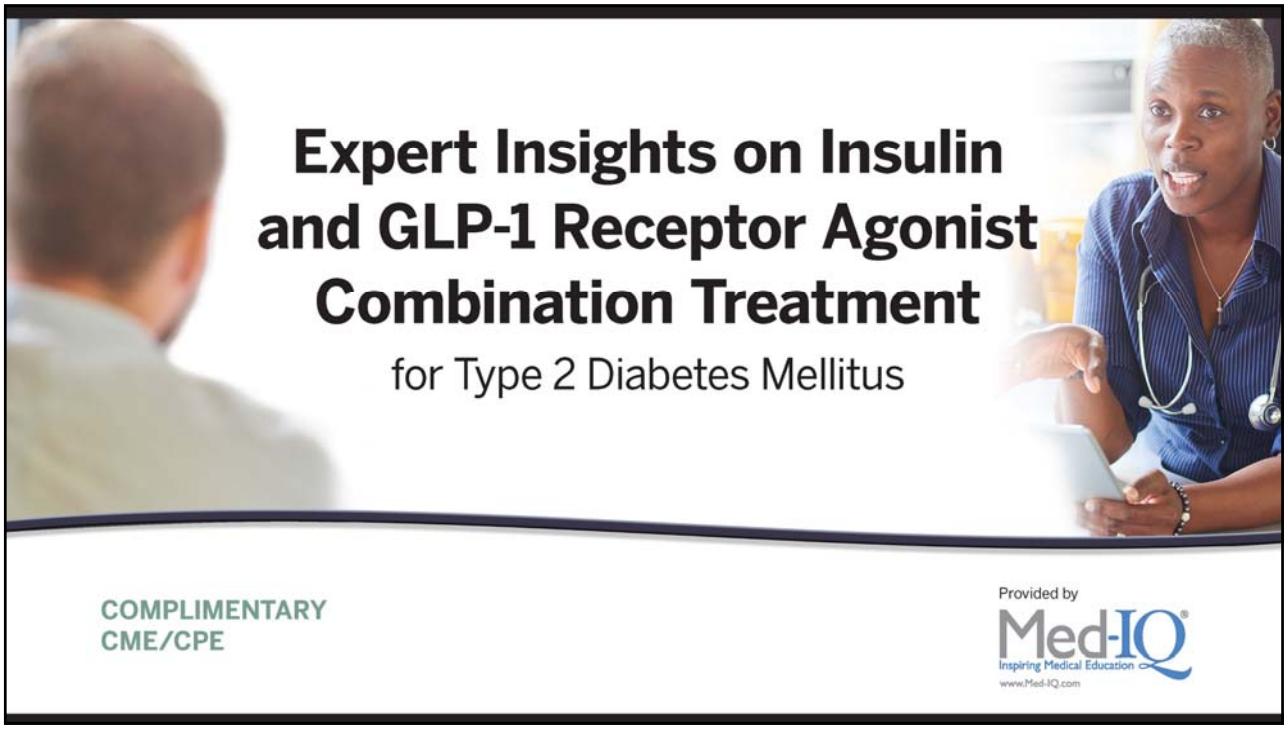


ADA and AACE Glycemic Targets

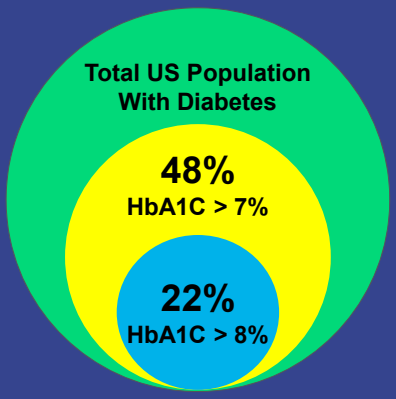
- HbA1C target should be individualized based on a number of factors including:
  - Age
  - Life expectancy
  - Comorbidities
  - Duration of diabetes
  - Risk of hypoglycemia
  - Patient motivation
  - Patient adherence

	Glycemic Control Targets	
Test	**ADA**	**AACE**
HbA1C	< 7%	≤ 6.5%
FPG	80-130 mg/dL	< 110 mg/dL
PPG	< 180 mg/dL (measured within 1-2 hours after the start of a meal)	< 140 mg/dL (2-hour value)

ADA. *Diabetes Care*. 2017;40:S48-56; Garber AJ, et al. *Endocr Pract*. 2016;22:84-113; Handelsman Y, et al. *Endocr Pract*. 2015;21:1-87.

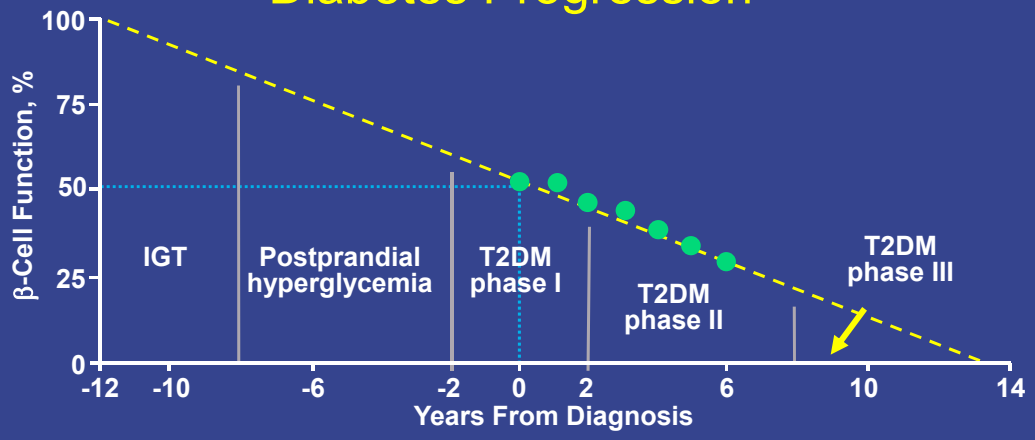
HbA1C Levels in Patients With Diabetes

- Many patients with diabetes have HbA1C levels above the ADA-recommended target of 7%
- As T2DM progresses, maintaining glycemic control becomes more difficult and often requires insulin therapy



Ali MK, et al. *N Engl J Med*. 2013;368:1613-24; Kahn SE, et al. *Lancet*. 2014;383:1068-83; Casagrande SS, et al. *Diabetes Care*. 2013;36:2271-9; Maiorino MI, et al. *Diabetes Care*. 2017;40:614-24.

Decline in β-Cell Function With Diabetes Progression



Dashed line shows extrapolation forward and backward from years 0 to 6 based on HOMA data from UKPDS.

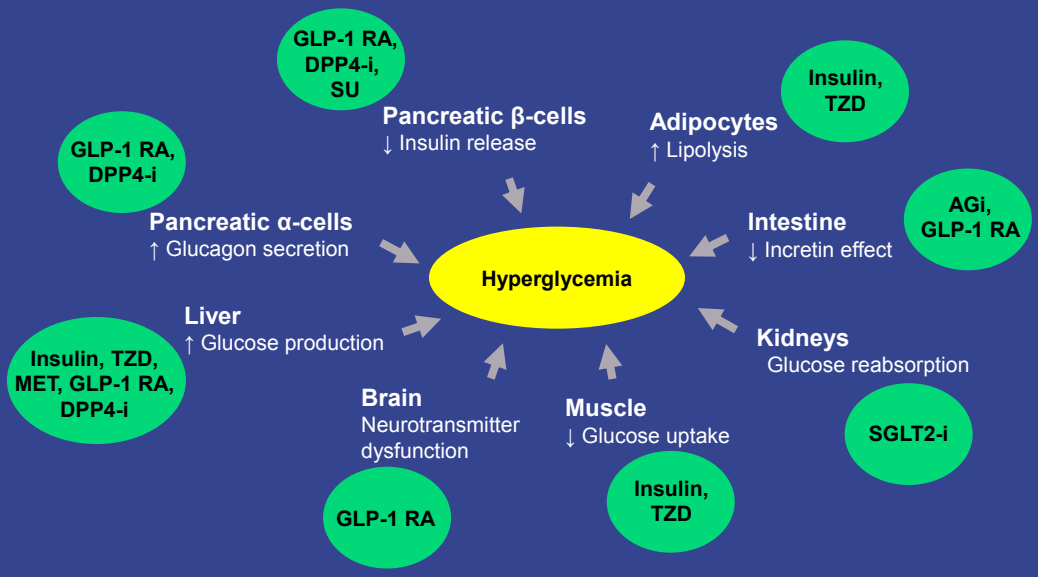
Lebovitz H. *Clin Chem*. 1999;45:1339-53; UKPDS Group. *Diabetes*. 1995;44:1249-58.

