

# Basal Insulin & Beyond

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# Case

- 66 female, DM-2 for 18 years.
- A1c in the last 2 years between 8.5-9.5%. On MF and Glimepiride 4 mg daily. Basal Insulin started 6 months ago.
- Since Insulin initiation A1c has been 8.7% and 8.4%
- Regimen Include: Lantus 12 units, MF full dose.

Name \_\_\_\_\_  
 DOB \_\_\_\_\_  
 Provider \_\_\_\_\_

Home # \_\_\_\_\_  
 Work # \_\_\_\_\_  
 Cell # \_\_\_\_\_

Fax Log  
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MONTH \_\_\_\_\_

Date	BB	2H	BL	2H	BD	2H
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5	143		157			
6	<del>129</del> 129					
7	160					
8	191					
9	127					
10	159					
11	163					
12	156					
13					150	
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15	218					
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17					158	
18	179					153
19						
20	140 ✓					
21	136 ✓					
22						
23	180 ✓					
24						
25						
26	198				190	
27						
28						
29	168					
30						
31					172	

BB- Before Breakfast

BL- Before Lunch

BD- Before Dinner

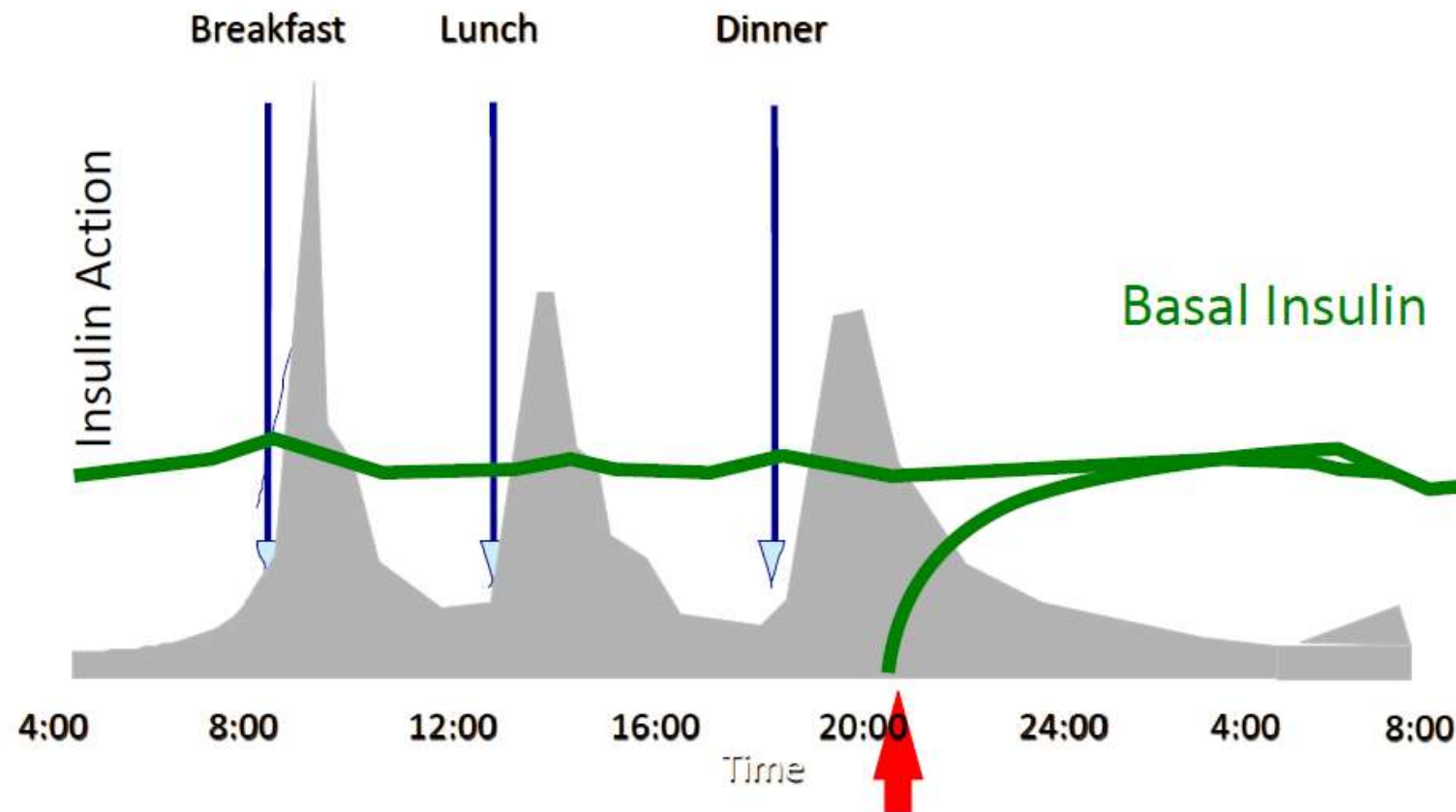
# Options

- Continue to titrate Lantus until AM blood sugars < 130.
- Add a rapid acting insulin before each meal.
- Add a rapid acting Insulin before dinner.
- Add GLP-1 RA once daily.
- Add SGLT-2 inhibitor.
- Add DPP-4 inhibitor.

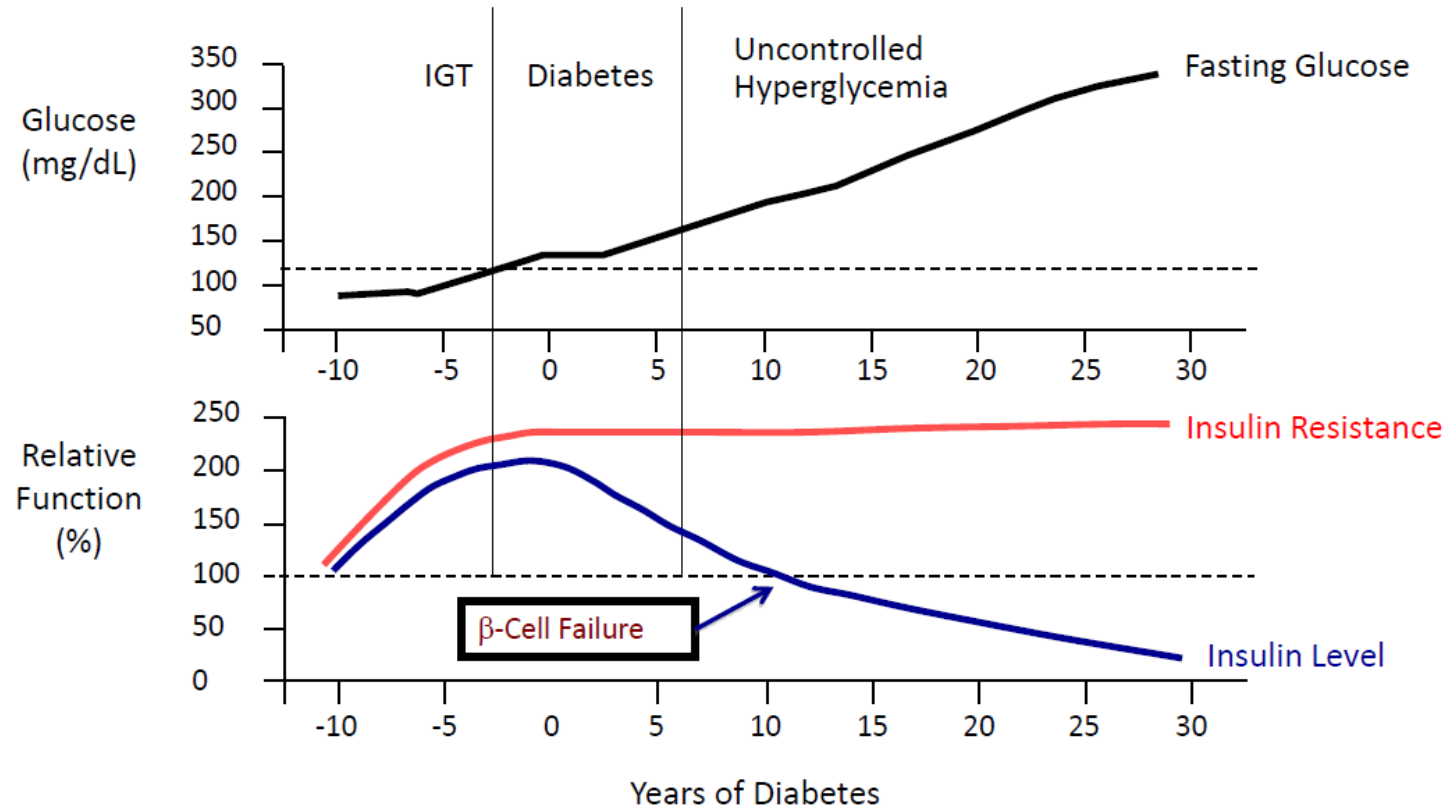
# Titration Basal Insulin.

