Objectives

- Apply current ADA/EASD recommendations for setting A1C and glucose targets and timely intensification of therapy in patients with type 2 diabetes
- Compare and contrast the clinical profiles of the different GLP-1 receptor agonists and assess their utility in reducing postprandial glucose
- Evaluate current data on fixed-ratio combinations of GLP-1 RAs and basal insulin for the treatment of type 2 diabetes
- Formulate evidence-based treatment regimens that optimize control of both fasting and postprandial glucose in patients requiring therapy intensification

Case 1 – Bruce

- Bruce is a 56-year-old man who presents for evaluation of fatigue and progressively increasing nocturia. Suspects prostate "acting up"
- Medical history includes hypertension, dyslipidemia, gout
- Current meds: ACE inhibitor, thiazide, statin, allopurinol
- Physical exam: weight 240 lbs, BMI 36, BP 128/77, abdominal obesity

Case 1 – Bruce cont'd

- On further questioning, he reported that he lost 10 pounds in the past 3 months, and "it was surprisingly easy." He also noted some blurry vision, but his optometrist just recommended reading glasses.
- Family history significant for diabetes in mother and 2 older brothers.

Case 1 – Bruce's Lab Results

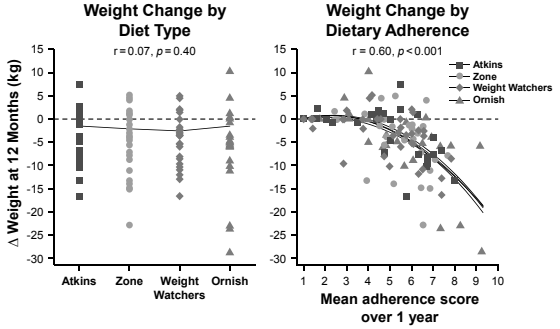
- Random serum glucose: 226 mg/dL
- Hemoglobin A1C: 7.8%
- **Bruce is diagnosed with type 2 diabetes**

Nutrition: Helpful Advice

- Portion size review; use plate method
- Snack choices
- Decreased soft drink and fruit juice intake
- Volumize high carbohydrate meals with vegetables, cutting down on carbohydrate, but increasing satiety

Courtesy of Dace Trence, MD.

Adherence Is More Important Than Diet Type for Weight Loss Success



Dansinger M. *JAMA*. 2005;293:43-53.

Case 1 – Bruce cont'd

- Goes to diabetes education
- Starts walking every other day and loses 14 pounds
- Starts monitoring his glucose levels
- Blood sugars fasting 160–180 mg/dL, and pre-meal blood sugars 140–160 mg/dL
- A1C now 7.5%

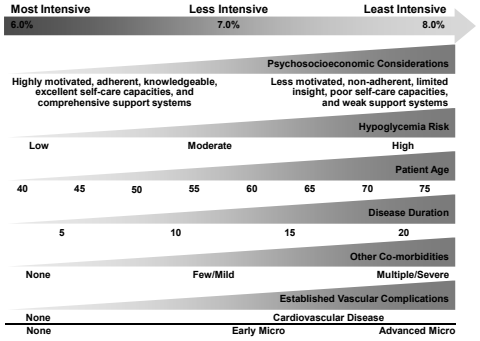
Normoglycemia and Recommended Glycemic Targets in T2DM

Glucose Control	Healthy Individuals[1–2]	ADA 2016[1]	ADA & AACE 2016
A1C, %*	<6.0	<7.0	**Individualized Target*** <7.0% most pts[1] ≤6.5% healthy pts[3]
Preprandial PG, mg/dL	<100	80–130	80–130
Peak postprandial PG, mg/dL	<140	<180[a]	<140-180[b]

a. Peak postprandial capillary plasma glucose; b. 2-hour postprandial glucose concentration. *A1C of 7–8% is reasonable in patients with known CVD or multiple co-morbidities. PG = plasma glucose; ADA = American Diabetes Association.

1. ADA. *Diabetes Care*. 2016;39(Suppl. 1):S1–S112. 2. ADA. *Diabetes Care*. 2001;24:775-778. 3. Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

Individualizing A1C Targets for Patients with T2DM

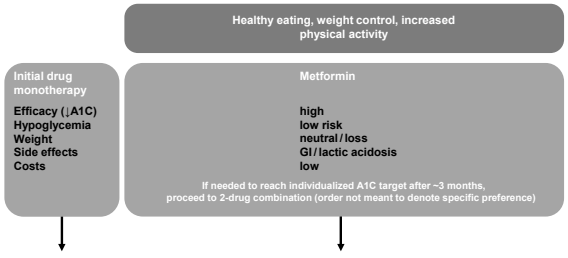


Data from Ismail-Beigi F, et al. *Ann Intern Med*. 2011;154(8):554-9.