T2DM

- T2DM is a complex, chronic disease characterized by multiple pathophysiologic abnormalities
- Most classes of drugs have multiple sites of action, leading to increased antihyperglycemic efficacy
- Combinations of oral and injectable therapies may be needed in T2DM patients to normalize glucose homeostasis, even those who are initially well controlled on monotherapy

Ferrannini E, et al. *Eur Heart J*. 2015;36:2288-96; ADA. *Diabetes Care*. 2017;40:S11-24.

Pathophysiologic Targets of T2DM Therapies



Ferrannini E, et al. *Eur Heart J*. 2015;36:2288-96.

ADA 2017 Guidelines for the Management of T2DM

Start With Monotherapy Unless:

HbA1C ≥ 9%, consider **Dual Therapy**

HbA1C ≥ 10%, BG ≥ 300 mg/dL, or patient is markedly symptomatic, consider **Combination Injectable Therapy**

Monotherapy: Metformin

Efficacy	Hypoglycemia risk	Weight	Side effects
High	Low	Neutral/loss	GI/lactic acidosis

Dual Therapy: Metformin +

	Basal insulin	DPP4-i	GLP-1 RA	SGLT2-i	SU	TZD
Efficacy	Highest	Intermediate	High	Intermediate	High	High
Hypoglycemia risk	High	Low	Low	Low	Moderate	Low
Weight	Gain	Neutral	Loss	Loss	Gain	Gain
Side effects	Hypoglycemia	Rare	GI	GUI, dehydration, fxs	Hypoglycemia	Edema, HF, fxs

Triple Therapy: Metformin +

Basal insulin + DPP4-i **or** GLP-1 RA **or** SGLT2-i **or** TZD	DPP4-i + basal insulin **or** SGLT2-i **or** SU **or** TZD
GLP-1 RA + basal insulin **or** SGLT2-i **or** SU **or** TZD	SGLT2-i + basal insulin **or** DPP4-i **or** GLP-1 RA **or** SU **or** TZD
SU + basal insulin **or** DPP4-i **or** GLP-1 RA **or** SGLT2-i **or** TZD	TZD + basal insulin **or** DPP4-i **or** GLP-1 RA **or** SGLT2-i **or** SU

If HbA1C target not achieved after ~3 months, proceed to **2-drug combination**

If HbA1C target not achieved after ~3 months, proceed to **3-drug combination**

Metformin should be started at diagnosis unless there are contraindications

GLP-1 RA or basal insulin should be considered early in the course of therapy

- If HbA1C target not achieved after ~3 months, and patient is on **(1) oral medication, move to basal insulin or GLP-1 RA, (2) GLP-1 RA, add basal insulin, or 3) optimally titrated insulin, add GLP-1 RA or mealtime insulin.**

ADA. *Diabetes Care*. 2017;40:S64-74.

Basal Insulin and GLP-1 RAs: Barriers to Intensification Strategies

- Provider barriers
  - Delay in initiating insulin therapy in patients with T2DM
  - Limited knowledge of GLP-1 RAs and how to choose among available GLP-1 RA therapies
  - Lack of experience with dose titration
- Patient barriers
  - Reluctance to accept an insulin-based strategy for glycemic control
    - Self-blame/feeling of failure
    - Belief that insulin therapy is complicated
    - Fear of injections

Peyrot M, et al. *Diabetes Care*. 2005;28:2673-9; Peyrot M, et al. *Diabetologia*. 2003;46:A89; Polonsky WH, et al. *Diabetes Care*. 2005;28:2543-5.

DAWN Study: Provider Barriers

- The DAWN study examined provider and patient attitudes toward insulin therapy
  - US physicians are significantly more likely to delay insulin therapy than physicians in other countries ($P < .05$ or $P < .001$ for all comparisons), except India and Japan
  - Only approximately 50% of MDs and RNs believe that insulin has a positive effect on care

Peyrot M, et al. *Diabetes Care*. 2005;28:2673-9.

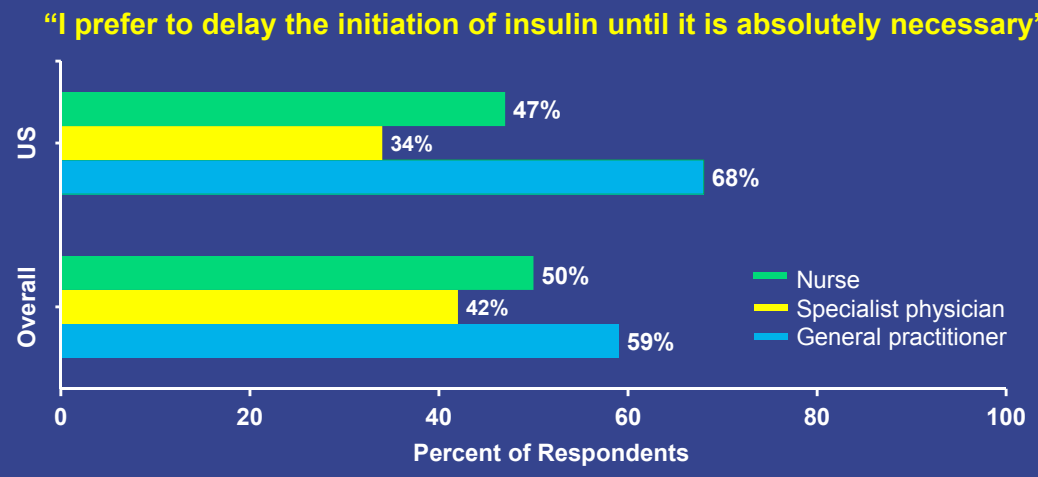
Polling Question 1:

Initiating Insulin Therapy

I prefer to delay the initiation of insulin until it is absolutely necessary.

a. Strongly agree
b. Agree
c. Disagree
d. Strongly disagree
e. N/A

DAWN Study: Delaying Insulin Therapy Is Common in the US



Peyrot M, et al. *Diabetes Care.* 2005;28:2673-9.

Self-Reported Comfort Level for Managing Diabetes by Professional Category

Derr RL, et al. *Diabetes Spectrum.* 2007;20:177-85.

Patient Barriers

- The DAWN study demonstrated that in patients with T2DM who were not on insulin (n = 2,061):
  - 57% had anxiety about initiating insulin therapy
  - US patients were more likely to report a lower belief in insulin efficacy[a] and self-blame[b] for insulin therapy than patients from any other country
- A separate study of 708 patients with T2DM who were not on insulin found that:
  - 28% were unwilling to administer insulin even if prescribed
  - < 25% were "very willing" to begin insulin therapy

[a]Significant difference from Germany ($P < .001$), India ($P < .01$), Japan ($P < .001$), Scandinavia ($P < .05$), and Spain ($P < .001$).
[b]Significant difference from Australia, Germany, India, and the Netherlands (all $P < .001$).

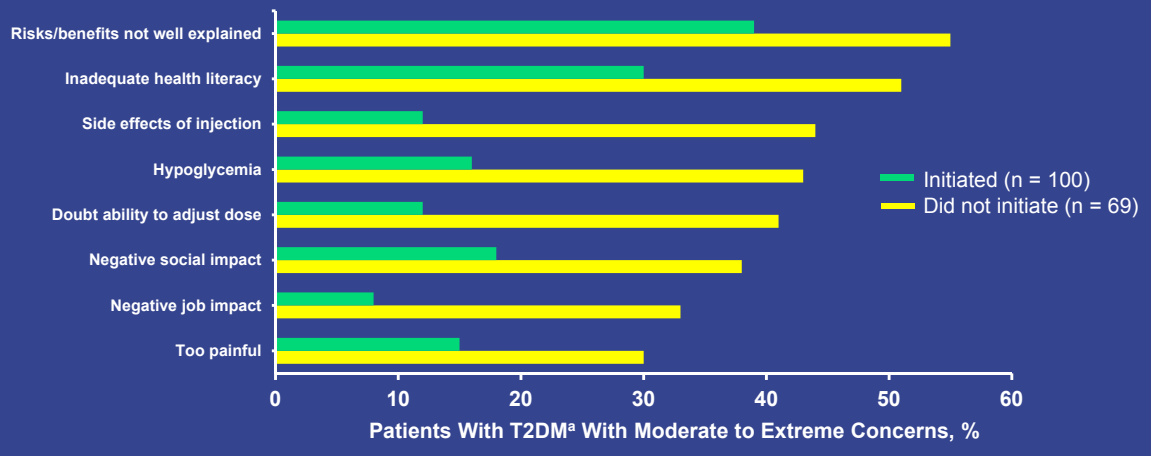
Peyrot M, et al. *Diabetologia*. 2003;46:A89;
Peyrot M, et al. *Diabetes Care*. 2005;28:2673-9;
Polonsky WH, et al. *Diabetes Care*. 2005;28:2543-5.