- AM Blood glucose consistently  $> 130$ -  $140$  increase basal by 2 units.
- Titrate Basal doses periodically to achieve AM targets.
- Ask patient about bedtime lows ( Night sweats, nightmares, waking up hungry)
- Check 3-4 AM blood sugars once a week during titration.

## Risk of Using Only Basal Insulin in Patients with Advanced Insulin Deficiency



# Disease Progression in Type 2 Diabetes (T2DM)



Adapted from: International Diabetes Center (Minneapolis, Minn.)

# Many Patients Fail to Achieve Glycemic Control with Basal Insulin

- Retrospective analysis of 39,074 patients with T2D on basal insulin<sup>1</sup>
  - At 3 months:
    - Only 27% of all basal insulin users achieved A1c < 7%
    - 20% had A1c of ≥ 9%
- Kaiser Permanente study of 1,139 patients started on basal insulin<sup>2</sup>
  - Only 40% reached A1c < 7%
    - More likely in those with baseline A1c < 8.2%

1. Dalal MR, et al. *Diabetes Res Clin Pract.* 2016;121:17-26.

2. Nichols GA, et al. *Diabetes Care.* 2012;35(3):495-497.



# When is it time to intensify basal insulin therapy?

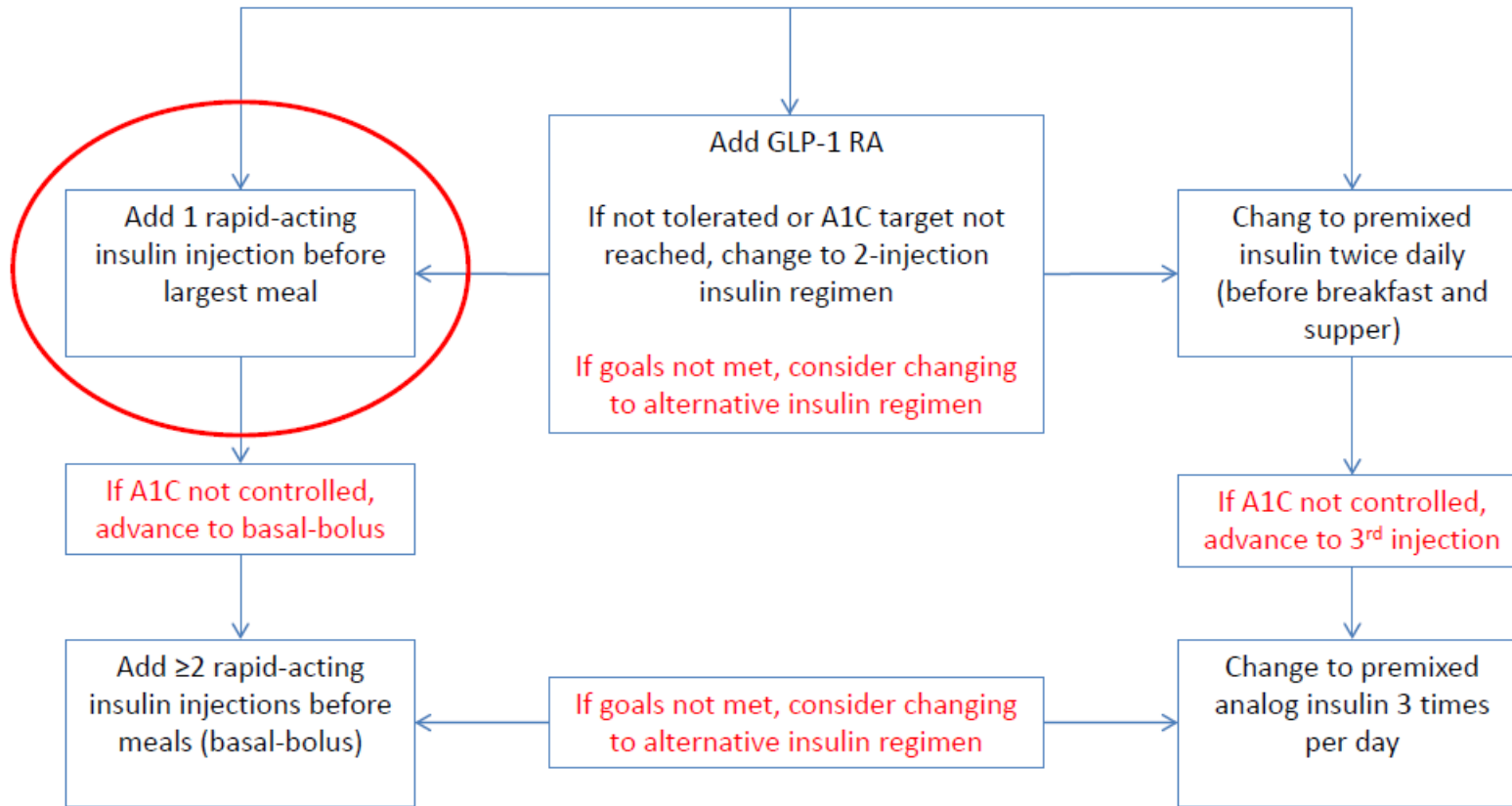
- Meta-analysis of 6 studies of glargine insulin in patients with type 2 diabetes<sup>1</sup>
  - A1c >7% associated with FBG < 130 mg/dl, suggests need for prandial insulin
  - A1c >7% with FBG < 130 mg/dl associated with more severe hypoglycemia
- Consider advancing when basal insulin > 0.5 U/kg/d

1. Shaefer C et al. *Diabetes* 61(Suppl 1) P959, 2012; 2. Hirsch IB, et al. *Endocrin Practice*. 2009;3. 15:343-348. Riddle MC, et al. *JCEM*. 2008;93:272-274.

