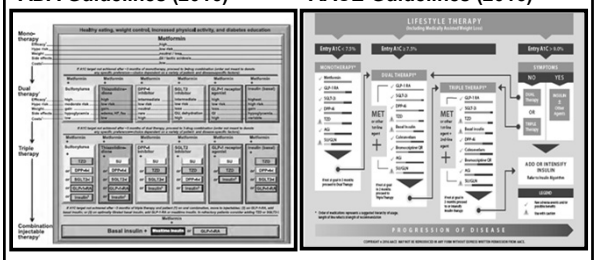
Program Learning Objectives

At the conclusion of this activity, participants should be able to:

- **Apply recent treatment guidelines when considering the role of GLP-1 receptor agonists in individualized, patient-centered treatment regimens at any stage in the progression of T2DM**
- **Evaluate recent evidence on therapeutic characteristics and safety of GLP-1 receptor agonists**
- **Address common perceptions or misperceptions surrounding the therapeutic effects and practical use of GLP-1 receptor agonists in the management of T2DM, including their use with insulin**

Current Treatment Algorithms Advocate GLP-1 RAs Beginning Early in the Progression of T2DM

ADA Guidelines (2016)[1] **AACE Guidelines (2016)[2]**



1. ADA. *Diabetes Care.* 2016;39(suppl 1):S1-S112.
2. Garber AJ, et al. *Endocr Pract.* 2016;22:84-113.

Current Treatment Algorithms Advocate GLP-1 RAs Beginning Early in the Progression of T2DM

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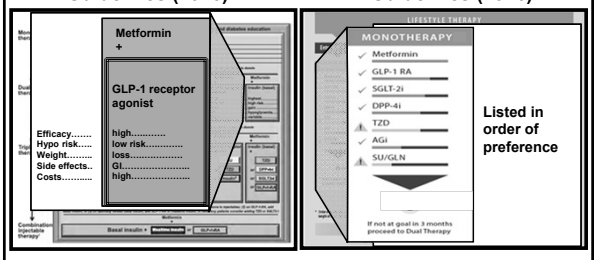


1. ADA. *Diabetes Care.* 2016;39(suppl 1):S1-S112.
2. Garber AJ, et al. *Endocr Pract.* 2016;22:84-113.

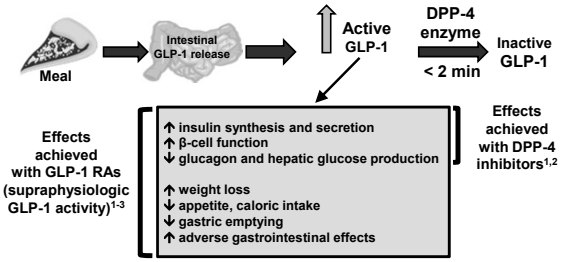
GLP-1 RAs Are Recommended Throughout the Progression of T2DM in Current Treatment Algorithms

Monotherapy	• **Patients intolerant of metformin or other oral agents[1,2]**
With 1-2 oral agents	• **Increased risk of hypoglycemia when used with insulin or sulfonylureas[1,2]** • **Use in any combination *except with DPP-4 inhibitors*[1,2]**
With insulin	• **Not a substitute for insulin[3]** • **Potential alternative to prandial insulin for patients unable to attain targets on basal insulin[1,2]** • **Increases likelihood of attaining A1C < 7% without hypoglycemia or weight gain relative to comparator regimens[4,5,6]**

1. ADA. *Diabetes Care.* 2016;39(suppl 1):S1-S111; 2. Garber AJ, et al. *Endocr Pract.* 2016;22:84-113;
3. Usui R, et al. *J Diabetes Investig.* 2013;27:4:585-594; 4. Freemantle N, et al. *Diabetes Ther.* 2015;573-591;
5. Blonde L, et al. *Lancet.* 2015;385:2057-2066; 6. Raccah D, et al. *J Diabetes Complications.* 2014;28:40-44.

Understanding the Incretin Effect and Incretin Therapies

Oral glucose load leads to secretion of incretin hormones, resulting in enhanced pancreatic insulin secretion[1-3]



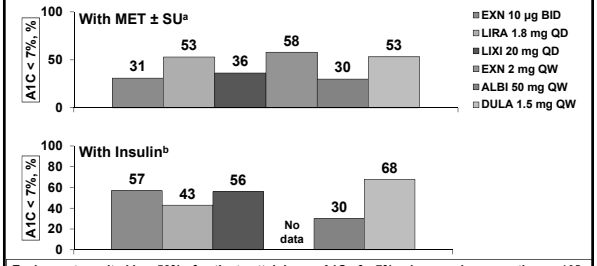
1. Baggio L, Drucker D. *Gastroenterology.* 2007;132:2131-2157.
2. Holst JJ, et al. *Trends Mol Med.* 2008;14:161-168.
3. Madsbad S. *Diabetes Obes Metab.* 2016;18:317-332.

