9:15 – 10:30 am

Finding the Right Combination: Using GLP-1 Receptor Agonist Therapy to Individualize T2DM Management

SPEAKERS

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Presenter Disclosure Information

The following relationships exist related to this presentation:

- James R. Gavin III, MD, PhD: Speakers Bureau for AstraZeneca; Boehringer Ingelheim Pharmaceuticals, Inc.; Lilly and Janssen Pharmaceuticals, Inc.; Medical Advisory Board for Abbott Laboratories; Intarcia Therapeutics, Inc. and Janssen Pharmaceuticals, Inc. Consultant for AstraZeneca and Boehringer Ingelheim Pharmaceuticals, Inc.
- Jay Shubrook, DO, FACOFP, FAAFP, BC-ADM: Medical Advisory Board for AstraZeneca; Lilly; and Novo Nordisk Inc. Research for sanofi-aventis U.S.

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Learning Objectives

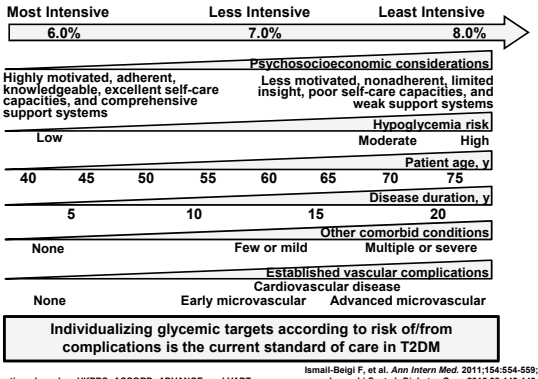
At the conclusion of this activity, participants should be able to:

- Compare and contrast characteristics of available GLP-1 RAs in the context of matching individual agents with specific patient needs and preferences
- Evaluate the individualized application of GLP-1 RAs in the context of common T2DM disease management scenarios
- Appraise recent evidence regarding the use of GLP-1 RAs across T2DM disease progression, especially in terms of their impact on disease management when used in combination with newer oral agents and/or with basal insulin

Outline: GLP-1 Receptor Agonists and Their Use With Oral Agents

- **Comparing currently available GLP-1 receptor agonists**
  - Glycemic control
  - Other treatment priorities (ie, weight, hypoglycemia, patient-related factors)
  - Safety and tolerability
- **Using GLP-1 receptor agonists in combination with oral antihyperglycemic agents**
  - GLP-1 receptor agonists added to metformin
  - Using GLP-1 receptor agonists with newer agents (ie, SGLT2 inhibitors)

Individualizing Glycemic Control in T2DM



Individualizing glycemic targets according to risk of/from complications is the current standard of care in T2DM

Considerations based on UKPDS, ACCORD, ADVANCE, and VADT.

Ismail-Beigi F, et al. *Ann Intern Med.* 2011;154:554-559; Inzucchi S, et al. *Diabetes Care.* 2015;38:140-149.

Individualizing T2DM Therapy With Currently Available GLP-1 Receptor Agonists

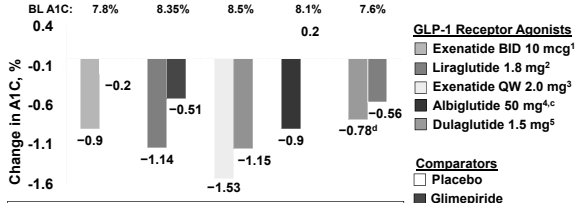
- **Current treatment guidelines emphasize individualized care and prioritize the use of GLP-1 RAs when avoidance of hypoglycemia or weight gain are important management goals for T2DM**
- **GLP-1 RAs may be used in patients with T2DM as:**
  - An adjunct to diet and exercise[1-5]
  - Monotherapy when metformin (MET) is contraindicated or not tolerated[3-5]
  - Part of dual or triple therapy[1-5]

US FDA-Approved Agent	Administration[1,2]
Exenatide BID (EXN BID)	• Subcutaneous injection, twice daily
Liraglutide (LIRA)	• Subcutaneous injection, once daily
Exenatide QW (EXN QW)	Subcutaneous injection, once weekly
Albiglutide (ALBI)	
Dulaglutide (DULA)	

1. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 2. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf; 3. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149; 4. American Diabetes Association. *Diabetes Care.* 2015;38(suppl 1):S1-S93; 5. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

COMPARING CURRENTLY AVAILABLE GLP-1 RECEPTOR AGONISTS

Relative Glycemic Efficacy of GLP-1 Receptor Agonists[a,b]



In head-to head trials:
- Dulaglutide, liraglutide and exenatide QW were more potent than exenatide BID, and albiglutide had an intermediate effect[6]
- Liraglutide had greater efficacy than exenatide QW and equivalent efficacy as dulaglutide[6]

[a] Phase 3 trials: 24-26 weeks for EXN trials, 52 weeks for LIRA and ALBI trials, 26 weeks for DULA trial; aged 52-56 years, disease duration 1-5.6 years.
[b] $P < .05$ vs comparator in all studies.
[c] ALBI 50 mg was started at 30 mg and increased to 50 mg at week 12.
[d] DULA superior to MET.