# Options for Intensification after basal insulin

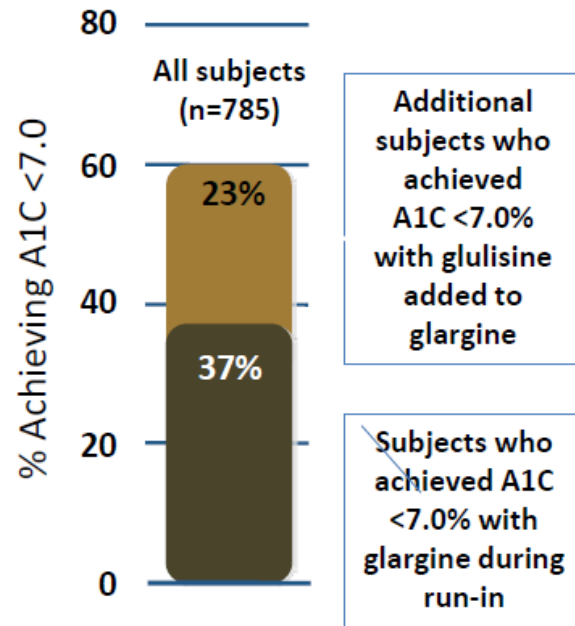
- Metformin
- RA Insulin 1 – 3/day
- Premixed insulin
- DPP-4i
- GLP-1 RA
- SGLT-2i

# Therapeutic Options in Patients Not Achieving Glycemic Goals with Basal Insulin: Consider Combination Injectable Therapy

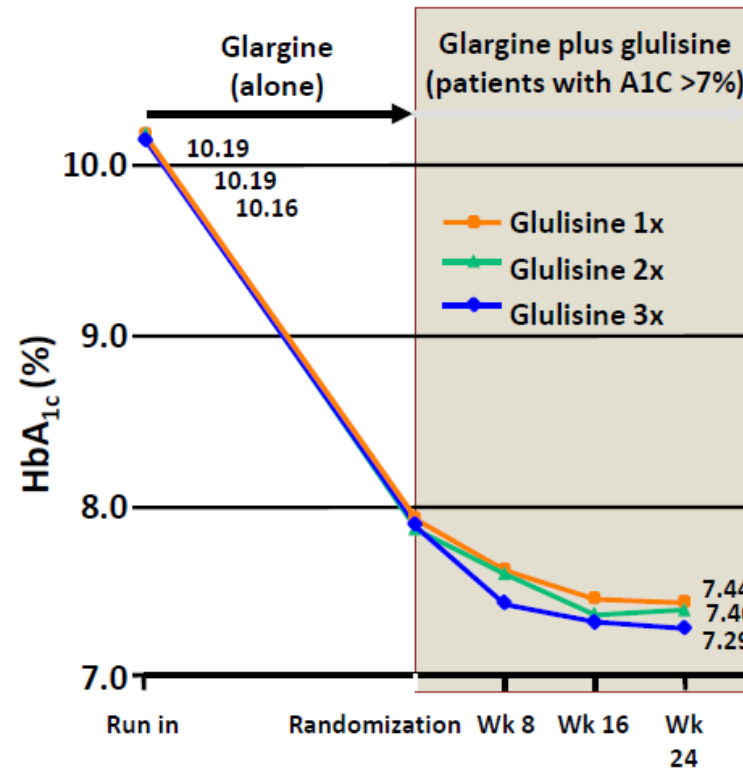


# 1.2.3 Study: Glargine Plus 1, 2, or 3 Doses of Glulisine

Responders in the whole population (n=785)

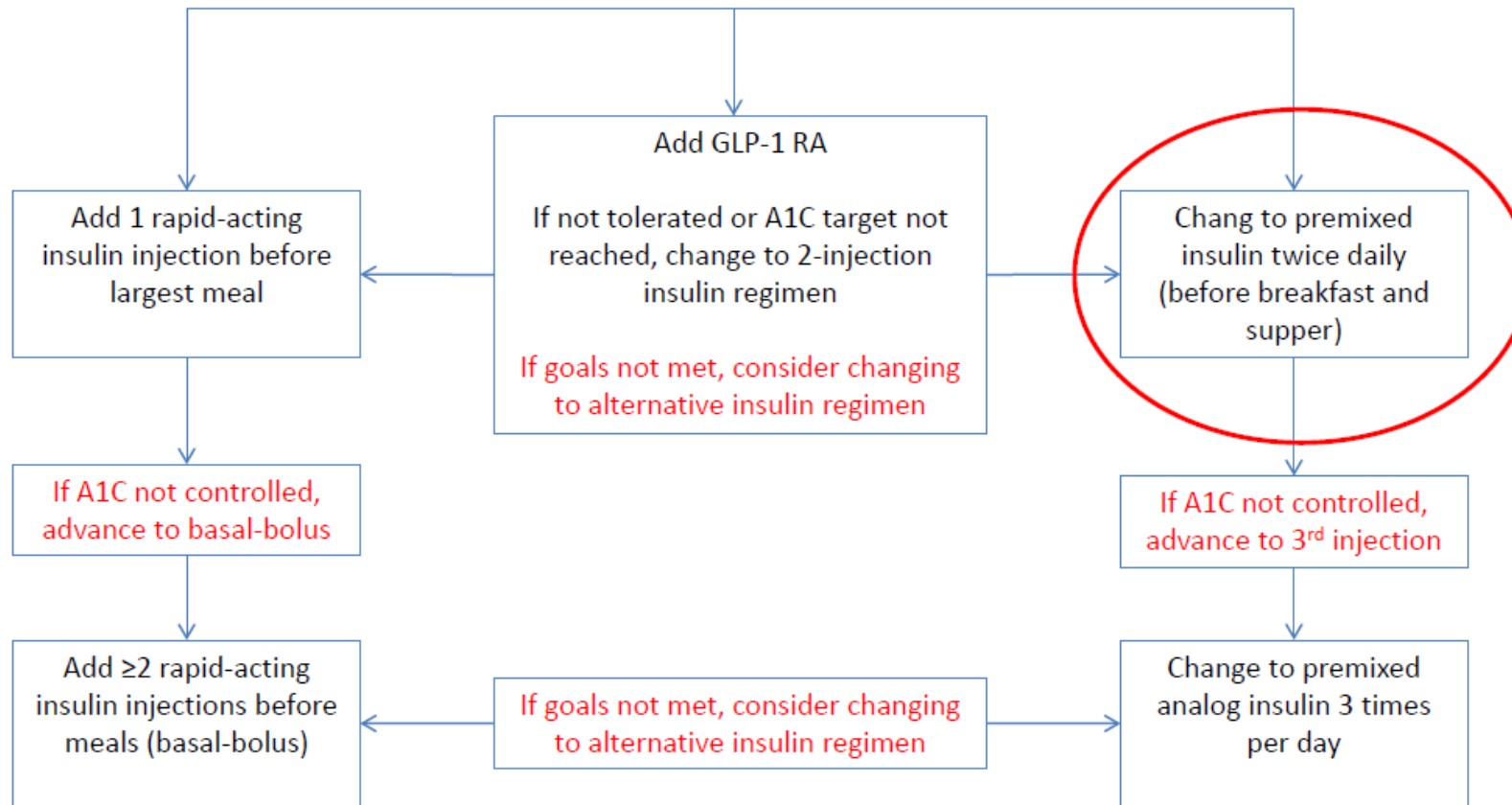


Evolution of A1C in the randomized population (n=343)



A1C in all subjects (n=785) = 9.8 at run-in and 7.3 at randomization

# Therapeutic Options in Patients Not Achieving Glycemic Goals with Basal Insulin: Consider Combination Injectable Therapy



