



Basal & GLP-1 Fixed Combination Use

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Learning Objectives

- Brief description of T2DM pathogenesis
- Guidelines approach to T2DM treatment according to ADA and AACE guidelines
- Rationale for starting basal insulin
- Role of GLP-1 Receptor agonists in the treatment of T2DM
- Rationale for combining GLP-1 RAs with basal insulin
- Basal insulin/GLP-1 RAs fixed combination: clinical trials



Age-adjusted Prevalence of Obesity and Diagnosed Diabetes Among US Adults

Obesity (BMI $\geq 30 \text{ kg/m}^2$)

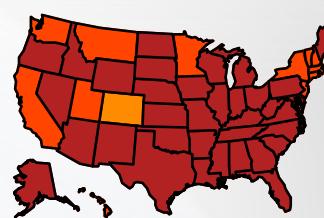
1994



2000



2015



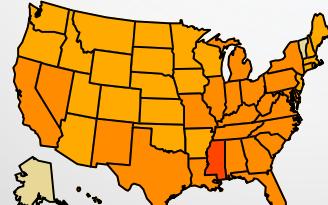
No Data <14.0% 14.0%-17.9% 18.0%-21.9% 22.0%-25.9% >26.0%

Diabetes

1994



2000

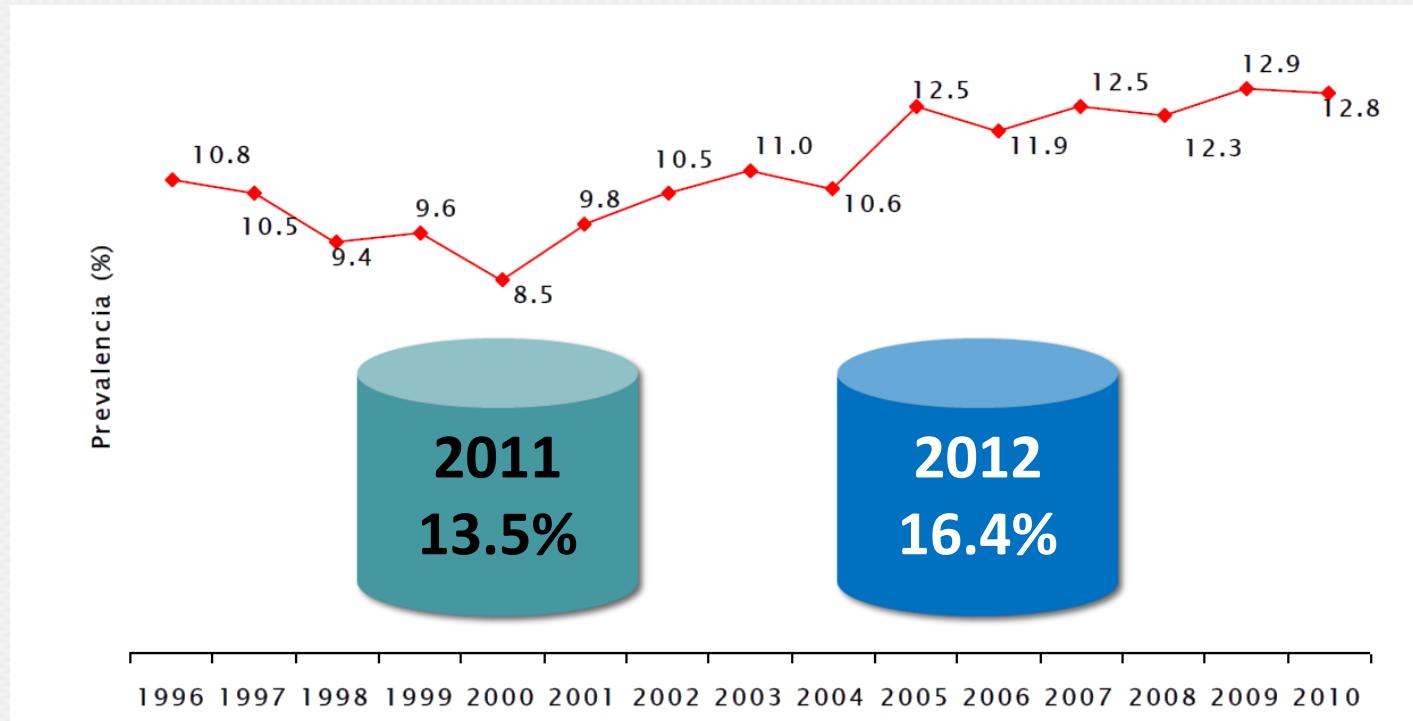


2015

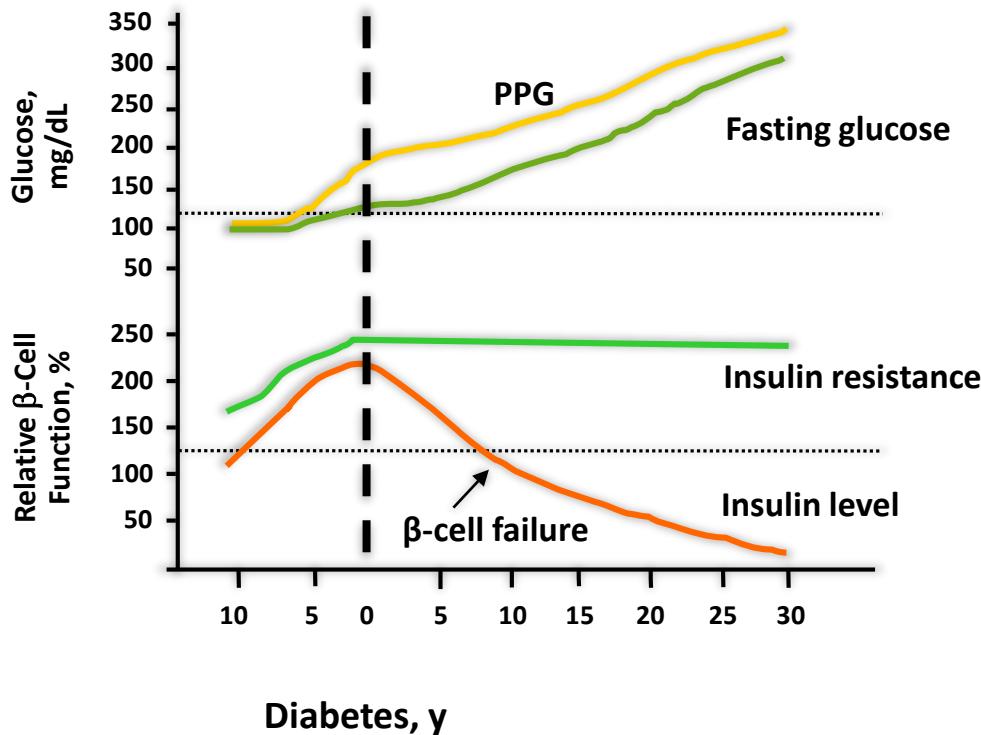


No Data <4.5% 4.5%-5.9% 6.0%-7.4% 7.5%-8.9% >9.0%

PREVALENCIA DE DIABETES EN PUERTO RICO, BRFSS, 1996-2010



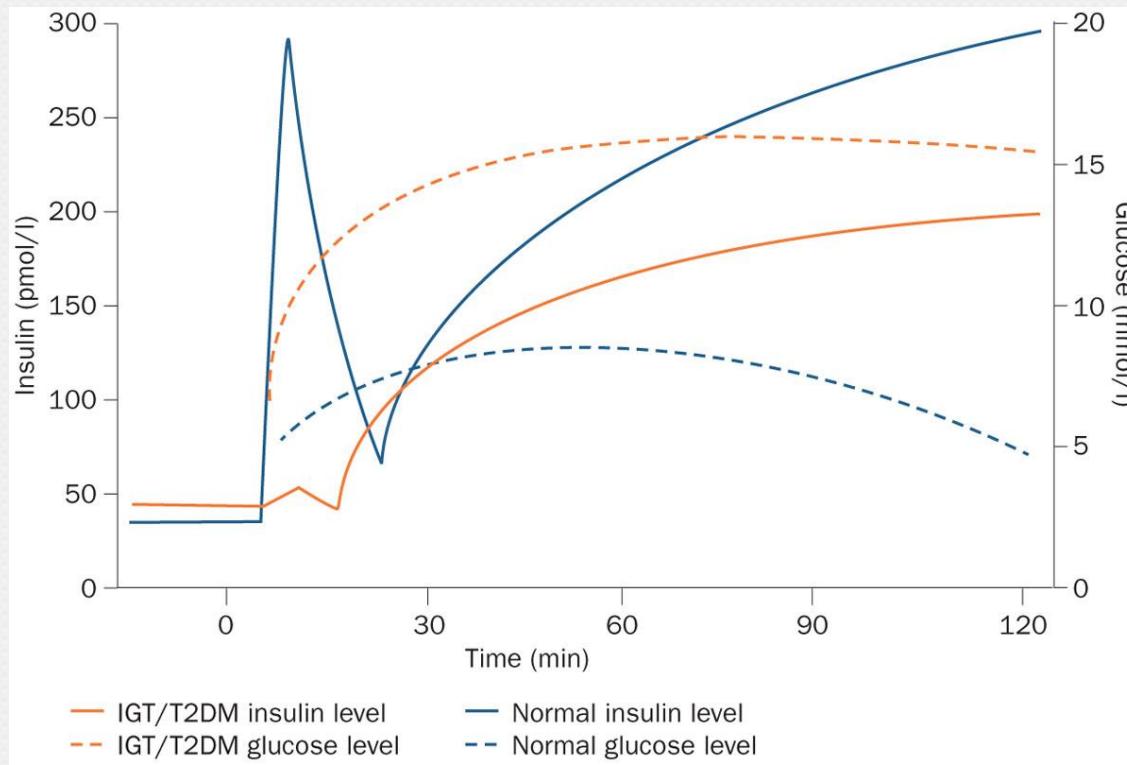
Natural History of T2DM



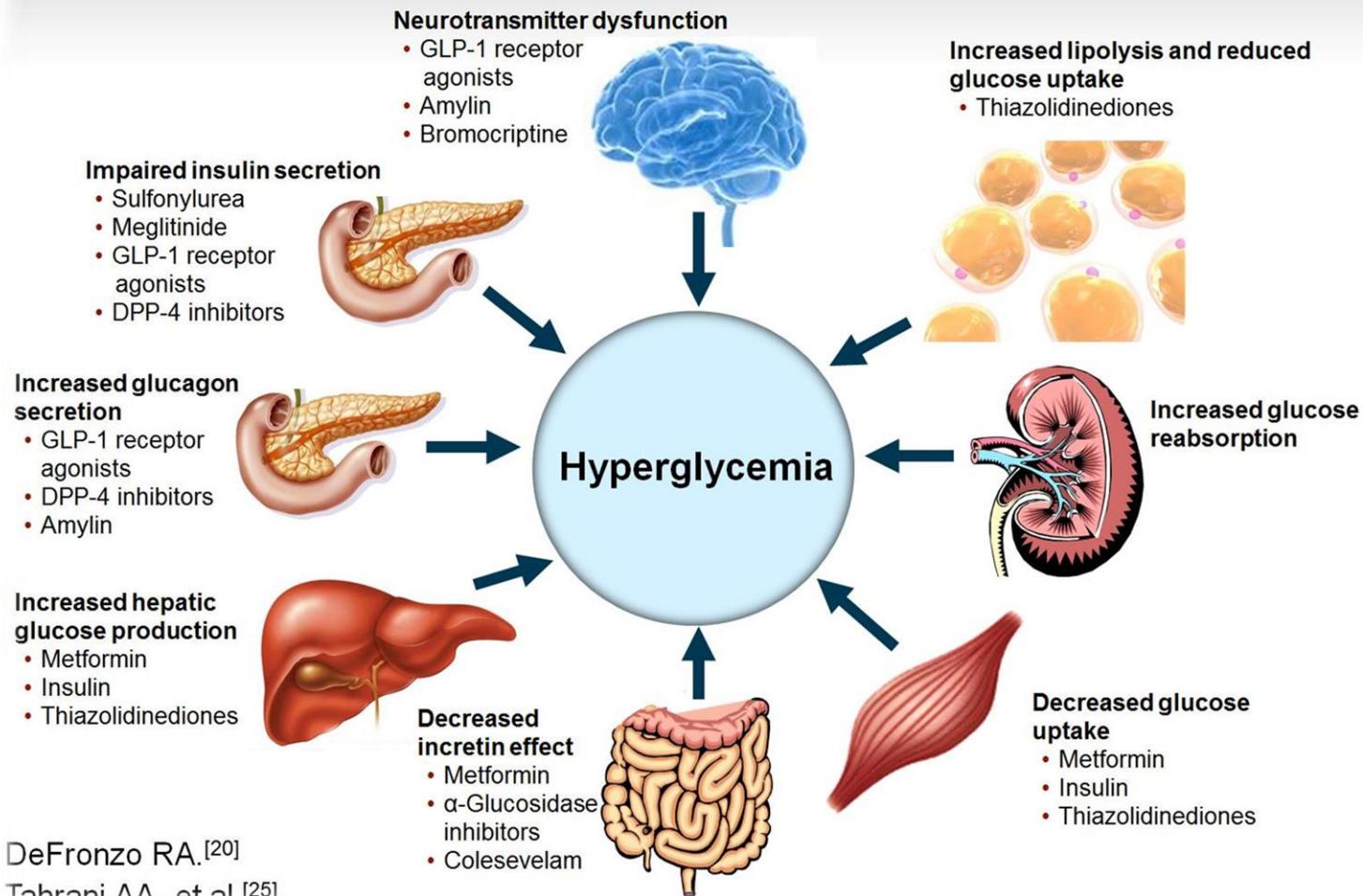
PPG = postprandial plasma glucose.

Adapted with permission from Bergenstal R et al. *Endocrinology*. Philadelphia, PA: WB Saunders Co; 2001:821-835.

Figure 1 First and second phase insulin release and corresponding glycaemia after an intravenous glucose challenge



Hyperglycemia in Type 2 Diabetes



Pathogenesis of type 2 diabetes:

Effective Tx of T2DM → multiple drugs in combination to correct multiple pathophysiological defects.

Tx should be based on known pathogenic abnormalities, NOT SIMPLY on A1C ↓

Tx must be started early in the natural Hx of T2DM → prevention of progressive β-cell failure.

Implications for therapy



GLYCEMIC CONTROL ALGORITHM



LIFESTYLE THERAPY

(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

Entry A1C ≥ 7.5%

Entry A1C > 9.0%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

DUAL THERAPY*

- MET
- or other
1st-line agent
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

TRIPLE THERAPY*

- MET
- or other
1st-line agent +
2nd-line agent
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

SYMPTOMS

NO YES

DUAL Therapy

OR

TRIPLE Therapy

INSULIN ± Other Agents

If not at goal in 3 months proceed to Dual Therapy

If not at goal in 3 months proceed to Triple Therapy

If not at goal in 3 months proceed to or intensify insulin therapy

ADD OR INTENSIFY INSULIN

Refer to Insulin Algorithm

LEGEND

✓ Few adverse events and/or possible benefits

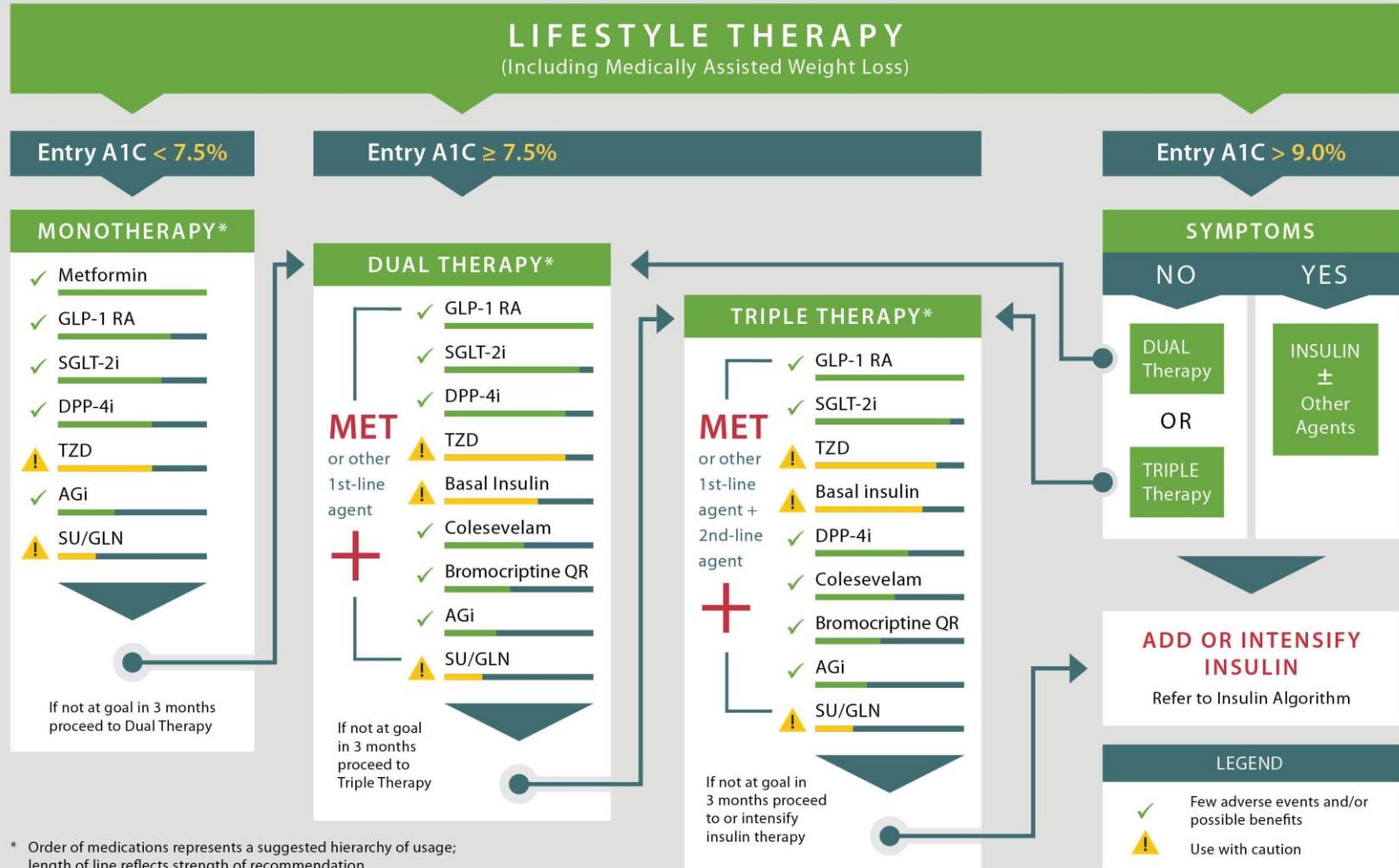
⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage;
length of line reflects strength of recommendation