Which Agent to Use?

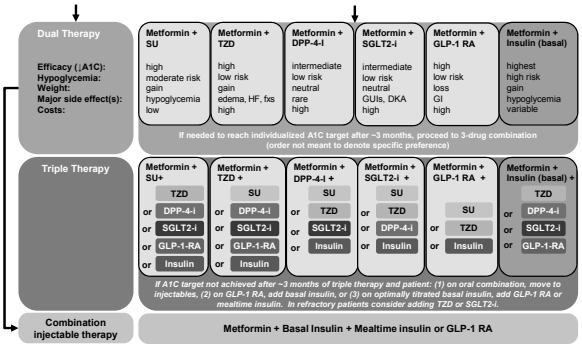
Do Guidelines Provide Direction?

ADA/EASD 2016 Guidelines



Adapted from American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

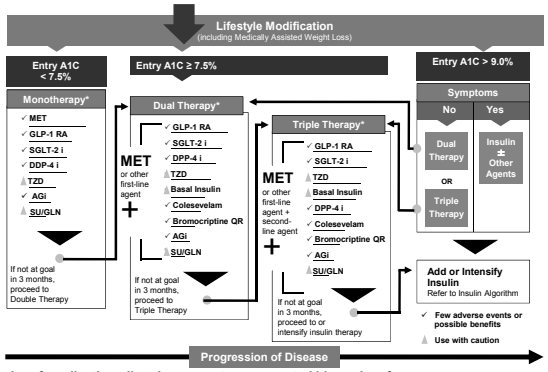
ADA/EASD 2016 Guidelines cont'd



DPP-4-i = dipeptidyl-deptidase 4 inhibitor; SGLT2-i = sodium-glucose cotransporter 2 inhibitor; GLP-1 RA = glucagon-like peptide-1 receptor agonists; GUI = genitourinary infections; DKA = diabetic ketoacidosis.

Adapted from American Diabetes Association. *Diabetes Care*. 2016;39(Suppl. 1):S1–S112.

AACE: Glycemic Control Algorithm for T2DM



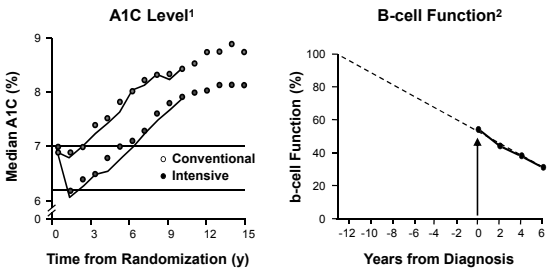
***Order of medications listed represents a suggested hierarchy of usage.**

Garber AJ, et al. *Endocr Pract.* 2016;22:84-113.

Case 1 – Bruce cont'd

- You recommend starting metformin. Bruce reports diarrhea; you suggest switching to extended-release. A1C drops to 6.9% at 3-month follow-up.
- Bruce maintained good glycemic control for about 2 years on metformin alone, then glimepiride was added.
- One year after adding the glimepiride, Bruce reports his job has changed to involve considerable travel. You note his weight is up 5 lbs. Fasting blood sugars have bumped up to 160–170 mg/dL, but postprandial glucose is stable A1C now 8.1%.

UKPDS: Progressive Deterioration in Glycemic Control Over Time



1. UKPDS Group. *Lancet.* 1998;352:837-853. 2. Holman RR. *Diabetes Res Clin Pract.* 1998;40(suppl):S21-S25.

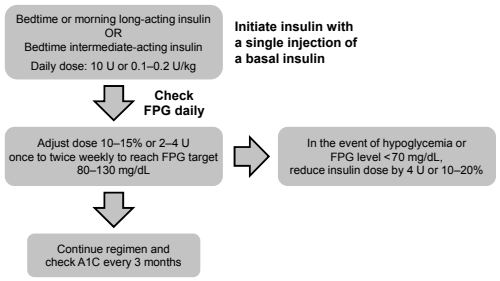
Basal Insulin in Type 2 Diabetes

- When to consider
  - When combination oral/injectable agents become inadequate (A1C >6.5% or higher)
  - High FPG >150 mg/dL
  - Unacceptable side effects of other agents
  - "Severely" uncontrolled*
- To be effective, basal insulin plus oral agents require presence of some endogenous B-cell function (oral agents are not effective in T1DM)

FPG = fasting plasma glucose; PPG = postprandial glucose.
***Defined as fasting glucose >250 mg/dL, random glucose >300 mg/dL, A1C >10%, ketonuria, or symptomatic (polyuria, polydipsia, and weight loss) by ADA 2009 Consensus Statement. After glucose is controlled, oral agents can be added and insulin withdrawn if preferred.**

Nathan DM, et al. *Diabetes Care.* 2009; volume 32,193-203. Inzucchi SE, et al. *Diabetes Care.* 2012;35(6):1364-1379. *ADA Diabetes Care.* 2014:37(suppl 1):S14-S80.