FDA-Approved GLP-1 Receptor Agonists

Twice-Daily Injections	
Exenatide BID	**Within 60 min of 2 main meals (usually breakfast and dinner), but ≥ 6 h apart**
Daily Injections	
Liraglutide	**Once daily, any time**
Lixisenatide	**Once daily, within 1 hour of first daily meal**
Weekly Injections	
Albiglutide	**Once weekly, any time**
Dulaglutide	**Once weekly, any time**
Exenatide QW	**Once weekly, any time**

US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

GLP-1 RAs Demonstrate Clinical Efficacy Across the Natural History of T2DM



Each agent resulted in ≈ 50% of patients attaining an A1C of < 7% when used as monotherapy[1,6,7]

1. US FDA. https://www.accessdata.fda.gov/scripts/cder/drugsatfda.
2. Rosenstock J, et al. *J Diabetes Complications.* 2014;28:386-392.
3. Giorgino F, et al. *Diabetes Care.* 2015;38:2241-2249.
4. Riddle MC, et al. *Diabetes Care.* 2013;36:2497-2503.
5. Blonde L, et al. *Lancet.* 2015;385:2057-2066.
6. Fonseca VA, et al. *Diabetes Care.* 2012;35:1225-1231.
7. Zhang L, et al. *Sci Rep.* 2016;6:18904.

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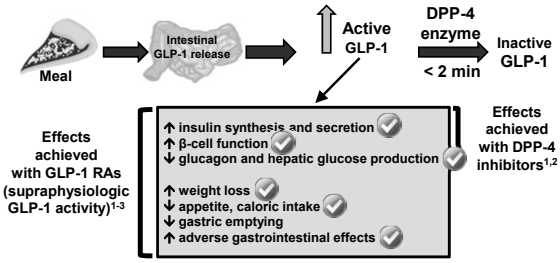
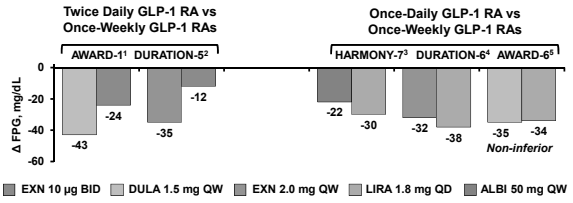


Effects more prominently associated with long-acting GLP-1 RAs

1. Baggio L, Drucker D. *Gastroenterology.* 2007;132:2131-2157.
2. Holst JJ, et al. *Trends Mol Med.* 2008;14:161-168.
3. Madsbad S. *Diabetes Obes Metab.* 2016;18:317-332.

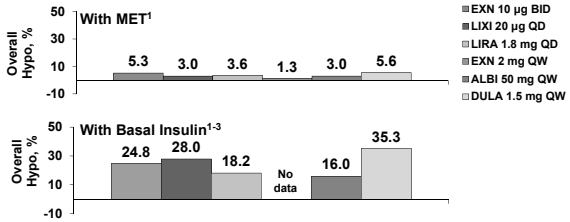
FPG and PPG Effects of GLP-1 RAs Differ



- *FPG improvement was similar with EXN BID and LIXI*[6]
- *FPG improved more with LIRA QD vs EXN BID or LIXI*[7,8]
- Significant PPG improvement from baseline observed with all GLP-1 RAs[1,9]

1. Wysham C, et al. *Diabetes Care.* 2014;37:2159-2167; 2. Blevins T, et al. *J Clin Endocrinol Metab.* 2011;96:1301-1310;
3. Pratley RE, et al. *Lancet Diabetes Endocrinol.* 2014;2:289-297; 4. Buse JB, et al. *Lancet.* 2013;381:117-124;
5. Dungan KM, et al. *Lancet.* 2014;384:1349-1357; 6. Rosenstock J, et al. *Diabetes Care.* 2013;36:2945-2951;
7. Nauck M, et al. *Diabets Care.* 2016;39:1501-1509; 8. Buse JB, et al. *Lancet.* 2009;374:39-47;
9. Drucker DJ, et al. *Lancet.* 2008; 372:1240-1250.

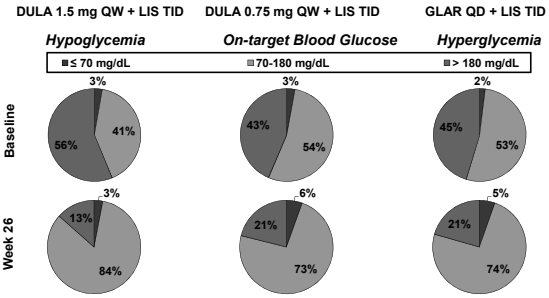
GLP-1 RAs Demonstrate a Low Risk of Hypoglycemia Across the Natural History of T2DM



Consider decreasing insulin dose to reduce hypoglycemia risk

1. Drugs@FDA. http://www.accessdata.fda.gov/scripts/cder/drugsatfda.
2. Ahmann A, et al. *Diabetes Obes Metab.* 2015;17:1056-1064.
3. Pozzilli P, et al. ADA Scientific Sessions 2016 [abstract 237-OR].