Psychological Barriers to Insulin Therapy

- For many patients, initiating insulin therapy represents a failure in self-care
  - 48% of patients believed they were to blame for not following physician instructions
- Other barriers to insulin use include:
  - Fear of injections
  - Belief that insulin use is complicated
  - Fear of loss of independence or a change in lifestyle
  - Stigma attached to needle use

Peyrot M, et al. *Diabetologia*. 2003;46:A89; Peyrot M, et al. *Diabetes Care*. 2005;28:2673-9.

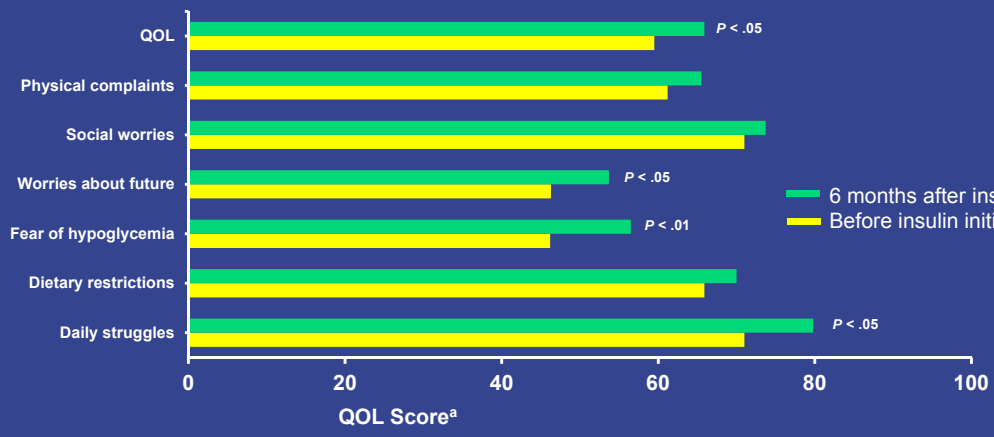
Barriers to Initiating Insulin Therapy Among Privately Insured Patients—New Jersey, 2010



Statistically significant factors influencing insulin use from a survey of 169 privately insured, insulin-naïve patients with poorly controlled T2DM; $P < .05$, not adherent vs adherent for all factors shown.
[a]Percentages of omitted responses not shown.

Karter AJ, et al. *Diabetes Care*. 2010;33:733-5.

Insulin Initiation Improves Quality of Life in T2DM



Results from 42 insulin-naïve older (mean age, 68.4 years) German adults with T2DM who initiated insulin with a structured diabetes education program.
[a]Higher scores indicate better QOL.

Braun A, et al. *Patient Educ Couns*. 2008;73:50-9.

Assessing and Addressing Common Patient Concerns

- Many patients fear:
  - Needles
  - Painful injections
  - Hypoglycemia
  - Weight gain
  - Adverse effects on lifestyle
  - Loss of personal freedom and independence
  - Complications caused by insulin
  - Effects on relationships with family and friends
- Additionally, patients may believe that taking insulin means their diabetes has gotten worse or may think that needing insulin indicates a personal failure

Funnell MM, et al. *Diabetes Educ*. 2004;30:274-80.

Patient Engagement: Assessment Questions

- What is your greatest concern about your diabetes?
- What is the hardest thing for you in taking care of your diabetes?
- How satisfied are you with your current therapy for diabetes?
- How satisfied are you with your current level of glucose control?
- What do you need to know to consider insulin therapy?
- What is your biggest fear about insulin?
- What problems do you think you will encounter?
- What do you see as the most negative?
- What do you see as the most positive?
- What support do you have to overcome barriers?
- Are you willing to start insulin? If not, what would cause/help you to start taking insulin?

Funnell MM, et al. *Diabetes Educ*. 2004;30:274-80.

Overcoming Patients' Fear of Injection

- Perform "dry run" injection
  - Insert needle without injecting any drug
- Administer the first injection in the office
- Use the smallest needle possible
- Present injection as a relatively painless process
  - Injection is into fatty tissue, not muscle (like an intramuscular vaccine)
- Discuss injection technique
  - Injection devices are quick and easy to use
  - Have a pen available for demonstration

Kruger DF, et al. *Diabetes Metab Syndr Obes*. 2015;8:49-56.

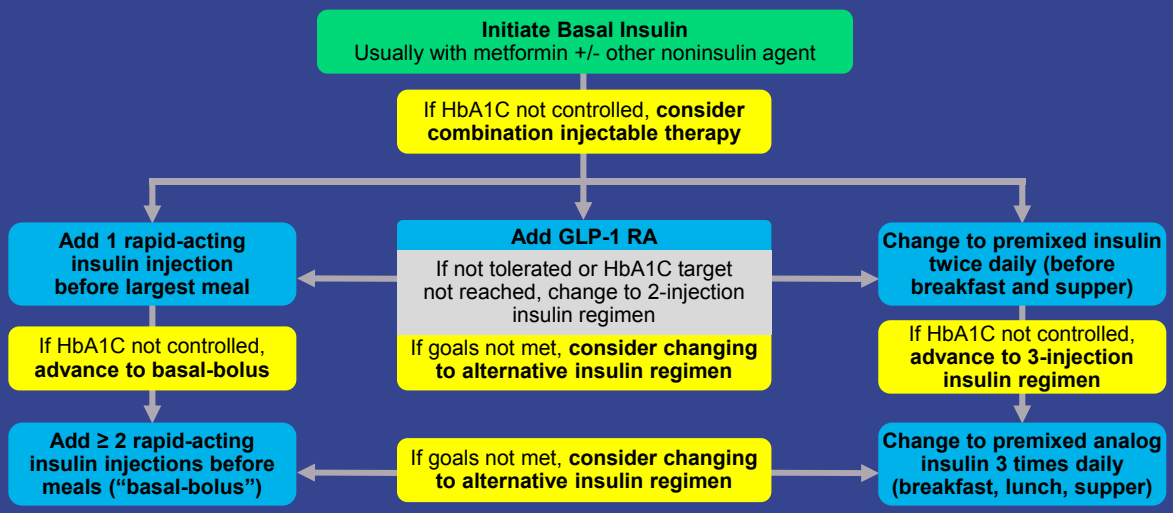
Polling Question 2:

Insulin Intensification Strategy

When a patient on basal insulin therapy is not achieving glycemic goals, which of the following is your preferred strategy for intensifying therapy?

a. Add a GLP-1 RA
b. Add oral noninsulin therapy
c. Add prandial insulin
d. Titrate insulin
e. Other

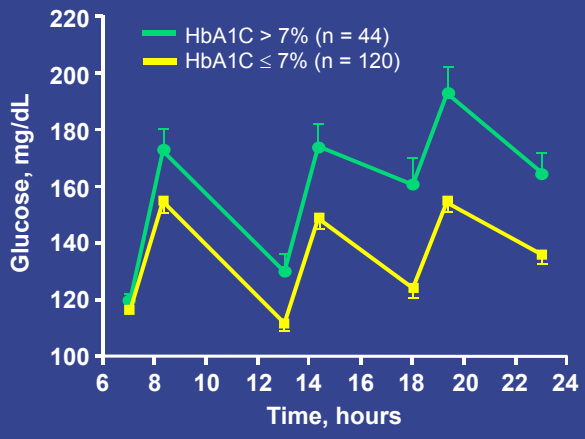
Therapeutic Options in Patients Not Achieving Glycemic Goals With Basal Insulin



ADA. *Diabetes Care*. 2017;40:S64-74.