Basal Insulin
The Simple Way to Add Insulin



Inzucchi S, et al. *Diabetes Care.* 2015;38:140-149.

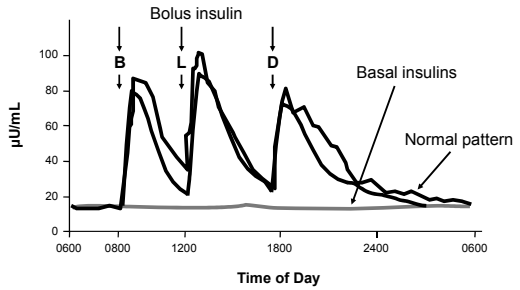
Case 1 – Bruce Follow-up:

- Bruce returns 3 months later, and he is feeling much better. He has up-titrated his basal insulin dose from 20 to 60 units every night.
- His meter download shows fasting glucose 100–110 mg/dL over the past several weeks.
- His A1C is now 7.2%.
- You congratulate and acknowledge his progress, and ask him to come back in 3 months.

Case 1 – Bruce Follow-up cont'd:

- Bruce returns in 5 months because he missed his last appointment. He reports that his job has required even more travelling.
- His fasting blood sugars have continued in the 100–130 mg/dL range, but postprandial glucoses are now in the 190–200 mg/dL range.
- His A1C is rechecked; now at 8.0%.

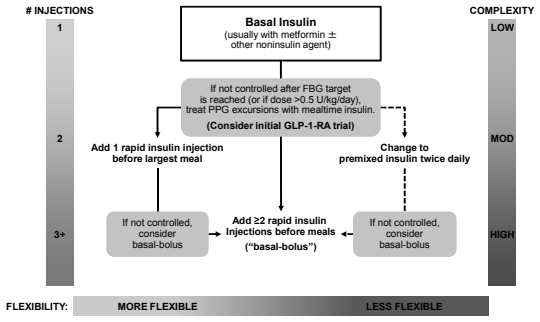
Physiologic (Basal-Bolus) Insulin Treatment Matching Insulin Administration to Insulin Needs



B = breakfast; L = lunch; D = dinner.

Adapted from Polonsky KS, et al. *N Engl J Med*. 1988;318:1231-9.

ADA Recommendations for Advancing Insulin



ADA. *Diabetes Care*. 2015;38(suppl 1):S41-S48.

Basal Plus Mealtime Insulin

- Use rapid-acting analogs (Aspart, Lispro, Glulisine), not regular insulin
  - Easier timing, less postprandial hypoglycemia
- Start with 1 injection at largest meal:
  - 4 units and titrate, OR
  - By weight: 0.1 U/kg
- Titrate to:
  - < 140 mg/dL 2 hours postprandial OR
  - < 110 mg/dL next meal or bedtime
- Consider a decrease or stopping oral secretagogues when prandial insulin is started
- Can continue metformin, TZD, AGI, GLP-1, DPP-4 inhibitor
- **Basal bolus dosing**
  - ~50% bolus insulin and ~50% basal insulin

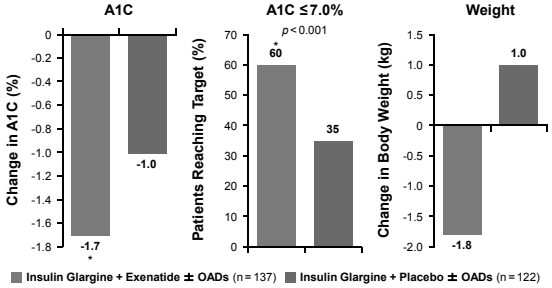
Garber AJ, et al. *Endocr Pract*. 2016;22:84-113.

Case 1 – Bruce Follow-up cont'd:

- Mealtime insulin of 10 units was added with his largest meal. His basal insulin was reduced to 50 units at bedtime and glimepiride was discontinued.
- At 3-month follow-up, his A1C was 6.8%. Over the next year Bruce continues to maintain good glycemic control, but did report a couple minor episodes of hypoglycemia. His weight has also increased.
- Bruce asks if there is anything that can be done to lower his risk of hypoglycemia. His current meds are metformin, mealtime insulin 10 units and basal insulin 50 units.
- His current A1C is 7.4%. He says he periodically skips his insulin dose to avoid hypoglycemia.