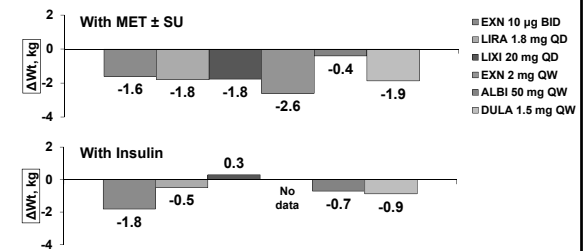
Glycemic Variability Is Reduced When a GLP-1 RA Is Used With Prandial Insulin



Data shown are mean number of CGM readings within the specified ranges from a substudy of AWARD-4.

Jendle J, et al. *Diabetes Obes Metab.* 2016 Jun 9. [Epub ahead of print].

GLP-1 RAs Demonstrate a Low Risk of Weight Gain Across the Natural History of T2DM



Each agent (except ALBI) resulted in 2- to 3-kg weight loss when used as monotherapy[1,7,8]

1. US FDA. https://www.accessdata.fda.gov/scripts/cder/drugsatfda. 2. Rosenstock J, et al. *J Diabetes Complications.* 2014;28:386-392.
3. Giorgino F, et al. *Diabetes Care.* 2015;38:2241-2249. 4. DeVries JH, et al. *Diabetes Care.* 2012;35:1446-1454.
5. Riddle MC, et al. *Diabetes Care.* 2013;36:2497-2503.6. Blonde L, et al. *Lancet.* 2015;385:2057-2066.7. Fonseca VA, et al. *Diabetes Care.* 2012;35:1225-1231.
8. Zhang L, et al. *Sci Rep.* 2016;6:18904.

Summary

- GLP-1 RAs are recommended early and throughout the progression of T2DM
  - Due to related mechanisms of action and the limited improvement in glycemic efficacy, GLP-1 RAs should not be used in combination with DPP-4 inhibitors
- For appropriate patients, GLP-1 RAs are as effective as insulin, with a lower risk of hypoglycemia and with the potential for weight loss
- Adding a GLP-1 RA to insulin therapy may reduce glycemic variability, an emerging risk factor for poor outcomes
- FPG and PPG effects of GLP-1 RAs differ
- Administration frequencies among GLP-1 RAs differ

Patient Priorities: Characteristics Desired in Injectable Antihyperglycemic Medications Ranked by Willingness to Pay[a]

1. Greater glycemic efficacy (1% A1C reduction)
2. Low risk of hypoglycemia
3. Weight loss (2-3 kg)
4. Avoid mixing (resuspension)
5. Fewer daily injections (reduce by 1 injection)

[a] Survey of 646 adults with T2DM treated with injectable agents from the United States and Canada. Both studies asked patients to compare the attributes of hypothetical agents.

Boegelund M, et al. *Diabetes*. 2015;64(suppl 1): A349 [abstract 1341-P].

Predicting Patient Preferences: Specific Characteristics Desired in GLP-1 RAs

Injection frequency
- Most important predictor of choice
- Weekly preferred more than daily

Needle size and pain
- Significant predictor
- Shorter (eg, 4-5 mm), thinner (eg, 31-32 G) preferred more than longer, thicker

Injection-site reactions
- Significant predictor
- Eliminating reactions preferred

Type of injection device
- Not a significant predictor

Refrigeration
- Not a significant predictor

[a] Discrete-choice experiment of 643 adults with T2DM treated with EXN QW , LIRA QD, insulin, or no injectable therapy.

Hauber AB, et al. *Curr Med Res Opin*. 2016;32:251-262.

Comparing Dosage and Administration of Current GLP-1 RAs: Daily GLP-1 RAs

Exenatide BID[a]	Liraglutide QD[a]	Lixisenatide QD[a]
Inject within 60 minutes prior to 2 main meals of the day, at least 6 h apart	Initiate at 0.6 mg once daily for 1 week[b]	Inject within 1 hour of the first daily meal
Initiate 5 µg per dose twice daily	After 1 week, increase to 1.2 mg	Initiate 10 µg dose once daily
Increase to 10 µg twice daily after 1 month, based on clinical response	Can increase to 1.8 mg if 1.2 mg does not provide acceptable glycemic control	Increase to 20 µg once daily at 15 days
Multidose pen	Multidose pen	Multidose pen

[a] May need needle prescription.
[b] Dose intended to reduce gastrointestinal symptoms during titration; not effective for glycemic control.

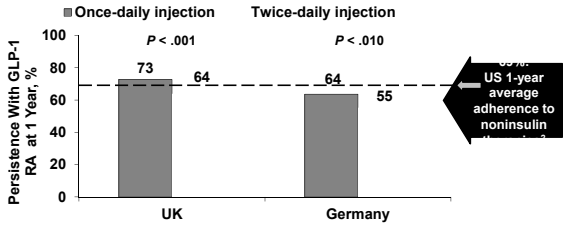
US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Comparing Dosage and Administration of Current GLP-1 RAs: Once-Weekly GLP-1 RAs

Exenatide QW	Albiglutide QW	Dulaglutide QW
23-G needle (supplied)	29-G needle (supplied)	29-G needle (supplied)
Administer 2 mg once weekly	Initiate at 30 mg once weekly	Initiate at 0.75 mg once weekly
No dose titration	Can increase dose to 50 mg if needed	Can increase dose to 1.5 mg if needed
Available in a single-use vial and syringe or in a single-dose pen	Available in a single-dose pen	Available in a single-dose pen

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Adherence to GLP-1 RAs Is Higher With Less-Frequent Administration—Studies From Europe



- Persistence to GLP-1 RAs was higher with once-daily than twice-daily dosing[1]
- Once-weekly GLP-1 RAs may further increase persistence and adherence[3]
- Generally, once-weekly dosing has higher adherence than once-daily dosing[4,a]

[a] Meta-analysis of medication possession ratios in 7 observational studies of osteoporosis medications.