PROGRESSION OF DISEASE



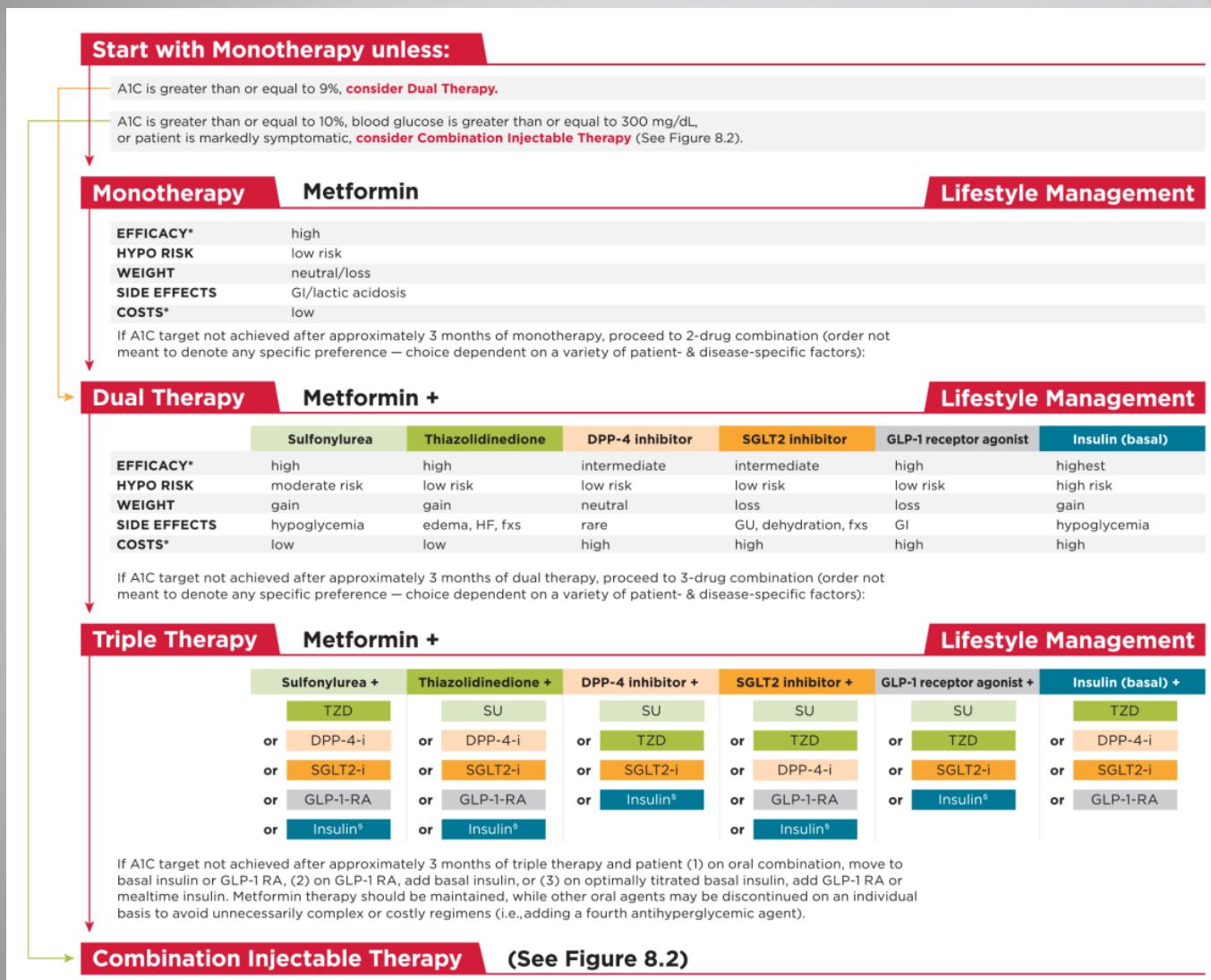
GLYCEMIC CONTROL ALGORITHM



* Order of medications represents a suggested hierarchy of usage;
length of line reflects strength of recommendation

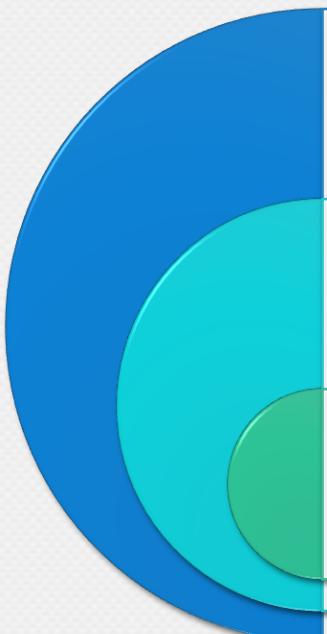
PROGRESSION OF DISEASE

Antihyperglycemic Therapy in T2DM





Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study

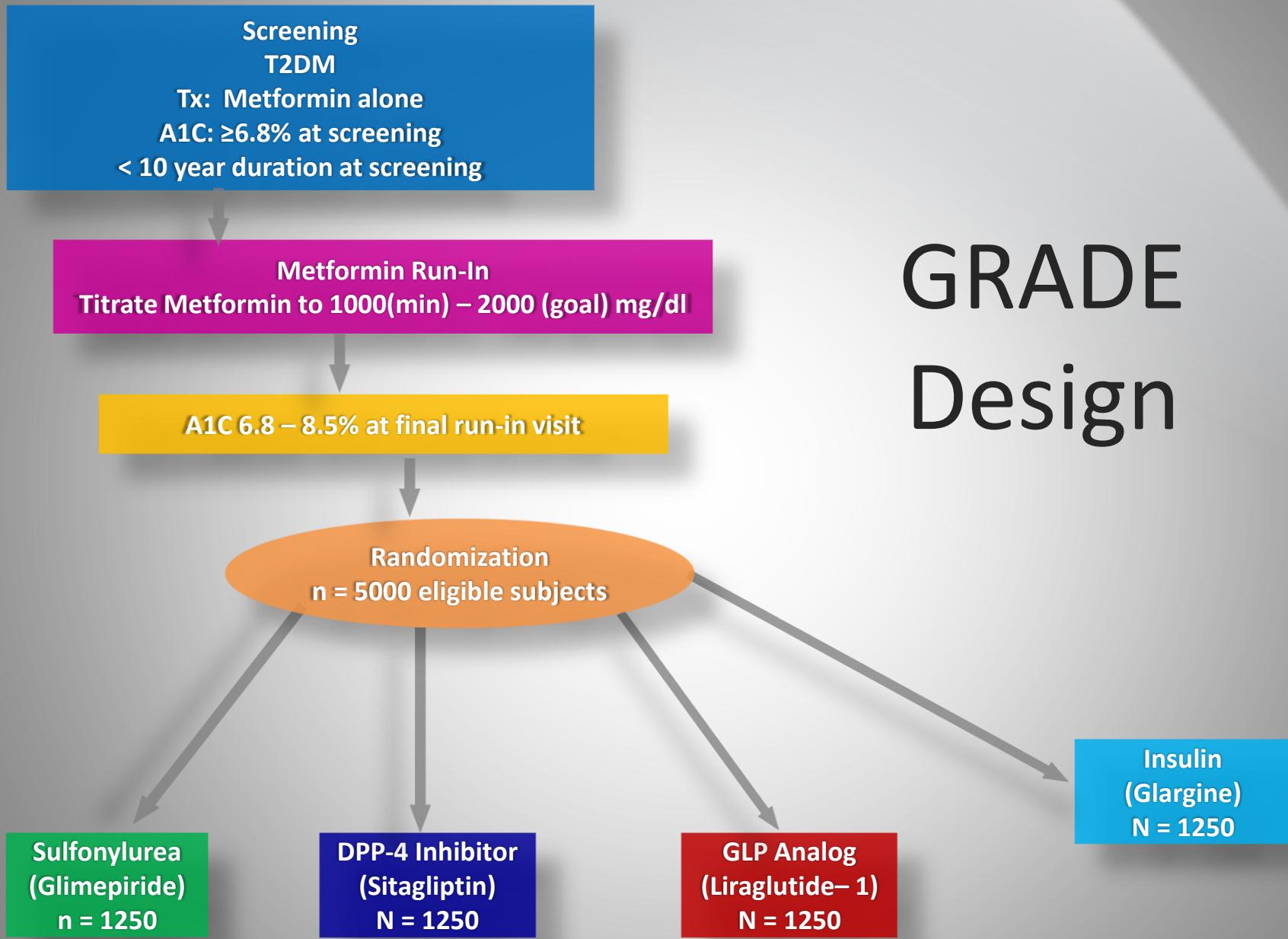


To provide unbiased comparison of most commonly used drugs to Tx DM in metformin treated patients with relatively recent-onset T2DM.

To determine patient characteristics and mechanisms associated with differential responses to medications to facilitate individualization of diabetes care.

To compare drugs over a clinically meaningful period of time (>4 years).

GRADE Design



Rationale for Starting Basal Insulin

Oral hypoglycemic agents no longer maintain control...

Adding basal insulin

↓
shown to ↓ entire 24-h fasting blood glucose profile¹

Suppression of overnight hepatic glucose production, through *direct* effects on the liver & *indirect* effects through suppression of free fatty release by adipose tissue

↓
improvement results from

Effective control with basal insulin added to oral hypoglycemic agents
Requires:
adequate dose titration

Target A1c &

hypoglycemia

Various studies: AVG doses of basal insulin from 0.33 units/kg BW (with insulin glargine)² to 0.78 units/kg (with insulin detemir)³...

If

Titration is stopped at lower doses

↓
optimal glycemic control

- Directly compared:
once-daily bedtime *insulin glargine*
- vs
- once-daily *NPH + oral hypoglycemic agents*
- Insulin titration: Fasting <100 mg/dl



- Similar mean fasting blood glucose and HbA1c between groups
- **42%** of patients treated with basal insulin and oral agents *did not achieve target HbA1c <7.0%*



Treat to Target trial

When Basal Insulin is Not Enough...

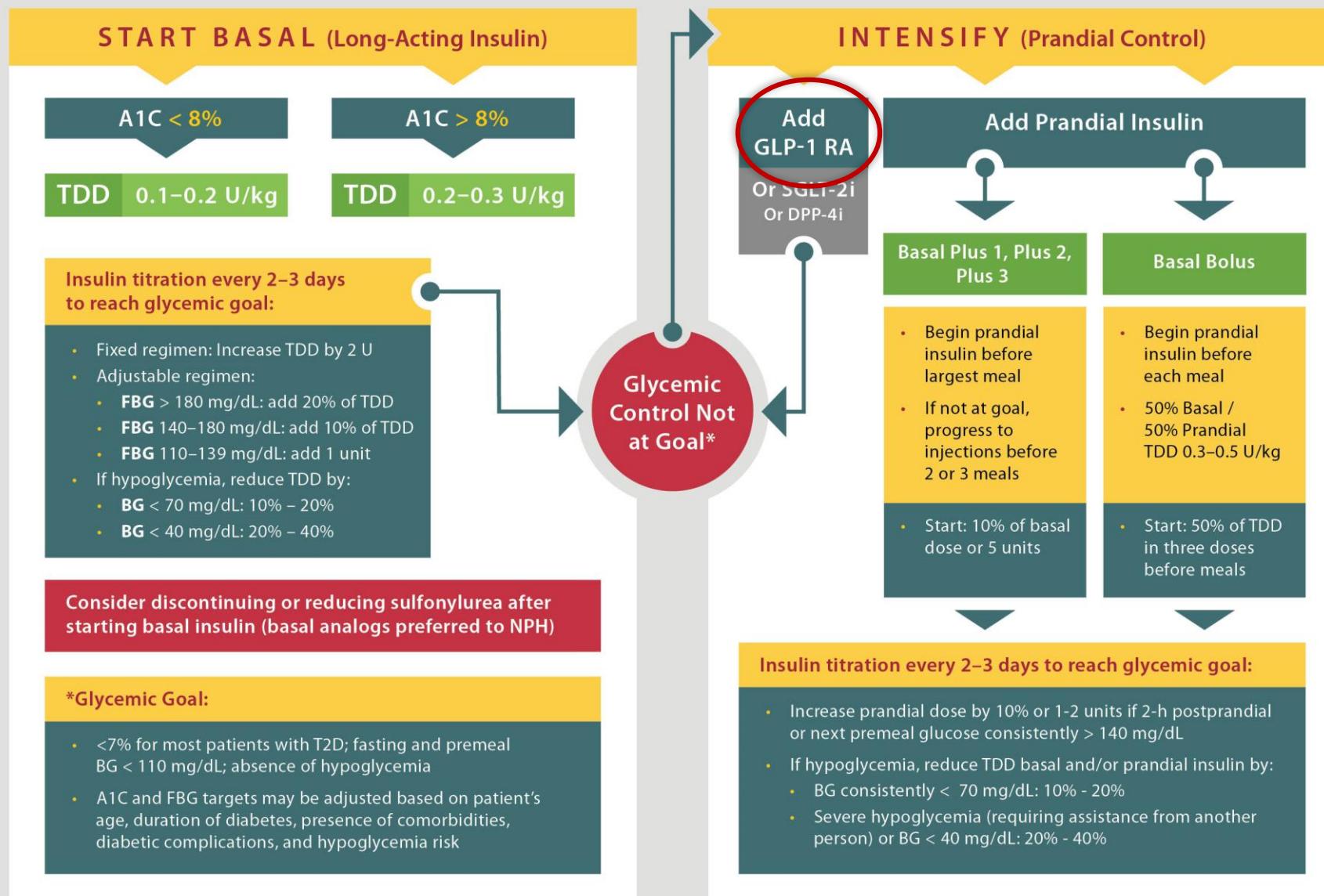
6 years after initiation of basal insulin...



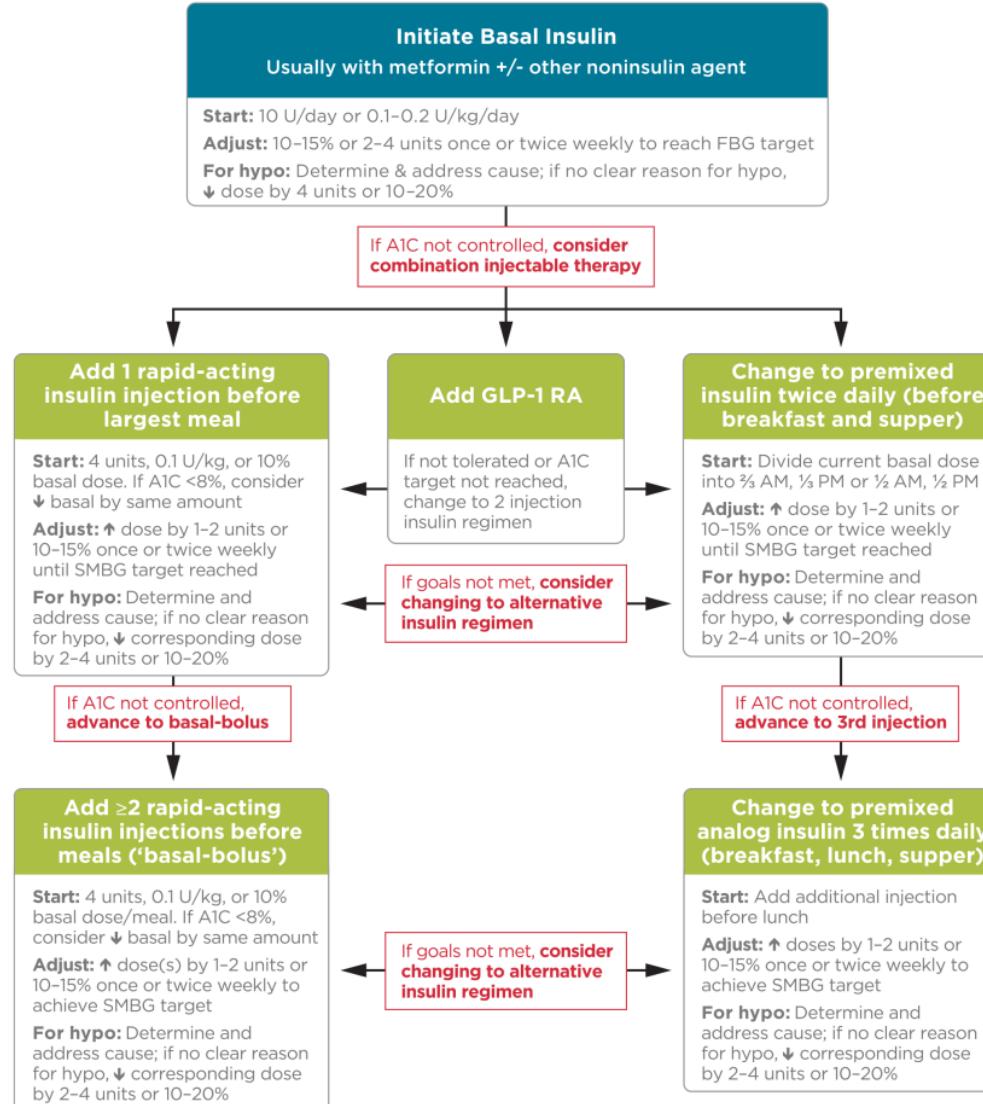
24% of patients needed additional short-acting insulin to limit hyperglycemia following meals



UKPDS



Combination Injectable Therapy in T2DM



Adding Prandial Insulin

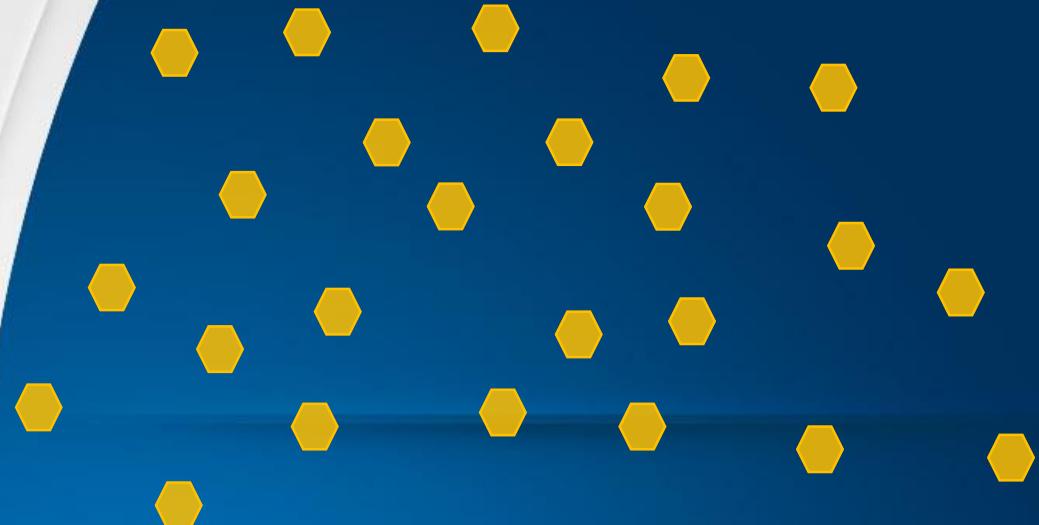
Advantages

What if we could
reduce risk of
hypoglycemia,
weight gain and
regimen complexity
in many or most
patients?