Postprandial Hyperglycemia Persists After Basal Insulin Therapy

- 164 patients with baseline HbA1C > 7.5% in 3-month intensified forced titration program
- Mealtime hyperglycemia persists after 3 months of intensive treatment



Woerle HJ, et al. *Diabetes Res Clin Pract*. 2007;78:280-5.

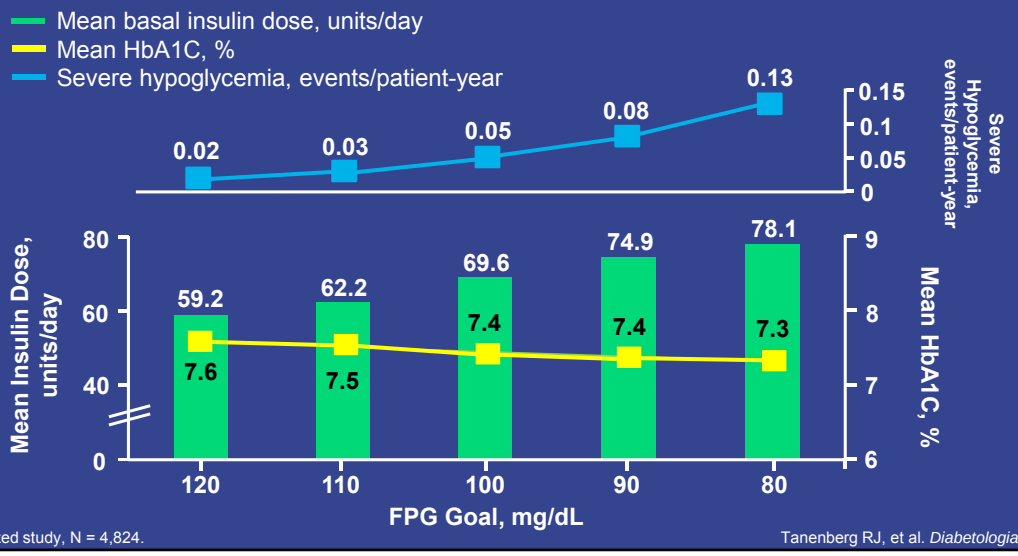
When to Stop Titrating Basal Insulin and Consider Prandial Control Options for T2DM Patients

The individual is not meeting glycemic targets on basal insulin and:

- **HbA1C still not at goal with 0.5 units/kg/day of basal insulin**
- **Elevated HbA1C despite normal FPG with basal insulin**
- **FPG with basal insulin is within target range, but PPG is persistently above goal**
- **Further increases in basal insulin result in hypoglycemia**

Inzucchi S, et al. *Diabetes Care*. 2012;35:1364-79; Davidson MB, et al. *Endocr Pract.* 2011;17:395-403.

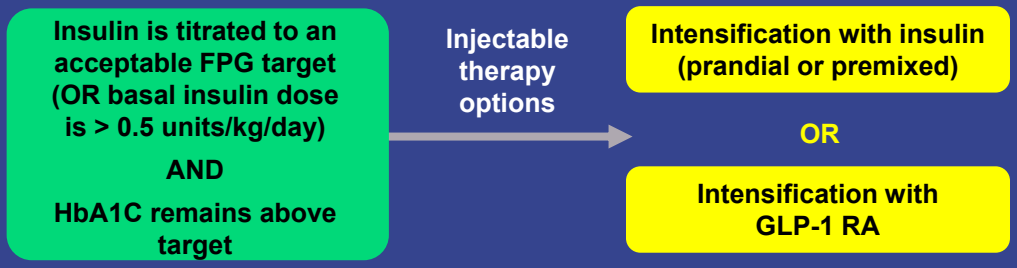
Aggressive Basal Dose Titration May Increase Severe Hypoglycemia Without Improving HbA1C



24-week randomized study, N = 4,824.

Tanenberg RJ, et al. *Diabetologia*. 2006;55:A135.

When to Consider Combination Injectable Therapy for T2DM Patients Using Basal Insulin



ADA. *Diabetes Care*. 2017;40:S64-74.

Basal Insulin and GLP-1 RAs: Benefits

- GLP-1 RAs increase insulin secretion in a glucose-dependent manner, suppress glucagon secretion, and delay gastric emptying through their activation of the GLP-1 receptor
- GLP-1 RA therapies effectively control glycemia and are not associated with weight gain or hypoglycemia
- Improvements in cardiovascular markers including blood pressure, triglycerides, and low-density lipoprotein cholesterol are also associated with GLP-1 RA therapy

Balena R, et al. *Diabetes Obes Metab*. 2013;15:485-502.

Benefits of Adding a GLP-1 RA to Basal Insulin vs Adding Prandial Insulin

Insulin is titrated to an acceptable FPG target (OR basal insulin dose is > 0.5 units/kg/day)

AND

HbA1C remains above target

Injectable therapy options

Intensification with insulin (prandial or premixed)

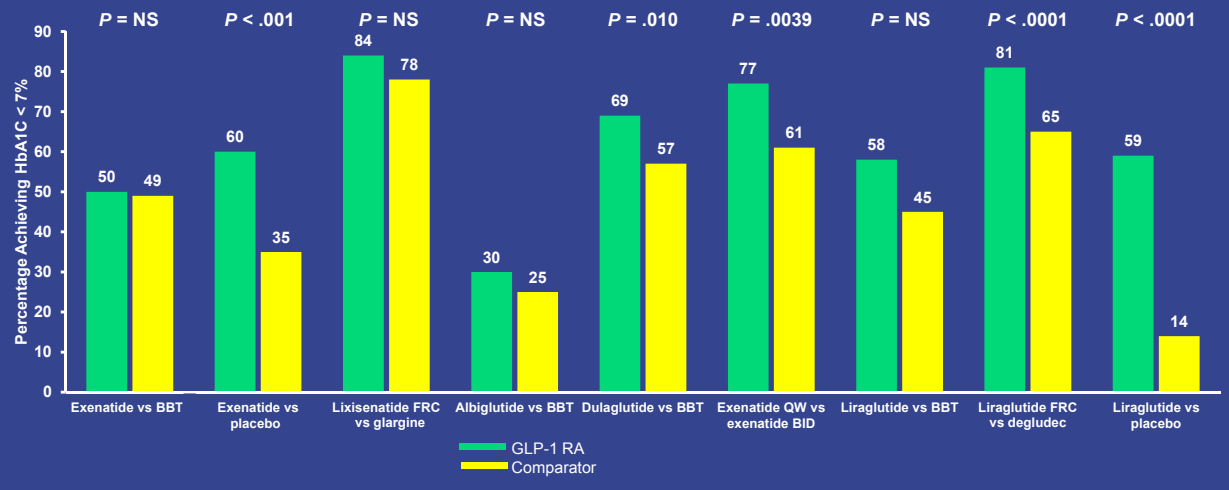
- More injections
- Increased risk of hypoglycemia
- Increased body weight
- Increased SMBG

Intensification with GLP-1 RA

- Fewer injections
- Complementary pharmacologic profile to insulin, especially with short-acting agents
- Lower risk of hypoglycemia (vs insulin)
- Decreased body weight
- Less SMBG (vs insulin)
- Large postprandial benefit, especially with short-acting agents

ADA. *Diabetes Care*. 2017;40:S64-74; Ahluwalia R, et al. *Diabetes Ther*. 2011;2:146-61; Inzucchi SE, et al. *Diabetes Care*. 2012;35:1364-79; Carris NW, et al. *Drugs*. 2014;74:2141-52.