1. Wilke T, et al. *Diabetes Ther*. 2016;7:105-124.
2. Kirkman MS, et al. *Diabetes Care*. 2015;38:604-609.
3. Garber AJ. *Lancet Diabetes Endocrinol*. 2014;2:266-267.
4. Iglay K, et al. *Clin Ther*. 2015;37:1813-1821.

Current GLP-1 RAs Vary Greatly in Their Ease of Use

	Agent	Patient must attach needle?	Patient must reconstitute from powder?	Patient must prime device before first use?	Patient can adjust dose?	Patient must count for dwell time (2-10 sec)?
Daily	Exenatide BID[1]	X		X	X	X
Daily	Liraglutide QD[2]	X		X	X	X
Daily	Lixisenatide QD[3]	X		X	X	X
Weekly	Exenatide QW (syringe)[4]	X	X[a]	X		X
Weekly	Exenatide QW (pen)[5]	X	X[a]	X		X
Weekly	Albiglutide QW[6]	X	X[a]	X		X
Weekly	Dulaglutide QW[7]					

[a] Consult prescribing information for specific instructions on how to reconstitute.

1. http://www.azpicentral.com/byetta/ifu_byetta.pdf;
2. http://www.novo-pi.com/victoza.pdf#guide;
3. http://www.accessdata.fda.gov/drugsatfda_docs/label/2016/208471Orig1s000lbl.pdf;
4. http://www.azpicentral.com/bydureon/ifu_bydureon.pdf;
5. https://www.bydureon.com/using-bydureon/how-to-use-bydureon.html (video);
6. https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Tanzeum/pdf/TANZEUM-PI-MG-IFU-COMBINED.PDF#page=35;
7. http://pi.lilly.com/us/trulicity-lowdose-ai-ifu.pdf.

Patient-Related Considerations When Introducing Patients With T2DM to GLP-1 Receptor Agonists

Identify a regimen that meets the patient's needs/desires/flexibility

Smaller pen needle size is effective and preferred

- Equivalent glycemic control for obese vs nonobese participants[1]

Have patient see/use pen and needle before leaving office with prescription[2]

1. Hirsch L, et al. *Curr Med Res Opin.* 2012;28:1305-1311.
2. Kruger DF, et al. *Diabetes Educ.* 2010;36(suppl 3):44S-72S.

Educating Patients About Their Medications May Improve Adherence and Reduce Patient Concerns That May Interfere With Adherence

Adherence Category	Received information from primary care doctor	Received information from other sources	Complaints about medication interfering with lifestyle	Worried about side effects of medications
Highly adherent 0%-10% doses missed	X	X		
Mostly adherent 11%-26% doses missed		X		
Somewhat nonadherent 27%-47% doses missed			X	
Nonadherent 47%-100% doses missed			X	X

Patients who were referred to CDEs and community programs had the highest adherence

Online survey of self-reported number of missed medication doses among 807 patients with diabetes (90% with T2DM).

Larkin AT, et al. *J Diabetes.* 2015;7:864-871.

Addressing and Assessing Patient Adherence: The Morisky Scale

Do you ever forget to take your medicine?

Are you careless at times about taking your medicine?

When you feel better do you sometimes stop taking your medicine?

Sometimes if you feel worse when you take the medicine, do you stop taking it?

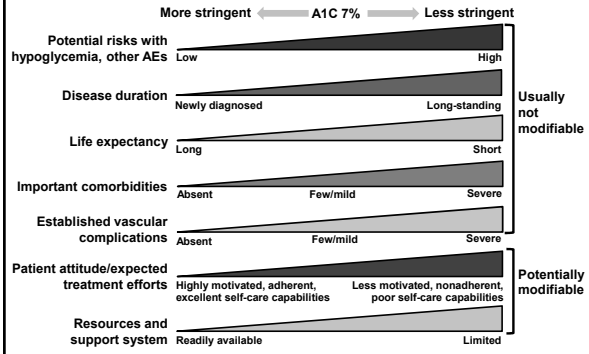
- Scoring (per question):
  - Yes = 0
  - No = 1
  - Add points for total score
- Interpreting the total score:
  - High adherence: 0 points
  - Medium adherence: 1-2 points
  - Low adherence: 3-4 points
- High adherence predicts better blood pressure control
  - 81% sensitivity
  - 44% specificity

Morisky DE, et al. *Med Care.* 1986;24:67-74.