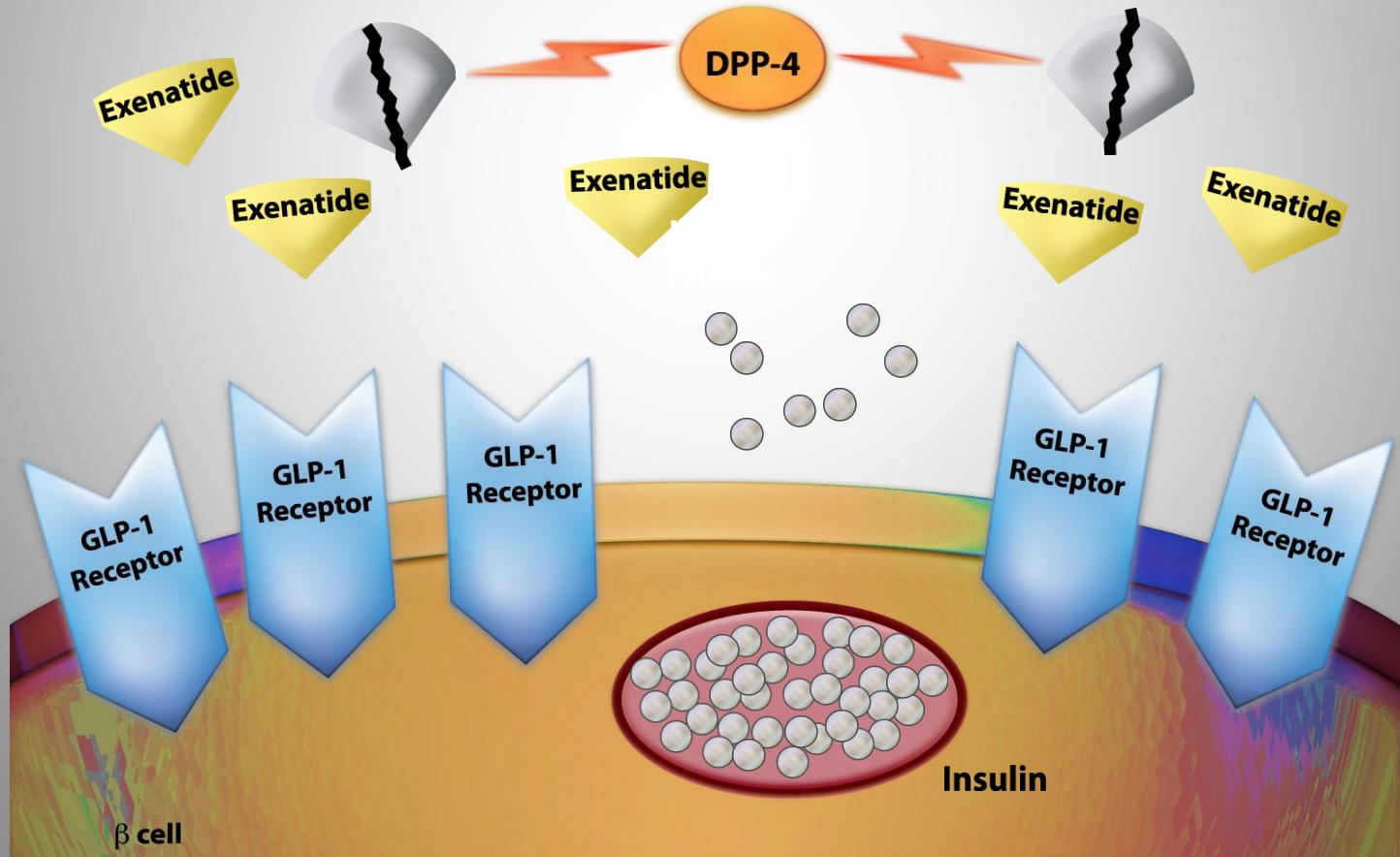
Disadvantages

- Weight gain
- Hypoglycemia
- Challenge for patients

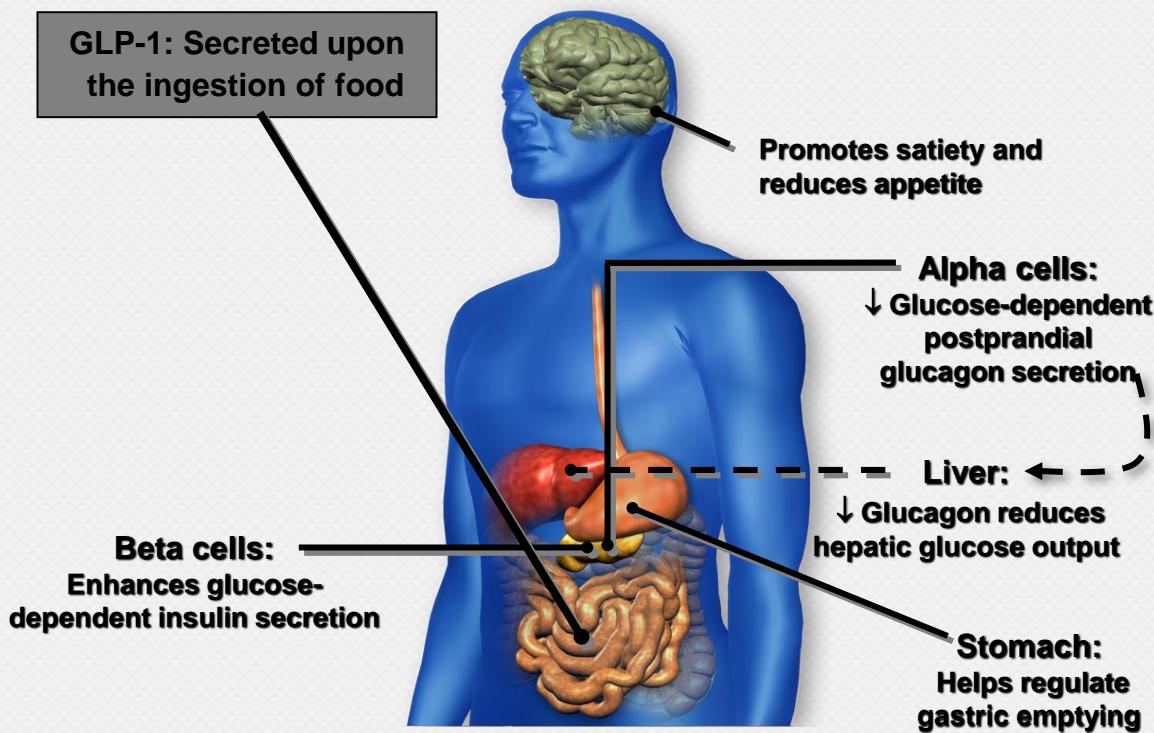
Rationale for Combining GLP-1 RAs with Basal Insulin



Exenatide Is Not Inactivated by DPP-4...



GLP-1 Modulates Numerous Functions in Humans



Data from Flint A, et al. J Clin Invest 1998;101:515-520. Data from Larsson H, et al. Acta Physiol Scand 1997;160:413-422.
Data from Nauck MA, et al. Diabetologia 1996;39:1546-1553. Data from Drucker DJ. Diabetes 1998;47:159-169.

Potential benefits of combining insulin with GLP-1 RAs

GLP-1 based therapies

- ↑ Insulin secretion
(glucose dependant)
- ↓ Glucagon secretion
- ↓ Body weight
- ↓ PPG/FPG

Low risk of
hypoglycemia

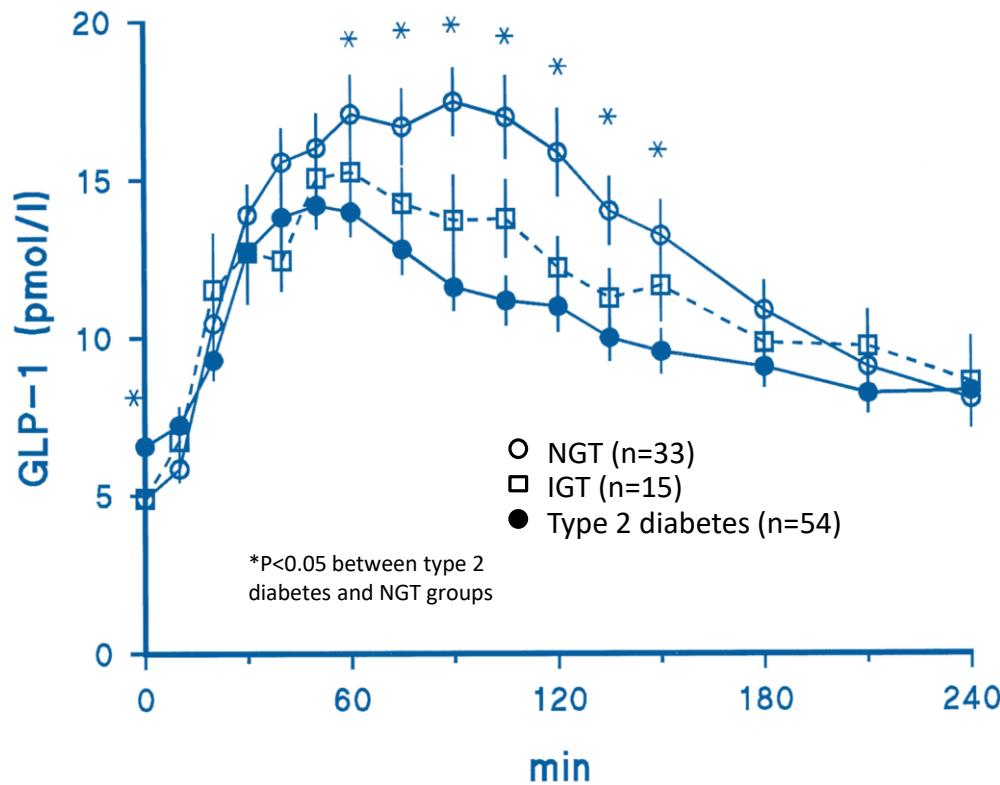
Basal insulin therapy

- ↑ Insulin levels
(non-insulin dependant)
- ↑ Beta cell rest
- ↑ Body weight
- ↓ FPG/PPG

Moderate risk of
hypoglycemia

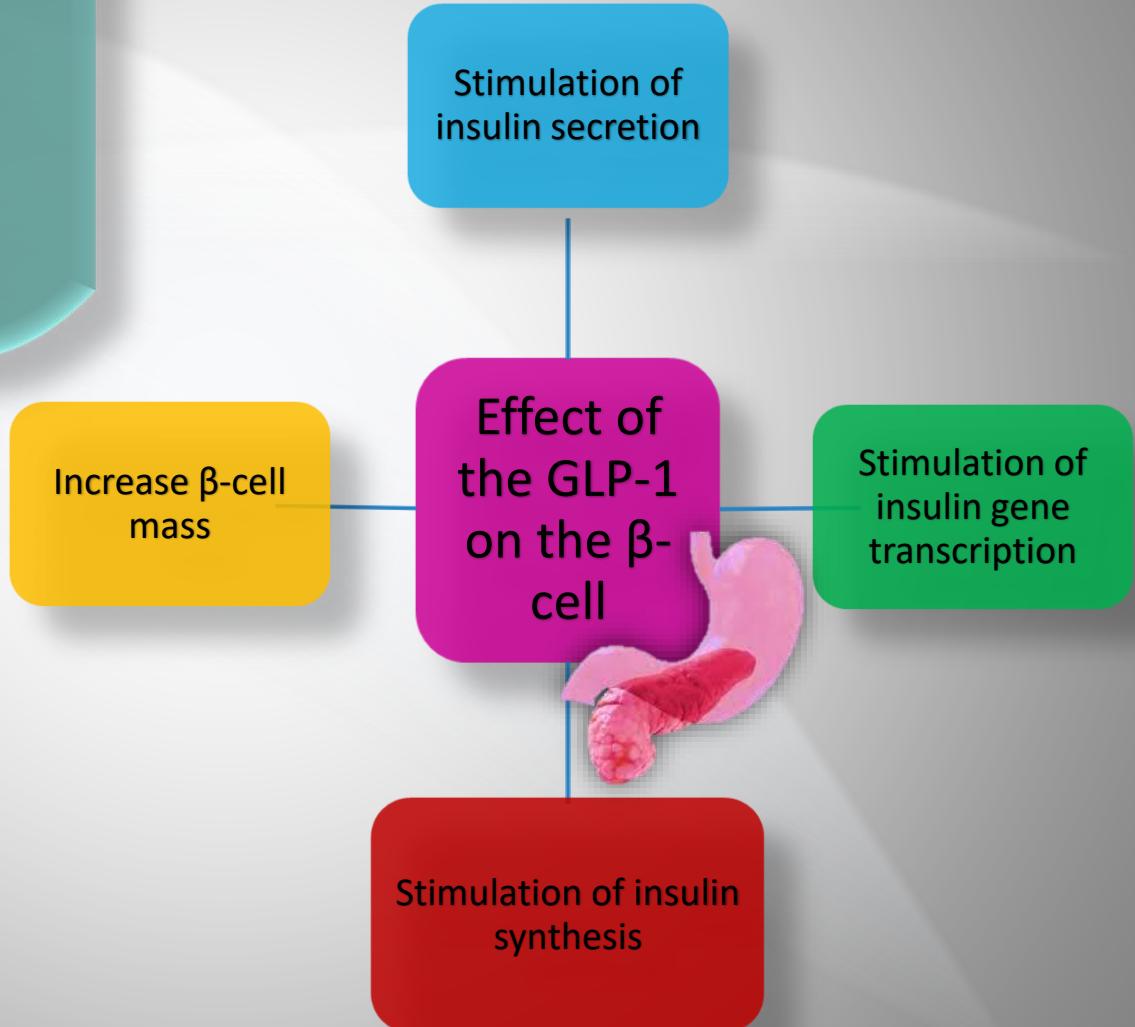
Potentially complementary benefits if
used in combination

GLP-1 Release is Reduced in Type 2 Diabetes



From: Determinants of the Impaired Secretion of Glucagon-Like Peptide-1 in Type 2 Diabetic Patients
J Clin Endocrinol Metab. 2001;86(8):3717-3723. doi:10.1210/jcem.86.8.7750

- Lixisenatide ↓ the number of apoptotic β cells by 50-60%
- An 80% reduction was seen with lixi + Glargin¹



1. TEWS D, ET AL. HORM METAB RES 2008; 40(3):172-180.

Comparison of physiologic effects of short-acting and long acting GLP-1 RAs.

Parameter	Short-acting GLP-1 RAs	Long-acting GLP-1 RAs
Molecule	Lixisenatide Exenatide BID	Liraglutide Exenatide LAR Albiglutide Dulaglutide
Half-life	2–5 h	12 h to several days
Effects		
Fasting blood glucose	Modest reduction	Marked reduction
Postprandial glucose excursion	Marked reduction	Modest reduction
Fasting insulin secretion	Modest stimulation	Marked stimulation
Postprandial insulin secretion	Reduction	Modest stimulation
Glucagon secretion	Reduction	Reduction
Gastric emptying rate	Marked deceleration	No effect or mild deceleration
Blood pressure	Reduction	Reduction
Heart rate	No effect or mild increase (0–2 bpm)	Moderate increase (2–9 bpm)
Reduction of body weight	1–5 kg	2–5 kg
Induction of nausea	20–50%, slow attenuation (from weeks to months)	20–40%, rapid attenuation (about 4–8 weeks)

BID, twice daily; bpm, beats per minute; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LAR, long-acting release. Reprinted by permission from Macmillan Publishers Ltd: *Nat Rev Endocrinol* (Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. 8:728–742), copyright (2012).

