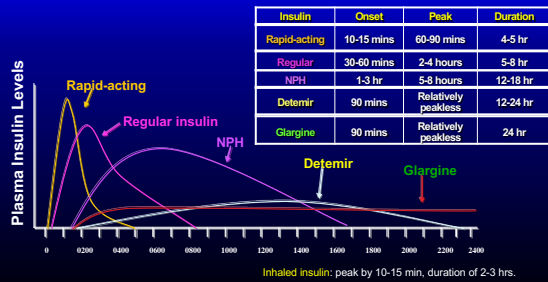
ADA Antihyperglycemic Therapy in Type 2 Diabetes: General Recommendations



Generic and Trade Names: Insulin

	Generic Name	Trade Name
Fast-Acting Insulin	Regular U-500 Regular Aspart/Fiasp Glulisine Lispro (U-100 and U-200) Inhaled Insulin	Humulin R, Novolin R Humulin R U-500 NovoLog Apidra Humalog Afrezza
Basal Insulin	Intermediate-Acting: NPH Long-Acting: Detemir Glargine (U-100) Glargine (U-300) Degludec (U-100/200) Follow-On Biologic Glargine (U-100)	Humulin N Novolin NPH Levemir Lantus Toujeo Tresiba Basaglar

Time Action Profiles: Traditional Insulins

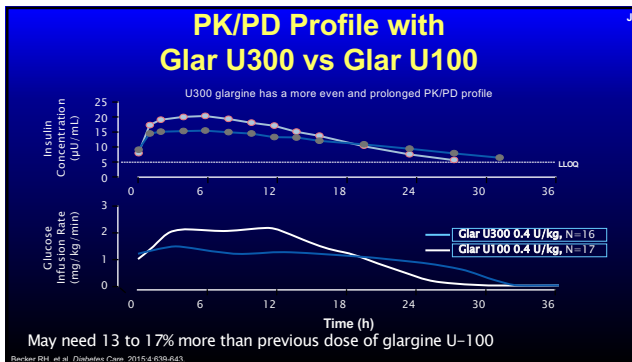


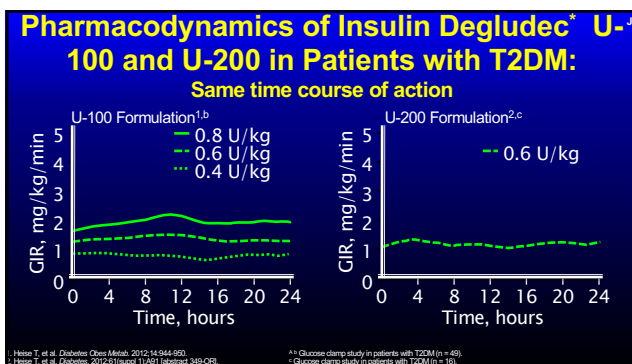
Shortcomings of Basal Insulins Include:

- › 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





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

Current SMBG (mg/dl) below:

	Pre-Breakfast	Pre-Lunch	Pre-Dinner	Bedtime
Monday	211	---	---	185
Tuesday	247	---	174	---
Wednesday	181	---	---	196
Thursday	226	---	179	---

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.

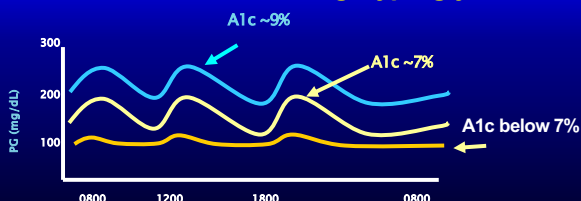
Start with basal insulin.
Titration the dose is essential (self titration can work well).

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.

Chapman RW, Henry RR. Diagnosis and management of Type 2 Diabetes. 12th Edition. Professional Communications, Inc., Greenwiche, CT. 288 pages. 2014.