Addition of Exenatide to Insulin Glargine

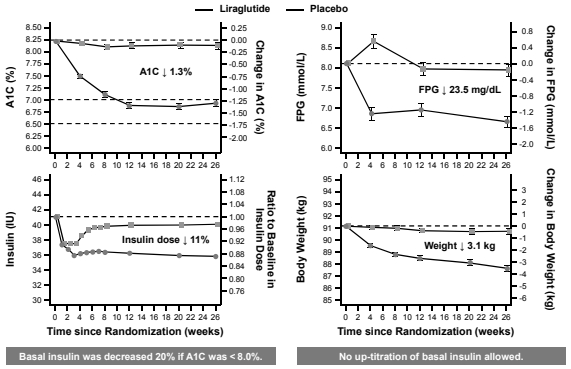
Basal insulin was decreased 20% initially if A1C was <8.0%.
Basal was titrated, and dose was greater in placebo group.
No increase in hypoglycemia.



Data are mean. *Significant vs placebo.

Buse JB, et al. *Ann Intern Med*. 2011;154:103-112.

Liraglutide Added to Basal Insulin



Ahmann A, et al. *Diab Obes Metab*. 2015;17:1056-64.

Case 1 – Bruce Follow-up cont'd:

- Mealtime insulin was discontinued.
- Bruce was advanced to liraglutide 1.8 mg daily, and his basal insulin was titrated to 44 units at night.
- At 6-month follow-up, his A1C was 6.9%, and he has not experienced any episodes of hypoglycemia. He reports a weight loss of 5 pounds.

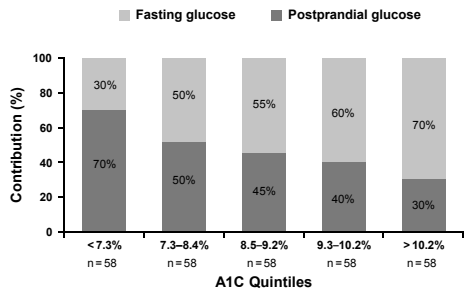
Case 2 – Ann

- Ann is a 64-year-old woman with a 14- year history of type 2 diabetes. She is active and works full time.
- Had been treated with metformin and glimepiride until bedtime insulin glargine was started 4 years ago. The dose was increased intermittently over the years.
- PMH: Hypertension, hyperlipidemia
- Medications:
  - Metformin 1000 mg bid
  - Glimepiride 4 mg qd
  - Glargine U100, 68 units hs
  - Lisinopril 20 mg qd
  - Atorvastatin 40 mg qd
  - HCTZ 12.5 mg qd

Case 2 – Ann cont'd

- PE:
  - BMI = 33.6
  - BP = 136/82
  - Central obesity
  - Decreased vibratory sensation and monofilament sensation in feet
- Lab tests:
  - A1C = 8.2%
  - LDL = 78 mg/dL
  - Creatinine = 0.89 mg/dL
- Glucose monitoring:
  - infrequent (<1x daily) — average = 152 mg/dL

Relative Contribution of FPG and PPG to A1C



Monnier L, et al. *Diabetes Care*. 2003;26:881-885.

Case 2 – Ann cont'd

- Ann agrees to monitor for 5 days before meals and bedtime
  - Mean glucose values:
    - Breakfast 138 mg/dL
    - Lunch 201 mg/dL
    - Dinner 184 mg/dL
    - Bedtime 182 mg/dL

Adding Prandial Insulin to Basal

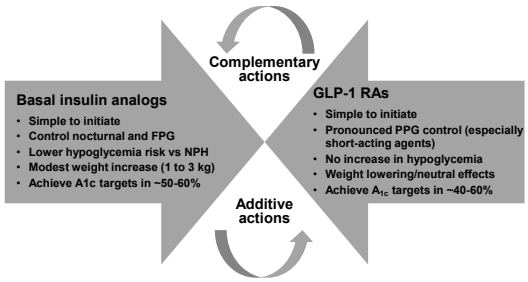
Advantages

- Treats postprandial hyperglycemia
- Increases success rate in achieving A1C < 7% compared to oral agents
- More effective than oral agents

Disadvantages

- Increases weight gain
- Increases hypoglycemia risk
- Less convenient with multiple injections

Combination of Basal Insulin with a GLP-1 RA Has a Scientific Logic



Little S, et al. *Diabetes Technol Ther*. 2011:13(suppl 1):S53-S64. Cohen ND, et al. *Med J Australia*. 2013;199(4):246-249. Carris NW, et al. *Drugs*. 2014;74(18):2141-2152.