Differences in mechanism of action and clinical profiles between short-acting and long-acting GLP-1 RAs: Head-to-head studies

Exenatide BID vs QW¹

Greater reduction in PPG with BID

Greater delay of gastric emptying with BID

Greater reduction in FPG and HbA1c with QW

Liraglutide QD vs Exenatide BID (added to Met, SU or both)²

Greater reductions in FPG and HbA1c with lira

Greater reduction in PPG with exenatide

Lixisenatide QD vs Liraglutide QD³

Greater reduction in PPG with lixi

Greater reductions in PP glucagon and insulin with lixi

1. DRUCKER DJ, ET AL. LANCET 2008; 372(9645): 1240-1250. 2. BUSE JB, ET AL. LEAD-6. LANCET 2009; 374(9683): 39-47. 3. KAPITZA C, ET AL. DIABETES OBES METAB 2013; 15(7): 642-649.

Differences in mechanism of action and clinical profiles between short-acting and long-acting GLP-1 RAs: Head-to-head studies

Lixi QD vs Lira QD as add-on to basal insulin¹

- Greater reduction in PPG with lixi
- No difference in A1c
- Delayed gastric emptying and glucagon suppression with lixi
- Increased insulin release with lira

Dulaglutide QW vs Exenatide BID (added to Met and pio)²

- Greater reduction in A1c with dulaglutide
- Greater reduction in prandial glucose excursions with exenatide
- Greater reduction in FPG and overall hyperglycemia with dulaglutide

1. Meier JJ, et al. Diabetes Care 2015; 38(7): 1263-1273. 2. Wysham C, et al. AWARD-1. Diabetes Care 2014; 37(8): 2159-2167.

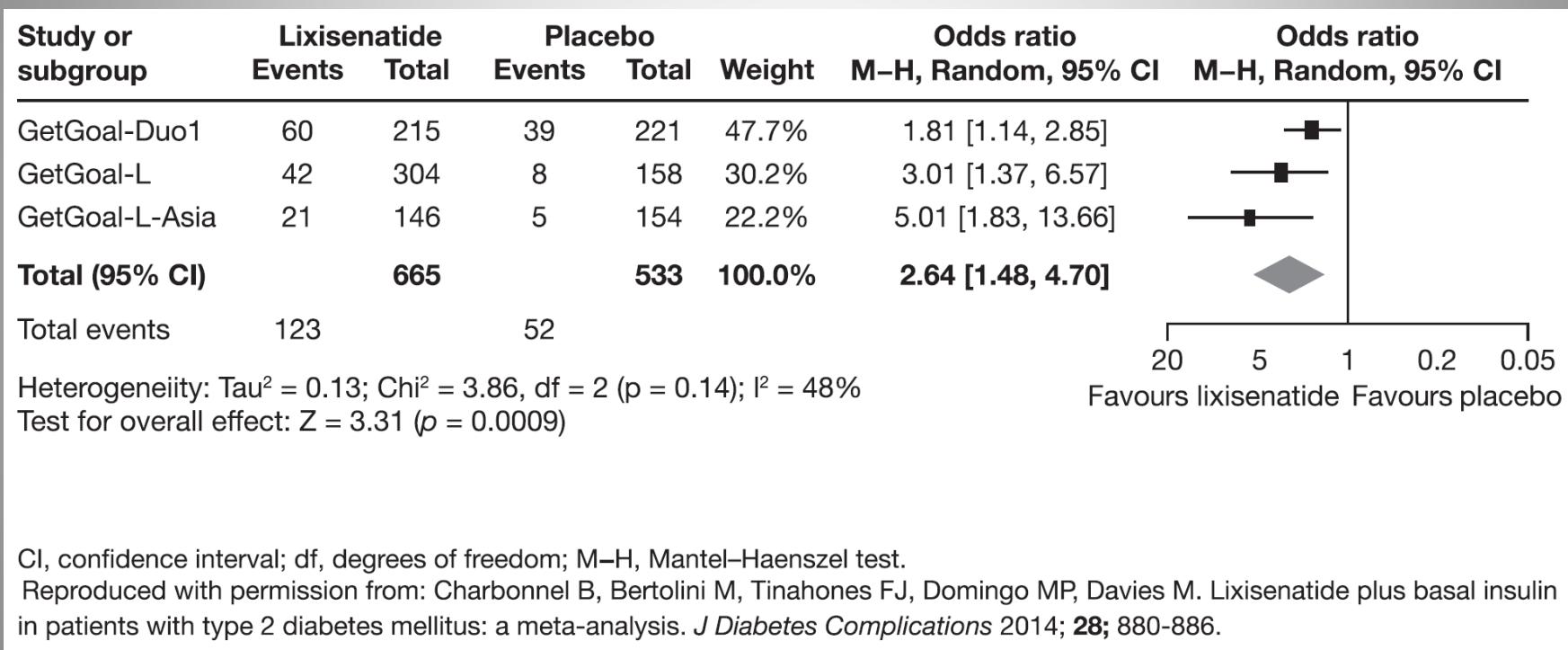
Glycemic parameters from clinical studies combining GLP-1 RAs and basal insulin

Reference	Treatments added to basal insulin	Patients (%) achieving HbA _{1c} ≤ 7.0%			Mean FPG change from baseline, mmol/L			Mean PPG change from baseline, mmol/L			Mean body weight change from baseline, kg		
		GLP-1 RA	Comparator	Between-group difference	GLP-1 RA	Comparator	Between-group difference	GLP-1 RA	Comparator	Between-group difference	GLP-1 RA	Comparator	Between-group difference
Buse <i>et al.</i> , 2011 [44]	Exenatide 10 µg BID versus placebo; 30 weeks	60 (51, 69)	35 (25, 45)	25 (12, 39); <i>p</i> < 0.001	-1.6 (-1.9, -1.3)	-1.5 (-1.8, -1.2)	-0.1 (-0.52, 0.32); <i>p</i> = 0.63	NR	NR	NR	-1.78 (-2.48, -1.08)	0.96 (0.23, 1.70)	-2.74 (-3.74, -1.74); <i>p</i> < 0.001
GetGoal-L Asia; Seino <i>et al.</i> , 2012 [20]	Lixisenatide 20 µg QD versus placebo; 24 weeks	35.6	5.2	30.4; <i>p</i> < 0.0001	-0.42	0.25	-0.67; <i>p</i> = 0.0187	-7.96	-0.14	-7.83 (-8.89, -6.77); <i>p</i> < 0.0001	-0.38	0.06	-0.44 (-0.925, 0.061); <i>p</i> = 0.0857
GetGoal-Duo1; Riddle <i>et al.</i> , 2013b [19]	Lixisenatide 20 µg QD versus placebo; 24 weeks	56	39	17; <i>p</i> = 0.0001	0.3 (0.2)	0.5 (0.2)	-0.1 (-0.5, 0.2); <i>p</i> = 0.5142	-3.1 (0.5)	0.1 (0.5)	-3.2 (-4.0, -2.4); <i>p</i> < 0.0001	0.3 (0.3)	1.2 (0.3)	-0.89 (-1.4, -0.4); <i>p</i> = 0.0012
GetGoal-L; Riddle <i>et al.</i> , 2013a [18]	Lixisenatide 20 µg QD versus placebo; 24 weeks	28.3	12.0	16.3; <i>p</i> < 0.0001	-0.6 (0.2)	-0.6 (0.3)	-0.1 (-0.6, 0.4); <i>p</i> = 0.7579	-5.5 (0.5)	-1.7 (0.5)	-3.8 (-4.7, -2.9); <i>p</i> < 0.0001	-1.8 (0.2)	-0.5 (0.3)	-1.3 (-1.8, -0.7); <i>p</i> < 0.0001
BEGIN: VICTOZA ADD-ON; Mathieu <i>et al.</i> , 2014 [48]	Liraglutide ≥1.8 mg QD versus insulin as part QD; 28 weeks	58.0	44.9	<i>p</i> = NS	-0.14	-0.04	-0.1; <i>p</i> = NS	-0.8*	-1.0*	<i>p</i> = NS	-2.8 (3.8)	0.9 (2.5)	-3.75 (-4.70, -2.79); <i>p</i> < 0.0001

Values in parentheses are 95% confidence intervals or standard error. These were not reported for all studies.
*Meal with largest decrease from baseline.

BID, twice daily; FPG, fasting plasma glucose; GLP-1 RA, glucagon-like peptide-1 receptor agonist; NS, nonsignificant; NR, not reported; PPG, postprandial plasma glucose; QD, once daily.

Meta-analysis showing the likelihood of patients reaching the composite endpoint of HbA1c <7% with no symptomatic hypoglycemia and no weight gain



Fixed-Combination Products Available

iDegLira

1 dose steps= 1 unit of insulin degludec + 0.036 mg of liraglutide

16 dose steps= 16 units of insulin degludec + 0.6 mg of liraglutide

32 dose steps= 32 units of insulin degludec + 1.2 mg of liraglutide

50 dose steps= 50 units of insulin degludec + 1.8 mg of liraglutide

LixiLan

2 units of insulin glargine + 1 mcg lixisenatide

10 units of glargine + 5 mcg lixisenatide

60 units of glargine + 30 mcg lixisenatide

IDegLira Clinical Trials: Summary of Trial Designs

	DUAL 1	DUAL II	DUAL III	DUAL IV	DUAL V
Trial Number	3697 (pivotal)	3912 (pivotal)	3851	3951	3952
Objective	IDegLira vs. IDeg vs. lira (3 arm factorial study)	IDegLira vs. IDeg with dose cap	IDegLira vs. GLP-1 analog 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 naive	Previous insulin users	Previous GLP1 analog users	Add on to OAD Insulin naive	Previous insulin users
Hypothesis test	NI to IDeg and Superiority to lira	Superiority	Superiority	Superiority	NI

Met= metformin \geq 1500 mg/day or maximum tolerated dose, Pio=pioglitazone \geq 30 mg/day, SU= sulfonylurea at (1/2 max of approved dose), IDegLira= insulin degludec and liraglutide, lira=liraglutide, IDeg=insulin degludec, OADs=oral antidiabetic drugs, FAS=Full analysis set, NI=non-inferiority

DUAL IV: IDegLira vs Placebo

Study Design

Subjects with
type 2 diabetes
(N=435)

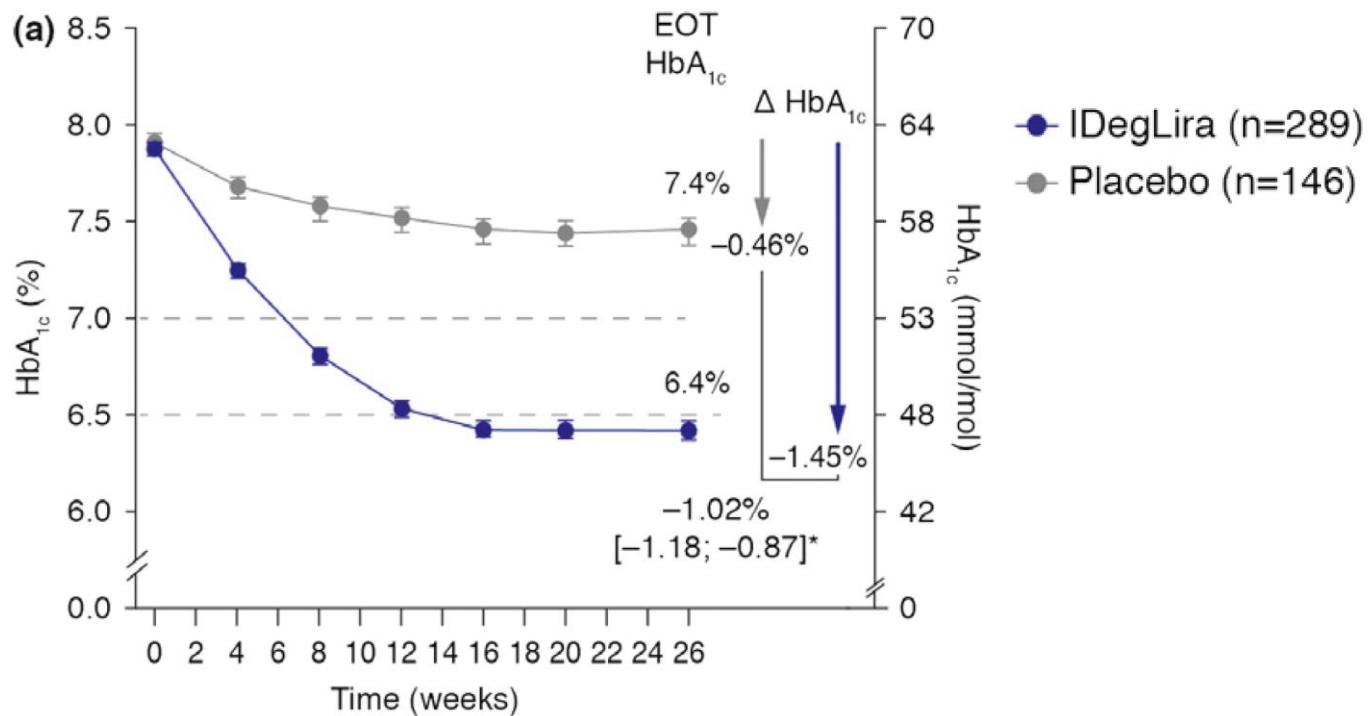


Inclusion Criteria

- Type 2 diabetes
- SU ± metformin
- HbA1c 7.0-9.0%
- Age ≥ 18 years
- BMI ≤ 40 kg/m²

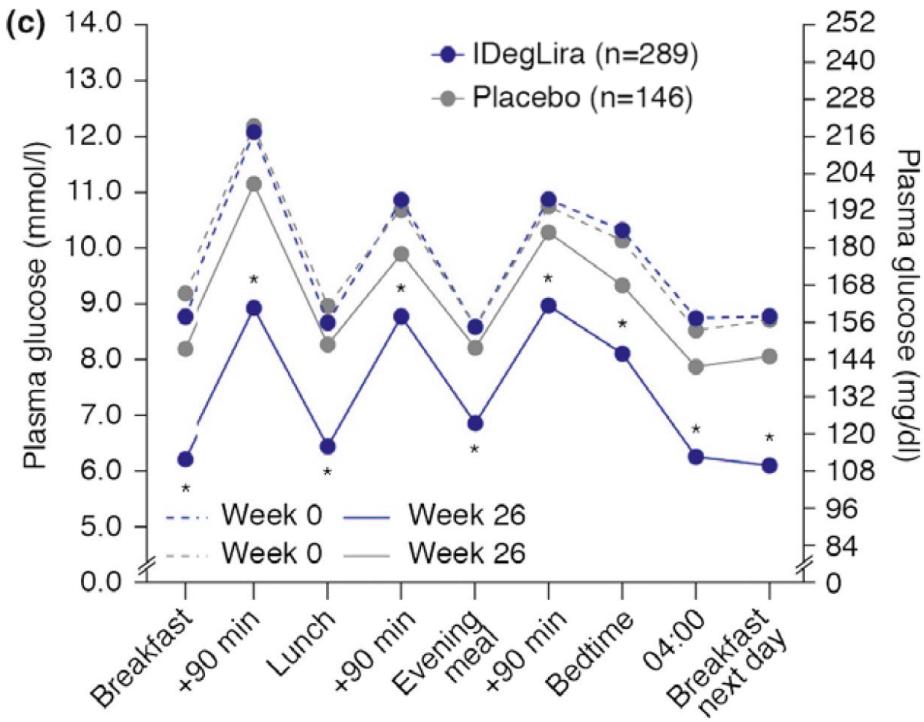
IDegLira/Placebo:
Starting Dose:
10 dose steps
Maximum Dose:
50 dose steps
Titrate to target
FPG 4-6 mmol/L
(72-108 mg/dl)

DUAL IV: HbA_{1c} over time



Mean observed values with error bars (standard error mean) based on full analysis set and last observation carried forward imputed data. Treatment difference estimated using ANCOVA model on full analysis set and last observation carried forward.

DUAL IV: 9-point SMBG profile

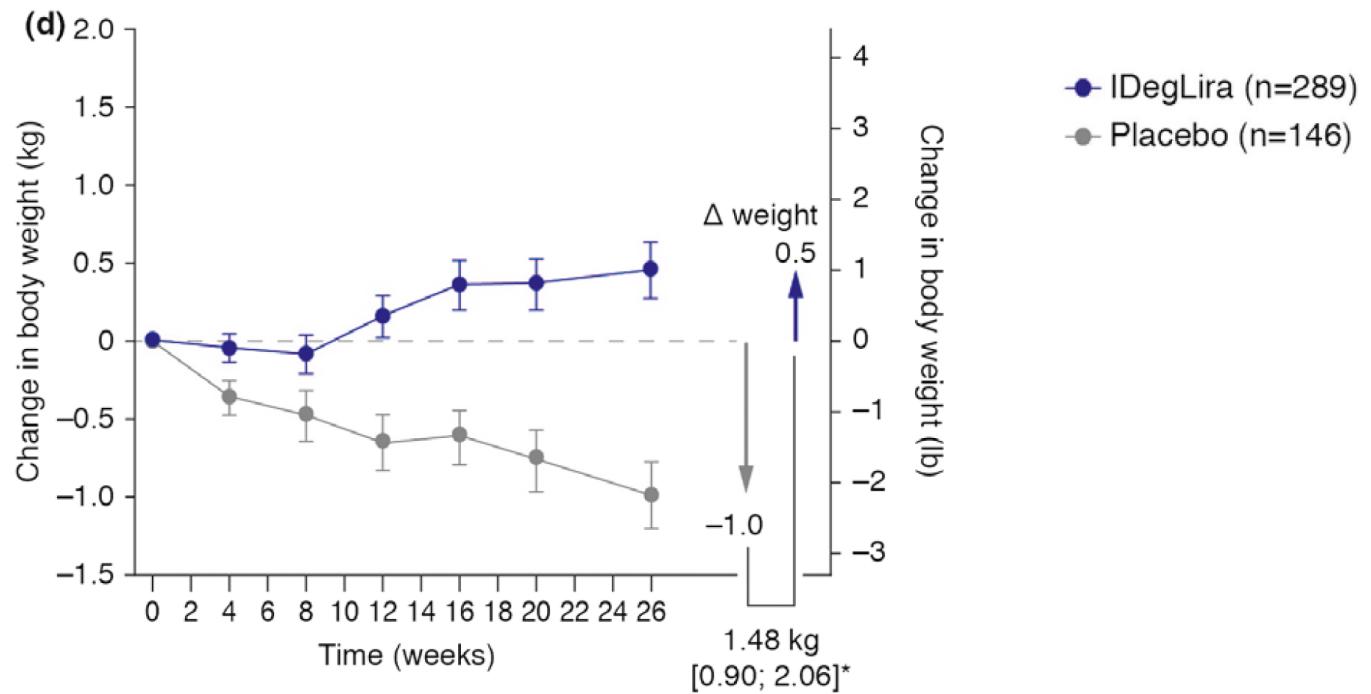


Greater reduction in
mean 9-P SMBG
profile with IDegLira vs
Placebo

Treatment difference
 -27.97 mg/dL ,
 $P < 0.001$

* $p < 0.05$ based on lineal mixed model with an unstructured residual covariance matrix. Mean observed values based on full analysis set and last observation carried forward imputed data.

