Activity Overview

In this audiocast, expert faculty focus on the discordance between the historic "treat-to-failure" or stepwise model and a more intensive management approach. They also explore the clinical evidence regarding the earlier use of GLP-1 receptor agonists with and without insulin therapy in patients with type 2 diabetes mellitus.

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Learning Objective

Upon completion, participants should be able to:

- Describe the benefits of earlier treatment intensification with injectable combination therapies versus the traditional stepwise approach to T2DM management

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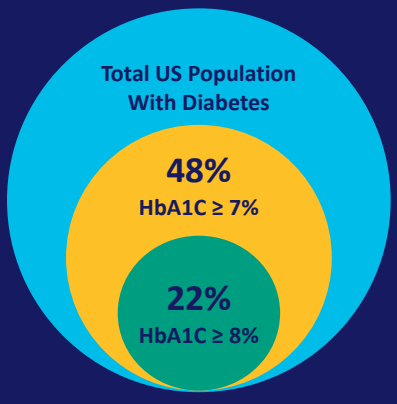
The Importance of Glycemic Control Across the Spectrum of the Disease

- Early and sustained glycemic control is critical
  - Observational data show that it is associated with delayed disease progression through preservation of beta-cell function and reduction in peripheral insulin resistance
  - Data also show that it is associated with reductions in diabetes-related complications and mortality (legacy effect)
    - Decreased rates of microvascular and neuropathic complications
    - Risk reduction for cardiovascular disease and cardiovascular events (MI, CVA)

Cefalu WT, et al. *Diabetes Care*. 2016;39:S1-110;
Wong J, et al. *Aust Fam Physician*. 2015;44:278-83; Hanefeld M, et al. *Diabetes Ther*. 2016;7:187-201.

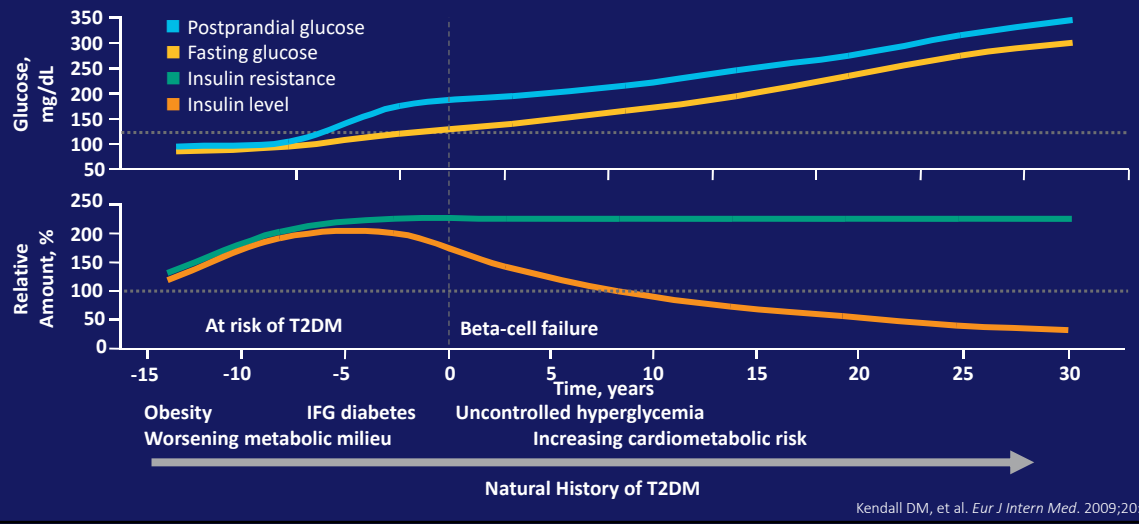
HbA1C Levels in Patients With Diabetes in the US

- Glycemic control is suboptimal despite advances in therapy
- As T2DM progresses, maintaining glycemic control becomes more difficult
- More-intensive treatment is usually required over time to meet therapeutic targets



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; Zafar A, et al. *Prim Care Diabetes*. 2010;4:203-7.

T2DM Is a Complex, Metabolic, Progressive Disease



Kendall DM, et al. *Eur J Intern Med*. 2009;20:S329-39.