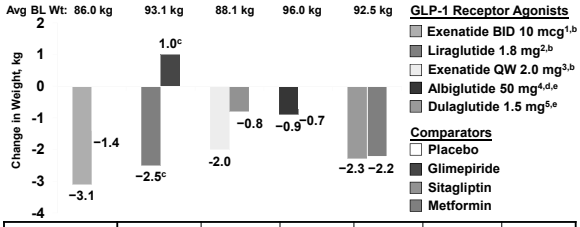
1. Moretto T, et al. *Clin Ther.* 2008;30:1448-1460;
2. Garber A, et al. *Lancet.* 2009;373:473-481;
3. Russell-Jones D, et al. *Diabetes Care.* 2012;35:252-258;
4. Reinhardt R, et al. EASD 2013 [abstract 903]. http://www.easdvirtualmeeting.org/resources/3898;
5. Umpierrez G, et al. *Diabetes Care.* 2014;37:2168-2176;
6. Trujillo JM, et al. *Ther Adv Endocrinol Metab.* 2015;6:19-28.

Comparing Other Glycemic Effects of Shorter- vs Longer-Acting GLP-1 Receptor Agonists

	Shorter-Acting GLP-1 RAs (EXN BID)	Longer-Acting GLP-1 RAs (LIRA, ALBI, DULA, EXN QW)
Half-life	2-5 hours	12 hours to several days
Fasting blood glucose levels	Modest reduction	Strong reduction
Postprandial glucose levels	Strong reduction	Modest reduction
Glucagon secretion	Reduction	Reduction

Meier JJ, et al. *Nat Rev Endocrinol.* 2012;8:728-742.

Relative Weight Effects of GLP-1 Receptor Agonists[a,b]

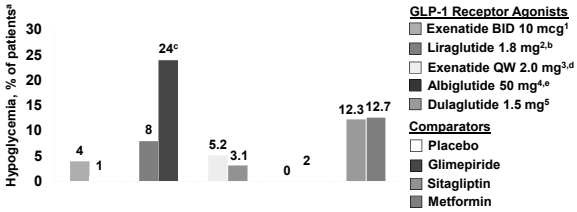


Agent	GLP-1 RAs	MET	SUs/ Glinides	TZDs	DPP-4 Inhibitors	SGLT2 Inhibitors
Weight change[6]	Loss	Slight loss	Gain	Gain	Neutral	Loss

[a] Phase 3 trials: 24-26 weeks for EXN trials, 52 weeks for LIRA and ALBI trials, 26 weeks for DULA trial, aged 52-56 years, disease duration 1-5.6 years; [b] $P < .05$ vs comparator; [c] Values are approximations; [d] ALBI 50 mg was started at 30 mg and increased to 50 mg at week 12; [e] $P > .05$ vs comparator, not significant.

1. Moretto T, et al. *Clin Ther.* 2008;30:1448-1460;
2. Garber A, et al. *Lancet.* 2009;373:473-481;
3. Russell-Jones D, et al. *Diabetes Care.* 2012;35:252-258;
4. Reinhardt R, et al. EASD 2013 [abstract 903]. http://www.easdvirtualmeeting.org/resources/3898;
5. Umpierrez G, et al. *Diabetes Care.* 2014;37:2168-2176;
6. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

GLP-1 Receptor Agonists Have a Relatively Low Risk of Hypoglycemia



Agent	GLP-1 RAs	MET	SUs/Glinides	TZDs	DPP-4 Inhibitors	SGLT2 Inhibitors
Hypoglycemia risk[6]	Neutral	Neutral	Moderate to severe/mild	Neutral	Neutral	Neutral

[a] No severe events reported. [b] Confirmed by BG measurement. [c] $P < .001$ between groups. [d] Not confirmed by BG measurement. [e] ALBI 50 mg was started at 30 mg and increased to 50 mg at week 12.

1. Moretto T, et al. *Clin Ther.* 2008;30:1448-1460; 2. Garber A, et al. *Lancet.* 2009;373:473-481; 3. Russell-Jones D, et al. *Diabetes Care.* 2012;35:252-258; 4. Reinhardt R, et al. EASD 2013 [abstract 903]. http://www.easdvirtualmeeting.org/resources/3898; 5. Umpierrez G, et al. *Diabetes Care.* 2014;37:2168-2176; 6. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

Potential Therapeutic Effects of GLP-1 Receptor Agonists Compared With Other Commonly Used Antihyperglycemic Agents[a]

Class or Agent	≈ Δ SBP, mm Hg	≈ Δ DBP, mm Hg	LDL Effect
GLP-1 RAs[1-4]	−4	−1	↓
TZDs/PIO[5,6]	−5	−4	Neutral
SU + MET[7]	NS vs MET	NS vs MET	NS vs MET
MET[8]	NS	NS	↓
DPP-4 inhibitors[9,10]	NS	NR	↓[b]
SGLT2 inhibitors[11,12]	−4[c] to −5[c]	−2[c] to −3[c]	↑

- As a class, GLP-1 RAs have the potential to reduce LDL, whereas SGLT2 inhibitors appear to increase LDL.