DUAL IV: Change in body weight over time



Mean observed values with error bars (SEM) based on FAS and LOCF imputed data. Treatment difference estimated using an ANCOVA model. ETD [95% CI], *P < 0.001.

DUAL IV: Confirmed hypoglycemia

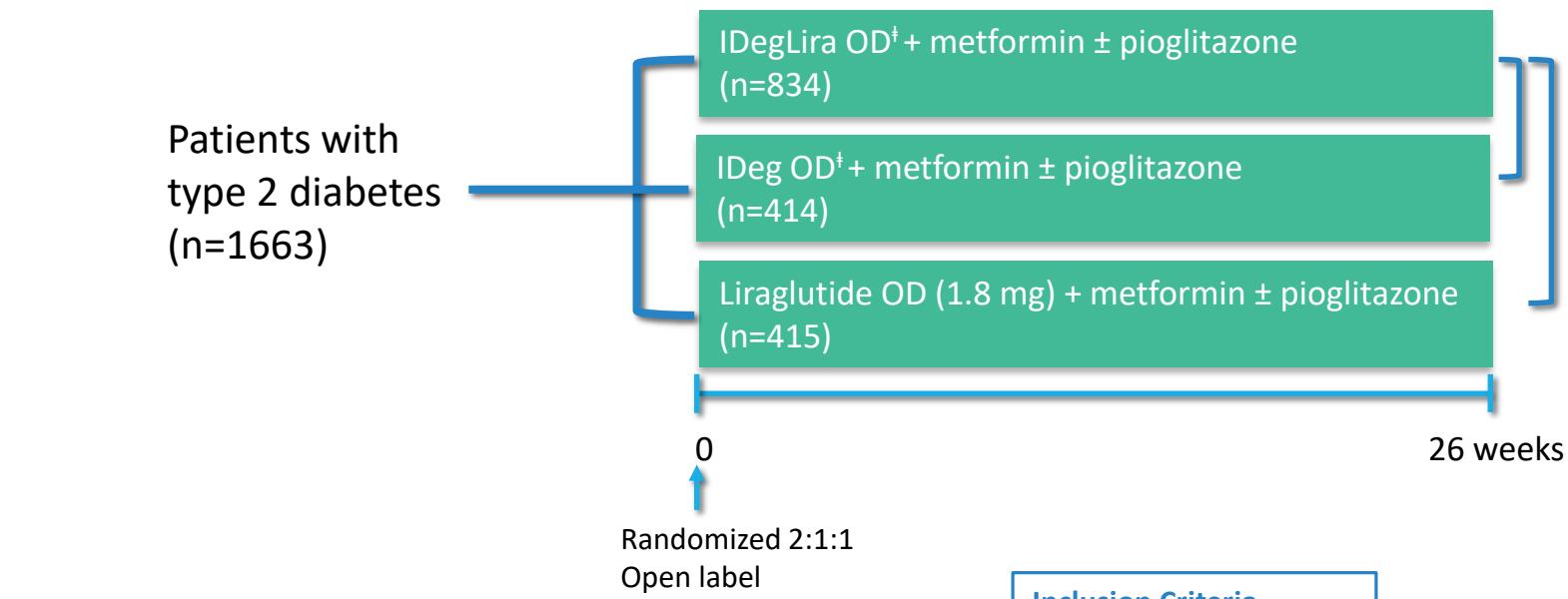
	IDegLira (n=288)		Placebo (n=146)	
	% Subjects (# subjects)	Rate (Episodes/PYE)	% Subjects (# subjects)	Rate (Episodes/PYE)
Severe	0.7% (2/288)	0.02	-	-
Confirmed	41.7% (120/288)	3.52	17.1% (25/146)	1.35*

End-of-trial HbA1c: IDegLira 6.4% Placebo 7.4%

*P<0.0001 for IDegLira vs Placebo

Data based on safety analysis set. Estimated treatment ratios are from a negative binomial model. %, percentage of participants; N, number of participants with ≥1 event.

DUAL I: IDegLira vs IDeg vs Liraglutide



Titration algorithm: IDegLira and IDeg

Mean Fasting PG		Dose Change
mg/dL	mmol/L	Dose steps or U
<72	<4.0	-2
72-90	4.0-5.0	0
>90	>5.0	+2

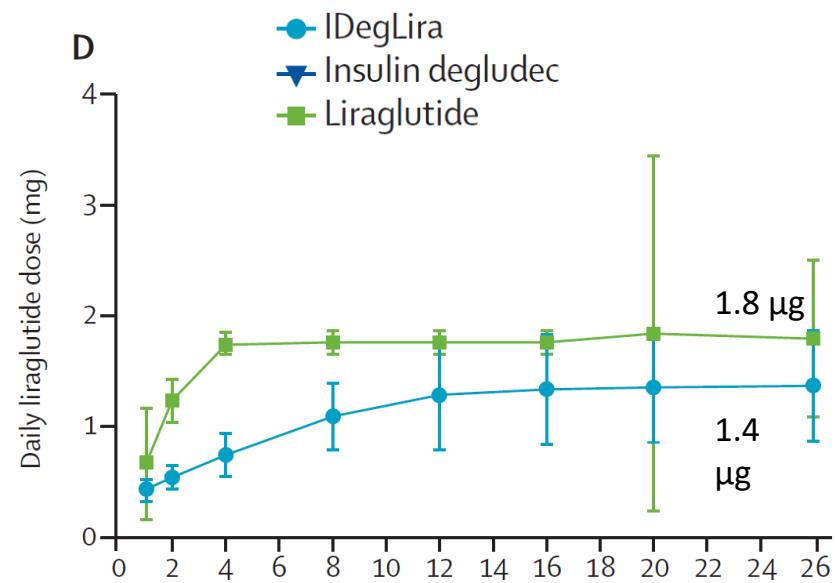
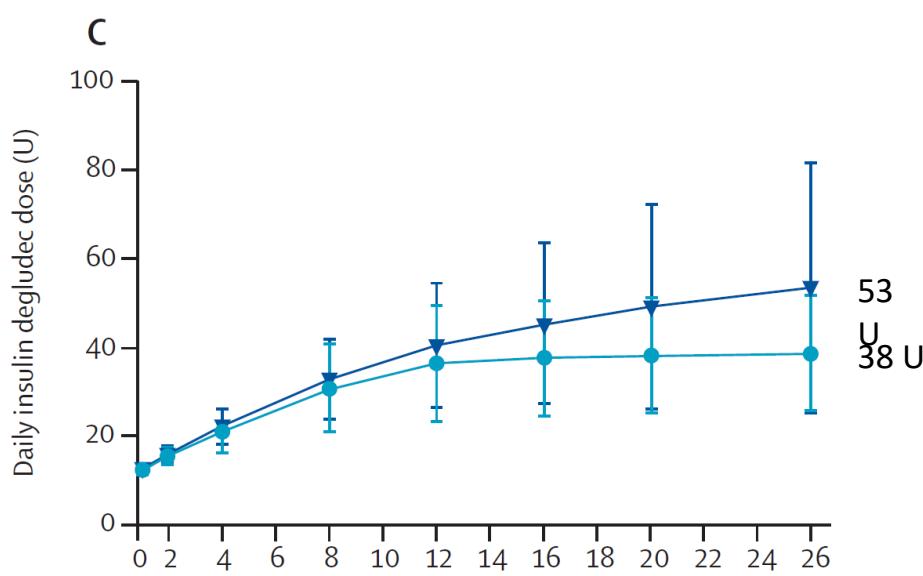
Inclusion Criteria

- Type 2 Diabetes
- Insulin naïve-treated
- with metformin ± pioglitazone
- HbA1c 7.0-10.0%
- BMI \leq 40 kg/m²
- Age \geq 18 years*