# Initiating and Titrating Prandial Insulin in T2DM: ADA Algorithm<sup>1</sup>

Initial dose	<p>If FBG target is reached or if basal dose &gt;0.5 U/kg/d, initiate prandial analogue before largest meal</p> <p>Initial dosing: 4 U or 0.1 U/kg or 10% of basal dose</p> <p>If A1C &lt;8%, consider reducing basal dose by same amount</p>
Titration	<p>1-2 U or 10%-15% once or twice weekly until SMBG target (eg. 80-130 mg/dL preprandially, &lt;180 mg/dL 2 hours postprandially) is reached</p> <p>Hypoglycemia: determine and address cause; reduce corresponding dose by 2-4 U or 10%-20%</p> <p>Follow same titration for second and third prandial dose, if needed</p>

# Pre-Mixed Insulins

70/30 Insulin (70% N/30% Regular)

Humalog Mix 75/25 (75% NPL/25% Lispro)

Humalog Mix 50/50 (50% NPL/50% Lispro)

Novolog Mix 70/30 (70% NPA/30% Aspart)

Deg/Asp Mix 70/30 (70% Deg/30% Aspart)

▼

**Change to premixed insulin twice daily (before breakfast and supper)**

**Start:** Divide current basal dose into  $\frac{2}{3}$  AM,  $\frac{1}{3}$  PM or  $\frac{1}{2}$  AM,  $\frac{1}{2}$  PM

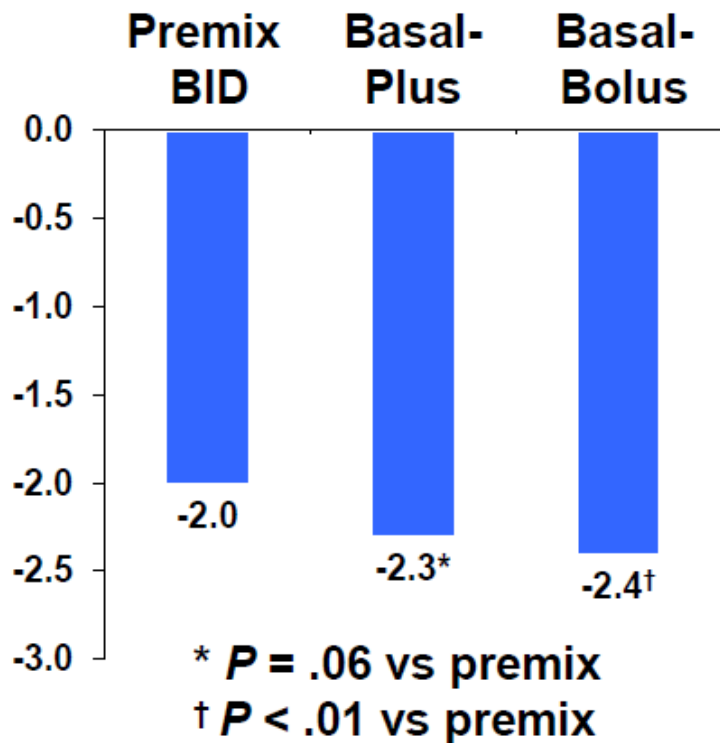
**Adjust:** ↑ dose by 1-2 units or 10-15% once or twice weekly until SMBG target reached

**For hypo:** Determine and address cause; if no clear reason for hypo, ↓ corresponding dose by 2-4 units or 10-20%

↓



# All to Target: Comparing Basal-Bolus, Basal-Plus, and Premixed Analogue Insulin Regimens

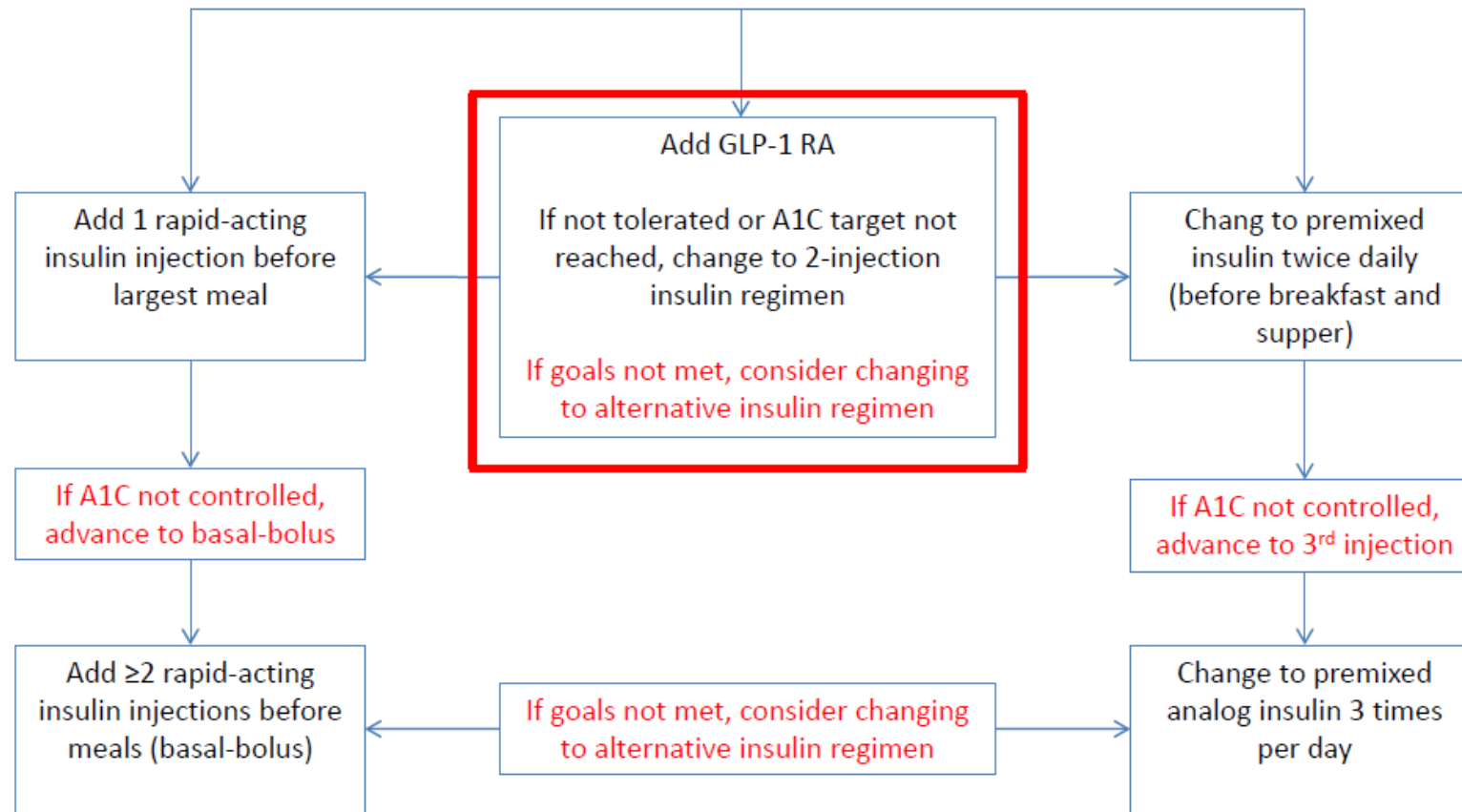


- A1C with basal-bolus vs premix ( $P < .01$ )
- A1C < 7%
  - Basal-plus: 49%
  - Premixed: 39% ( $P < .05$ )
- Hypoglycemia (BG < 50 mg/dL): incidence 30%-35% lower with basal-bolus vs premix ( $P < .01$ )
- Similar insulin doses and weight gain in all groups