Summary

- With proper patient education, GLP-1 RAs may be very easy to use
- Current GLP-1 RAs range from twice-daily to once-weekly agents
- Instructions for use vary by agent and have the potential to influence adherence
- Factors associated with greater likelihood of adherence include receiving education from primary care provider *and* community programs

Many Different Aspects of Care Are Used to Individualize Management of T2DM



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

GLP-1 RAs May Decrease the Risk of Cardiovascular Events in Patients With T2DM

Completed Studies	Endpoint/Parameter	Outcome
LEADER (liraglutide)[1]	MACE (CV death, nonfatal MI, nonfatal stroke)	*Decreased risk for 3-point MACE*
	Rate of hospitalization for heart failure	*No increased risk*
	Mortality	*15% reduced risk*
ELIXA (lixisenatide)[2]	MACE (CV death, MI, stroke, or hospitalization for unstable angina)	*No increased risk*
	Rate of hospitalization for heart failure	*No increased risk*
	Mortality	*No increased risk*
SUSTAIN 6 (semaglutide)[3,a]	MACE (CV death, nonfatal MI, nonfatal stroke)	*16% reduced risk*[4]

Cardiovascular outcomes trials for exenatide QW, dulaglutide, and albiglutide are in progress[3]

[a] Not approved by US FDA.

1. Marso SP, et al. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print].
2. Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-2257.
3. https://clinicaltrials.gov/ct2/show/record/NCT01720446.
4. Marso SP, eta. *NEJM.* 2016. .Sep 16 [Epub ahead of print].

Large "Real-World" Study Shows No Increased Risk of Heart Failure Hospitalization With GLP-1 RAs

Treatment	Patients *Without* a History of HF, aHR (95% CI)	Patients *With* a History of HF, aHR (95% CI)
≥ 2 OADs	Reference	Reference
Incretin class	No difference	No difference
DPP-4 inhibitors	No difference	No difference
GLP-1 RAs	No difference	No difference
Duration of treatment with incretin-based drugs		
< 365 days	No difference	No difference
365-729 days	21% lower risk[a]	No difference
≥ 730 days	No difference	No difference

aHR, adjusted hazard ratio.
[a] $P < .05$, incretin-based drugs vs ≥ 2 OADs.

Filion KB, et al. *N Engl J Med.* 2016;374:1145-1154.

Most Commonly Reported Adverse Events With GLP-1 Receptor Agonist Use—Prescribing Information[1,2,a]

	Agent	Nausea	Vomiting	Diarrhea	Headache	Upper Respiratory Tract Infection	Injection-Site Reaction
Daily	Exenatide BID	X	X	X	X		
	Liraglutide	X	X	X	X		
	Lixisenatide	X	X	X	X		
Weekly	Exenatide QW	X	X	X	X		X
	Albiglutide	X		X		X	X
	Dulaglutide	X	X	X			

[a] Adverse events reported in ≥ 5% of patients.

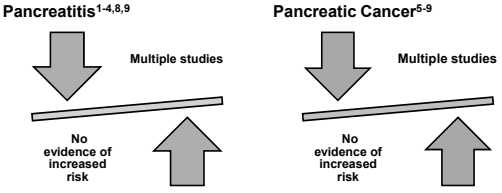
1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
2. Trulicity (dulaglutide) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2015.

Important Points for Patient Education Regarding Gastrointestinal Adverse Events

- Discuss expectations (eg, nausea is transient, sense of fullness)[1]
- Titrate slowly[1]
- Suggest behavioral changes (eg, decrease portion sizes and fat content, keep a log of foods that cause nausea)[1]
- Be aware of persistent abdominal pain and pancreatitis risk[1,2]

1. Kruger DF, et al. *Diabetes Educ.* 2010;36 (suppl 3):44S-72S.
2. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Pancreatitis and Pancreatic Cancer Are Rarely Reported in Clinical Trials or Observational Studies of GLP-1 RAs



- However, providers should be aware and counsel their patients[10,11]:
- Persistent severe abdominal pain is a hallmark symptom of pancreatitis
  - *Discontinue promptly if pancreatitis symptoms occur: upper abdominal or back pain (may be sudden), nausea, vomiting*
  - Risk factors include previous pancreatitis, alcoholism, gallstones, and hypertriglyceridemia

1. Monami M, et al. *Diabetes Obes Metab.* 2015;17:32-41; 2. Li L, et al. *BMJ.* 2014;348:g2366; 3. Wang T, et al. *Diabetes Obes Metab.* 2015;17:32-41; 4. Giorda CB, et al. *Endocrine.* 2015;48:461-471; 5. Guo X, et al. *Clin Drug Investig.* 2016 Mar 15. [Epub ahead of print]; 6. Knapen LM, et al. *Diabetes Obes Metab.* 2016;18:259-265; 7. Azoulay L, et al. *BMJ.* 2016;352:i581; 8. Pfeffer MA, et al. *N Engl J Med.* 2015;373:2247-2257; 9. Marso SP, et al. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print]; 10. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 11. http://www.mayoclinic.org/diseases-conditions/pancreatitis/basics/symptoms/con-20028421.