First Goal: Correct Fasting Hyperglycemia



Second Goal: Control Postprandial Hyperglycemia If A1c Still >7% (or above individual goal)

Adapted with permission from Cefalu WT. In: Leahy J, Cefalu W, eds. Insulin Therapy. New York: Marcel Dekker; 2002:1-11.

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

Epidemiol. V. Henry RR. Diabetes and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages. 2014.

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



Time	Blood glucose range	Blood glucose average
Pre-Breakfast	148 - 229 mg/dL	(~175 mg/dL)
Pre- Lunch	111 - 182 mg/dL	(~147 mg/dL)
Pre- Dinner	91 - 155 mg/dL	(~139 mg/dL)
Bedtime	148 - 231 mg/dL	(~184 mg/dL)
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)

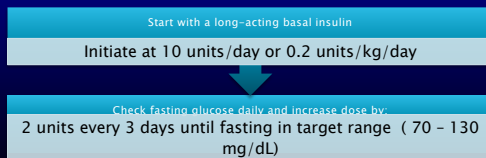
- Insulin degludec U-200 was added at night (20 units) and titrated up to 120 units over the next 10 weeks
- He was asked to test 2x/day (pre-breakfast and bedtime)
- It is important to make sure the patient is not going to bed high

Pre-Breakfast	82 - 155 mg/dL	(~122 mg/dL)
Pre- Lunch	---	---
Pre- Dinner	---	---
Bedtime	128 - 183 mg/dL	(~155 mg/dL)

- 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:



ADA, American Diabetes Association; EASD, European Association for the Study of Diabetes.
Muller et al. Diabetes Care. 2009;32:143-149.

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 \leq 120 mg/dL

EXAMPLE

Less than 100: decrease by 2 units

Between 100 and 150: no change

Over 150: increase by 2 units

The goal can be individualized

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

*Adjust dose subsequently to patient's need.

†Dose was not increased that week if there were any episodes of documented hypoglycemia (<72 mg/dL) during the preceding week. FPG, fasting plasma glucose.

Gerstein HC et al. Diabet Med. 2008;23:736-742.

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.

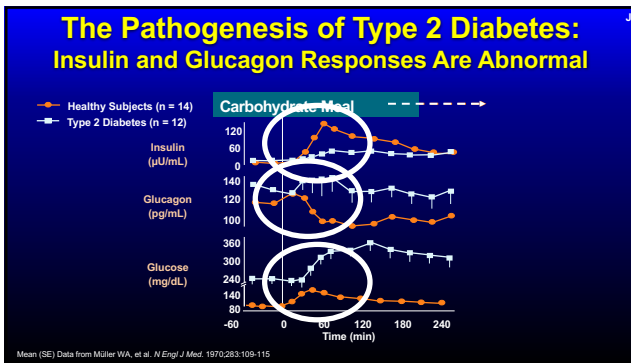
Edelman SJ, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages. 2014.

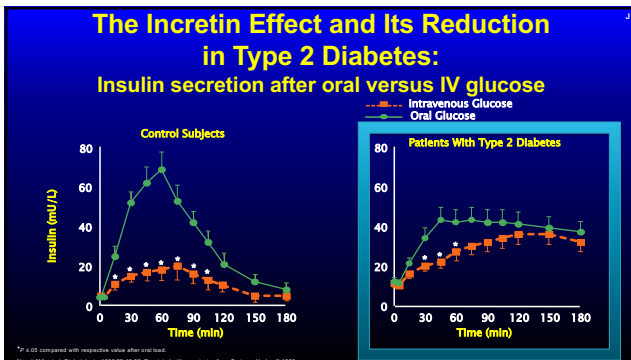
Clinical Pearls: Combination Therapy with Basal Insulin

-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.) <u>relatively soon</u>
-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.

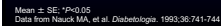
Edelman SJ, Henry RR. Diagnosis and management of type 2 diabetes. 12th Edition. Professional Communications, Inc., Greenwich, CT. 288 pages. 2014.