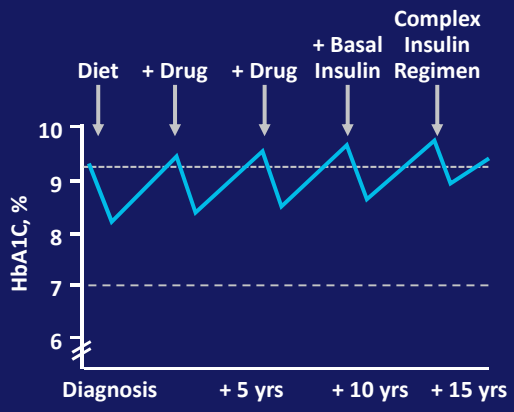
Mechanisms Affecting Beta-Cell Function

- The major clinical factors for progressive loss of beta-cell function and mass are:
  - Glucotoxicity—leads to beta-cell damage due to prolonged exposure to elevated transient or chronic physiologic glucose concentrations
  - Lipotoxicity—increased circulating FFAs and changes in lipoprotein profile impair insulin secretion
  - Incretins—abnormalities in the incretin axis result in progressive beta-cell failure, deficiency of GLP-1, and resistance to action of GIP
  - Leptin and proinflammatory cytokines (adipocyte-secreted cytokines and hormones)
  - Islet cell amyloid
  - Linkage of reduced beta-cell mass and dysfunction

Wajchenberg BL. *Endocr Rev*. 2007;28:187-218.

Models of Pharmacologic Management: Stepwise or "Treat-to-Failure" Model

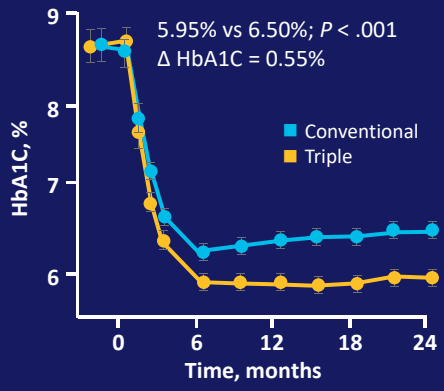
- "One-size-fits-all" model of treatment
- Based on algorithmic approach with the stepwise addition of antihyperglycemic agents over time
- Involves adding or titrating agents when HbA1C targets are not achieved or maintained
- Generally, patients do not achieve durable glycemic control, and underlying pathophysiology of the disease is not adequately addressed



Campbell IW. *Br J Cardiol*. 2000;7:625-31;
Stolar MW. *Mayo Clin Proc*. 2010;85:S50-9; Phillips LS, et al. *Diabetes Care*. 2014;37:2668-76.

"Treat-to-Success" Model Allows for Sustained HbA1C Lowering

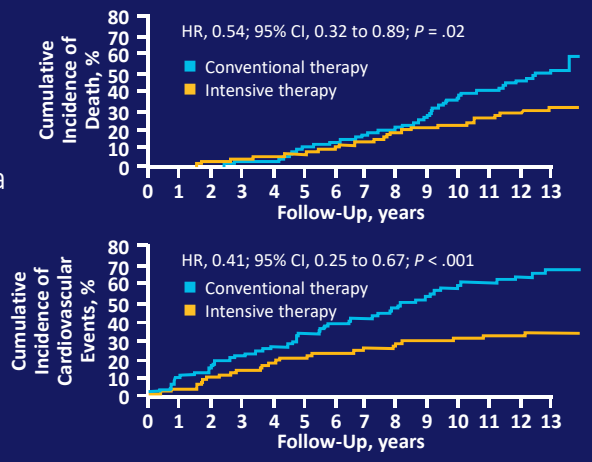
- Treatment-naïve patients with T2DM were randomized to receive intensive triple therapy (metformin/pioglitazone/exenatide) or conventional therapy (escalating dose of metformin followed by sequential addition of sulfonylurea and glargine insulin)
- Patients receiving intensive therapy achieved an HbA1C < 6.0% and maintained levels for 2 years
- Patients receiving intensive therapy also demonstrated:
  - 7.5-fold lower rate of hypoglycemia
  - 1.2-kg mean weight loss (vs 4.1-kg weight gain; $P < .01$)



Abdul-Ghani MA, et al. *Diabetes Obes Metab*. 2015;17:268-75.