Recent Findings Regarding GLP-1 RAs and Thyroid Cancer

Long-term exposure to GLP-1 RAs in rodents, <u>but not monkeys or humans</u>, has been associated with thyroid C-cell hyperplasia and tumors[1]

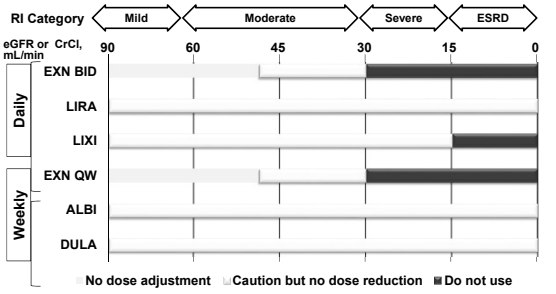
→ **FDA black box warning on product inserts of long-acting GLP-1 RAs[2,a]; contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2**

- Pooled analysis showed no increased risk of thyroid cancer[3,b]
- 1 MTC case reported for dulaglutide in 1 trial, but it was determined to have been pre-existing[4]
- No thyroid events reported for lixisenatide; no increased risk for liraglutide[5,6]

[a] All approved GLP-1 RAs except EXN BID.
[b] 24-30 weeks; all studies—DURATION-1 through -6 and Asian studies; EXN QW (n = 1934), EXN BID (n = 606), non-GLP (non–GLP-1 comparator, n = 1338), EXN QW (n = 461), LIRA (n = 450).

1. Knudsen LB, et al. *Endocrinology.* 2010;151:1473-1486; 2. Drugs@FDA.gov; 3. MacConell L, et al. *Diabetes Metab Syndr Obes.* 2015;8:241-253. 4. Jendle J, et al. *Diabetes Metab Res Rev.* 2016 Apr 21. [Epub ahead of print]; 5. Pfeffer MA, et al. *N Engl J Med.* 2016;373:2247-2257; 6. Marso SP, et al. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print].

Recommendations for Current GLP-1 RAs in Patients With Renal Impairment[1]



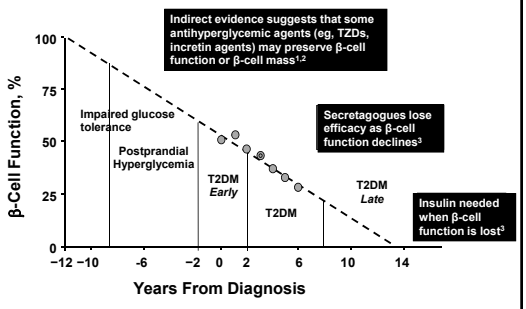
- *Patients who are dehydrated are at increased risk of renal injury from GLP-1 RAs*[1]
- Liraglutide is associated with a *decreased* risk of renal events[2]

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.
2. Marso SP, et al. *N Engl J Med.* 2016 Jun 13. [Epub ahead of print].

Summary

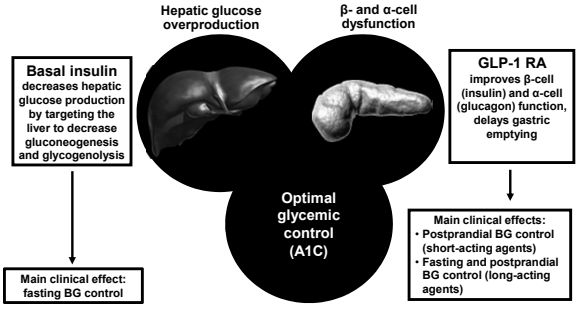
- GLP-1 RAs have shown to date a neutral to favorable effect on cardiovascular risks
- GI effects such as nausea are common but tend to diminish with time and proper patient education/counseling
- Counsel patients to recognize symptoms of pancreatitis; consider other classes of agents in patients with a history of pancreatitis
- Some agents should not be used in patients with a personal or family history of certain rare thyroid tumors
- Most GLP-1 RAs can be used in patients with renal impairment, although indications vary among agents—consult prescribing information

β-Cell Function Is Gradually Lost as T2DM Progresses



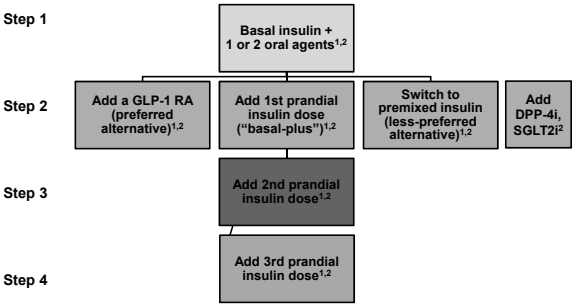
1. Buchanan TA, et al. *Diabetes.* 2002;51:2796-2803.
2. Salehi M, et al. *Endocr Rev.* 2008;29:367-379.
3. Lebovitz HE. *Diabetes Rev.* 1999;7:139-153.

Complementary Actions of Basal Insulin and GLP-1 RAs[1-4]



1. Baggio LL, Drucker DJ. *Gastroenterology.* 2007;132:2131-2157.
2. Balena R, et al. *Diabetes Obes Metab.* 2013;15:485-502.
3. Holst JJ. *Physiol Rev.* 2007;87:1409-1239.
4. Madsbad S. *Diabetes Obes Metab.* 2016;18:317-332.