[a] Not approved for treatment of hypertension or dyslipidemia.[11]
[b] Sitagliptin only.
[c] Dapagliflozin only.

1. Vilsbøll T, et al. *BMJ.* 2012;344:d7771; 2. Drucker DJ, et al. *Lancet.* 2008;372:1240-1250; 3. Buse JB, et al. *Lancet.* 2009;374:39-47; 4. Buse JB, et al. *Lancet.* 2013;381:117-124; 5. Qayyum R, et al. *J Clin Hypertens (Greenwich).* 2006;8:19-28; 6. Chiquette E, et al. *Arch Intern Med.* 2004;164:2097-2104; 7. Zhang F, et al. *Endocrine.* 2013;44:548-558; 8. Wulffelé MG, et al. *J Intern Med.*2004;256:1-14; 9. Monami M, et al. *Diabetes Obes Metab.* 2013;15:112-120; 10. Derosa G, et al. *Fundam Clin Pharmacol.* 2014;28:221-229; 11. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 12. Abdul-Ghani MA, et al. *Curr Diab Rep.* 2012;12:230-238.

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

Agent	Nausea	Vomiting	Diarrhea	Headache	Upper Respiratory Tract Infection	Injection-Site Reaction
EXN BID	X	X	X	X		
LIRA	X		X	X		
EXN QW	X	X	X	X		X
ALBI	X		X		X	X
DULA	X	X	X			

Except for DULA, occurrence of GI adverse events is lower with most longer-acting agents[3] (LIRA and EXN QW vs EXN BID; EXN QW and ALBI vs LIRA)

1. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;
2. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf;
3. Meier JJ, et al. *Nat Rev Endocrinol*. 2012;8:728-742.

Renal Safety of GLP-1 Receptor Agonists Compared With Other Oral Antihyperglycemic Agents[1,2]

Agent	Renal Safety
GLP-1 RAs[1,4]	Exenatide BID or QW: should not use in severe renal impairment (RI)[a] or ESRD; use with caution in moderate RI or renal transplant[b]
	Liraglutide: no dose adjustment recommended; use with caution in RI. In ESRD, reduced dose and prolonged titration may reduce GI adverse effects.
	Albiglutide and dulaglutide: no dose adjustment; use with caution, monitor renal function in RI and severe gastrointestinal adverse effects
MET[1,5]	Contraindicated in CKD if SCR ≥ 1.5 mg/dL (males) or ≥ 1.4 mg/dL (females); new ADA guidelines suggest dose reduction if eGFR < 60 and discontinuation if eGFR < 30
SUs/Glinides[4]	Use with caution in RI; lower starting doses are recommended
TZDs[4]	No dose adjustment recommended
DPP-4 Inhibitors[1,4]	Dose adjustment may be necessary (except linagliptin)
SGLT2 Inhibitors[1]	Canagliflozin: dose limitation if eGFR[c] 45 to < 60; do not use if eGFR[c] < 45
	Dapagliflozin: do not use if eGFR[c] < 60
	Empagliflozin: do not use if eGFR[c] < 45

- Direct nephrotoxicity has not been demonstrated with GLP-1 RAs
- Altered renal function has been reported with GLP-1 RAs; some events have occurred in conjunction with nausea/vomiting or agents affecting renal function and/or volume status

[a] Creatinine clearance < 30 mL/min.
[b] Creatinine clearance 30 to 50 mL/min.
[c] eGFR in mL/min/1.73 m^2.

1. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/;
2. Idorn T, et al. *Diabetes Care*. 2015 Aug 17. [Epub ahead of print].
3. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf;
4. Garber AJ, et al. *Endocr Pract*. 2015;21:438-447; 5. Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149.

Risk of Pancreatitis With GLP-1 Receptor Agonists

- US FDA/EMA statement regarding potential pancreatitis risk with GLP-1 receptor agonists[1]
  - "...assertions concerning a causal association between incretin-based drugs and pancreatitis or pancreatic cancer...are inconsistent with the current data..."
  - "...current knowledge is adequately reflected in the product information and labeling..."
- Findings from a recent study in Denmark suggest that incretin therapies (both GLP-1 RAs and DPP-4 inhibitors) are not associated with increased acute pancreatitis risk[2]

Discontinue promptly if pancreatitis symptoms occur

⇩

Consider other agents if patient has a history of pancreatitis

⇩

If acute pancreatitis is confirmed, do not restart GLP-1 RA

⇩

Report cases of pancreatitis to www.fda.gov/medwatch[a]

[a] Risk evaluation and mitigation strategies (REMS) information can be found at http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm111350.htm.

1. Egan AG, et al. *N Engl J Med*. 2014;370:794-797; 2. Thomsen RW, et al. *Diabetes Care*. 2015;38:1089-1098; 3. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 4. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.