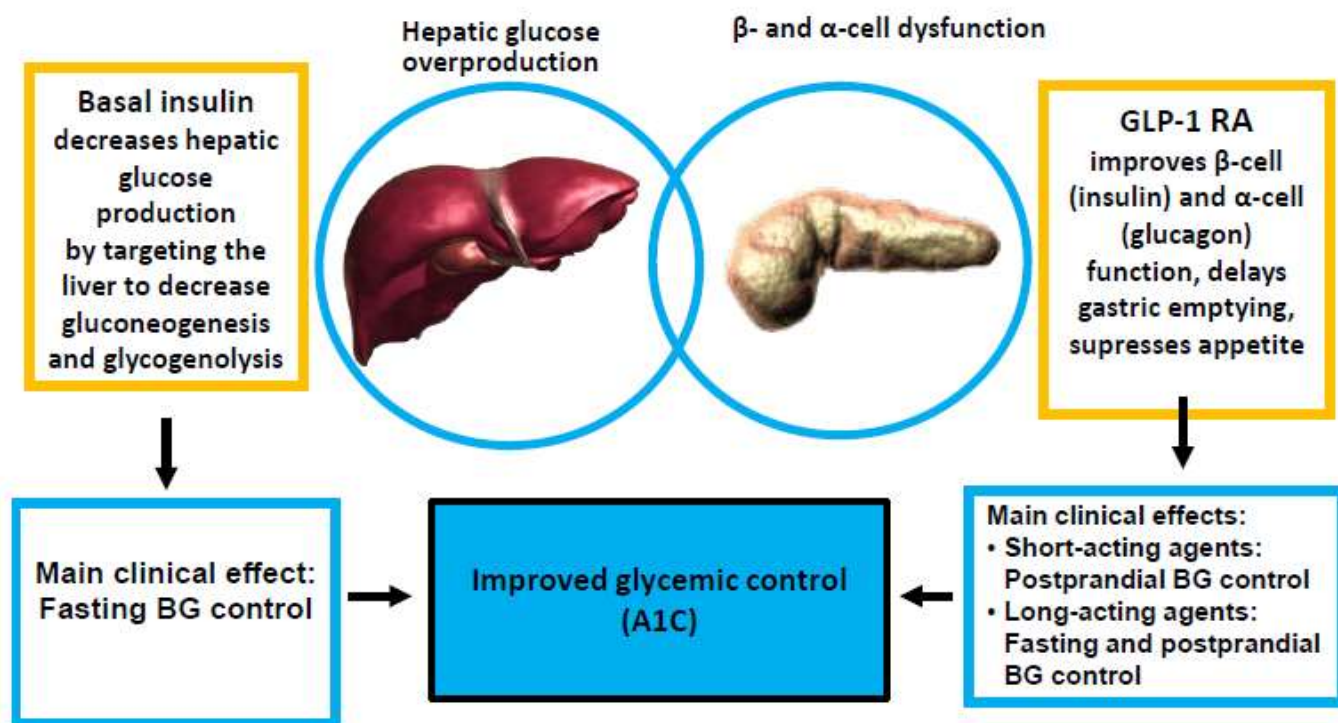
# Intensifying Basal Insulin – Insulin Options

Option	Therapeutic consideration	Weight gain	Hypoglycemia
Basal +	1 additional injection	+	+
Basal bolus	3 additional injections More complex	++	++
Premixed	1 – 2 additional injections Decreased flexibility	++	++

# Therapeutic Options in Patients Not Achieving Glycemic Goals with Basal Insulin: Consider Combination Injectable Therapy

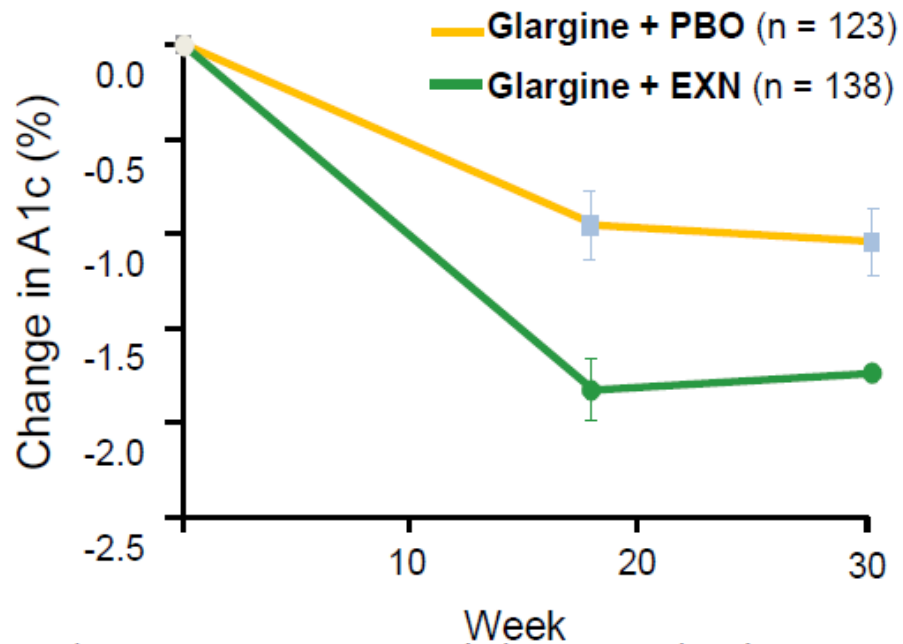


# Complimentary Actions of Basal Insulin and GLP-1 RAs<sup>1-4</sup>



# Exenatide BID Added to Basal Insulin Efficacy and Safety

Adults with T2DM and A1c of 7.1% to 10.5% receiving glargine ± metformin ± pioglitazone were randomized to exenatide (10 mcg twice a day) or placebo for 30 weeks.