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





Glucoregulatory Role of Incretins



A1c and Weight



GLP-1 Receptor Agonists

Mechanism of Action	* Mimic the effects of human GLP-1
Benefits	<ul style="list-style-type: none"> * Significant A1c reductions (1.0 to 2.0%) * Shorter acting GLP-1 RAs have greater effects on PPG * Statistically significant weight loss * No hypoglycemia (due to GLP-1 RA directly) * Once daily and once weekly formulations
Concerns	<ul style="list-style-type: none"> * 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	<ul style="list-style-type: none"> * 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

Exenatide SV, Henry RH. Diagnosis and management of type 2 diabetes. Elsevier Edition. Professional Communications, Inc., Greenwich, CT. 1998:1000-1011.

Generic and Trade Names: GLP-1 RAs

	Generic Name	Trade Name
GLP-1 Receptor Agonists	Exenatide Once-weekly Twice-daily Liraglutide Once-daily Dulaglutide Once-weekly Albiglutide Once-weekly Lixisenatide Once-daily Semaglutide Once-weekly	Bydureon Byetta Victoza Trulicity Tanzeum Adlyxin Ozempic
Basal Insulin/GLP-1 Receptor Agonist Fixed Combination	Glargine/lixisenatide Degludec/liraglutide	Soliqua , iGlarLixi Xultophy, iDegLira

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

TECHNOLOGY

- Previously-approved delivery system
- Small micropump
 - Maintains stability at temps $\approx 37^{\circ}\text{C}$
 - Maintains stability for ≥ 12 months



MEDICINE: EXENATIDE

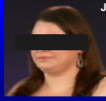
- Previously-approved GLP-1 therapeutic with demonstrated:
 - Glycemic control
 - Weight loss
 - Safety



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%



FBS (mg/dl)	PPG (mg/dl)
Mean 191	Mean 265

What would you recommend now for Megan?

A	Start a SGLT-2 inhibitor
B	Try to convince her to start basal insulin
C	Start a GLP-1 receptor agonist (discontinue the DPP-4 inhibitor)
D	Start a fixed combination of a basal insulin and a GLP-receptor agonist (discontinue the DPP-4 inhibitor)

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?

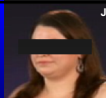
Before GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 191	Average 265

After GLP-1*

FBS (mg/dl)	PPG (mg/dl)
Average 131	Average 167

* Increased frequency of SMBG testing not a requirement with GLP-1 receptor agonists



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



	May 2013	May 2014	November 2016
A1c (%)	7.2	8.6	7.7
FPG (mg/dL)	~156	~220	81 – 144
PPG (mg/dL)	NA	NA	NA

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

Home glucose monitoring data:

HS = at bedtime; ---- = did not test.

	Breakfast	Lunch	Dinner	HS
Monday	117	184	-----	184
Tuesday	91	-----	119	210
Wednesday	111	161	105	239
Thursday	79	-----	131	221

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

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/1.8mg lira)

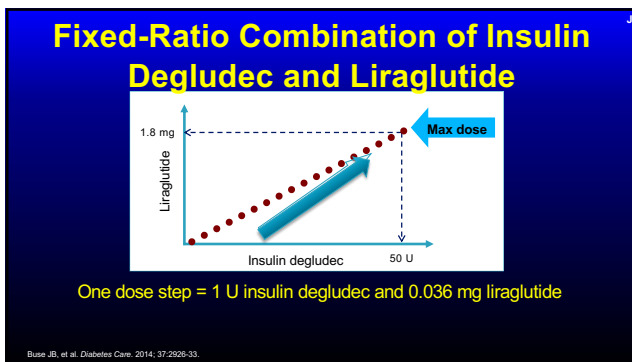


1 unit of IGlarLixi has 0.33 mcg lixisenatide (maximum dose is 60 iGlar/20 mcg lixi)