Risk of Thyroid C-Cell Tumors With GLP-1 Receptor Agonists

- AACE/ACE Statement on Diabetes and Cancer indicates that current evidence does not support an increased risk of MTC with GLP-1 RA use[1]
  - ALBI, DULA, EXN QW, and LIRA are contraindicated in patients with MEN2 or a personal or family history of MTC
- With the exception of EXN BID, all GLP-1 RAs have approved REMS[a]

Clinical Recommendations[2,3]

Counsel patients regarding MTC risk and symptoms of thyroid tumors	Value of routine calcitonin and/or ultrasound monitoring is uncertain and may lead to unnecessary procedures	Patients with thyroid nodules or elevated serum calcitonin levels identified for other reasons should be sent to an endocrinologist

To monitor potential associations, report all cases of MTC, regardless of regimen: http://www.fda.gov/medwatch

[a] More REMS information can be found at http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2011/021773s031ltr.pdf.

1. Handelsman Y, et al. *Endocr Pract*. 2013;19:675-693;
2. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA;
3. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.

Other Patient-Related Considerations With 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]

Agent	Administration[3,4]	Pen Needle Size[5-7]
Exenatide BID	• Twice daily; within 60 min of 2 main meals, but ≥ 6 h apart	29, 30, or 31G
Liraglutide	• Daily, any time of the day	30 or 32G
Exenatide QW	Weekly, any time of the day	23G
Albiglutide		29G
Dulaglutide		29G

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; 3. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 4. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf; 5. Shomali M. *Clin Diabetes*. 2014;32:32-43; 6. RxList. http://www.rxlist.com/tanzeum-drug/indications-dosage.htm; 7. Lilly USA, LLC. https://www.trulicity.com/healthcare-professionals-glp-1-ra-therapy-and-administration.aspx.

USING GLP-1 RAs IN COMBINATION WITH ORAL ANTIHYPERGLYCEMIC AGENTS

GLP-1 RAs Offer Complementary Actions to Common Oral Antihyperglycemic Agents

- Increased insulin secretion/sensitivity and decreased hepatic glucose production are common actions associated with many oral antihyperglycemic agents (MET, SU, glinides, TZDs)

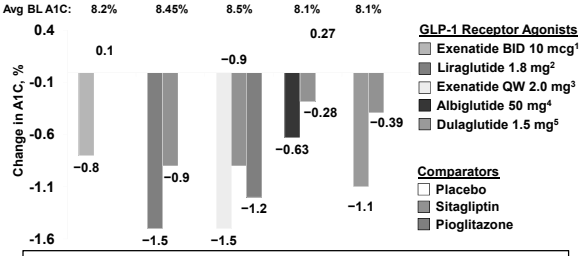
Oral glucose load leads to secretion of incretin hormones, resulting in enhanced pancreatic insulin secretion (impaired in patients with T2DM)	GLP-1 RAs mediate glucose-dependent changes • Increase insulin • Decrease glucagon • Slow gastric emptying • Increase satiety	GLP-1 activity is higher with GLP-1 RAs (≈ 9 × baseline) vs DPP-4 inhibitors (≈ 2 × baseline)

- Data regarding use of GLP-1 RAs and SGLT2 inhibitors in combination is limited at this time[1]
- GLP-1 RAs should not be used in combination with DPP-4 inhibitors[2,a,b]

[a] Due to lack of efficacy and/or increased risk of adverse effects. [b] Consult 2015 guideline for current recommendation; this guideline has been announced but was not publicly available as of April 24, 2015.

1. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149; 2. Garber AJ, et al. *Endocr Pract.* 2013;19(suppl 2):1-48; 3. Baggio L, Drucker D. *Gastroenterology.* 2007;132:2131-2157; 4. DeFronzo RA, et al. *Curr Med Res Opin.* 2008;24:2943-2952.

Glycemic Efficacy of GLP-1 RAs[a,b] vs Common Oral Antihyperglycemic Agents When Added to Metformin

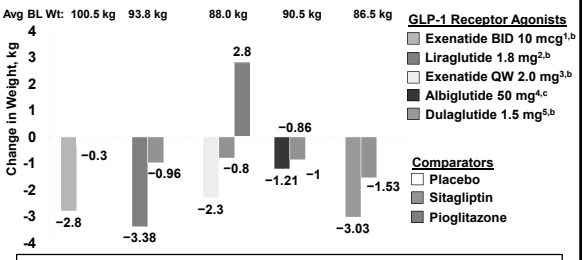


Head-to-head trials of GLP-1 RAs added to common antihyperglycemic regimens with 2 or more OADs showed similar results[6-9]

[a] Phase 3 trials, 26-30 weeks, except 104 weeks for ALBI trial, 52 weeks for DULA trial; aged 52-56 years, disease duration 5-7 years. [b] $P < .05$ vs comparator in all studies.

1. DeFronzo R, et al. *Diabetes Care.* 2005;28:1092-1100; 2. Pratley R, et al. *Lancet.* 2010;375:1447-1456; 3. Bergenstal R, et al. *Lancet.* 2010;376:431-439; 4. Ahren B, et al. *Diabetes Care.* 2014;37:2141-2148; 5. Nauck M, et al. *Diabetes Care.* 2014;37:2149-2158; 6. Buse JB, et al. *Lancet.* 2009;374:39-47; 7. Buse JB, et al. *Lancet.* 2013;381:117-124; 8. Pratley R, et al. *Lancet Diabetes Endocrinol.* 2014;2:289-297; 9. Wysham C, et al. *Diabetes Care.* 2014;37:2159-2167.