Intensive Therapy Associated With Lower Risk of Cardiovascular Causes and Events

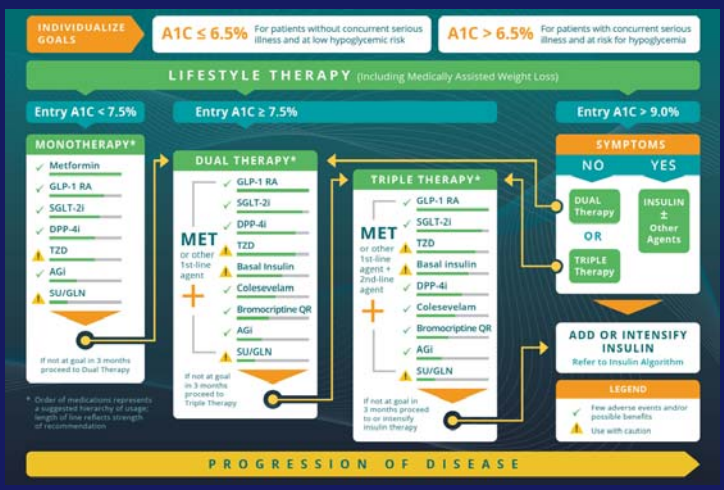
- Patients with T2DM and persistent microalbuminuria were randomized to receive either intensive therapy or conventional therapy
- Intensive therapy was associated with a lower risk of death from cardiovascular causes and cardiovascular events
- Fewer patients receiving intensive therapy required retinal photocoagulation (relative risk, 0.45; 95% CI, 0.23 to 0.86; *P* = .02)



Gaede P, et al. *N Engl J Med*. 2008;358:580-91.

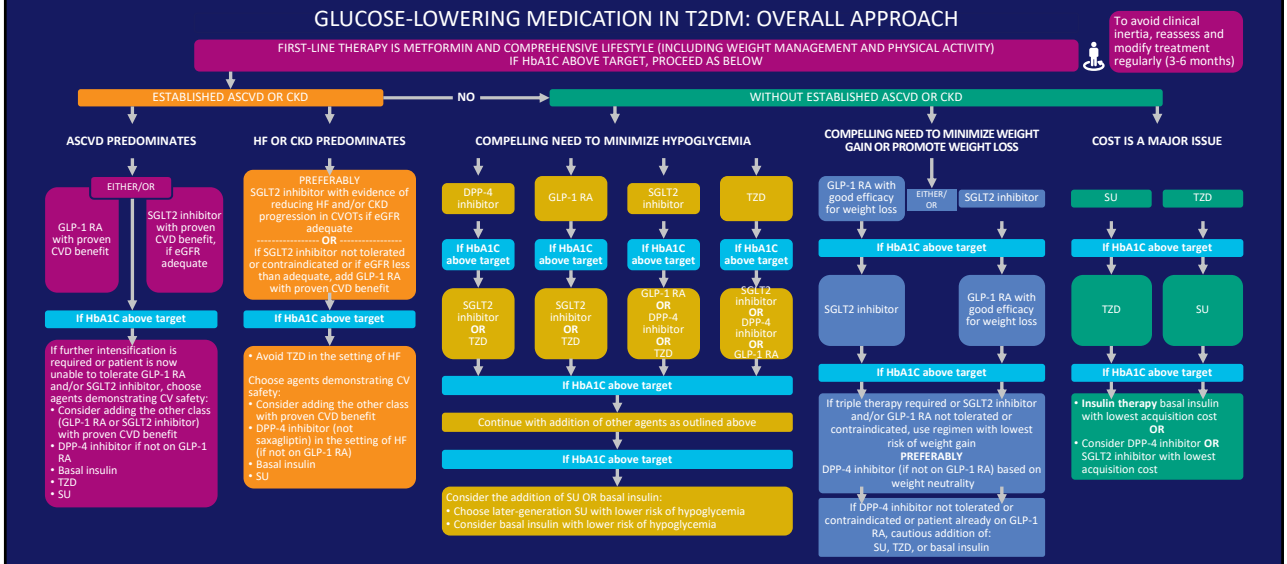
AACE 2018: Standards of Medical Care in Diabetes

- GLP-1 RA—at the top of the "suggested hierarchy of usage" in combination with metformin