Intensification of Antihyperglycemic Therapy in T2DM, Starting With Basal Insulin: Current Recommendations



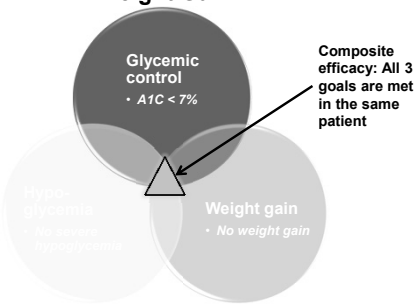
1. ADA. *Diabetes Care.* 2016;39(suppl 1):S1-S112.
2. Garber AJ, et al. *Endocr Pract.* 2016;22:84-113.

Approval Status for Use of GLP-1 RAs in Combination With Insulin

Class	Agent	Basal	Prandial	Not Recommended
Daily	Exenatide 5-10 μg BID[1]	X		
	Liraglutide 0.6-1.8 mg QD[1]	X	Tested[2]	
	Lixisenatide 10-20 μg QD[1]	X		
Weekly	Exenatide 2 mg QW[1]			X
	Albiglutide 30-50 mg QW[1]	X		
	Dulaglutide 0.75-1.5 mg QW[1]	Tested[3]	X	X (Basal)

1. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;
2. de Wit HM, et al. *J Intern Med.* 2016;279:283-292;
3. Pozzilli P, et al. *Diabetes.* 2016;65(suppl 1):A62 [abstract 237-OR].

Defining Composite Efficacy in Diabetes Therapy: Glycemic Control, Hypoglycemia, and Weight Gain



Zinman B, et al. *Diabetes Obes Metab.* 2012;14:77-82.

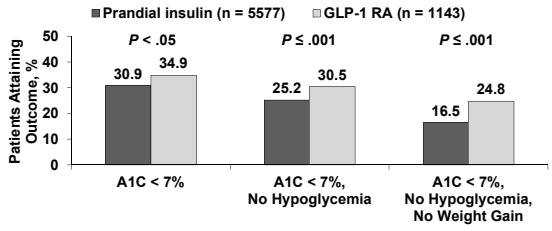
GLP-1 RA vs Prandial Insulin Added to Long-Acting Basal Insulins—Meta-Analysis

Comparison	A1C	Hypoglycemia	Weight
GLP-1 RA + basal insulin vs other agents + basal insulin[a]	0.44% additional reduction with GLP-1 RA (*P* < .05)	No increased relative risk with GLP-1 RA (RR, 0.99; *P* = NS)	Mean reduction of 3.22 kg with GLP-1 RA (*P* < .05)
GLP-1 RA + basal insulin vs basal-bolus insulin therapy[b]	0.1% additional reduction with GLP-1 RA (*P* < .05)	33% lower risk with GLP-1 RA (*P* < .05)	Mean reduction of 5.66 kg with GLP-1 RA (*P* < .05)

[a] Background OADs included MET, SU, TZD, GLN, AGI.
[b] Background OADs included MET, PIO.

Eng C, et al. *Lancet.* 2014;384:2228-2234.

GLP-1 RA vs Prandial Insulin Added to Long-Acting Basal Insulins—Real-World Data



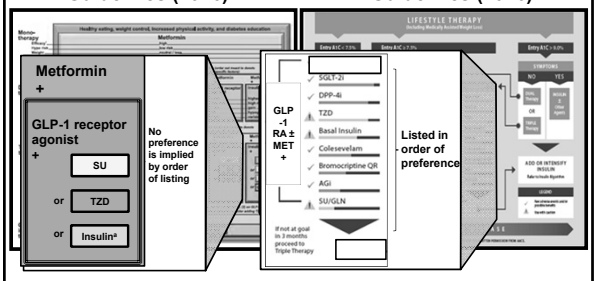
Patients initiating GLP-1 RAs also had significantly fewer ED visits, hospitalizations, and specialist referrals than patients initiating prandial insulin

US database study reporting results 1 year after addition of prandial insulin or a GLP-1 RA to basal insulin among patients matched for age, A1C, and body mass at baseline.

Digenio A, et al. *Postgrad Med.* 2014;126:49-59.

Intensification of Antihyperglycemic Therapy in T2DM, Starting With a GLP-1 RA: Current Recommendations

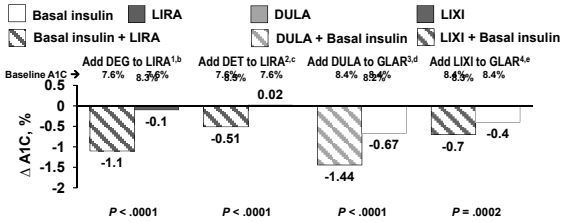
ADA Guidelines (2016)[1] **AACE Guidelines (2016)[2]**



[a] Usually a basal insulin (NPH, glargine, detemir, degludec).