Weight Effects of GLP-1 RAs[a] vs Common Oral Antihyperglycemic Agents When Added to Metformin



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[a] Phase 3 trials, 26-30 weeks, except 104 weeks for ALBI trial, 52 weeks for DULA trial; aged 52-56 years, disease duration 5-7 years. [b] $P < .05$ for GLP-1 RA vs comparator. [c] $P > .05$ vs comparator, not significant.

1. DeFronzo R, et al. *Diabetes Care.* 2005;28:1092-1100; 2. Pratley R, et al. *Lancet.* 2010;375:1447-1456; 3. Bergenstal R, et al. *Lancet.* 2010;376:431-439; 4. Ahren B, et al. *Diabetes Care.* 2014;37:2141-2148; 5. Nauck M, et al. *Diabetes Care.* 2014;37:2149-2158; 6. Buse JB, et al. *Lancet.* 2009;374:39-47; 7. Buse JB, et al. *Lancet.* 2013;381:117-124; 8. Pratley R, et al. *Lancet Diabetes Endocrinol.* 2014;2:289-297; 9. Wysham C, et al. *Diabetes Care.* 2014;37:2159-2167.

Increased Risk of Hypoglycemia With GLP-1 RA Use in Combination With SUs

Hypoglycemia; Patients Reporting ≥ 1 Event, %		
	Without SU	With SU
Exenatide BID[1,2]	1-11	15-42
Liraglutide[1,3,4]	1-6	12-33
Albiglutide QW[5]	2-3	13-17
Exenatide QW[2,3]	0-4	15
Dulaglutide QW[6]	–	39-40

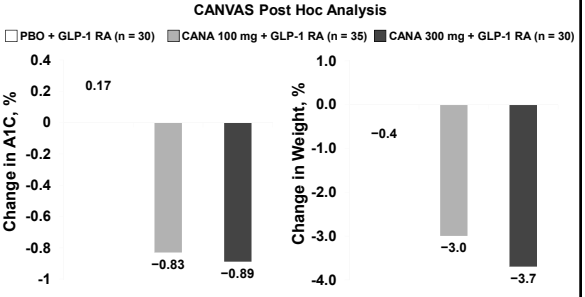
Possible increased hypoglycemia risk when used with SU

Consider a lower dose of SU to decrease hypoglycemia risk[5,6]

Educate or review hypoglycemia recognition and treatment

1. Buse JB, et al. *Lancet.* 2009;374:39-47; 2. Drucker DJ, et al. *Lancet.* 2008;372:1240-1250; 3. Buse JB, et al. *Lancet.* 2013;381:117-124; 4. DeVries JH, et al. *Diabetes Care.* 2012;35:1446-1454; 5. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 6. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.

Glycemic Efficacy and Weight Change of a GLP-1 RA Used in Combination With an SGLT2 Inhibitor



Post hoc analysis of CANVAS data at 18 weeks, limited to participants who were using GLP-1 RAs at baseline, with or without other agents (N = 95).
Baseline A1C = 8.1%; baseline BMI = 37.4 kg/m^2.

Wysham C, et al. *Diabetes.* 2013(suppl 1):A279 [abstract 1080-P].

Clinical Pearls: GLP-1 Receptor Agonists and Their Use With Oral Agents

- Compared with other classes of antihyperglycemic therapy, therapeutic intensification with GLP-1 RAs offers:
  - Robust A1C lowering
  - Lower rates of hypoglycemia, except when used in combination with sulfonylureas
  - Favorable weight effects
- GLP-1 RAs complement the actions of many oral antihyperglycemic agents, except for DPP-4 inhibitors
- GLP-1 RAs offer considerable flexibility with regard to matching agents to an individual patient's needs and preferences
- Consider patient risk factors
  - History of thyroid tumors
  - History of pancreatitis
- Educate patients about potential risks and/or adverse effects associated with GLP-1 RAs
  - Nausea and other gastrointestinal effects

Outline: GLP-1 Receptor Agonists and Their Use With Insulin

- Advancing antihyperglycemic therapy beyond 2 to 3 oral agents
  - Adding a GLP-1 receptor agonist vs basal insulin
- Intensifying insulin
  - Using GLP-1 receptor agonists in combination with insulin therapy
  - Adding a GLP-1 receptor agonist vs prandial or basal to intensify insulin therapy

ADVANCING ANTIHYPERGLYCEMIC THERAPY BEYOND 2 TO 3 ORAL AGENTS

Adding a GLP-1 Receptor Agonist vs Basal Insulin

Mechanisms of Action: Insulin Compared With GLP-1 Receptor Agonists

Class of Agent	Mechanism(s) of Action	Administration
Insulin[1,2]	↓ Hepatic glucose production ↑ Glucose disposal ↑ Glucose uptake in muscle	Subcutaneous injection
GLP-1 Receptor Agonists[1,3,4]	↑ Insulin secretion ↓ Hepatic glucose production ↓ Gastric emptying/glucose absorption ↑ Satiety	Subcutaneous injection

1. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149;
2. Aronoff SL, et al. *Diabetes Spectrum.* 2004;17:183-190;
3. Drucker D, et al. *Diabetes Care.* 2010;33:428-433;
4. Handelsman Y, et al. *Endocr Pract.* 2015;21(suppl 1):1-87.