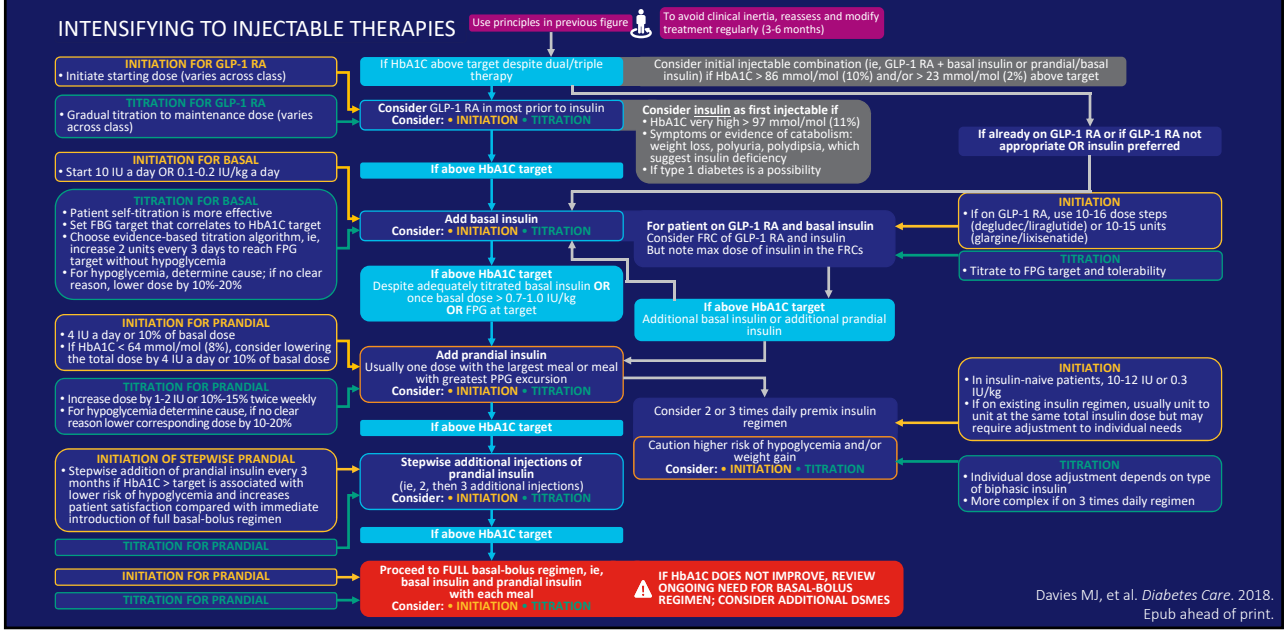
Garber AJ, et al. *Endocr Pract*. 2018;24:91-120.

ADA-EASD 2018 Guideline Recommendations



Davies MJ, et al. *Diabetes Care*. 2018. Epub ahead of print.

ADA-EASD 2018 Guideline Recommendations



Davies MJ, et al. *Diabetes Care*. 2018. Epub ahead of print.

Factors to Consider When Choosing Treatment Intensification

- Would there be a delay in deterioration of glycemic control? Better durability? Better beta-cell function over time? Does this approach address the pathophysiology better?
- Does it allow for assessing individual response?
- Are the costs appropriate? Would this approach result in cost savings and reduction in complications over time?
- Is the risk-to-benefit ratio acceptable?
- Would it improve unmet clinical needs (eg, weight gain, hypoglycemia)?
- Would adherence/compliance be an issue?

Cahn A, et al. *Diabetes Care*. 2016;39:S137-45.

Pharmacologic Profile of Basal Insulins

Basal Insulin Classification	Insulin Preparation	Onset (h)	Peak (h)	Variability (CV%)	Duration (h)	Timing of Administration
Intermediate acting	NPH	1-3	4-6	68	12-16	Usually twice daily
Long acting	Detemir	0.5-2	Flat, some peak at 7-14	~27	~20	Once or twice daily
	Glargine	0.5-2	Flat, some peak at 4-12	~32-82	~24	Once daily, same time of day
Ultra long acting	Degludec	ND	Flat, no peak	20	> 24	Once daily, any time of day
	Glargine U300	ND	Flat, no peak	17-35	> 24	Once daily ± 3 h