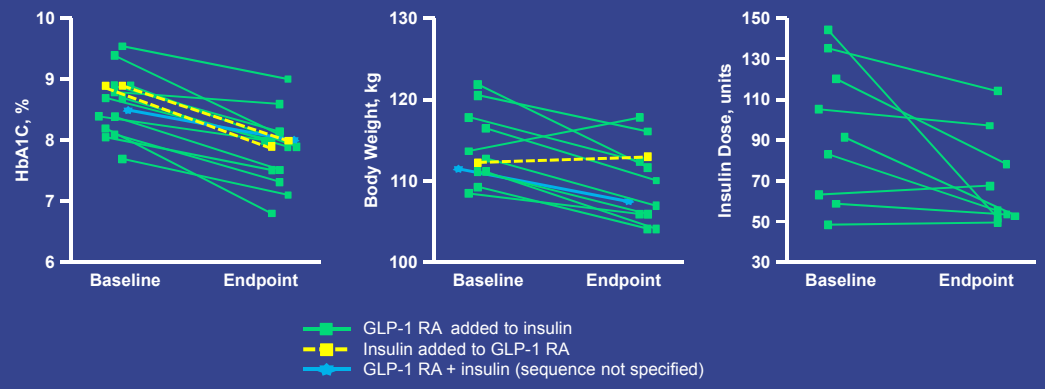
GLP-1 RAs Improve Glycemic Control in Patients With T2DM



Diamant M, et al. *Diabetes Care*. 2014;37:2763-73; Mathieu C, et al. *Diabetes Obes Metab.* 2014;16:636-44; Gough SC, et al. *Lancet Diabetes Endocrinol.* 2014;2:885-93; Rosenstock J, et al. *Diabetologia*. 2014;57:abstr 241; Blonde L, et al. *Lancet*. 2015;385:2057-66; Buse JB, et al. *Ann Intern Med.* 2011;154:103-12; Ahmann A, et al. *Diab Obes Metab*. 2015;17:1056-64; Drucker DJ, et al. *Lancet*. 2008;372:1240-50; Rosenstock J, et al. *Diabetes Care*. 2014;37:2317-25.

GLP-1 RAs Improve Glycemia and Are Associated With Weight Loss and Reduced Insulin Dose

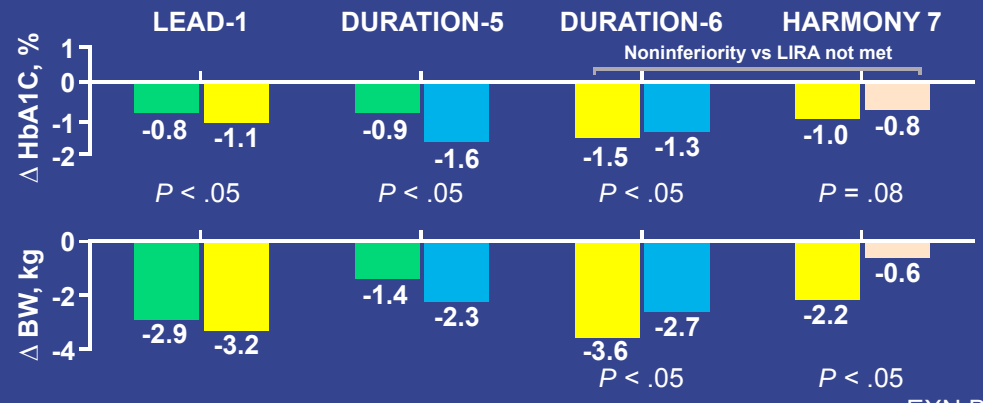
- 7 RCTs and 15 clinical practice or observational studies including ≥ 30 patients with T2DM



Each line represents a study.

Balena R, et al. *Diabetes Obes Metab*. 2013;15:485-502.

Head-to-Head Trials of GLP-1 RAs: Efficacy and Weight

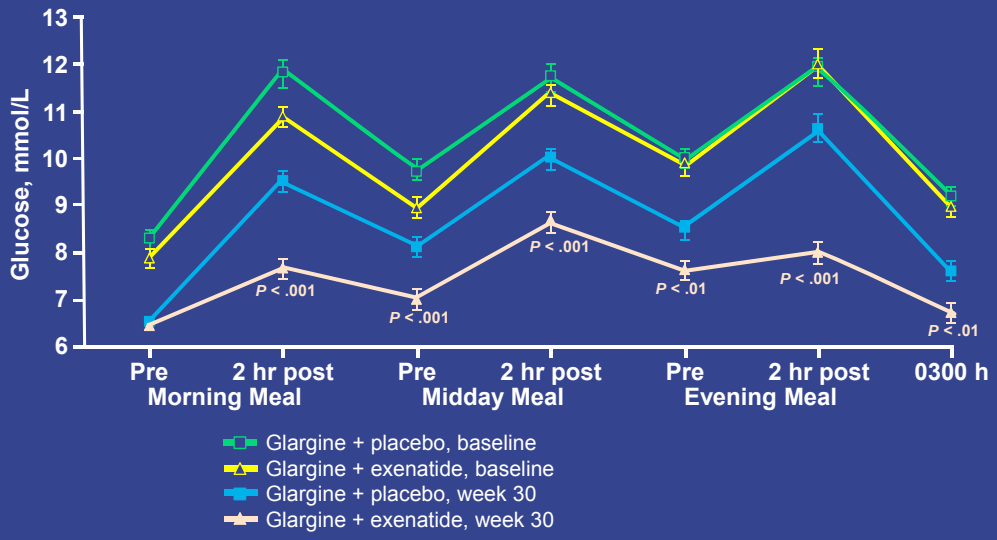


- Occurrence of GI adverse effects is generally lower with longer-acting agents (LIRA and EXN QW vs EXN BID[a]; EXN QW and ALBI vs LIRA)
- Injection-site reactions are more common with EXN QW and ALBI

[a]Nausea rates initially similar for LIRA vs EXN BID, but rates were lower with LIRA (8%) vs EXN BID (16%) by week 6.

Buse JB, et al. *Lancet*. 2009;374:39-47; Blevins T, et al. *J Clin Endocrinol Metab*. 2011;96:1301-10; Buse JB, et al. *Lancet*. 2013;381:117-24; Pratley R, et al. *Lancet Diabetes Endocrinol*. 2014;2:289-97.

GLP-1 RAs Significantly Lower PPG Levels



Balena R, et al. *Diabetes Obes Metab.* 2013;15:485-502.

Polling Question 3:

GLP-1 RA Selection

In your practice, what is your GLP-1 RA dosing frequency preference?

a. I prefer to prescribe a GLP-1 RA that is taken once daily
b. I prefer to prescribe a GLP-1 RA that is taken once weekly
c. I prefer to prescribe a GLP-1 RA that is taken twice daily
d. N/A, I have no preference

Choosing the Appropriate GLP-1 RA to Achieve Patient Treatment Goals

- GLP-1 RA biomedical factors
  - Targeting of FPG vs PPG
  - Duration of action
  - Body weight reduction
  - Severity of side effects
- Patient psychosocial factors
  - Comfort with injections
  - Frequency of contact with healthcare provider
  - Meal pattern
  - Adherence

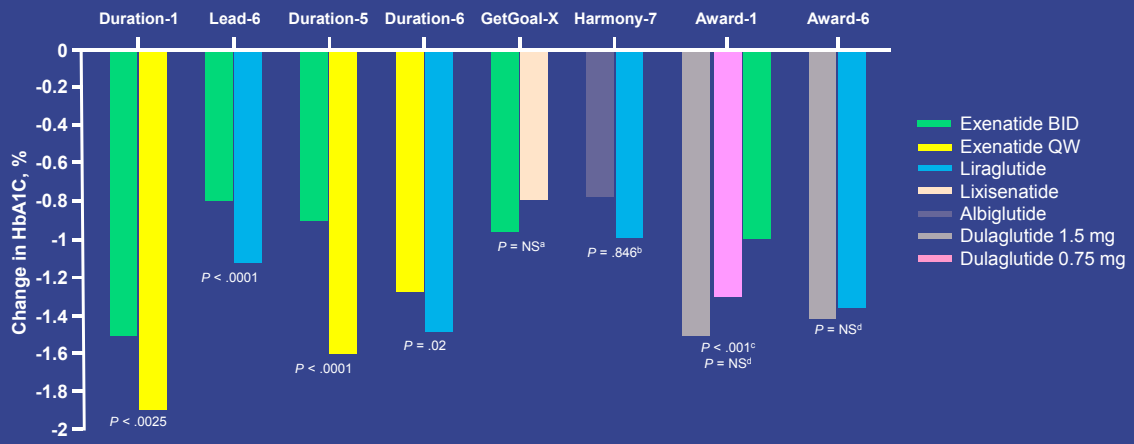
Kalra S. *Diabetes Ther*. 2014;5:333-40.