*Singapore age >21 years

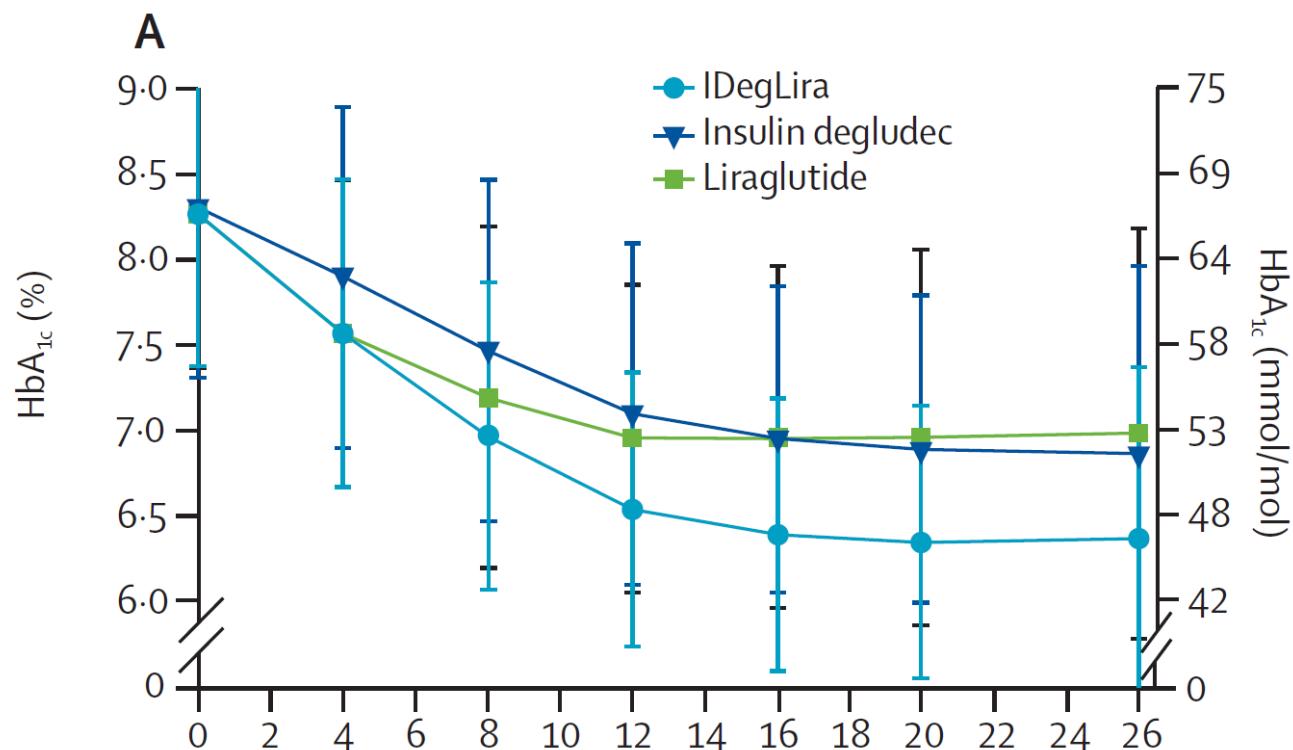
DUAL I: IDegLira vs IDeg vs Liraglutide

Mean Daily Doses



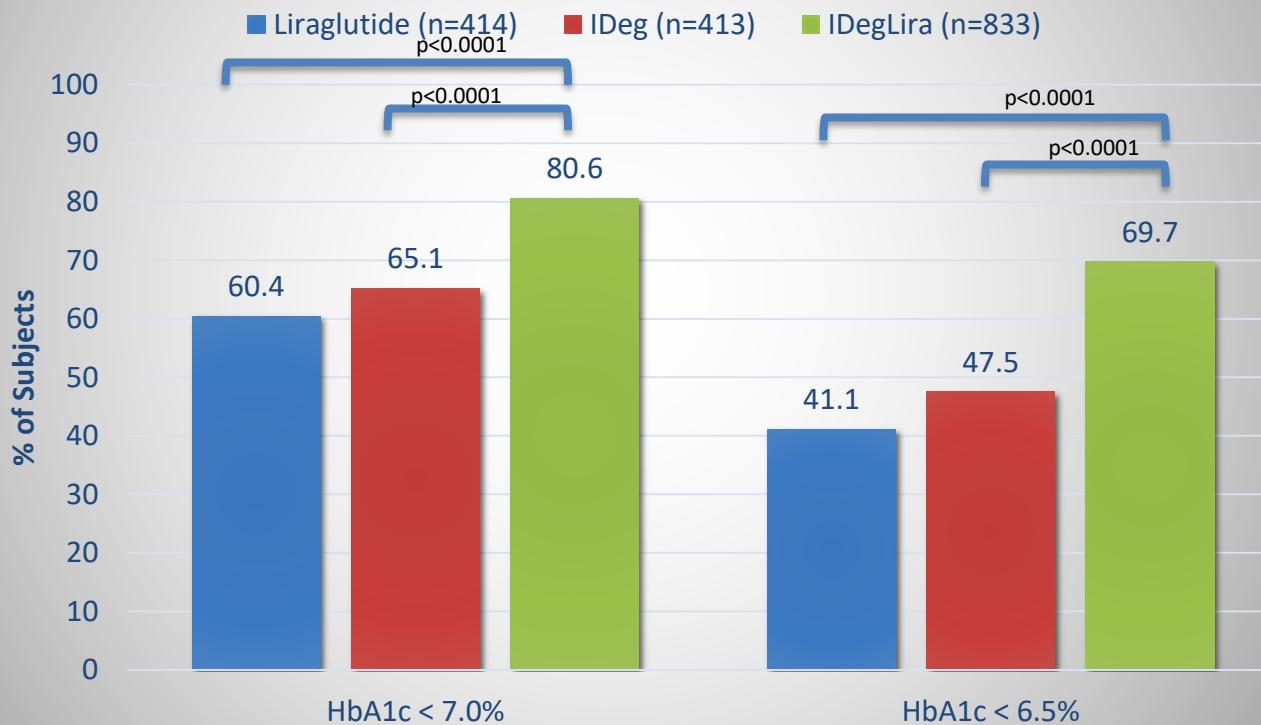
DUAL I: IDegLira vs IDeg vs Liraglutide

HbA_{1c} over time



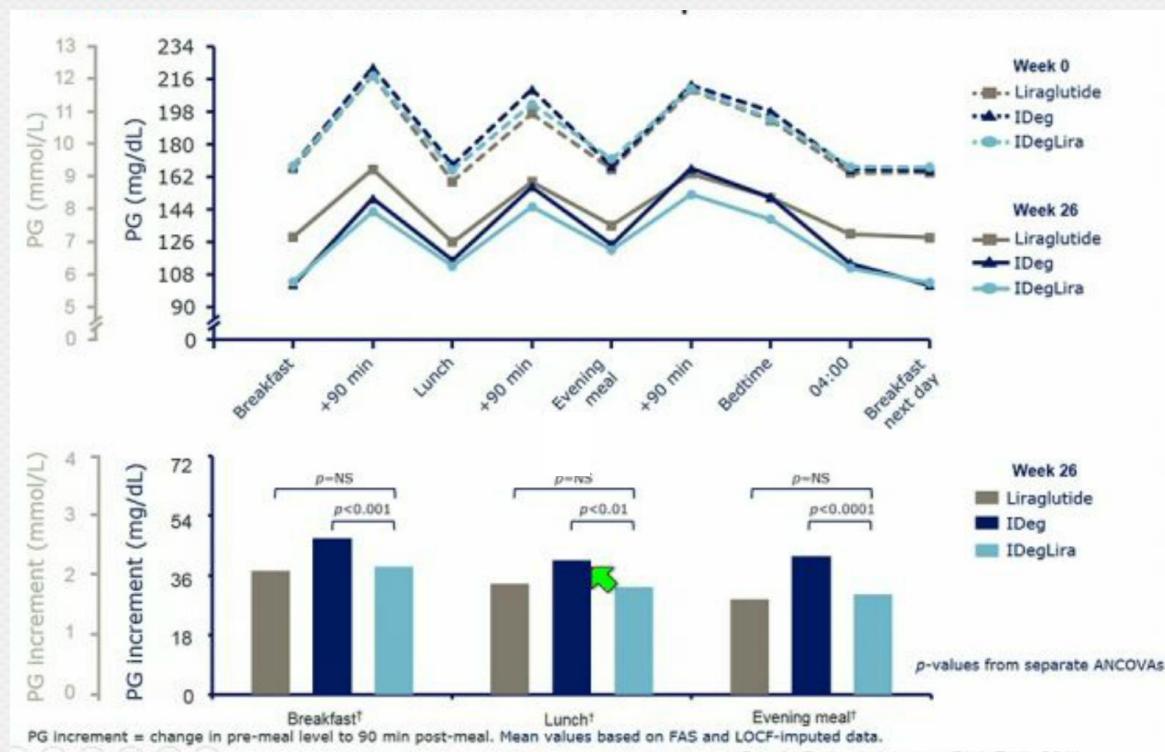
DUAL I: IDegLira vs IDeg vs Liraglutide

Percentage of subjects to target

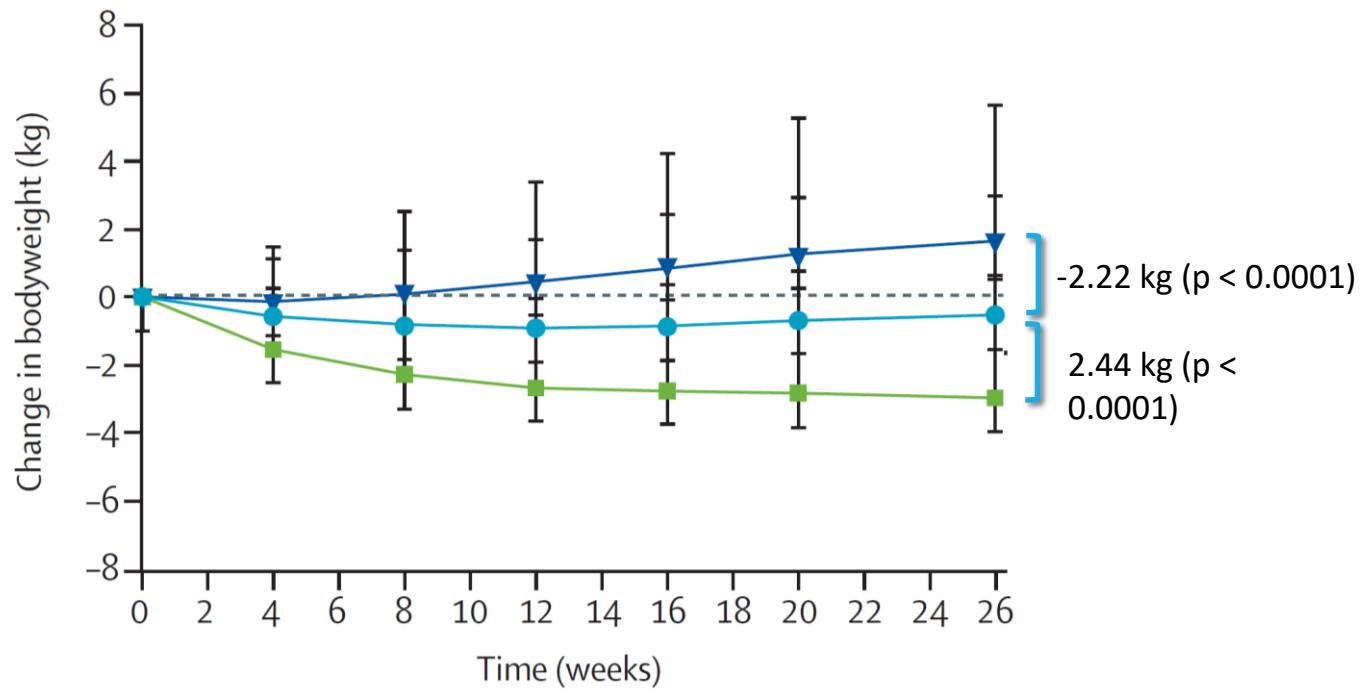


Gough, Bode Et al. Lancet Diab Endo 2014

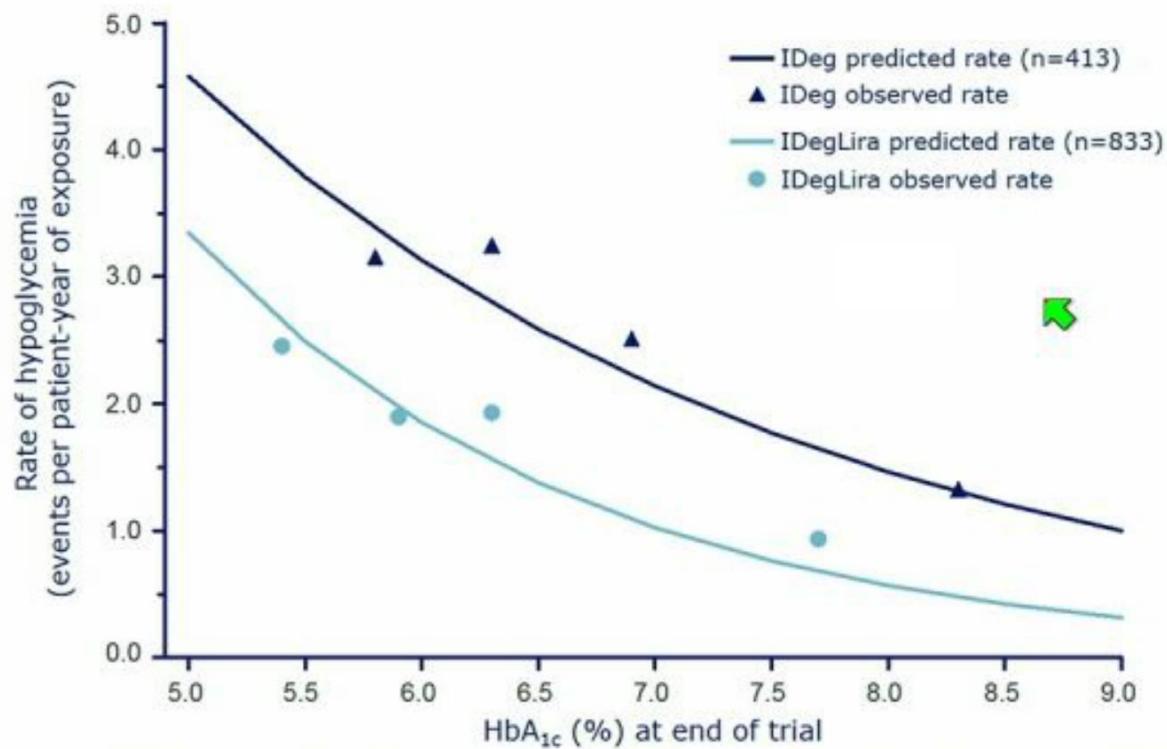
DUAL I: 9-point SMBG: Post-prandial PG increment



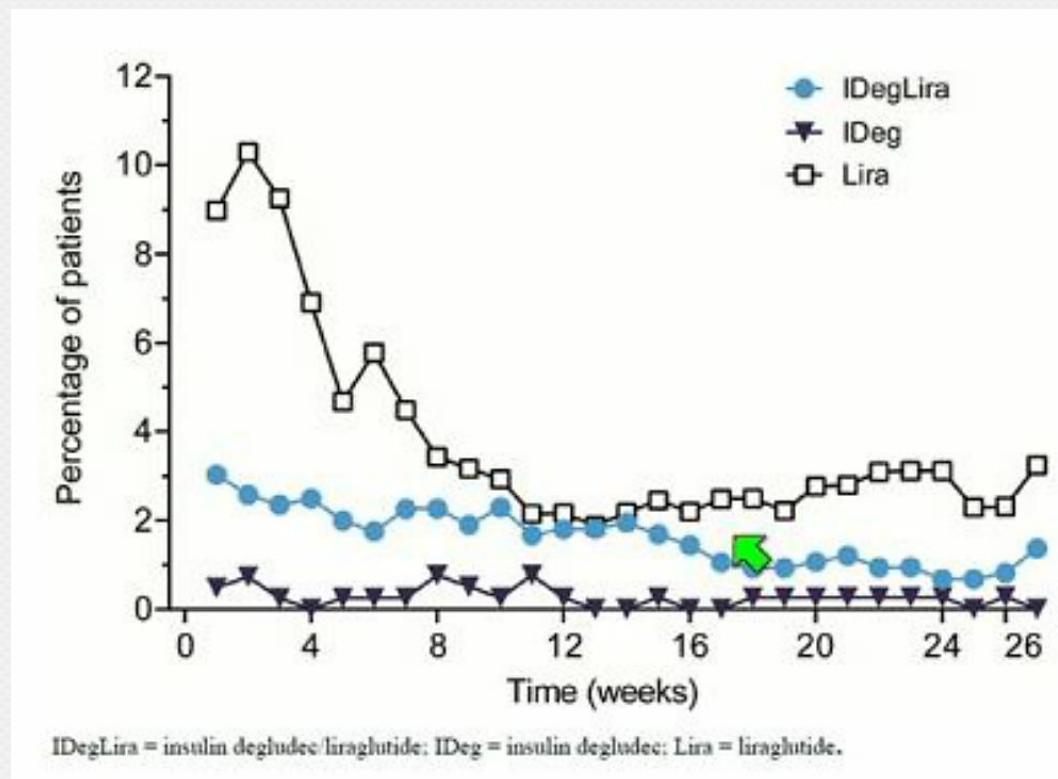
DUAL I: Change in body weight over time



DUAL I: Rate of confirmed hypoglycemia by HbA_{1c}

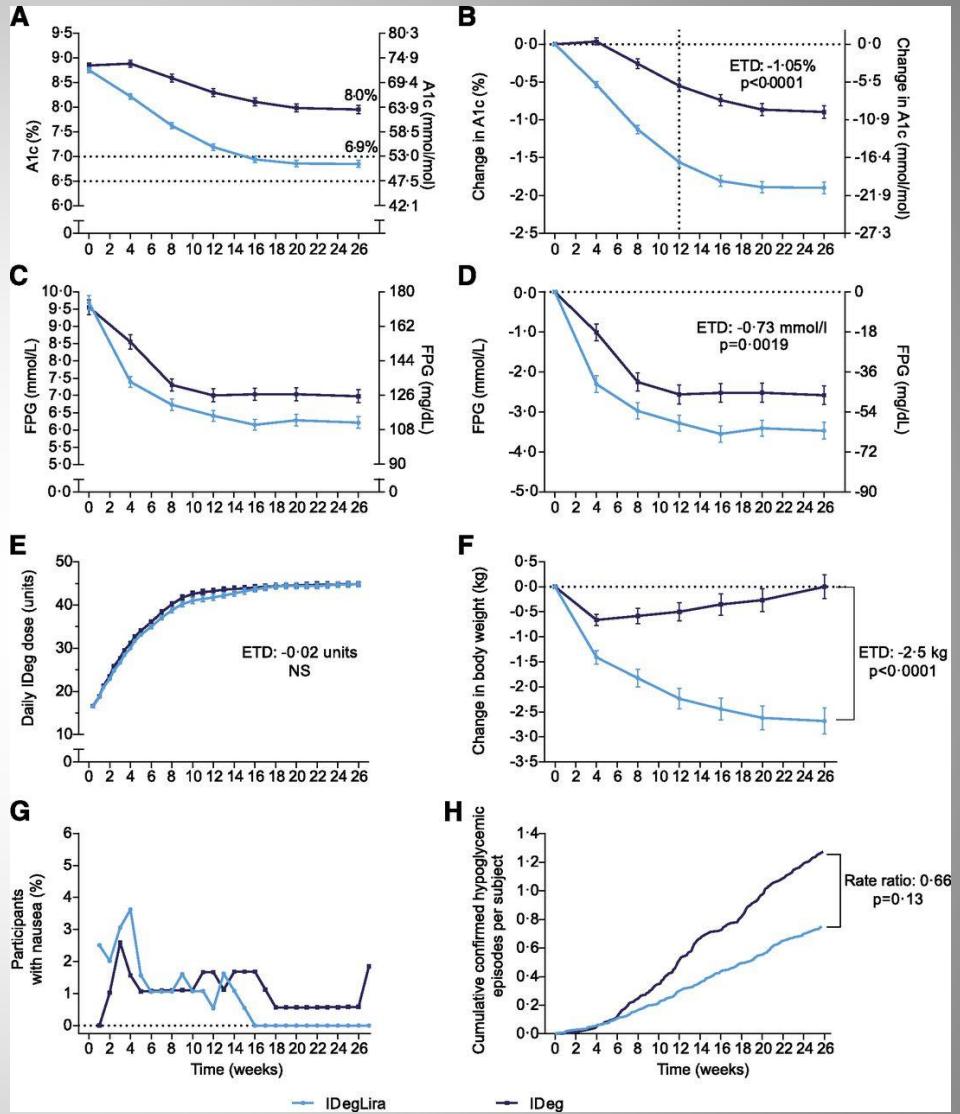


DUAL I: Nausea over time

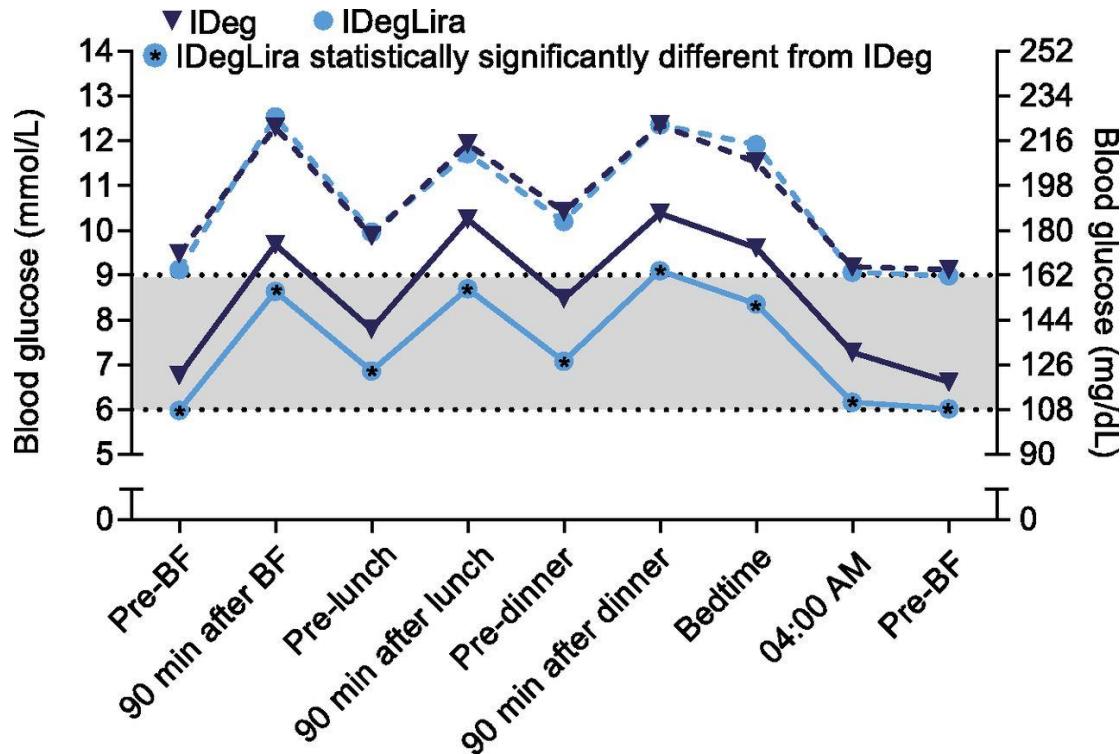


DUAL II: IDegLira vs Degludec in patients on basal insulin

- 199 patients per group
- Glycemic efficacy, insulin dose, body weight, and AEs.
- Data are means (SE).



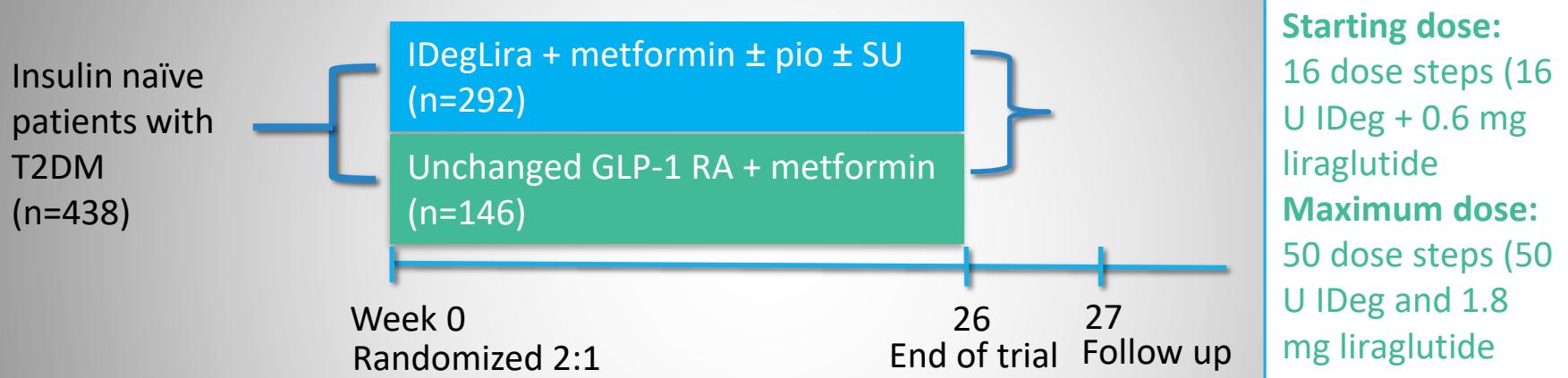
DUAL II: IDegLira vs Degludec in patients on basal insulin



Mean 9-point self-monitored blood glucose profiles at baseline (dotted line) and after 26 weeks (full line).