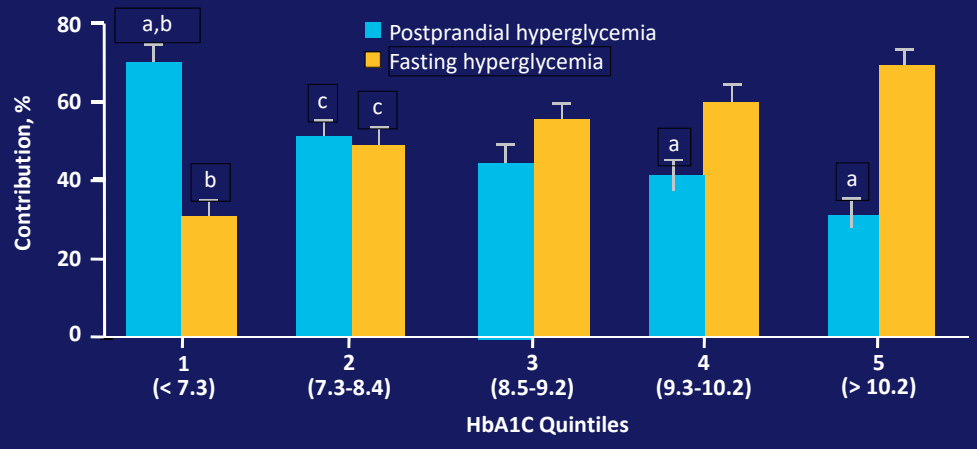
Standl E, et al. *Diabetes Care*. 2016;39:S172-9.

Comparison of Select Basal Insulins

Consideration	NPH	Detemir	Glargine U100	Glargine U300	Degludec
Risk of hypoglycemia	Present	Low	Low	Least	Least
Risk of nocturnal hypoglycemia	Present	Low	Low	Least	Least
Risk of severe hypoglycemia	Present	Low	Low	Least	Least
Weight gain	Present	Low	Low	Low	Low
Use in renal impairment	Dose needs to be adjusted	Safe	Safe	Safe	Safe
Use in hepatic impairment	Dose needs to be adjusted	Safe	Safe	Safe	Safe

Freemantle N, et al. *BMJ Open*. 2016;6:e009421.

Contributions of Fasting and Postprandial Plasma Glucose to HbA1C in Diabetes



[a]Significant difference was observed between fasting and postprandial plasma glucose (paired *t* test).
[b]Significantly different from all other quintiles (ANOVA).
[c]Significantly different from quintile 5 (ANOVA).

Adapted from Monnier L, et al. *Diabetes Care*. 2003;26:881-5.

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

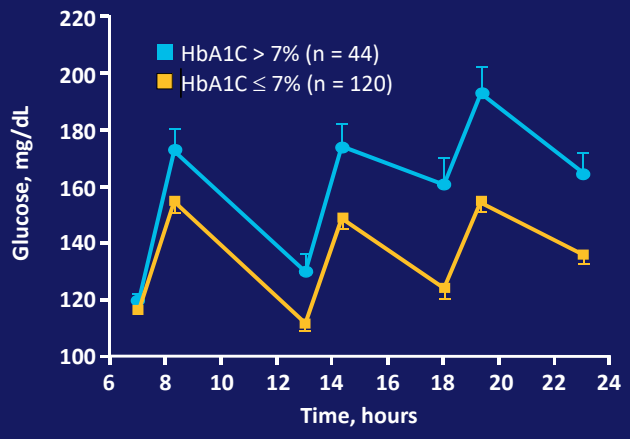
The individual is not meeting glycemic targets on basal insulin and:

- **HbA1C is still not at goal with 0.5 units/kg/day of basal insulin**
- **HbA1C is elevated 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.

Postprandial Glucose Excursions and Glycemic Control

- 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.

Key Efficacy and Safety Data in the Intensification of Basal Insulin Plus Prandial Insulin

	Change from baseline in HbA1C (%)	Change from baseline in PPG (mmol/L)	Change from baseline in FPG (mmol/L)	Change from baseline in body weight (kg)	Hypoglycemia (% of patients)
Data from 8 studies examining the efficacy of "basal-plus" regimens in T2DM	-0.4 to -1.1	-0.8 to -3.9	-0.8	0.5 to 1.8	Symptomatic: 46 to 52 Severe: 0 to 2 Nocturnal: 11 to 22

Darmon P, et al. *Diabetes Metab.* 2015;41:6S21-7.