Considerations for Advancing Therapy to Include GLP-1 Receptor Agonists or Insulin

GLP-1 Receptor Agonists

Advantages
- Robust A1C change
- Low hypoglycemia risk
- Weight loss/avoidance of weight gain
- Multiple dosing options with available agents
- No dose titration for meal size, exercise

Limitations
- Training required for injection
- GI adverse effects
- Contraindicated/not recommended in some populations[a]

Insulin

Advantages
- Theoretically unlimited efficacy
- Universal effectiveness

Limitations
- Training required for injection
- SMBG (dose adjustment, hypoglycemia avoidance)
- Hypoglycemia
- Weight gain
- Dose titration with meals, exercise

Insulin can be added before adding a GLP-1 RA, or a GLP-1 RA can be added before adding insulin; more studies are needed to determine the optimal order of initiation[5]

[a] Patients with MEN2 or with a personal or family history of MTC (ALBI, DULA, EXN QW, LIRA); patients with a history of pancreatitis (all); patients with severe RI/ESRD (EXN BID, EXN QW).

1. Handelsman Y, et al. *Endocr Pract.* 2015;21(suppl 1):1-87;
2. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149;
3. US http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/;
4. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.
5. Goldenberg R. *Curr Med Res Opin.* 2014;30:431-445.

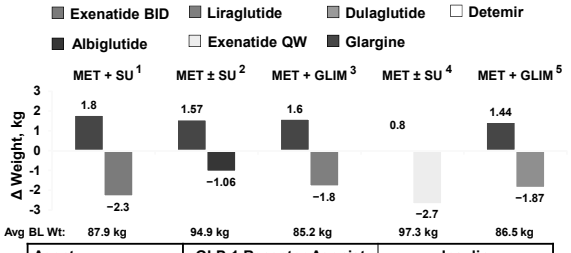
Glycemic Efficacy of GLP-1 RAs Compared With Basal Insulin When Intensifying Oral Therapy

Background Therapy	Change in A1C, % GLP-1 RA	Change in A1C, % Basal Insulin
MET + SU[1,a,b]	−1.1 Exenatide BID[f]	−1.1 Glargine
MET + SU[2,a,c]	−0.7 Albiglutide[f]	−0.8 Glargine
MET + GLIM[3,a,b]	−1.3 Liraglutide[g]	−1.1 Glargine
MET ± SU[4,a,b,d]	−1.3 Exenatide QW[g]	−0.9 Detemir
MET + GLIM[5,a,e]	−1.1 Dulaglutide[g]	−0.6 Glargine

[a] BL A1C, 8.1% to 8.4%; aged 55.5-59.8 y; disease duration 7-10 y.
[b] 26 weeks.
[c] 52 weeks, 82% on MET + SU background.
[d] = 70% on MET + SU background.
[e] 52 weeks.
[f] Noninferior vs insulin.
[g] $P < .05$ vs insulin.

1. Heine R, et al. *Ann Intern Med.* 2005;143:559-569;
2. Weissman PN, et al. *Diabetologia.* 2014;57:2475-2484;
3. Russell-Jones D, et al. *Diabetologia.* 2009;52:2046-2055;
4. Davies M, et al. *Diabetes Care.* 2013;36:1368-1376;
5. Giorgino F, et al. *Diabetes.* 2014;63(suppl 1):A87.

Weight Effects With GLP-1 RAs Compared With Basal Insulin When Intensifying Oral Therapy[a]



Agent	GLP-1 Receptor Agonist	Insulin
Impact on weight[6]	Loss	Gain

[a] $P < .05$ for between-group difference; phase 3 studies, 26-52 weeks; BL A1C, 8.1% to 8.4%; aged 55.5-59.8 y; disease duration 7-10 y.

1. Heine R, et al. *Ann Intern Med.* 2005;143:559-569;
2. Weissman PN, et al. *Diabetologia.* 2014;57:2475-2484;
3. Russell-Jones D, et al. *Diabetologia.* 2009;52:2046-2055;
4. Davies M, et al. *Diabetes Care.* 2013;36:1368-1376;
5. Giorgino F, et al. *Diabetes.* 2014;63(suppl 1):A87;
6. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

Risk of Hypoglycemia With GLP-1 RAs Compared With Basal Insulin When Intensifying Oral Therapy