DUAL III: IDegLira vs unchanged GLP-1 RA

Study Design



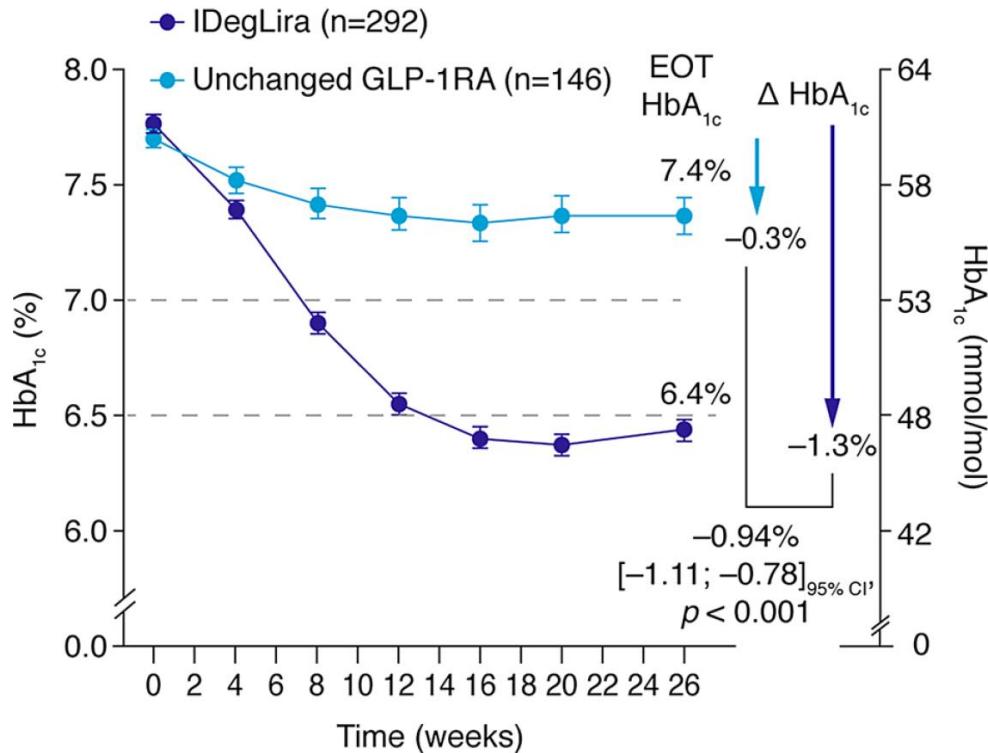
Inclusion Criteria

Type 2 diabetes
GLP-1 RA max dose + met
± pio ± SU
HbA1c 7.0-9.0%
Age ≥ 18 years
BMI ≤ 40 kg/m²

Mean Fasting PG		Titration Dose Change
mg/dL	mmol/L	Dose steps/U
<72	<4.0	-2
72-90	4.0-5.0	0
>90	>5.0	+2

DUAL III: IDegLira vs unchanged GLP-1 RA

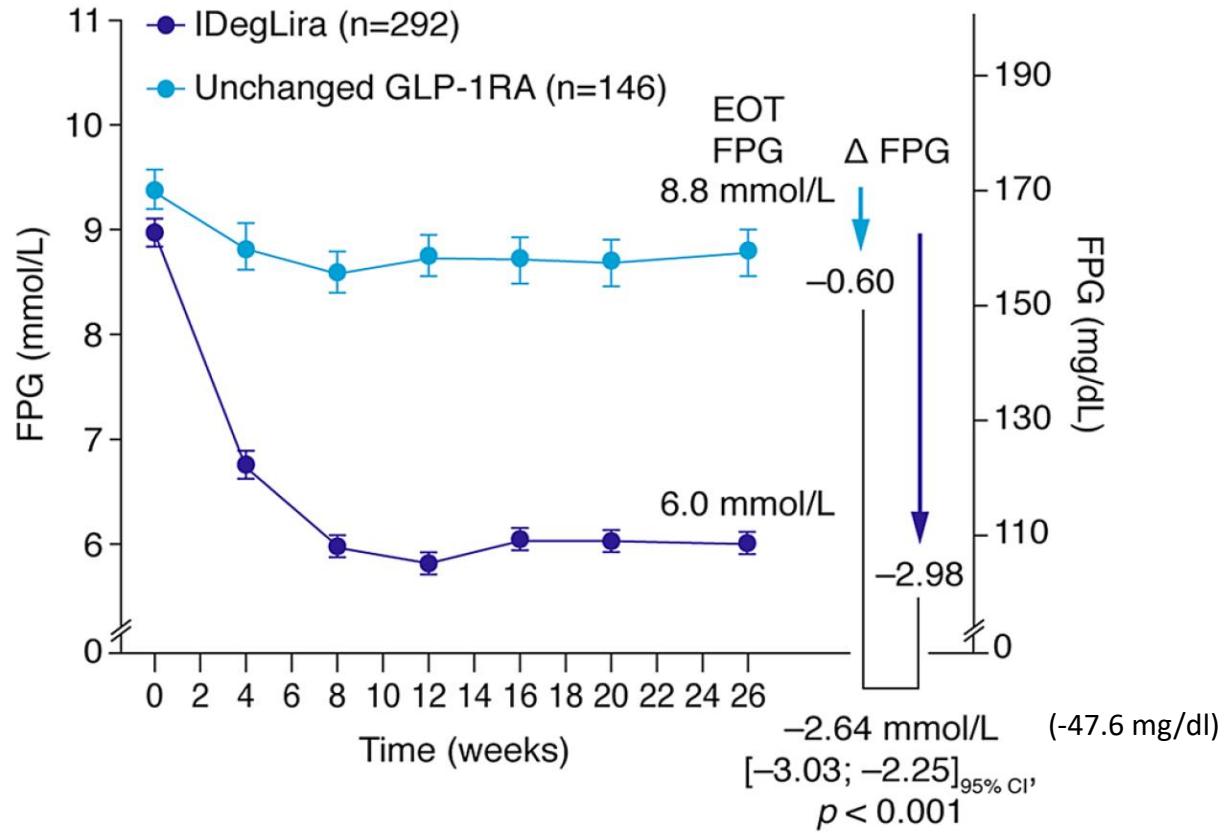
HbA_{1c} over time



Mean observed values with error bars (standard error of the mean) based on FAS and LOCF imputed data. ETD is from ANCOVA analysis, and change in HbA_{1c} (Δ) values are observed; both are based on FAS and LOCF imputed data. Dotted lines represent ADA/EASD and AACE HbA_{1c} targets of 7.0% and 6.5%, respectively.

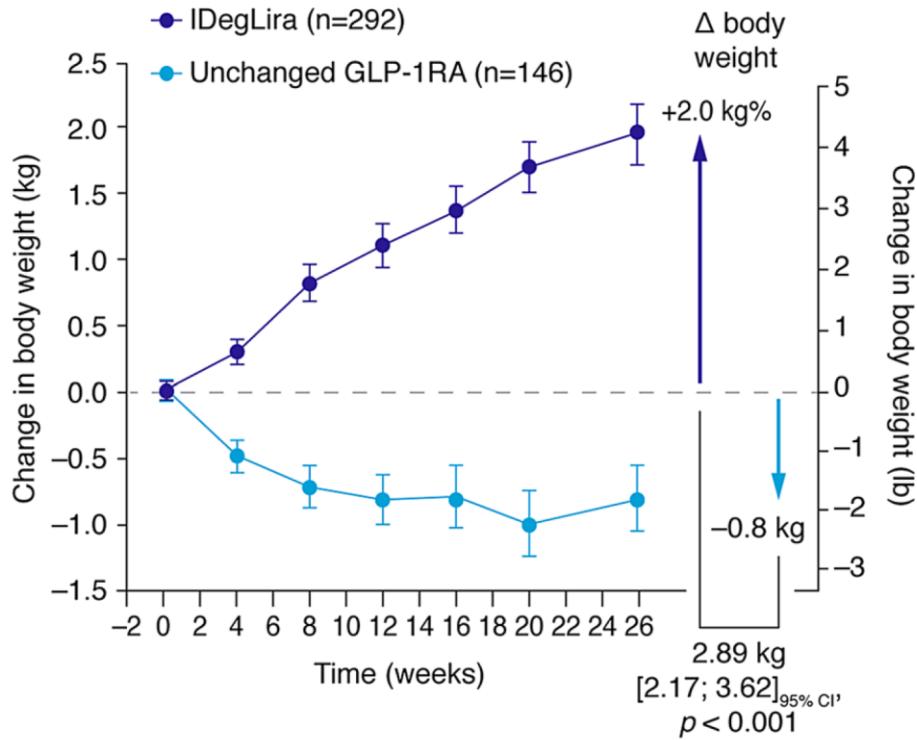
DUAL III: IDegLira vs unchanged GLP-1 RA

FPG over time



DUAL III: IDegLira vs unchanged GLP-1 RA

Change
in body
weight
over
time

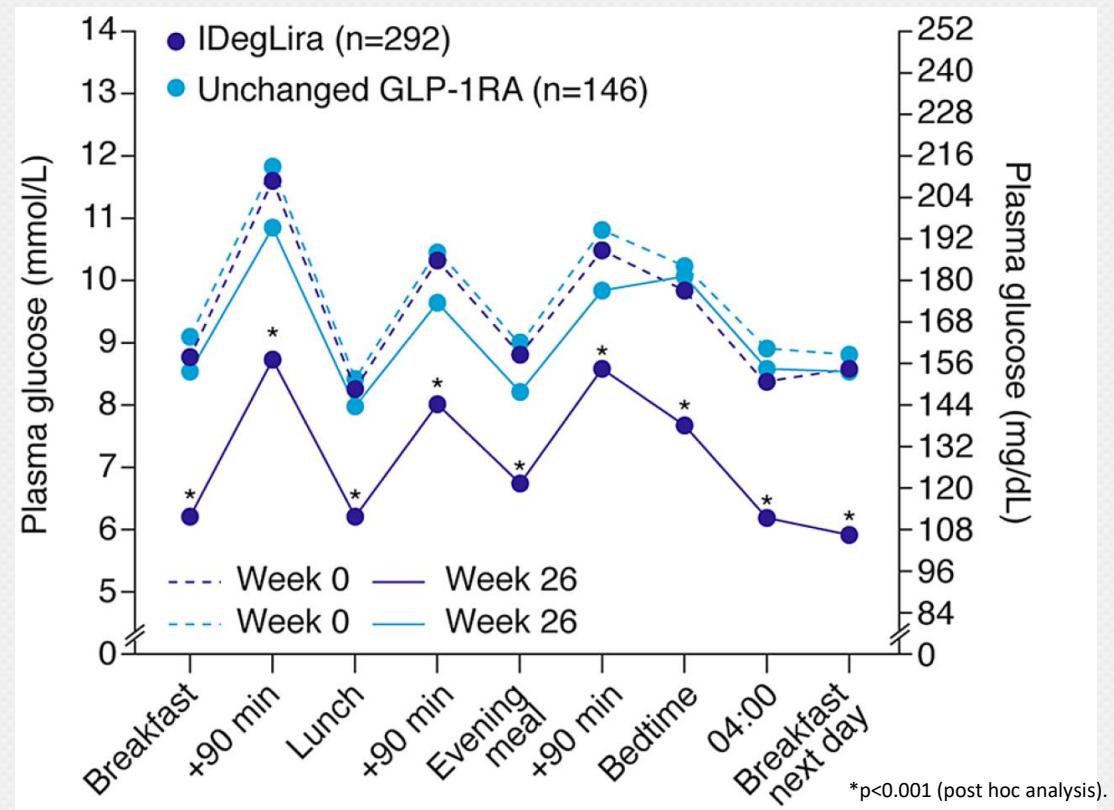


DUAL III: IDegLira vs unchanged GLP-1 RA

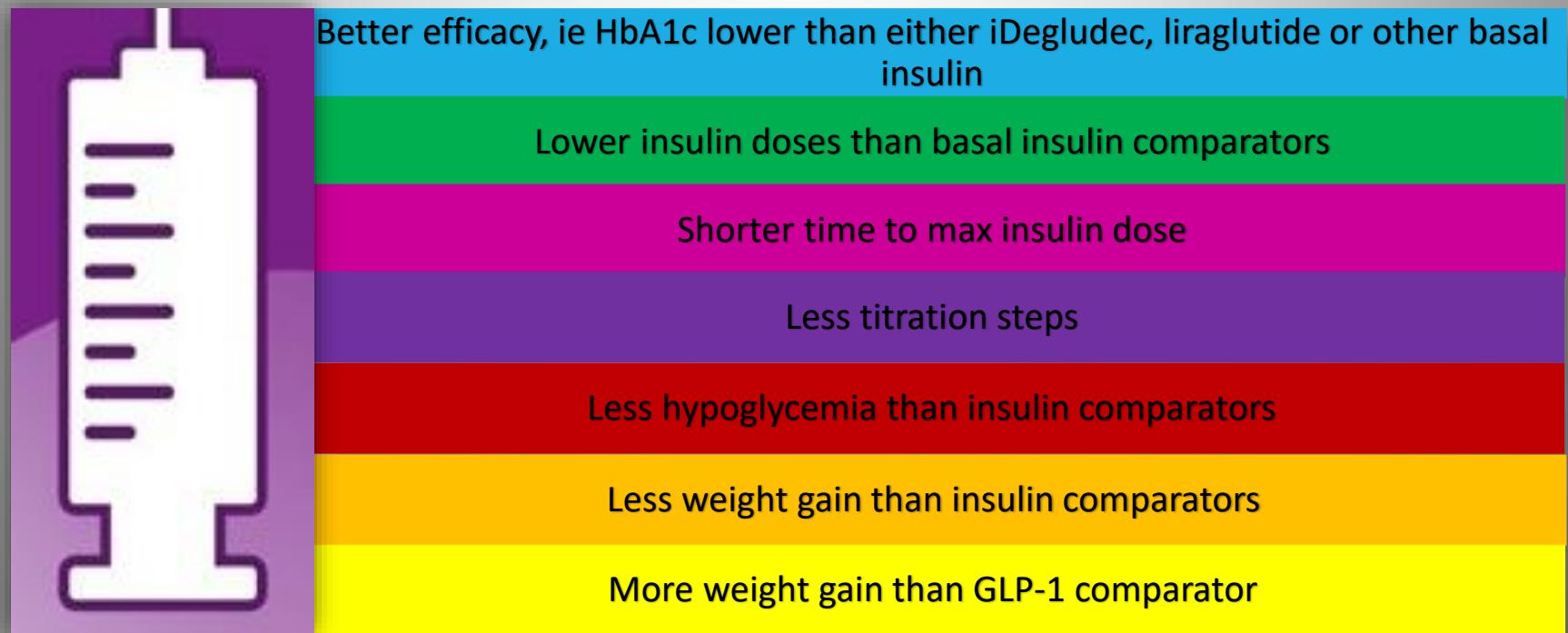
9-point SMBG profile

Greater reduction in mean 9-P SMBG profile with IDegLira versus GLP-1 RA

Treatment difference:
<32 mg/dl,
 $P<0.001$



DUAL Studies: IDegLira Fixed Dose Combination vs Comparators

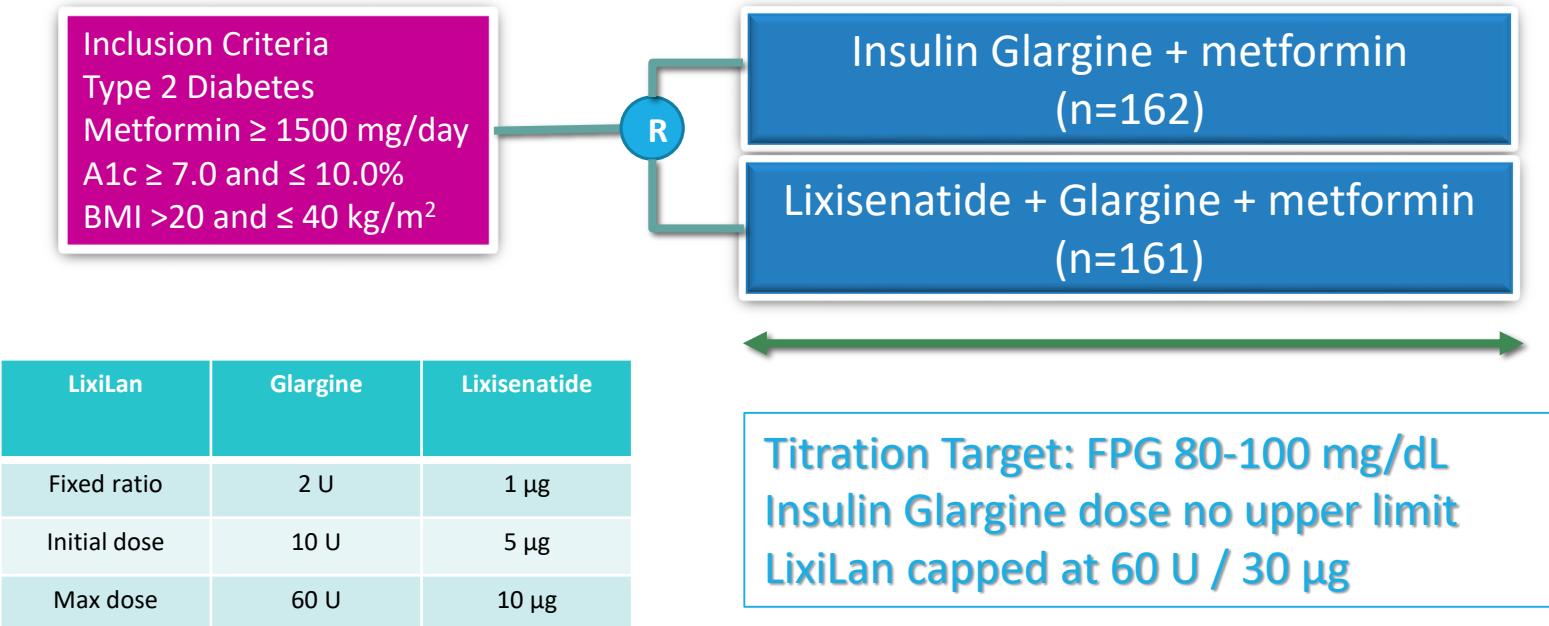


LixiLan Proof of Concept

Lixilan vs iGlargine in insulin Naïve T2DM Patients

Parameter	LixiLan	iGlargine
Baseline HbA1c	$8.1 \pm 0.8\%$	$8.0 \pm 0.8\%$
Week 26 HbA1c	6.3%	6.5%
Final daily insulin doses	36 Units	39 Units
Symptomatic hypoglycemia	21.7%	22.8%
Nausea	15.5%	9.3%
AEs leading to discontinuation	3.7%	0

LixiLan Proof of Concept: Study Design



GetGoal Duo 2 Trial

Lixisenatide + Basal Insulin vs Insulin Glulisine either as basal-plus or basal-bolus in T2DM

- ➡ Entry criteria: patients with T2DM on OAD + basal insulin
- ➡ 298 patients per group
 - Lixisenatide 20 mcg once daily
 - Insulin glulisine once daily
 - Insulin glulisine 3x daily
- ➡ Screening HbA1c 8.5%, after run-in, 7.8-7.9%
- ➡ Insulin glargine dose: screening 39 - 41 units, after run-in, 65 – 68 units