Considerations for Basal Plus Prandial Insulin

- Prandial insulin:
  - Can be started with largest meal of the day with additional meal injections as indicated (typically up to 3 injections of meal insulin daily)
  - Can be tailored to meet the glycemic needs of each meal
  - Is safe to use with many of the common comorbidities that accompany diabetes
- Stop sulfonylureas and glinides, stop thiazolidinediones due to edema risk, and consider stopping DPP-4 inhibitors
- Risks/considerations:
  - Weight gain
  - Hypoglycemia
  - Cost

Edelman S, et al. *Osteopath Med Prim Care.* 2007;1:9; Darmon P, et al. *Diabetes Metab.* 2015;41:6S21-7.

Considerations for Basal Plus GLP-1 RA

- GLP-1 RA:
  - Can be added to basal insulin twice daily, once daily, or once weekly (soon implantable quarterly)
  - Twice and once daily can be given before meals
  - Once weekly does not have to be timed with meals
- Hypoglycemia risk is lower with GLP-1 RAs than with prandial insulin
- Weight reduction is possible with GLP-1 RAs
- Reduce or stop sulfonylureas to mitigate hypoglycemia, do not use with DPP-4 inhibitors, and reduce basal insulin by ~20% if hypoglycemia is a concern (then re-titrate)
- Risks/considerations:
  - Nausea/vomiting/diarrhea, pancreatitis, acute renal injury
  - Not indicated with history of MTC or MEN2
  - Cost

Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-9;
ADA. *Diabetes Care*. 2018;41:S1-159; Handelsman Y, et al. *Endocr Pract*. 2015;21:1-87; Garber AJ, et al. *Endocr Pract*. 2018;24:91-120.

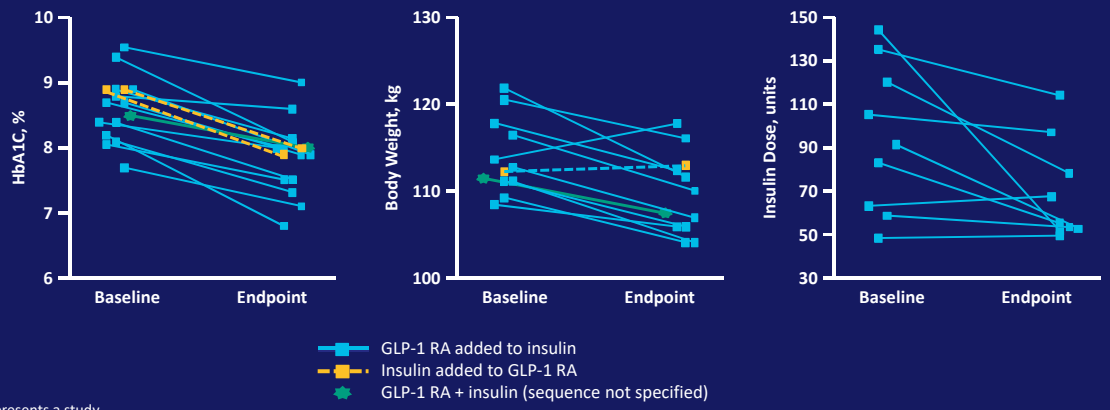
Comparison of Short-Acting vs Long-Acting GLP-1 RAs

	Short-Acting GLP-1 RAs		Long-Acting GLP-1 RAs			
	Exenatide	**Lixisenatide**	**Dulaglutide**	**Exenatide-ER**	**Liraglutide**	**Semaglutide**
Half-life	2.4 hours	2-4 hours	5 days	2 weeks	13 hours	7 days
Dosing	Twice daily	Once daily	Once weekly	Once weekly	Once daily	Once weekly
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;
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; Aroda VR, et al. *Lancet Diabetes Endocrinol*. 2017;5:355-66.