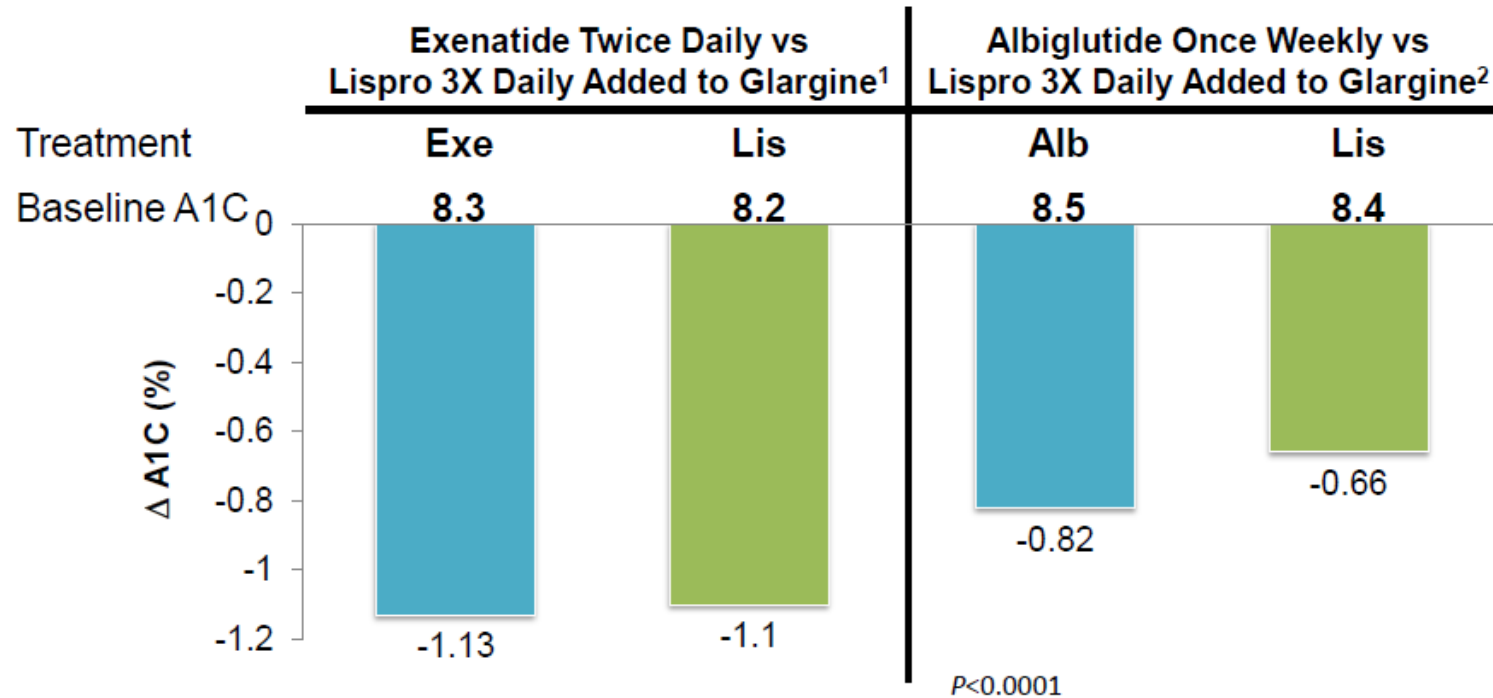


Outcome	PBO	EXN BID	<i>p</i> - Value
Hypoglycemia† (%)	1.2	1.4	0.49
Discontinuation due to adverse events (% of pts)	1	9	<0.01
Δ Weight (kg)	1.0	-1.8	<0.001

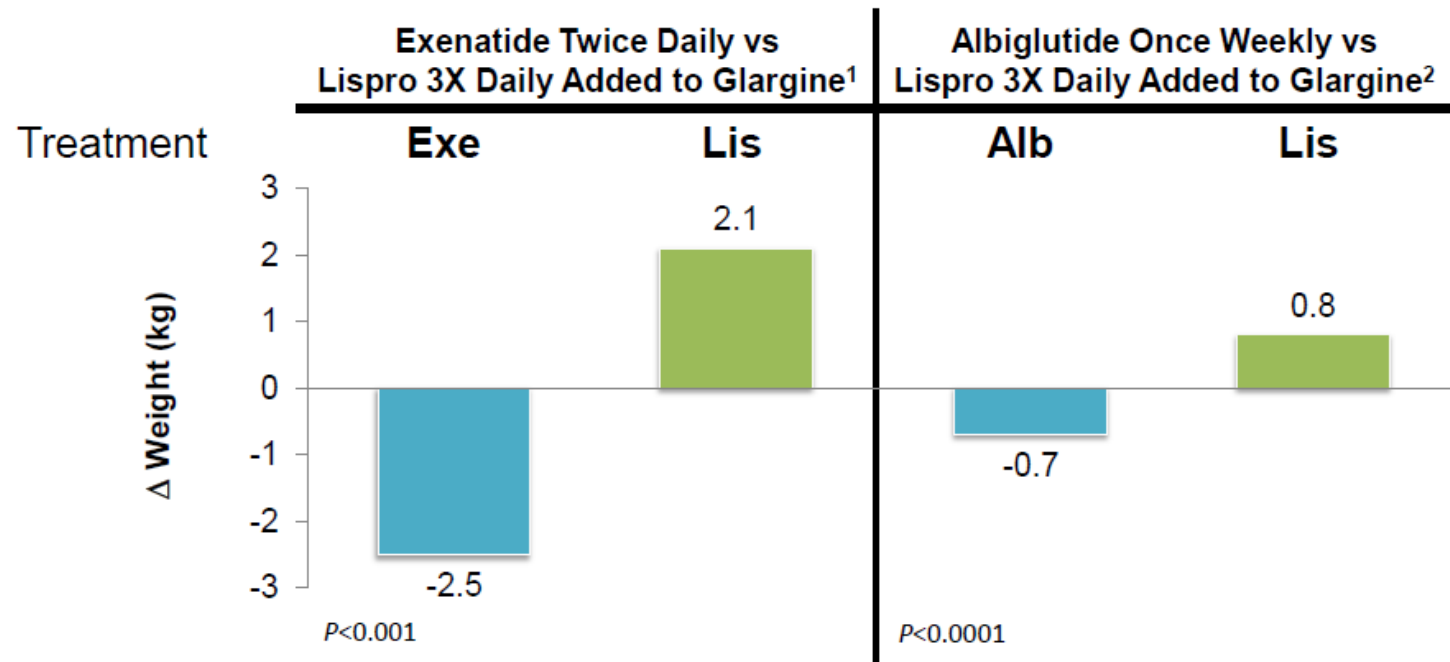
# GLP-1 Receptor Agonists with Basal Insulin

- FDA approved
  - Exenatide BID
  - Liraglutide
  - Dulaglutide
  - Fixed ratio insulin + GLP-1 RA
    - iGlarLixi
    - iDegLira
  - Exenatide QW