Pharmacokinetic Profile of GLP-1 RAs

Drug	Dosing	Half-life	Duration of Action
Exenatide	5–10 mcg SC twice daily	2.4 hours	**Short-acting**
Lixisenatide	10–20 mcg SC daily	2–4 hours	**Short-acting**
Albiglutide	30–50 mg SC once weekly	6–7 days	**Long-acting**
Dulaglutide	0.75–1.5 mg SC once weekly	5 days	**Long-acting**
Exenatide ER	2 mg SC once weekly	2.4 hours	**Long-acting**
Liraglutide	0.6–1.8 mg SC once daily	13 hours	**Long-acting**

ER = extended release.

Pinelli NR and Hurren KM. *The Annals of Pharmacotherapy*. 2011;45(7-8):850-860. American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S41-S48. US FDA. Drugs@FDA Website. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/. EU EMA. Medicines@EMA Website. http://www.ema.europa.eu/ema/.

Some General Characteristics of GLP-1 Receptor Agonists

- **Short-acting agents (exenatide, lixisenatide)**
  - **Have greater effect on postprandial glucose**
  - Possibly more nausea
- **Long-acting agents (albiglutide, exenatide ER, dulaglutide, liraglutide)**
  - **Less effect on postprandial glucose but greater fasting glucose reduction**
  - May have variable efficacy and weight loss
    - Albiglutide appears to have lower efficacy and less weight loss but has proven effective in combination with basal insulin

Considerations for GLP-1 RAs

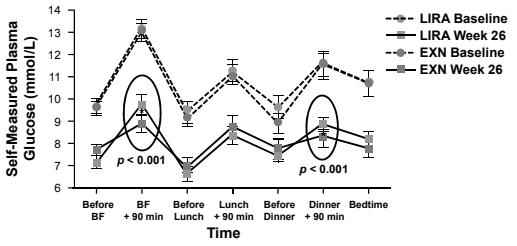
- Renal impairment
  - Reduced clearance of exenatide
  - Exenatide should not be used in patients with severe renal impairment or ESRD (CrCl<30 mL/min)
  - Hypovolemia due to nausea and vomiting
- Pancreatitis
  - No causal relationship confirmed
  - Not for use in patients with history of pancreatitis
  - Educate patients about signs and symptoms; stop therapy if signs and symptoms present
  - Do not restart therapy if pancreatitis is confirmed
- Personal or family history of MTC or MEN2
  - Contraindicated

ESRD = end-stage renal disease; MTC = medullary thyroid carcinoma; MEN2 = multiple endocrine neoplasia syndrome type 2.

Linnebjerg H, et al. Br J Clin Pharmacol. 2007;64:317-327. Egan AG, et al. N Engl J Med. 2014;370(9):794-7. Exenatide, liraglutide, albiglutide and dulaglutide at www.pdr.net. Accessed April 2, 2106.

Postprandial Glucose Effect of Short- and Long-Acting GLP-1 RAs: EXN vs. LIRA

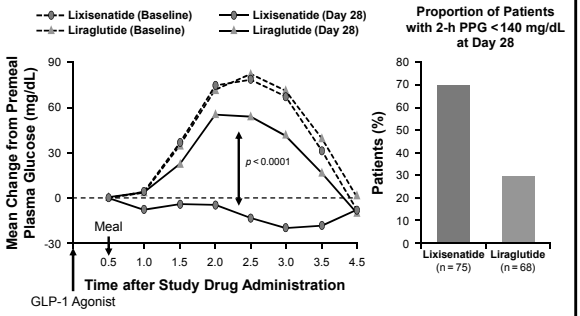
EXN twice daily preferentially affects PPG compared to liraglutide.
EXN twice daily reduced PPG significantly more after breakfast and dinner than LIRA, $p<0.001$



PPG = postprandial glucose; BF = breakfast; EXN = exenatide; LIRA = liraglutide.

Buse JB, Rosenstock J, Sesti G, et al. *Lancet*. 2009;374:39-47.

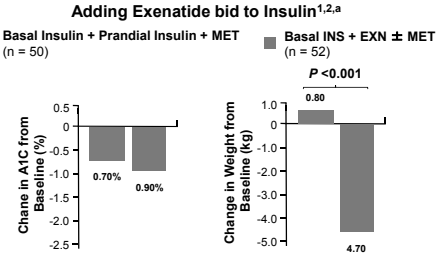
PPG Effect of Short- and Long-Acting GLP-1 RAs: LIXI vs LIRA



LIXI = lixisenatide; PPG = postprandial glucose.