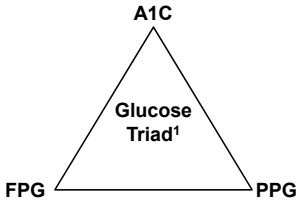
Hypoglycemia Type	Comparison
Severe hypoglycemia	Dulaglutide ≈ Glargine[1] "Minimal"
	Liraglutide > Glargine (0.06 vs 0 events per year [EPY])[2]; (2 vs 0 events over 24 weeks)[3]
Nocturnal hypoglycemia	Exenatide BID < Glargine[4,5]
	Liraglutide < Glargine[2]
Minor hypoglycemia	Exenatide QW ≈ Detemir[7]
	Exenatide QW < Glargine[6]
Overall hypoglycemia	Albiglutide < Glargine[8]
	Dulaglutide < Glargine[3]
	Liraglutide < Glargine[2]

Agent	GLP-1 Receptor Agonist	Insulin
Risk of hypoglycemia[9]	Neutral	Moderate to severe

1. D'Alessio D, et al. *Diabetes Obes Metab.* 2015;17:170-178; 2. Giorgino F, et al. *Diabetes.* 2014;63(suppl 1):A87; 3. Russell-Jones D, et al. *Diabetologia.* 2009;52:2046-2055; 4. Heine R, et al. *Ann Intern Med.* 2005;143:559-569; 5. Davies M, et al. *Diabetes Obes Metab.* 2009;11:1153-1162; 6. Diamant M, et al. *Lancet.* 2010;375:2234-2243; 7. Davies M, et al. *Diabetes Care.* 2013;36:1368-1376; 8. Weissman PN, et al. *Diabetologia.* 2014;57:2475-2484; 9. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

USING GLP-1 RAs IN COMBINATION WITH INSULIN

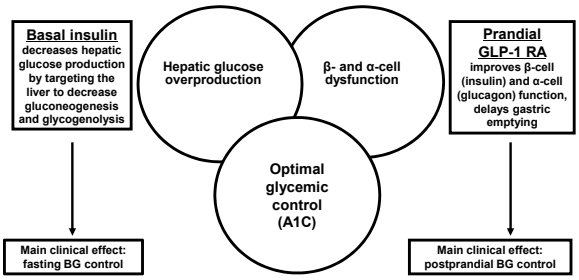
Postprandial Glucose (PPG) Can Remain Uncontrolled With Basal Insulin Therapy



- Patients with T2DM can experience significant PPG excursions, even with good control according to A1C and FPG measurements[1]
- 40% of patients treated with oral therapy and basal insulin had controlled FPG, but not A1C[2]

1. Monnier L, et al. *Diabetes Metab.* 2006;32:S11-S16; 2. Colclough HA, et al. *Diabetes.* 2012;63(suppl 1):A87.

Complementary Actions of Basal Insulin and GLP-1 RAs



Baggio LL, Drucker DJ. *Gastroenterology.* 2007;132:2131-2157; Balena R, et al. *Diabetes Obes Metab.* 2013;15:485-502; Holst JJ. *Physiol Rev.* 2007;87:1409-1439.

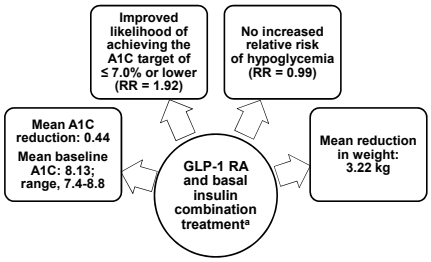
Specific Guidance Regarding the Use of GLP-1 RAs in Combination With Insulin

Of the 5 currently available GLP-1 receptor agonists[1-4]:

Approved for use in combination with basal insulin	Not studied nor approved for use in combination with basal insulin	Approved for use with prandial insulin
• Albiglutide • Exenatide BID • Liraglutide	• Dulaglutide • Exenatide QW (prescribing information cautions against combination use)	• Dulaglutide

1. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 2. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf; 3. Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149; 4. Garber AJ, et al. *Endocr Pract.* 2015;21:438-447.

Using GLP-1 Receptor Agonists and Basal Insulin in Combination

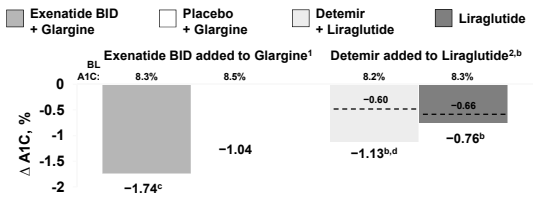


Compared to treatment with a basal-bolus insulin regimen, the combination of a GLP-1 RA and basal insulin has been associated with a lower risk of hypoglycemia

[a] Meta-analysis of 15 eligible studies; N = 4348; mean trial duration, 24.8 weeks (range, 12-36 weeks); mean duration of diabetes, 12.2 years (range, 7.9-17.1 years).

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

Combining GLP-1 RAs[a] With Basal Insulin: Glycemic Control Based on Order of Addition



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, and ALBI are approved for use with basal, but not prandial, insulin.[5]
[b] Includes ΔA1C from 12-wk run-in with LIRA alone in both groups (dashed lines and black text).
[c] $P < .001$ for combination; [d] $P < .0001$.