Comparison of Short-Acting vs Long-Acting GLP-1 RAs

	Short-Acting GLP-1 RAs		Long-Acting GLP-1 RAs			
	Exenatide	Lixisenatide	Albiglutide	Dulaglutide	Exenatide-ER	Liraglutide
Half-life	2.4 hours	2-4 hours	6-7 days	5 days	2 weeks	13 hours
Dosing	Twice daily	Once daily	Once weekly	Once weekly	Once weekly	Once daily
Control of HbA1C	Effective					
Control of FPG	Suitable		**More suitable**			
Control of PPG	**More suitable**		Suitable			
Body weight reduction	1-5 kg		**2-5 kg**			
Directly observed therapy	Not feasible		**Feasible**			
Injection-site reactions	**Rare**		Common; seldom for liraglutide			
GI symptoms	More common		**Less common**			
Increase in pulse rate	**Less common**		More common			

Kalra S. *Diabetes Ther*. 2014;5:333-40; Pinelli NR, et al. *Ann Pharmacother*. 2011;45:850-60; ADA. *Diabetes Care*. 2017;40:S64-74; Anderson SL, et al. *Ther Adv Chronic Dis*. 2016;7:4-17; Murphy CE. *Ann Pharmacother*. 2012;46:812-21; Meier JJ. *Nat Rev Endocrinol*. 2012;8:728-42.

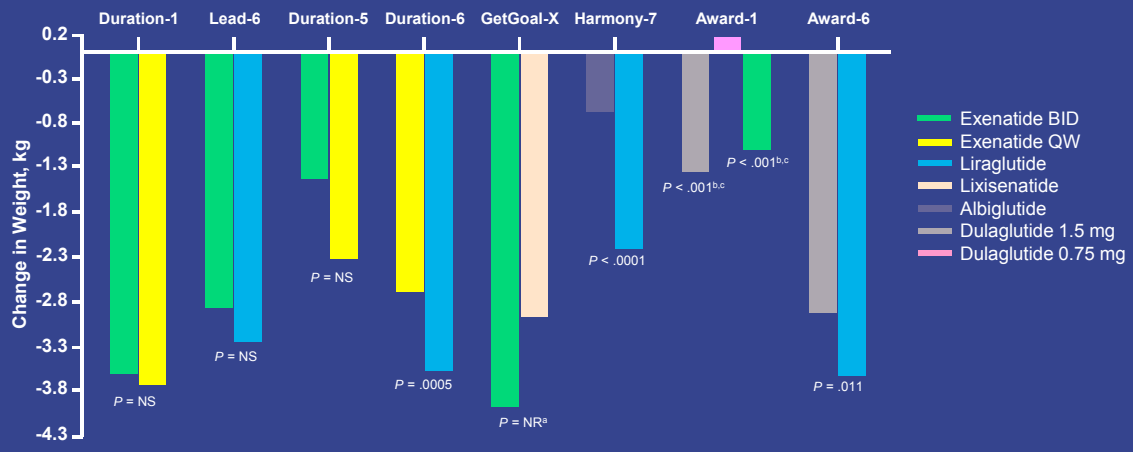
Changes in HbA1C Values in Head-to-Head GLP-1 RA Clinical Trials



P values are for statistical superiority unless otherwise noted as noninferiority.
[a]Noninferiority *P* value not reported (95% CI, 0.033-0.297, meeting predefined noninferiority margin).
[b]Noninferiority *P* value (not meeting predefined noninferiority margin).
[c]*P* value for both doses of dulaglutide vs exenatide BID.
[d]Noninferiority *P* value < .0001 (meeting predefined noninferiority margin).

Trujillo JM, et al. *Ther Adv Endocrinol Metabl*. 2015;6:19-28.

Changes in Weight in Head-to-Head GLP-1 RA Clinical Trials



P values are for statistical superiority unless otherwise noted as noninferiority.
[a]*P* value not reported for weight difference of 1.02 kg (95% CI, 0.456-1.581).
[b]*P* value vs dulaglutide 0.75 mg.
[c]*P* value not significant between dulaglutide 1.5 mg vs exenatide BID.

Trujillo JM, et al. *Ther Adv Endocrinol Metabl*. 2015;6:19-28.

FDA-Approved Basal Insulin/GLP-1 RA FRCs

- Two FRCs currently available
  - Insulin degludec/liraglutide
  - Insulin glargine/lixisenatide
- Benefits
  - Better efficacy than either component given alone
  - Improved FPG and PPG levels
  - Lower rates of hypoglycemia and weight gain vs insulin monotherapy
  - Slow uptitration reduces GI effects vs GLP-1 RA alone
  - Simplified regimen may increase patient adherence
- Limitations
  - Nausea remains problematic
  - Dose titration is required

Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-35; Aroda VR, et al. *Diabetes Care*. 2016;39:1972-80; Gough S, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-9; Buse JB, et al. *Diabetes Care*. 2014;37:2926-33.

Insulin Degludec/Liraglutide Phase 3 Clinical Trials

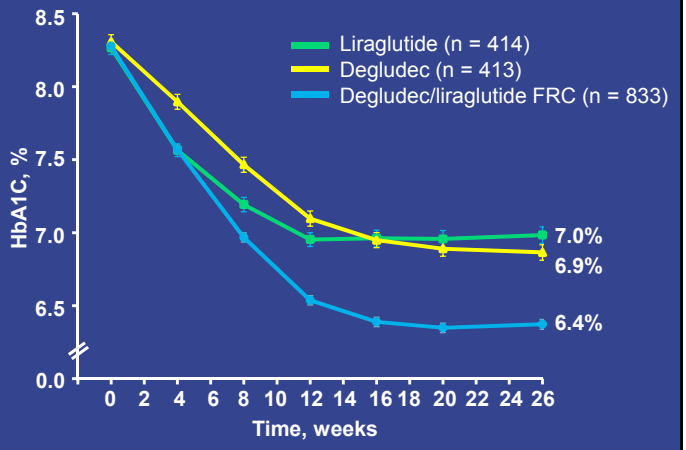
Trial Number	Dual I 3697 (pivotal)	Dual II 3912 (pivotal)	Dual III 3851	Dual IV 3951	Dual V 3952
Objective	IDegLira vs IDeg vs lira (3-arm factorial study)	IDegLira vs IDeg with dose cap	IDegLira vs GLP-1 RA alone	IDegLira vs placebo	IDegLira vs insulin glargine
HbA1C entry criteria	7%-10%	7.5%-10%	7%-9%	7%-9%	7%-10%
Blinding	Open	Blind	Open	Blind	Open
Control	Active (IDeg and lira)	Active (IDeg)	Active (exenatide and lira)	Placebo	Active (glargine)
Duration	26 weeks + **26-week extension**	26 weeks	26 weeks	26 weeks	26 weeks
Background therapy	MET ± PIO	MET	MET ± SU ± PIO	MET ± SU	MET
Randomization ratio	2:1:1 (IDegLira:IDeg:lira)	1:1	2:1	2:1	1:1
Population	Add on to OAD **Insulin naïve**	Previous insulin users	Previous GLP-1 analog users	Add on to OAD **Insulin naïve**	Previous insulin users
Hypothesis test	Noninferiority to IDeg and superiority to lira	Superiority	Superiority	Superiority	Noninferiority

IDeg = insulin degludec; IDegLira = insulin degludec and liraglutide; lira = liraglutide.
MET ≥ 1,500 mg/day or maximum tolerated dose; PIO ≥ 30 mg/day; SU at 1/2 max of approved dose.

Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-93; Buse JB, et al. *Diabetes Care*. 2014;37:2926-33; Linjawi S, et al. *Diabetes Ther*. 2017;8:101-14; Rodbard HW, et al. *Diabet Med*. 2017;34:189-96; Lingvay I, et al. *JAMA*. 2016;315:898-907; Gough SC, et al. *Diabetes Obes Metab*. 2015;17:965-73.