Kapitza C, et al. *Diabetes Obes Metab*. 2013;15(7):642-9.

Exenatide + Basal Insulin as an Alternative to Prandial Insulin + Basal Insulin

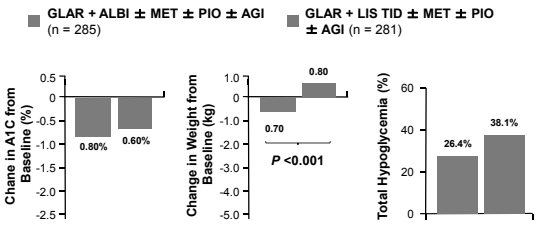


Glycemic variability (MAGE) was improved in the EXN *bid* group but not in the prandial insulin group[2]. No severe hypoglycemia events reported in either group.

a. EXN administered at 2-3 meals daily, prandial insulin administered at 3 meals daily[1]

1. FLAT-SUGAR Trial Investigators. *Diabetes Care*. 2015;38:1558-1566. 2. Hirsch IB, et al. *Diabetes*. 2015; 64(suppl 1):A100 [abstract 385-OR].

Albiglutide as an Alternative to Prandial Insulin to Intensify Basal Insulin

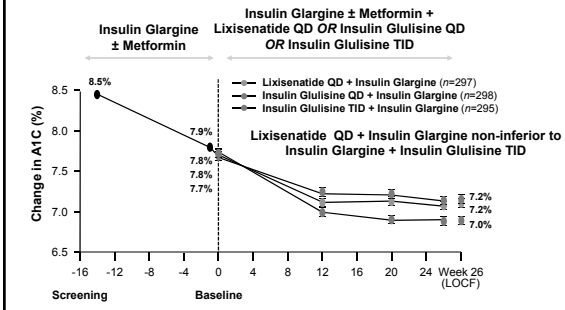


Documented symptomatic hypoglycemia was more frequent in the lispro group; 2.3 vs 0.9 events/pt/y (*p* value not reported)

ALBI = albiglutide; GLAR = glargine; LIS = lispro; MET = metformin; PIO = pioglitazone; AGI = alpha-glucosidase inhibitor.

Rosenstock J, et al. *Diabetes Care*. 2014;37:2317-2325.

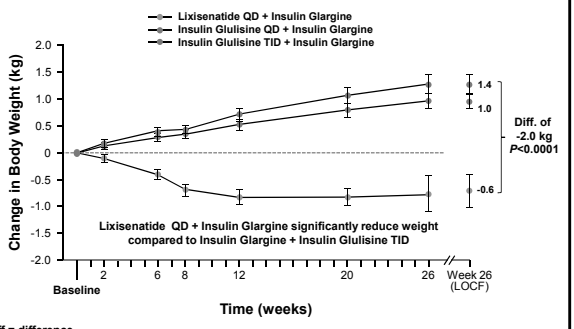
Lixi/Basal vs Basal/Plus, Basal/Bolus: Change in A1C



QD = daily; TID = three times daily; LOCF = last observation carried forward.

Rosenstock J, et al. *Diabetes Care*. 2016;39:1318-1328.

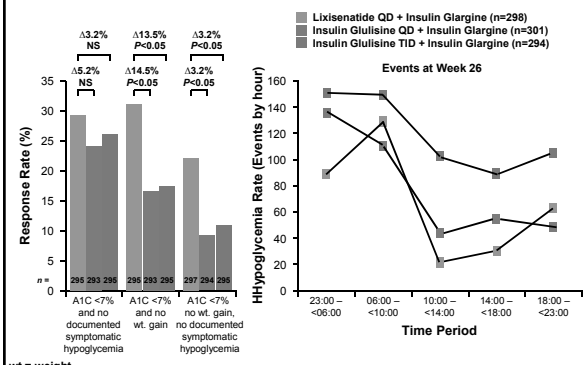
Lixi/Basal vs Basal/Plus, Basal/Bolus: Change in Weight



Diff = difference.

Rosenstock J, et al. *Diabetes Care*. 2016;39:1318-1328.

Efficacy and Safety



wt = weight.

Rosenstock J, et al. *Diabetes Care*. 2016;39:1318-1328.