# Glucose Control With GLP-1 Receptor Agonists vs Prandial Insulin Added to Basal Insulin

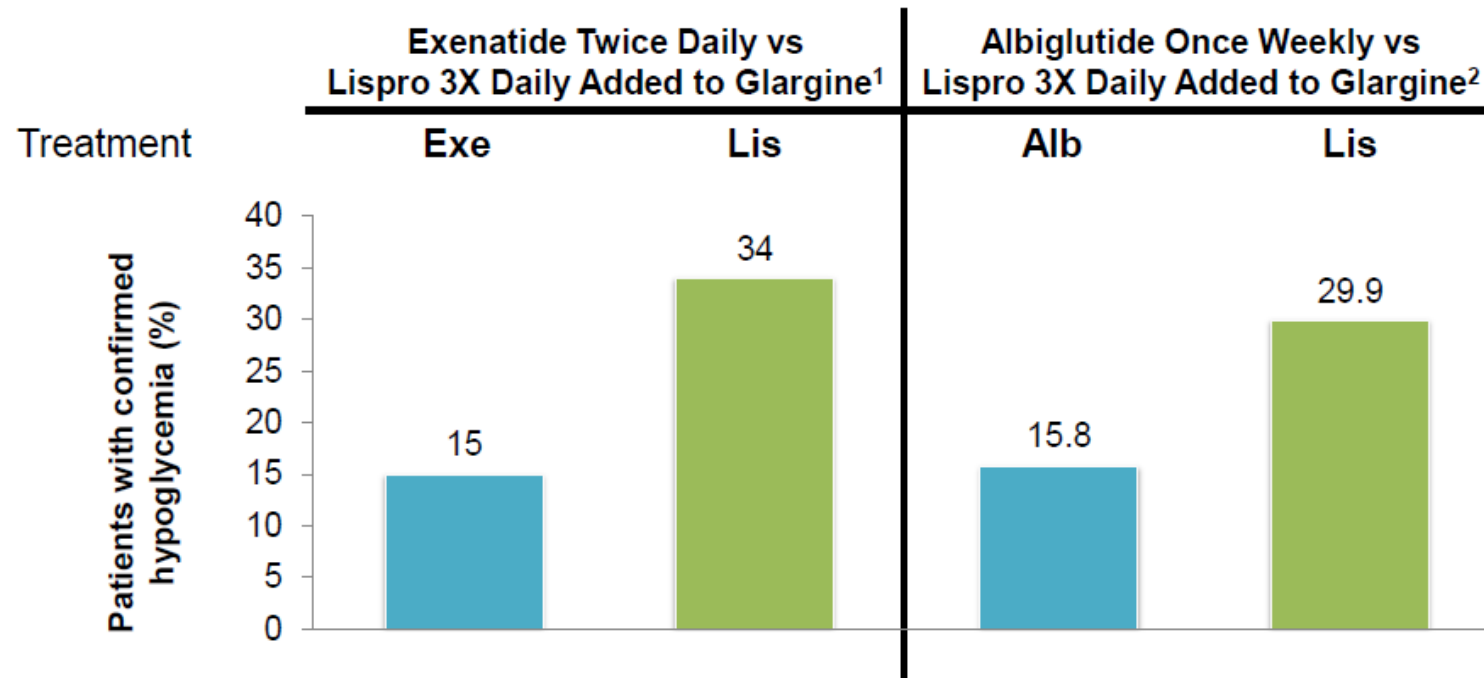


# Weight Change With GLP-1 Receptor Agonists vs. Prandial Insulin Added to Basal Insulin





# Hypoglycemia With GLP-1 Receptor Agonists vs. Prandial Insulin Added to Basal Insulin



# Intensifying Insulin Therapy With a GLP-1 RA vs Prandial Insulin

- Compared with adding prandial insulin, adding a GLP-1 RA<sup>1,2</sup>:
  - Is equally, if not more, effective at lowering A1c
  - Has a lower risk of hypoglycemia
  - Is less likely to cause weight gain
  - Is associated with less glycemic variability throughout the day

**A1C  $\leq$  7.0%<sup>a</sup>**  
Equivalent  
glycemic control  
( $P = \text{NS}$ )<sup>1,3,4</sup>

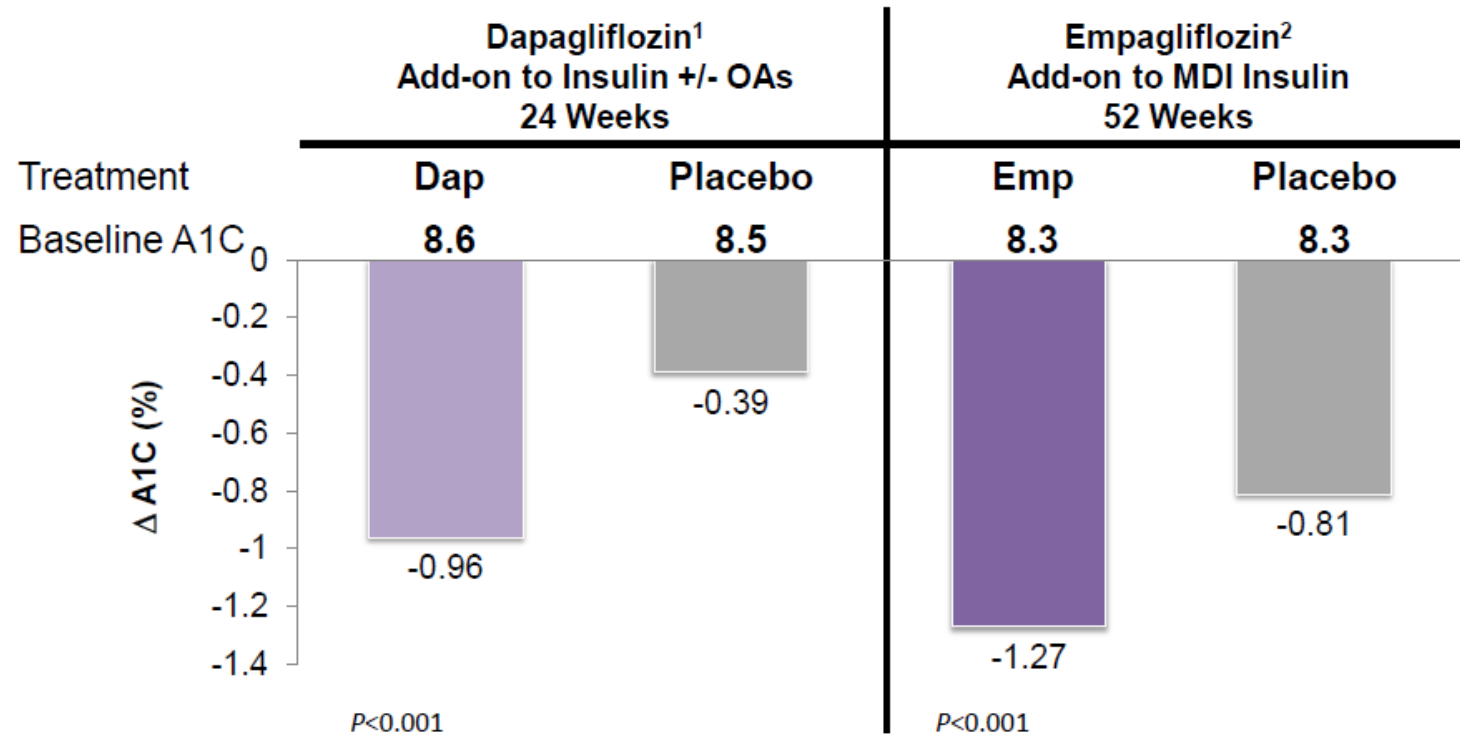
**Hypoglycemia<sup>b</sup>**  
33% fewer events  
per patient-year  
with GLP-1 RA  
( $P < .05$ )<sup>1,3-5</sup>