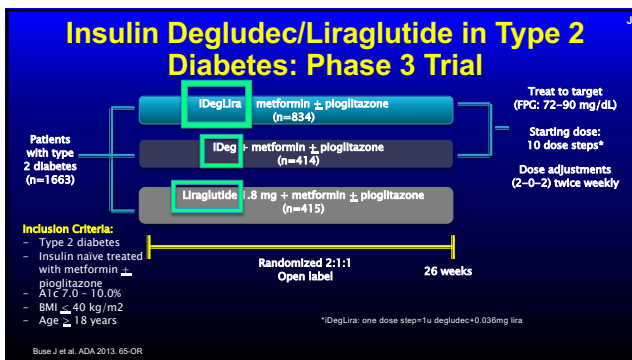
Lancet Diabetes Endocrinol. 2014 Nov;2(11):856-8. 2017 PDR. Pix

Insulin Degludec/Liraglutide vs. Insulin Glargine/Lixisenatide	
100 units/ml of insulin degludec 3.6 mg/ml of liraglutide	100 units/ml of insulin glargine 3.3 mcg/ml of lixisenatide
10 units of insulin degludec has 0.36 mgs of liraglutide 50 units of insulin degludec has 1.8 mgs of liraglutide	15 units of insulin glargine has 5 mcg of lixisenatide 30 units of insulin glargine has 10 mcg of lixisenatide 60 units of insulin glargine has 20 mcg of lixisenatide
Starting dose: 16 units of insulin degludec which has 0.58 mgs of liraglutide	Starting dose: If insulin glargine dose is <30, start at 15 units of combo If insulin glargine dose is >30 units, start with 30 units
Titrate as if you were using basal insulin alone	Titrate as if you were using basal insulin alone
Maximum dose is 50 units of insulin degludec and 1.8 mgs of liraglutide	Maximum dose is 60 units of insulin glargine and 20 mcgs of lixisenatide

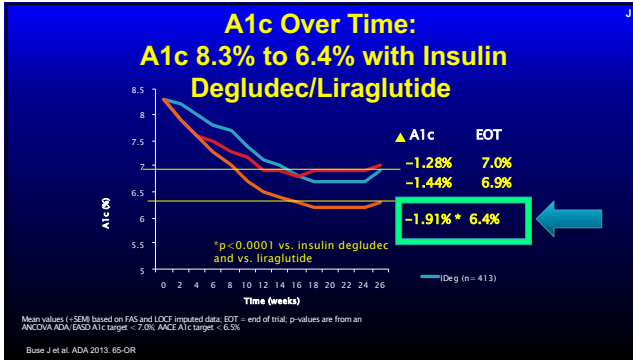
DDP-101 (n=1663) 2017

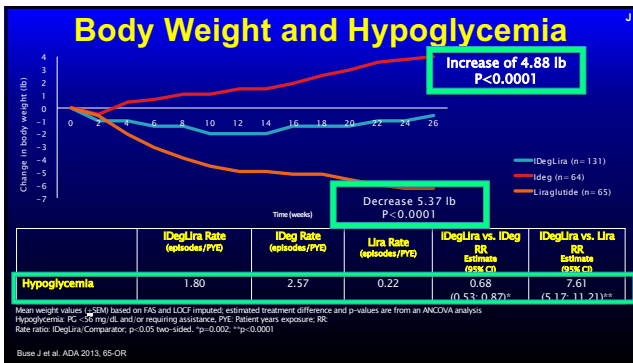


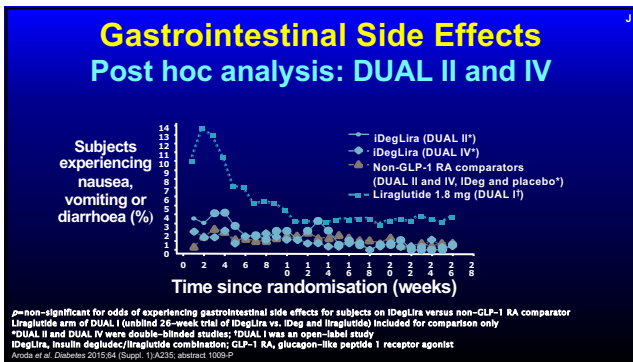
Buse JB, et al. Diabetes Care. 2014; 37:2926-33.