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

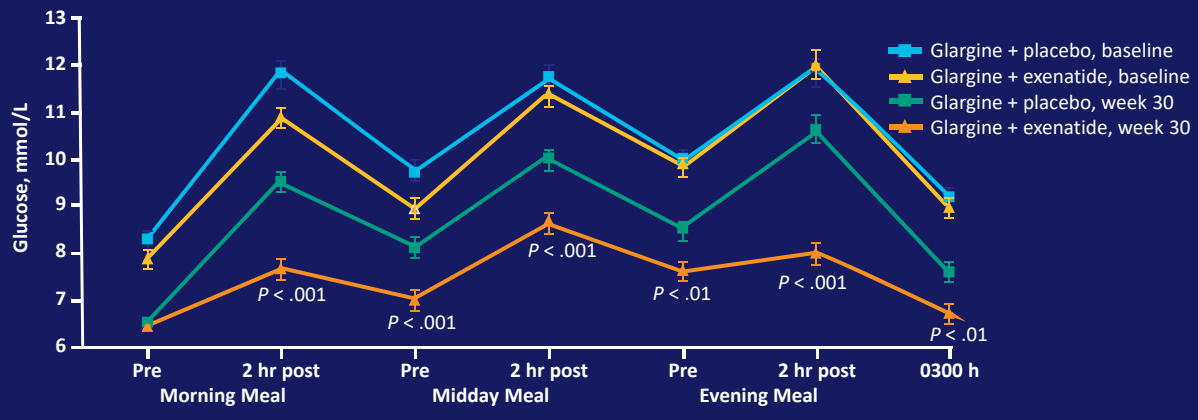
- 7 RCTs and 15 clinical practice or observational studies including ≥ 30 patients with T2DM



Each line represents a study.
GLP-1 RA and insulin delivered in separate injections.

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

GLP-1 RAs Significantly Lower PPG Levels



GLP-1 RA and insulin delivered in separate injections.

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

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
  - Risk 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.

Safety Considerations: GLP-1 RAs

	Dulaglutide	Exenatide BID	Exenatide QW	Liraglutide	Lixisenatide	Semaglutide
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			
Use caution in patients with renal impairment	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])	X
Adverse events: GI (nausea, diarrhea, vomiting), injection-site irritation	X	X	X	X	X	X

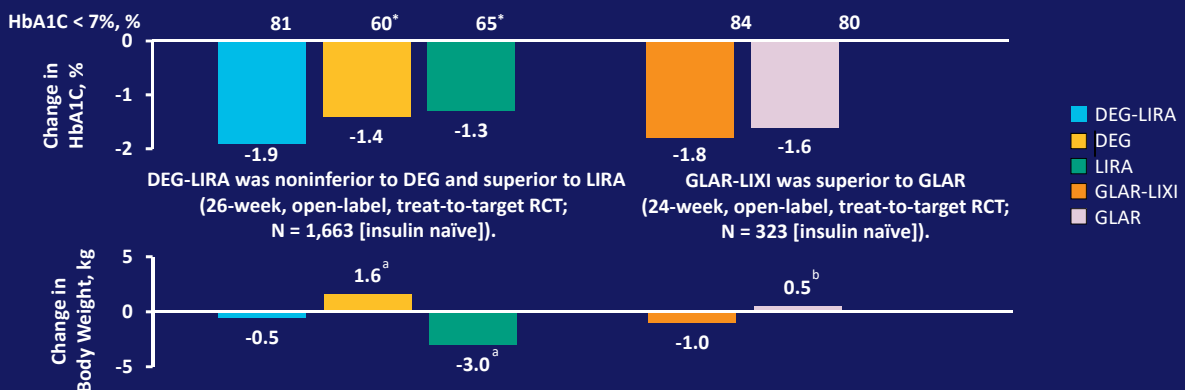
Prescribing information for individual agents.

Basal Insulin/GLP-1 RA Fixed-Ratio Combinations

- Two fixed-ratio combinations 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 up-titration 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.

Basal Insulin/GLP-1 RA Fixed-Ratio Combinations



- ≤ 3 severe hypoglycemic episodes per group
- Lower rate of hypoglycemia for LIRA vs DEG or DEG-LIRA (overall and nocturnal)
- Lower rate of hypoglycemia for GLAR-LIXI than for GLAR (overall)

[a]*P* < .0001 vs DEG-LIRA.
[b]*P* < .0001 vs GLAR-LIXI.

Gough SC, et al. *Lancet Diabetes Endocrinol*. 2014;2:885-93; Rosenstock J, et al. *Diabetes Care*. 2016;39:1579-86.

Basal Insulin/GLP-1 RA Fixed-Ratio Combinations

- Practical considerations
  - A reasonable choice for patients who are on GLP-1 RA or basal insulin but are not at goal
  - Consider for patients when further intensification of therapy is delayed due to concerns regarding weight gain and hypoglycemia
  - Taking both medications in a once-daily formulation may improve adherence vs taking the medications individually
  - Dose range is based on the units of insulin but is limited by the maximum dose of the GLP-1 RA
  - The risks, benefits, and contraindications of the individual medications also apply to the fixed-ratio combinations
  - Insurance coverage remains a challenge for many

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