**$\Delta$  Weight<sup>a</sup>**  
5.66-kg more weight  
loss with GLP-1 RA  
( $P < .05$ )<sup>1,3-5</sup>

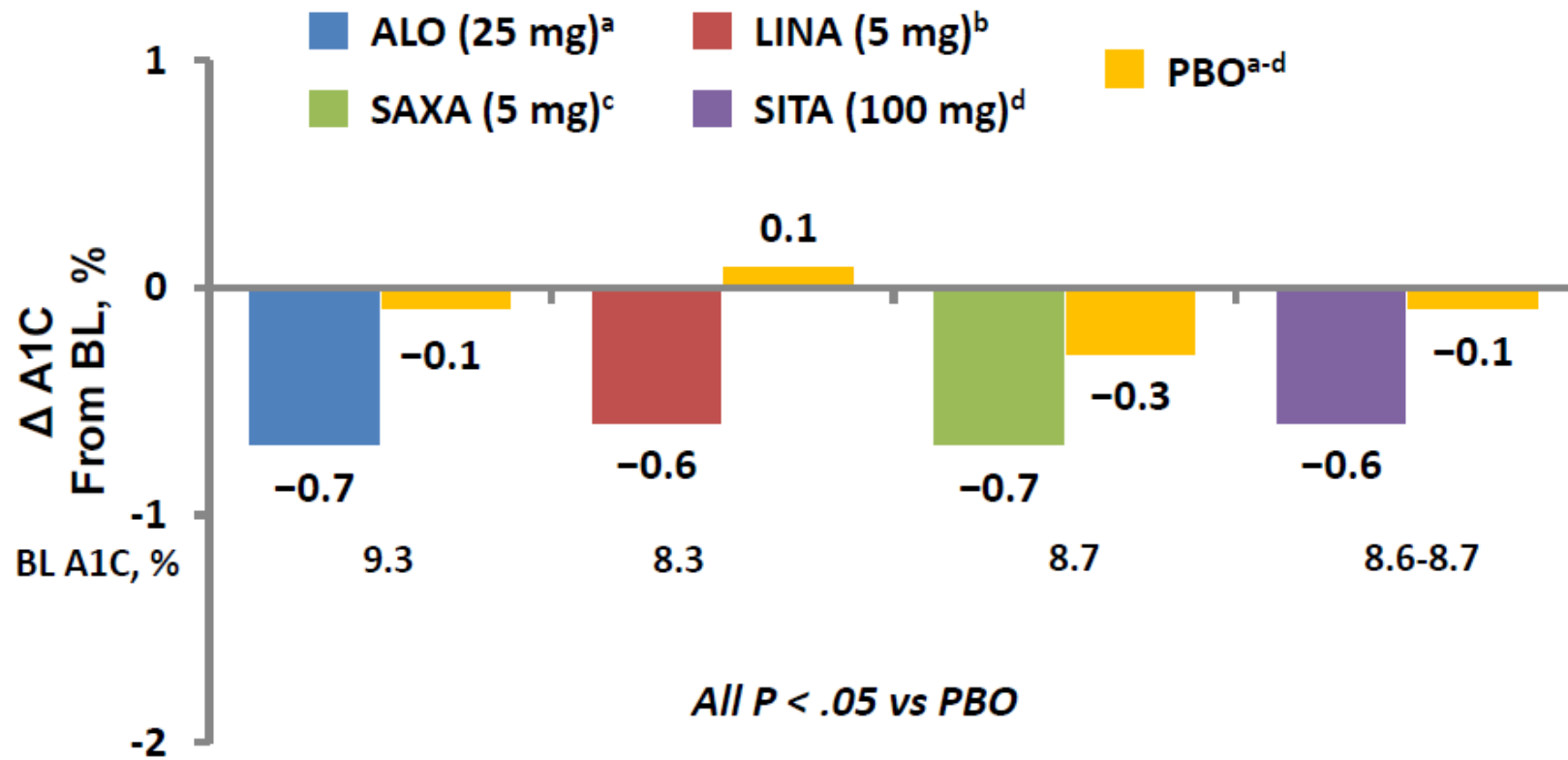
## Advantages of GLP-1 RA+ Basal Insulin over Basal-Bolus Insulin

- Equivalent A1c control
- Less weight gain (or even some loss)
- Less hypoglycemia
- Less glucose monitoring needed
- Fewer injections (as few as one per day if using fixed dose combinations) or one insulin injection per day + 1 GLP-1 RA injection per week
- Disadvantages: cost, GI side effects

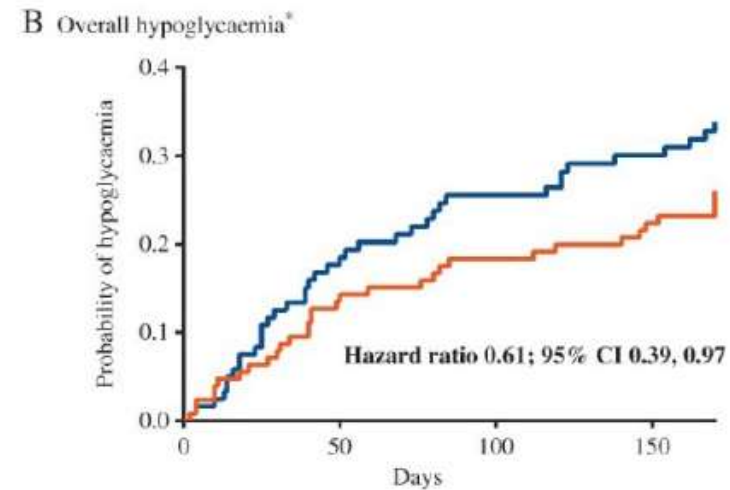
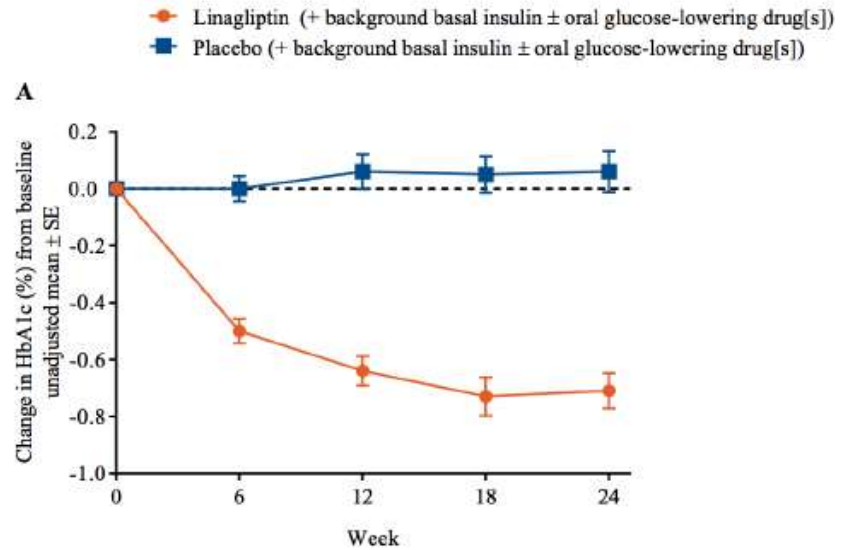
# Glucose Control With SGLT2 Inhibitors Added to Insulin Regimens



# Improved Glycemic Efficacy With DPP-4 Inhibitors Added Insulin



# Lower Risk of Hypoglycemia when Linagliptin is add to Insulin in the Elderly



# Intensifying Basal Insulin: Non-insulin Options

Option	Therapeutic considerations	Weight change	Hypoglycemia
DPP-4 inhibitor	Simple Elderly Renal impairment	Weight neutral	Less
GLP-1 RA	Injections CVD benefit GI SE	Weight loss	Equal comp to basal Less comp to BBI
SGLT-2 inh	Simple CVD benefit DKA	Weight loss	Equal

## Some Clinical Considerations for Intensification Options

- CKD
  - Exenatide not recommended for eGFR < 30 ml/min/1.73 m<sup>2</sup>
  - SGLT-2 inhibitors not recommended for eGFR < 45 ml/min/1.73 m<sup>2</sup>
  - Of DPP-4, all but Linagliptin require dose adjustment for CKD.
- Acute Kidney Injury
  - Reported with GLP-1 RA, SGLT-2, but not seen in CVOT
  - Mitigate risk by avoiding dehydration and hypotension
- Gastrointestinal disease
  - GLP-1 RA increase risk for nausea/vomiting – short acting > long acting
- Cardiovascular disease – consider SGLT-2 inhibitor or Liraglutide
- Peripheral vascular disease - Lower extremity amputations with canagliflozin
- Elderly -Consider DPP-4 as first step in intensification



# A practical approach and algorithm for intensifying beyond basal insulin in type 2 diabetes