1. ADA. *Diabetes Care.* 2016;39(suppl 1):S1-S112.
2. Garber AJ, et al. *Endocr Pract.* 2016;22:84-113.

Combining GLP-1 RAs[a] With Basal Insulin: Does Order of Addition Matter?



GLP-1 RA and basal insulin combination treatment improves glycemic control relative to basal insulin or GLP-1 RA alone, regardless of order of addition[1-4]

[a] Only EXN BID, LIRA, LIXI, and ALBI are currently approved for use with basal insulin[2]; [b] 24 -to 28-week randomized trials.

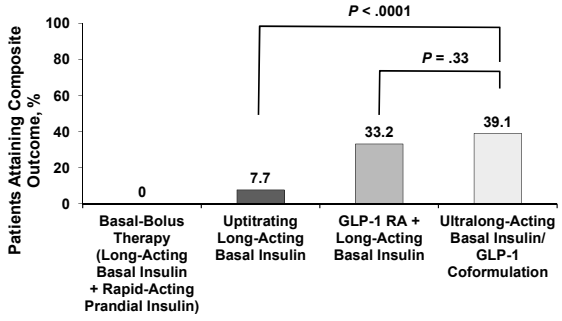
1. Aroda VR, et al. *Diabetes Obes Metab.* 2016;18:663-6702; 2. DeVries J, et al. *Diabetes Care.* 2012;35:1446-1454; 3. Pozzilli P, et al. *Diabetes.* 2016;65(suppl 1):A62 [abstract 237-OR]; 4. Riddle MC, et al. *Diabetes Care.* 2013;36:2489-2496; 5. US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Shared Decision-Making Points for Comparing a GLP-1 Receptor Agonist vs a Basal Insulin

Aspect of Care	GLP-1 Receptor Agonist	Basal Insulin Analogue
Number of injections per week	1 to 14	7 to 14
Dose adjustment for meals required?	No	Yes
Dose adjustment for exercise required?	No	Yes
Glucose monitoring needed multiple times daily?	No	Maybe
Most common adverse events?	GI distress	Hypoglycemia

US FDA. Drugs@FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

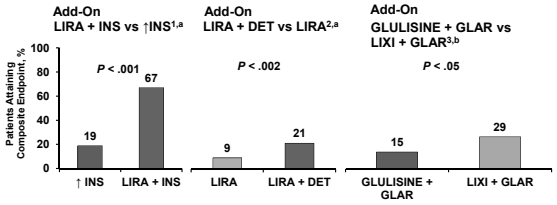
Comparing 4 Different Strategies for Intensifying a Basal Insulin Regimen—Composite Efficacy[a]



[a] Pooled analysis and indirect comparison of 5 randomized controlled trials. Composite efficacy: A1C < 7% without hypoglycemia or weight gain.

Freemantle N, et al. *Diabetes Ther.* 2015;6:573-591.

GLP-1 RA + Basal Insulin vs Other Intensification Strategies

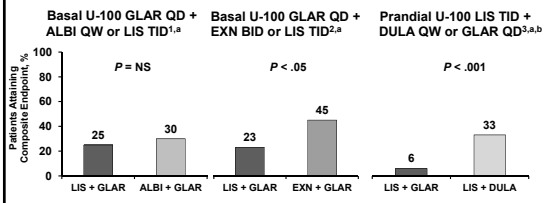


Fixed-ratio coformulations of basal insulin and a GLP-1 RA have been recommended for FDA approval[4,5]

[a] 12- to 26-week randomized controlled trials, BL A1C 8.2%-8.8%, BL Wt 86-99 kg. [b] Meta-analysis of 5 randomized controlled trials.

1. Li CJ, et al. *Cardiovasc Diabetol.* 2012;11:142.
2. DeVries JH, et al. *Diabetes Care.* 2012;35:1446-1454.
3. Raccah D, et al. *J Diabetes Complications.* 2014;28:40-44.
4. http://www.medpagetoday.com/endocrinology/diabetes/58115.
5. http://www.medpagetoday.com/washington-watch/fdageneral/58141.

GLP-1 RA + Insulin (Basal or Prandial) vs Lispro/Glargine Basal Bolus Therapy



[a] 26- to 30-week randomized trials, BL A1C 8.4%-8.5%, BL Wt 89-92 kg. [b] Composite endpoint at 52 wks was attained by 52% on LIS/DULA 1.5 mg and by 14% on LIS/GLAR.

1. Rosenstock J, et al. *Diabetes Care.* 2014;37:2317-2325.
2. Diamant M, et al. *Diabetes Care.* 2014;37:2763-2773.
3. Blonde L, et al. *Lancet.* 2015;385:2057-2066.

Summary

- GLP-1 RAs or basal insulins can be initiated in either order
- GLP-1 RAs are less burdensome for patients than insulin regimens—SMBG and dose adjustments for meals and exercise are not required
- GLP-1 RAs used in combination with basal or prandial insulin is highly advantageous in terms of composite efficacy (A1C reduction, hypoglycemia, weight gain) relative to most comparator strategies
- GLP-1 RAs have varying indications for use with insulin—consult prescribing information
- Fixed-ratio combination therapies—GLP-1 RA + basal insulin—have recently been recommended for FDA approval