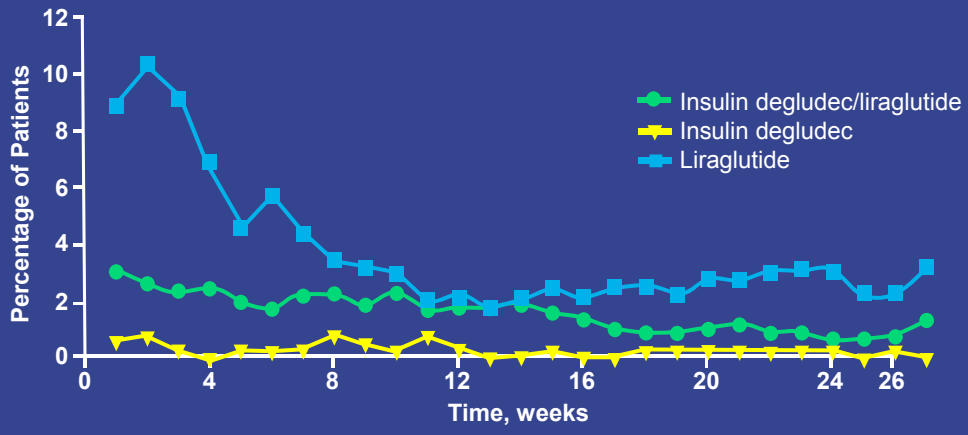
DUAL I: Insulin Degludec/Liraglutide vs Degludec vs Liraglutide

- Degludec/liraglutide FRC significantly reduces HbA1C and body weight vs degludec and liraglutide given alone (all $P < .0001$)
- Rates of hypoglycemia lower with degludec/liraglutide FRC vs degludec alone



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

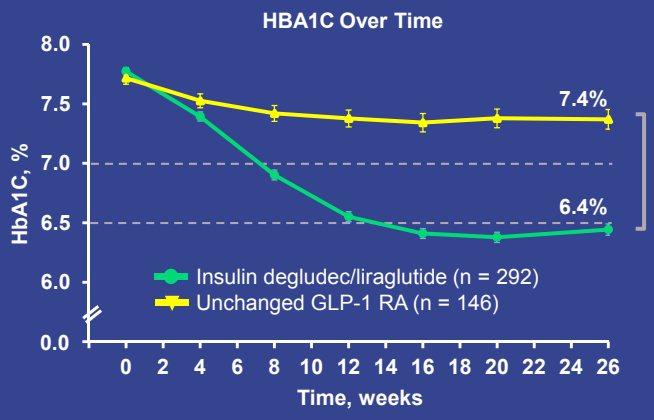
DUAL I: Rates of Nausea Over Time



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

DUAL III: Insulin Degludec/Liraglutide vs Unchanged GLP-1 RA

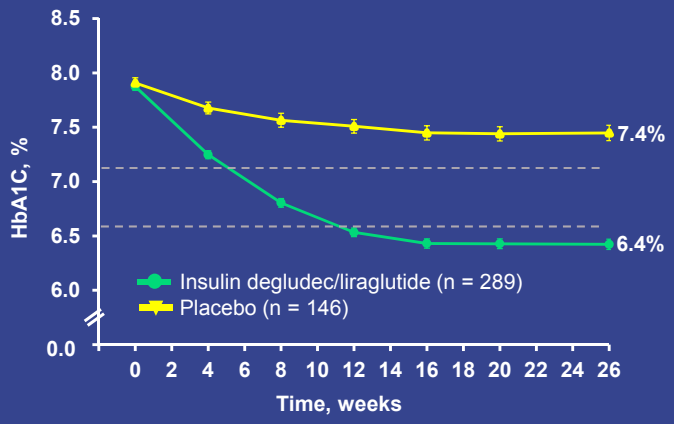
- Degludec/liraglutide FRC significantly reduces HbA1C vs unchanged GLP-1 RA (*P* < .001)
- FRC associated with significant increase in weight vs GLP-1 RA (*P* < .001)



Linjawi S, et al. *Diabetes Ther*. 2017;8:101-14.

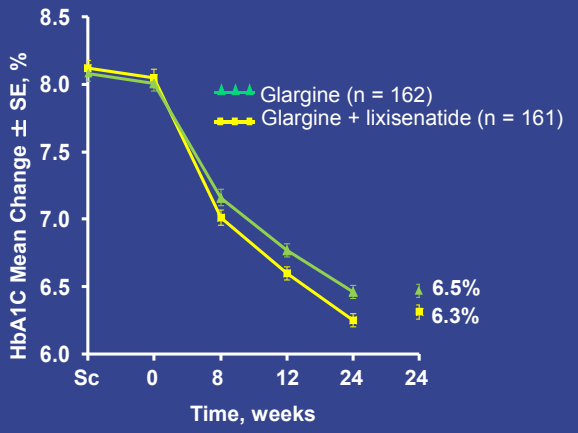
DUAL IV: Insulin Degludec/Liraglutide vs Placebo

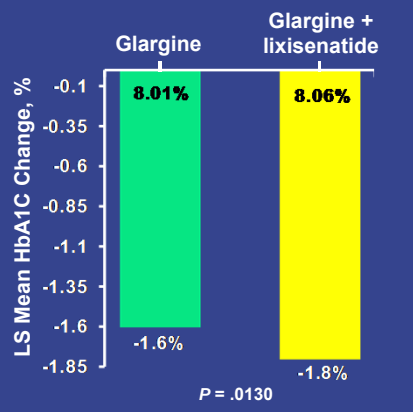
- Degludec/liraglutide FRC significantly reduces HbA1C over time vs placebo (treatment difference, 1.02%; *P* < .0001)
- Greater reduction in mean 9-point SMBG profile with FRC vs placebo (treatment difference, 1.55 mmol/L; *P* < .001)



Rodbard HW, et al. *Diabet Med.* 2017;34:189-96.

Insulin Glargine/Lixisenatide vs Glargine

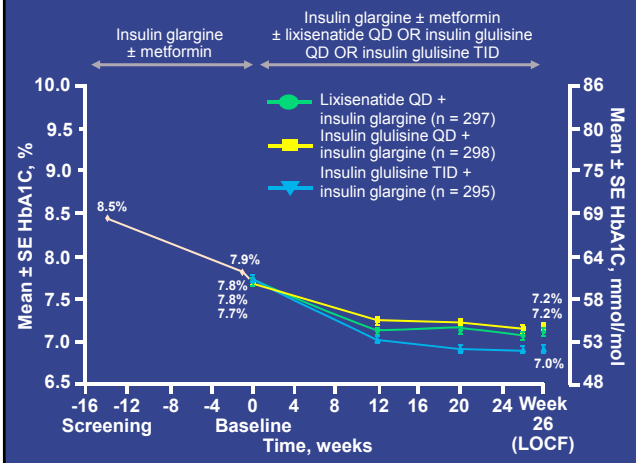


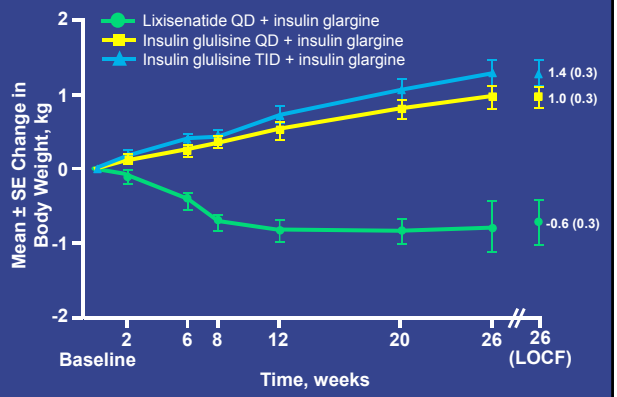


LS mean difference glargine/lixisenatide vs glargine = -0.17% (95% CI, -0.312 to -0.037)

Rosenstock J, et al. EASD 2014. Vienna, Austria. Abstract 241.