1. Buse JB, et al. *Ann Intern Med*. 2011;154:103-112; 2. DeVries J, et al. *Diabetes Care*. 2012;35:1446-1454; 3. Pawaskar M, et al. *Endocr Pract*. 2012;18:700-711; 4. Li CJ, et al. *Cardiovasc Diabetol*. 2012;11:142; 5. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA.

Rates of Hypoglycemia May Increase When GLP-1 RAs Are Added to Insulin Compared to GLP-1 RA Monotherapy

Hypoglycemia; Patients Reporting ≥ 1 Event, %			
	GLP-1 RA Alone	GLP-1 RA + Insulin	Basal Insulin Alone
Exenatide BID[1-3]	1-11	25-53	29-41
Liraglutide[1,4-6]	1-6	9-12	31
Albiglutide QW[7]	2-3	16	30
Exenatide QW[2,4]	0-4	–	–
Dulaglutide QW[8]	–	80-85 (Lispro)	–

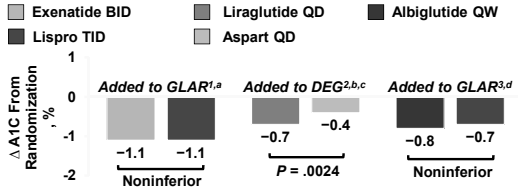
Possible increased hypoglycemia risk when GLP-1 RAs are used with insulin or sulfonylurea

Consider a lower dose of insulin or sulfonylurea to decrease hypoglycemia risk[7,8]

Educate or review hypoglycemia recognition and treatment

1. Buse JB, et al. *Lancet*. 2009;374:39-47; 2. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250; 3. Balena R, et al. *Diabetes Obes Metab*. 2013;15:485-502; 4. Buse JB, et al. *Lancet*. 2013;381:117-124; 5. Li CJ, et al. *Cardiovasc Diabetol*. 2012;11:142; 6. DeVries JH, et al. *Diabetes Care*. 2012;35:1446-1454; 7. US FDA. http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA; 8. Dulaglutide prescribing information. http://pi.lilly.com/us/trulicity-uspi.pdf.

Comparing Effects of GLP-1 RAs vs Prandial Insulin When Intensifying Basal Insulin



Outcome	EXN BID vs LIS[1]		LIRA vs ASP[2]		ALBI QW vs LIS[3]	
Δ Weight, kg	−2.5[e]	2.1	−2.8[e]	0.9	−0.7[e]	0.8
Hypoglycemia[f]	30%	41%	1.0 EPY[e]	8.2 EPY	0.9 EPY; 15.8%	2.3 EPY; 29.9%
Nausea, %	32	2	LIRA > ASP, first 2 wk		11	1

[a] 30 weeks, BL A1C 8.2% to 8.3%. [b] Insulin degludec is not approved in the US, but has been accepted for review by the US FDA. [c] ~ 26 weeks, BL A1C 7.7%. [d] ≥ 26 weeks, BL A1C 8.4% to 8.5%. [e] $P < .05$ between groups.
[f] Rates of severe hypoglycemia were low across groups.

1. Diamant M, et al. *Diabetes Care*. 2014;37:2763-2773; 2. Mathieu C, et al. *Diabetes Obes Metab*. 2014;16:636-644; 3. Rosenstock J, et al. *Diabetes Care*. 2014;37:2317-2325; 4. http://www.reuters.com/article/2015/04/07/us-novo-nordisk-fda-idUSKBN0MY21420150407.

Comparing Glycemic Efficacy of GLP-1 RA and Basal Insulin When Used With Prandial Insulin

Prandial Insulin	Change in A1C, % GLP-1 RA	Change in A1C, % Basal Insulin
Lispro TID[a]	−1.5 Dulaglutide QW	−1.2 Glargine QD

Outcome	Dulaglutide vs Glargine	
Δ Weight, kg	−0.35[b]	2.89
Hypoglycemia, EPY[c]	31.0	39.9
Severe hypoglycemia, n	11	22
Nausea, %	25.8	3.4

[a] 52 wk, N = 884, $P < .02$.
[b] $P < .05$ between groups.
[c] BG ≤ 70 mg/dL and symptoms.

Jendle J, et al. *Diabetes*. 2014;63(suppl 1):A246-A247.

Clinical Pearls: GLP-1 Receptor Agonists and Their Use With Insulin

- Consider patient-specific goals and needs when making therapeutic selections
- Consider combination therapy with a GLP-1 RA and insulin in patients who do not reach A1C goals with dual or triple therapy
- GLP-1 RA + basal insulin combinations have been shown to improve glycemic control comparably with or to a greater extent than each agent alone
  - Current treatment guidelines include the use of basal insulin in combination with GLP-1 RA therapy as T2DM progresses
  - GLP-1 RAs in combination with insulin carry a higher risk of hypoglycemia when compared to GLP-1 RA monotherapy; reducing the insulin dose is recommended when combining basal insulin and a GLP-1 RA
- GLP-1 RAs offer the potential for fewer injections, greater flexibility, favorable weight effects, and less hypoglycemia compared with prandial insulin