Benefits of Adding a GLP-1 RA to Basal Insulin as Compared with Adding Prandial Insulin

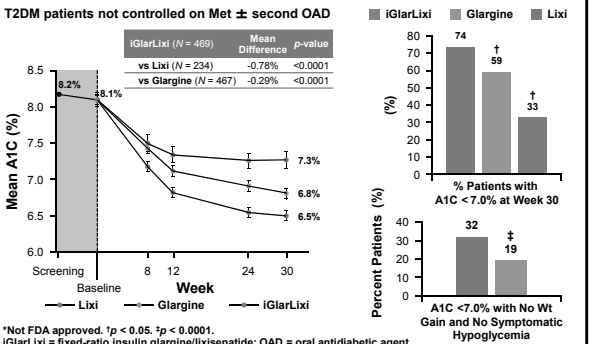
- Fewer injections
- Weight loss
- Lower hypoglycemic risk
- Reduce insulin doses
- Postprandial benefit, particularly with short-acting agents

Carris NW, et al. *Drugs*. 2014;74(18):2141-2152.

Case 2 – Ann Follow-up

- In addition to her current meds, Ann was started on lixisenatide 20 mcg once daily to better manage her postprandial hyperglycemia.
- At 1-month follow-up, her A1C is 6.9%.

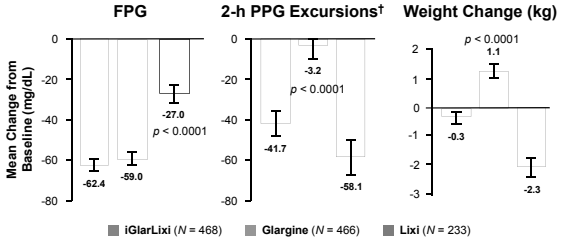
Efficacy of Fixed-Ratio iGlarLixi* in Insulin Naïve T2DM Patients



*Not FDA approved. †$p < 0.05$. ‡$p < 0.0001$.
iGlarLixi = fixed-ratio insulin glargine/lixisenatide; OAD = oral antidiabetic agent.

Rosenstock J, Aronson R, Grunberger G, et al. *Diabetes Care*. 2016 Aug 15. pii: dc160917. [Epub ahead of print]

Fixed-Ratio iGlarLixi* in Insulin Naïve T2DM Patients: Glucose and Weight Effects

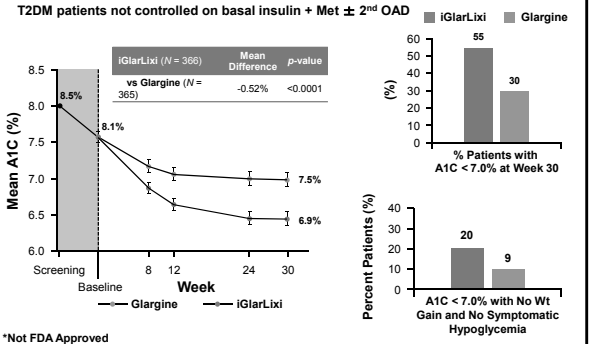


With iGlarLixi, nausea that occurred mostly over the first 6-8 weeks was the most common (10%) side effect, which is significantly less than Lixi alone (24%)

*Not FDA approved †PPG changes are mean for all 3 meals.

Rosenstock J, Aronson R, Grunberger G, et al. *Diabetes Care*. 2016 Aug 15. pii: dc160917. [Epub ahead of print]

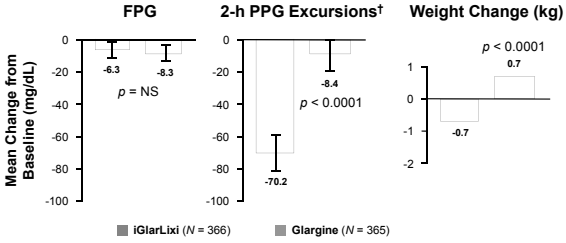
Efficacy of Fixed-Ratio iGlarLixi* in T2DM Patients Not Controlled on Basal Insulin



*Not FDA Approved

iGlarLixi Briefing Document. www.fda.gov. Accessed May 25, 2016. (Results not yet validated under FDA review.)

Fixed-Ratio iGlarLixi* in T2DM Patients Not Controlled on Basal Insulin: Glucose and Weight Effects



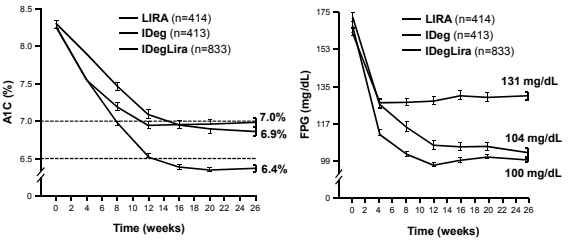
*Not FDA Approved †PPG changes are mean for all 3 meals.

iGlarLixi Briefing Document. www.fda.gov. Accessed May 25, 2016. (Results not yet validated under FDA review.)