Get Goal Duo-2: Lixisenatide Plus Basal Insulin vs Insulin Glulisine (Basal-Plus or Basal-Bolus)

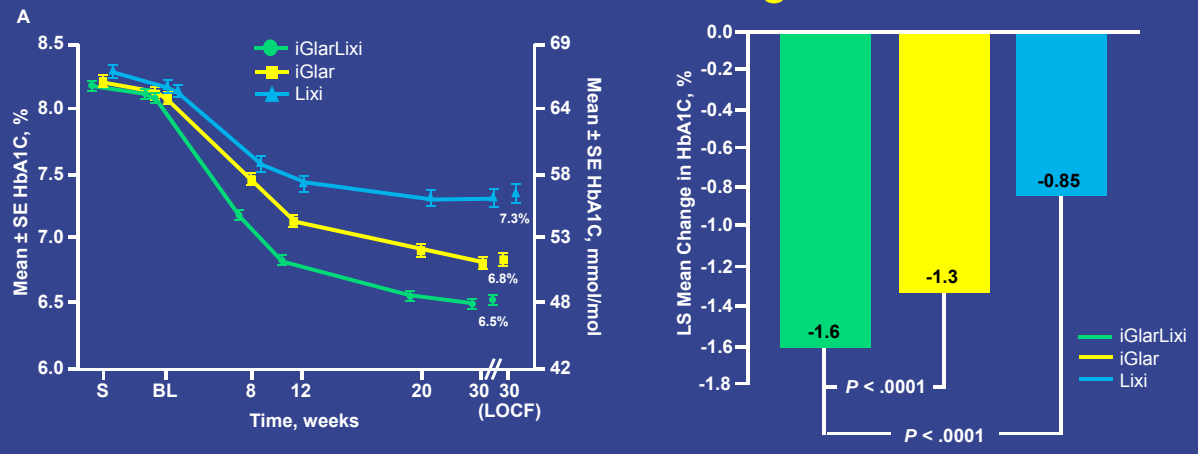




- Patients receiving lixisenatide were twice as likely to achieve HbA1C < 7% without weight gain or documented symptomatic hypoglycemia

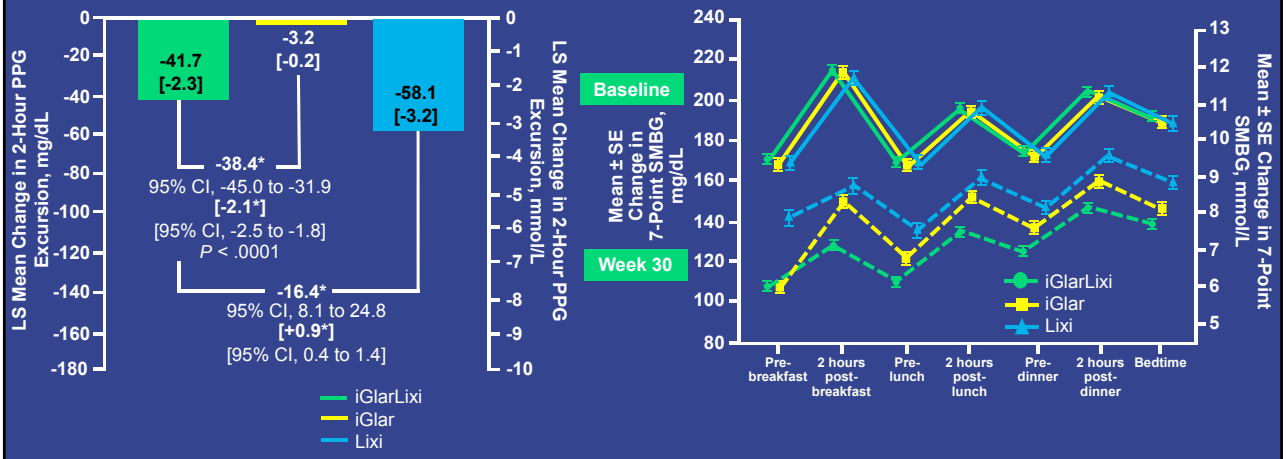
Rosenstock J, et al. *Diabetes Care*. 2016;39:1318-28.

Insulin Glargine/Lixisenatide vs Lixisenatide vs Glargine



Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-35.

Insulin Glargine/Lixisenatide vs Lixisenatide vs Glargine



Rosenstock J, et al. *Diabetes Care*. 2016;39:2026-35.

Basal Insulin/GLP-1 RA FRCs

- Insulin degludec/liraglutide 100/3.6
  - 1 dose step = 1 unit of insulin degludec + 0.036 mg of liraglutide
  - 16 dose steps = 16 units of degludec + 0.6 mg of liraglutide
  - 32 dose steps = 32 units of degludec + 1.2 mg of liraglutide
  - 50 dose steps = 50 units of degludec + 1.8 mg of liraglutide
- Insulin glargine/lixisenatide 100/33
  - 15 units of insulin glargine + 5 mcg lixisenatide
  - 30 units of glargine + 10 mcg lixisenatide
  - 60 units of glargine + 20 mcg of lixisenatide

Prescribing information for individual agents.

Basal Insulin/GLP-1 RA FRCs: Dosing and Titration

Product	Starting Dose	Dose Range	Titration
Insulin degludec/ liraglutide 100/3.6	16 units/0.58 mg	Lowest dose: 10 units/0.36 mg Max dose: 50 units/1.8 mg	**Every 3 to 4 days** Above target: + 2 units Within target: 0 units Below target: -2 units
Insulin glargine/ lixisenatide 100/33	15 units/5 mcg (if < 30 units basal insulin or lixisenatide) 30 units/10 mcg (if 30-60 units basal insulin)	Lowest dose: 15 units/5 mcg Max dose: 60 units/20 mcg	**Weekly** Above target: + 2 units Within target: 0 units Below target: -2 units

Prescribing information for individual agents.

Safety Considerations: GLP-1 RAs

	Albiglutide	Dulaglutide	Exenatide BID	Exenatide QW	Liraglutide	Lixisenatide
Thyroid C-cell tumors in preclinical studies; do not use if personal or family history of MTC or MEN2	X	X		X	X	
Prior severe hypersensitivity to agent	X	X	X	X		X
Discontinue if pancreatitis is suspected	X	X	X	X	X	X
Not recommended for patients with preexisting or severe GI disease	X	X	X	X		
Use caution in patients with renal impairment	X	X	X (Not recommended in patients with severe renal impairment [CrCl < 30 mL/min])	X (Not recommended in patients with severe renal impairment [CrCl < 30 mL/min])	X	X (Not recommended in patients with end-stage renal disease [eGFR < 15 mL/min])
Adverse events: GI (nausea, diarrhea, vomiting), injection-site irritation	X	X	X	X	X	X

Prescribing information for individual agents.

Conclusions

- Basal insulin and GLP-1 RAs have different and complementary mechanisms of action that result in the improvement of both FPG and PPG control
- Clinical trials demonstrate the efficacy of a basal insulin/GLP-1 RA combination in the management of T2DM
- FRCs allow greater ease of use of a basal insulin/GLP-1 RA combination in one injection
- Addressing patient concerns about injections and discussing the efficacy of combination insulin and GLP-1 RA therapy can help mitigate barriers to injectable treatment for T2DM

Question/Answer Session With Faculty

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Contact Information

Call (toll-free) 866 858 7434
E-mail info@med-iq.com

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Abbreviations and Acronyms

AACE = American Association of Clinical Endocrinologists
ADA = American Diabetes Association
AGi = alpha-glucosidase inhibitor
BBT = basal insulin glargine, bolus insulin lispro, and metformin therapy
BG = blood glucose
BID = twice daily
BW = body weight
CrCl = creatinine clearance
DDP4-i = dipeptidyl-peptidase 4 inhibitor
eGFR = estimated glomerular filtration rate
ER = extended release
FDA = Food and Drug Administration
FPG = fasting plasma glucose
FRC = fixed-ratio combination
fxs = fractures
GI = gastrointestinal
GLP-1 = glucagon-like peptide-1
GUI = genitourinary infections
HbA1C = hemoglobin A1C
HF = heart failure
HOMA = homeostasis model assessment
IGT = impaired glucose tolerance
LOCF = last observation carried forward
LS = least squares
MEN2 = multiple endocrine neoplasia type 2
MET = metformin
MTC = medullary thyroid carcinoma
OAD = oral antidiabetic drug
PIO = pioglitazone
PPG = postprandial glucose
QD = daily
QOL = quality of life
QW = once weekly
RA = receptor agonist
RCT = randomized controlled trial
SE = standard error
SGLT2-i = sodium-glucose cotransporter 2 inhibitor
SMBG = self-monitoring of blood glucose
SMPG = self-monitoring of plasma glucose
SU = sulfonylurea
T2DM = type 2 diabetes mellitus
TID = three times daily
TZD = thiazolidinedione
UKPDS = United Kingdom Prospective Diabetes Study
US = United States