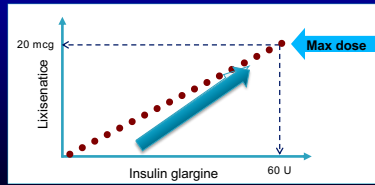
Buse J et al. ADA 2013. 65-OR







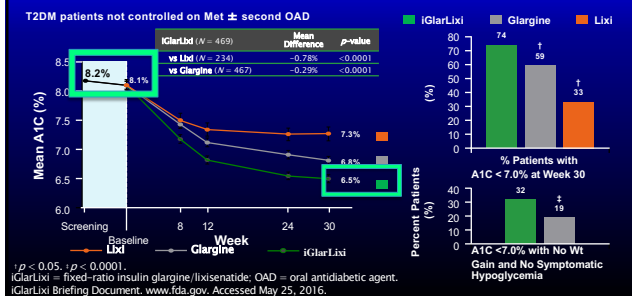
Fixed-Ratio Combination of Insulin Glargine and Lixisenatide



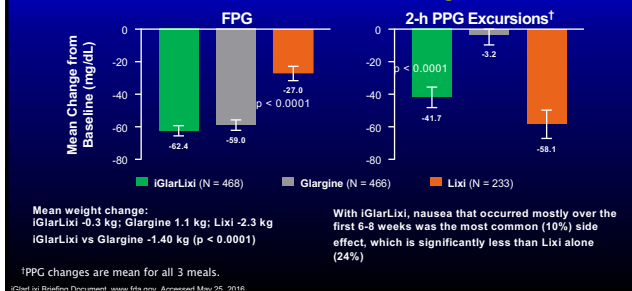
One dose step = 1 U insulin glargine and 0.33 mcg lixisenatide

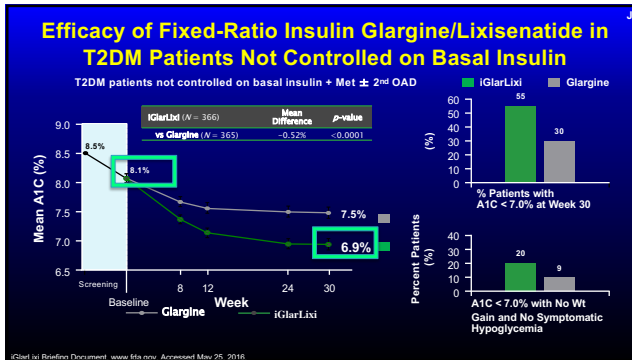
Buse JB, et al. Diabetes Care. 2014; 37:2928-33.

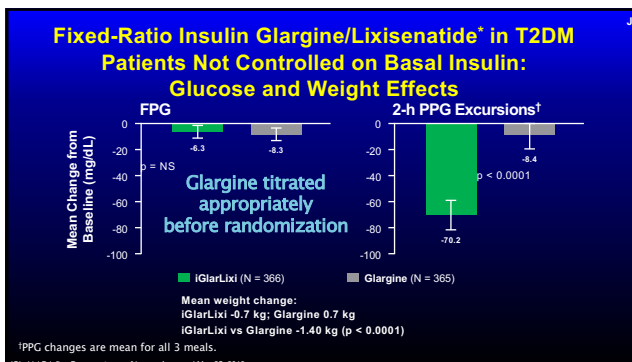
Efficacy of Fixed-Ratio Insulin Glargine/Lixisenatide in Insulin Naïve T2DM Patients



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







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



Time	Blood glucose range	Blood glucose average
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Bedtime	159 – 231 mg/dL	(~194 mg/dL)
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