Efficacy of Fixed-Ratio IDegLira* in Insulin Naïve T2DM Patients not Controlled on OADs

Deg/Lira was superior (p<0.001) to Lira and non-inferior to insulin Deg in reducing A1C

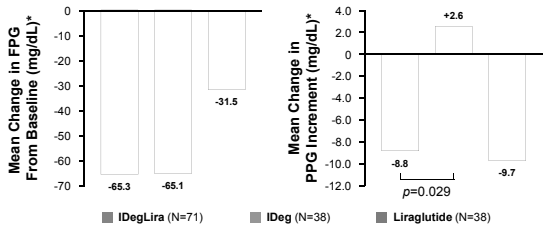
Deg/Lira significantly reduced FPG compared to Lira (p<0.001)



OADs = metformin ±pioglitazone; LIRA = liraglutide; IDeg = insulin degludec; IDegLira = fixed-ratio insulin degludec/liraglutide. *Not FDA Approved.

Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-93.

Fixed-Ratio IDegLira† in Insulin Naïve T2DM Patients: Glucose and Weight Effects



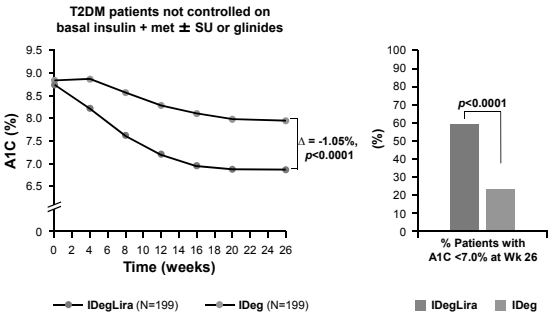
Hypoglycemia rate:
IDegLira vs LIRA: rate ratio 7.61, p<0.0001
IDegLira vs IDeg: rate ratio 0.68, p=0.0023

Mean treatment difference in Wt.:
IDegLira vs IDeg: -2.2 kg, p<0.0001
IDegLira vs LIRA: +2.44 kg, p<0.0001

***Mean change from baseline at wk 26 in PPG increment across all meals based on continuous glucose monitoring data. †Not FDA Approved.**

Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-93. NDA 208583 Briefing Document. www.fda.gov. Accessed May 25, 2016 (Results not yet validated under FDA review)

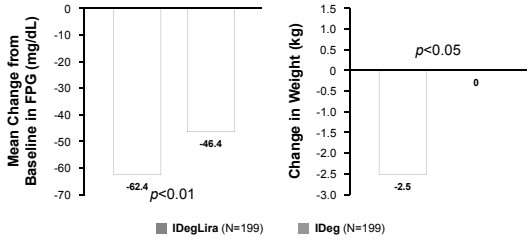
Efficacy of Fixed-Ratio IDegLira* in T2DM Patients Not Controlled on Basal Insulin



***Not FDA Approved**

NDA 208583 Briefing Document. www.fda.gov. Accessed May 25, 2016 (Results not yet validated under FDA review) .

Fixed-Ratio IDegLira* in T2DM Patients Not Controlled on Basal Insulin: Glucose and Weight Effects

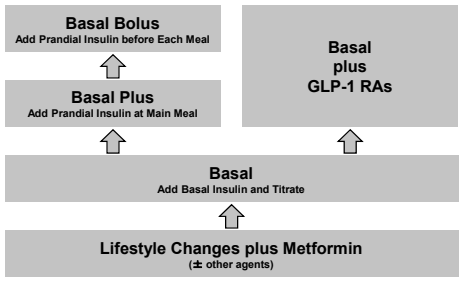


Nausea was most common side effect with IDegLira (7.8%) which occurred mostly over the first 6 weeks which is significantly less than LIRA alone (15.1%)

***Not FDA Approved**

NDA 208583 Briefing Document. www.fda.gov. Accessed May 25, 2016 (Results not yet validated under FDA review).

When Basal Is Not Enough



Summary

- Type 2 diabetes is characterized by progressive beta cell dysfunction requiring advancing therapy.
- Following one or two oral agents, GLP-1 receptor agonists or basal insulin are equally effective agents.
- When the combination of oral agents and basal insulin fails, the problem is often postprandial hyperglycemia.
- In T2DM, when glucose control is lost after basal insulin, GLP-1 receptor agonists often hold advantages over rapid-acting insulin analog therapy.
- Premixed basal insulin with a GLP-1 receptor agonist in a single injection may be useful in the future.