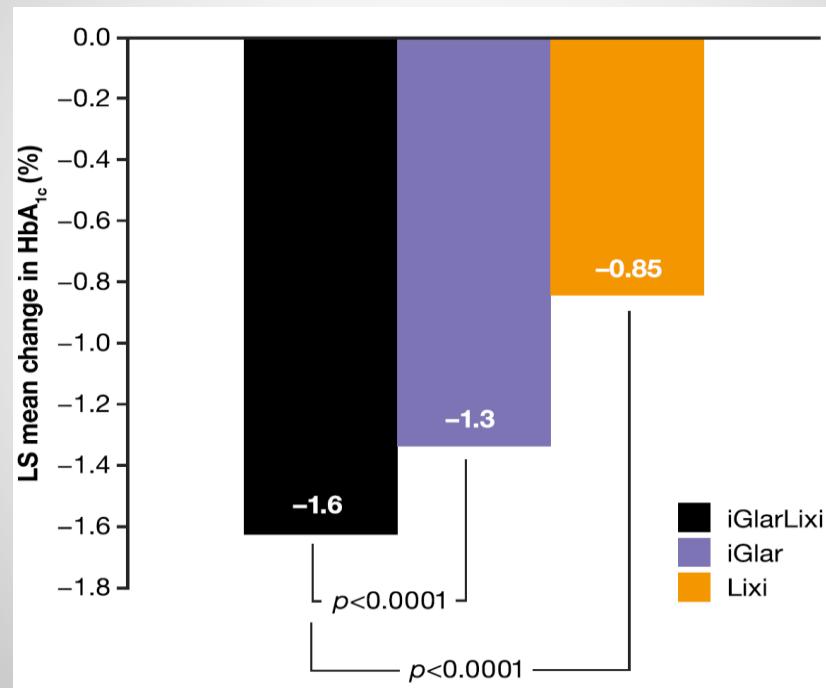
GetGoal-2 Trial: Results

Parameter	Lixi 20 µg daily	iGulisine 1x	iGulisine 3x
HbA1c, % baseline	7.8	7.8	7.8
HbA1c, % week 26	7.2	7.2	7.0
Change body weight	-0.6 kg	+1.0 kg	+1.4 kg
iGlargine dose, units/day	67	65	65
iGulisine dose, units/day	-	10 ± 8	20 ± 13
TDD	67 ± 32	74 ± 39	81 ± 34
Symptomatic hypoglycemia	35.9%	46.5%	52.4%
Lixi vs iGlu Hypo		0.75	0.49

ROSENSTOCK J, ET AL. DIABETES CARE 2016; 39: 1318-1328

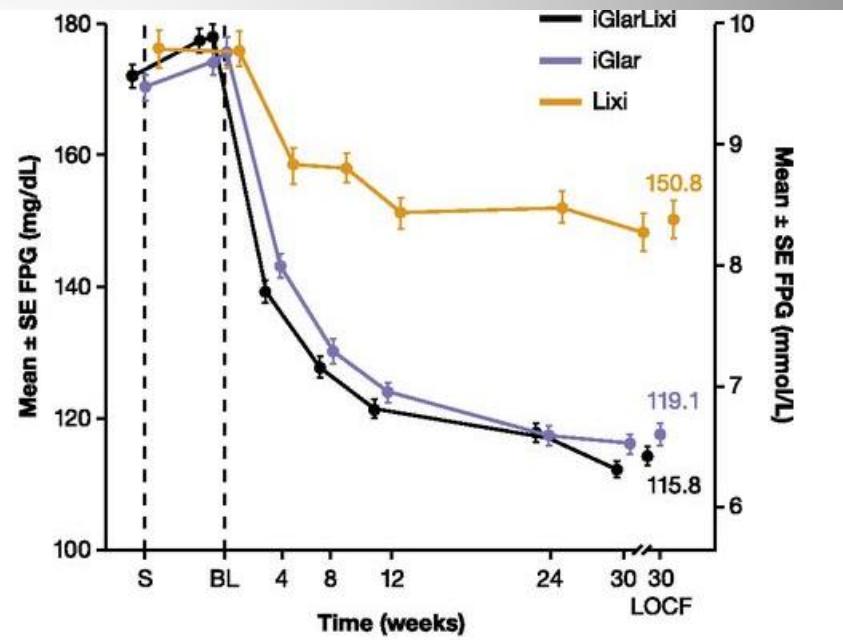
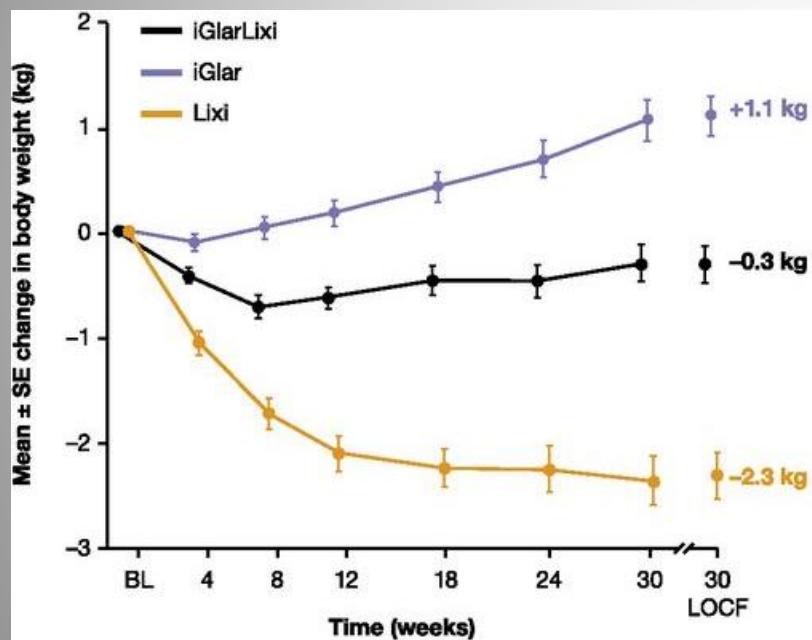
LixiLan-O: LixiLan vs Lixi vs Glargine

Change in FBG and Weight



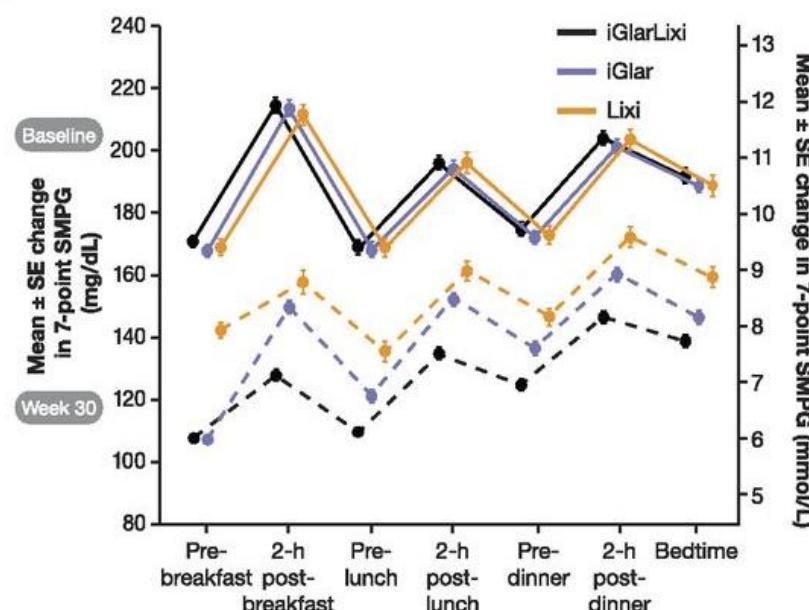
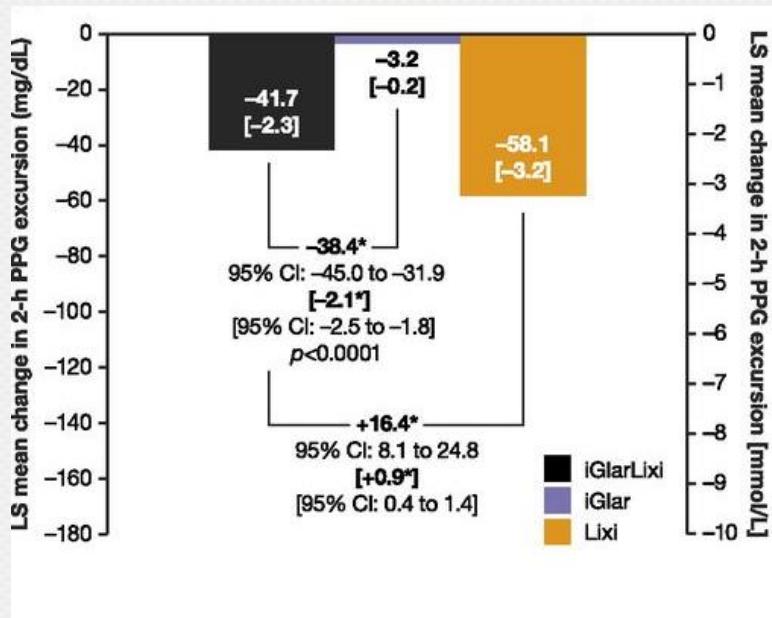
Rosenstock J, et al. Diabetes Care 2016; 39: 1318-1328

LixiLan-O: LixiLan vs Lixi vs Glargine Change in FBG and Weight

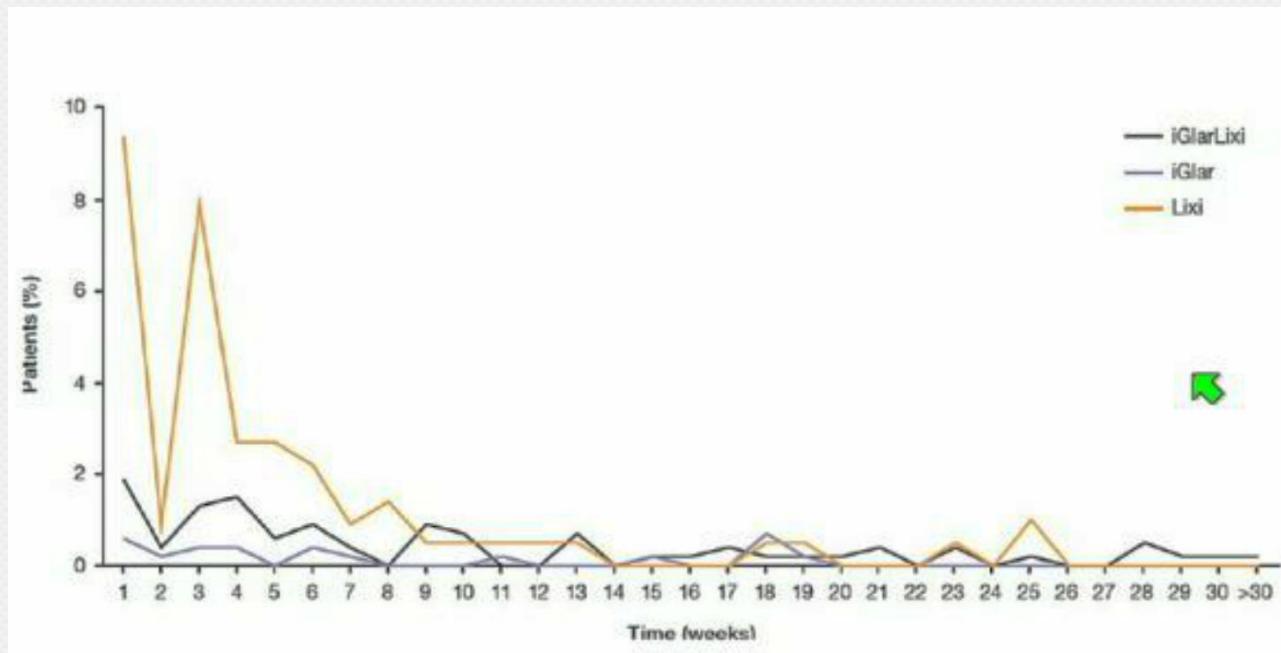


Rosenstock J, et al. Diabetes Care 2016;
39:2026-2035

LixiLan-O: LixiLan vs Lixi vs Glargine Change in 2-h PPG and 7-pt profile



LixiLan-O: LixiLan vs Lixi vs Glargin



GLP-1 RA and Insulin: Efficacy Outcomes

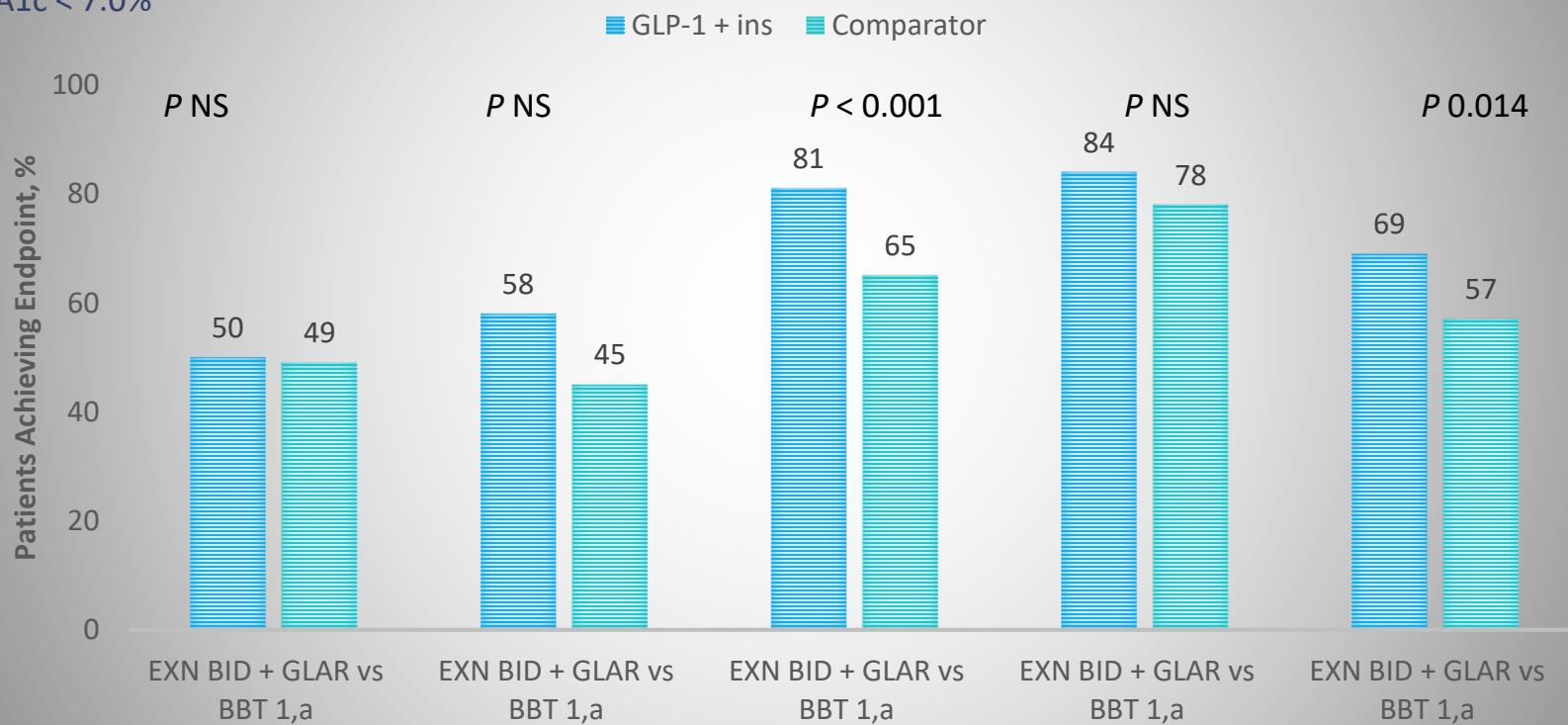
Study	Study Drug and Comparator	Overall Hypoglycemia	Severe Hypoglycemia	Overall Hypoglycemia Definition
Diamant ^{1,a}	EXN BID + GLAR BBT	335 events 881 events	3 events 11 events	Minor symptomatic or self-treated, BG < 54 mg/dL
Mathieu ^{2,b}	LIRA QD + DEG BBT	1.00 EPY 8.15 EPY	0 events 0 events	Confirmed, BG < 56 mg/dL or severe
Gough ^{3,c,f}	LIRA FRC QD DEG	1.77 EPY 2.79 EPY	3 events 2 events	Confirmed, BG < 56 mg/dL or severe
Rosenstock ^{4,d}	LIXI FRC QD GLAR	22% 23%	0 events 0 events	Confirmed, BG < 70 mg/dL
Blonde ^{5,e}	DULA QW + LIS BBT	10.42 EPY 13.23 EPY	0.06 EPY 0.09 EPY	Documented symptomatic, PG < 54 mg/dL

a. BL A1c 8.5%, BL Wt 89 kg; 30 weeks; b. 26-weeks, BL A1c 7.7%, BL Wt 91-95 kg, BL BMI 32-33 kg/m², age 61 y, diabetes duration 12-13 y; c. 26-weeks BL A1c 8.3%, BL Wt 87 kg; d. 24 weeks, BL A1c 8.0%, BL BMI 32.1 kg/m², e. DULA 1.5 mg, BL A1c 8.5%, BL Wt 91 kg, 26 wk results

1. Diamant M, et al. Diabetes Care 2014; 37: 2763-2773.
2. Mathieu C, et al. Diabetes Obes Metab, 2014; 16: 636-644.
3. Gough SC, et al. Lancet Diabetes Endocrinol. 2014; 2: 885-893.
4. Rosenstock J, et al. Diabetologia 2014; 57 (suppl 1) [abstract 241].
3. Blonde L, et al. Lancet 2015; 385: 2057-2066.

GLP-1 RA and Insulin: Efficacy Outcomes

HbA1c < 7.0%

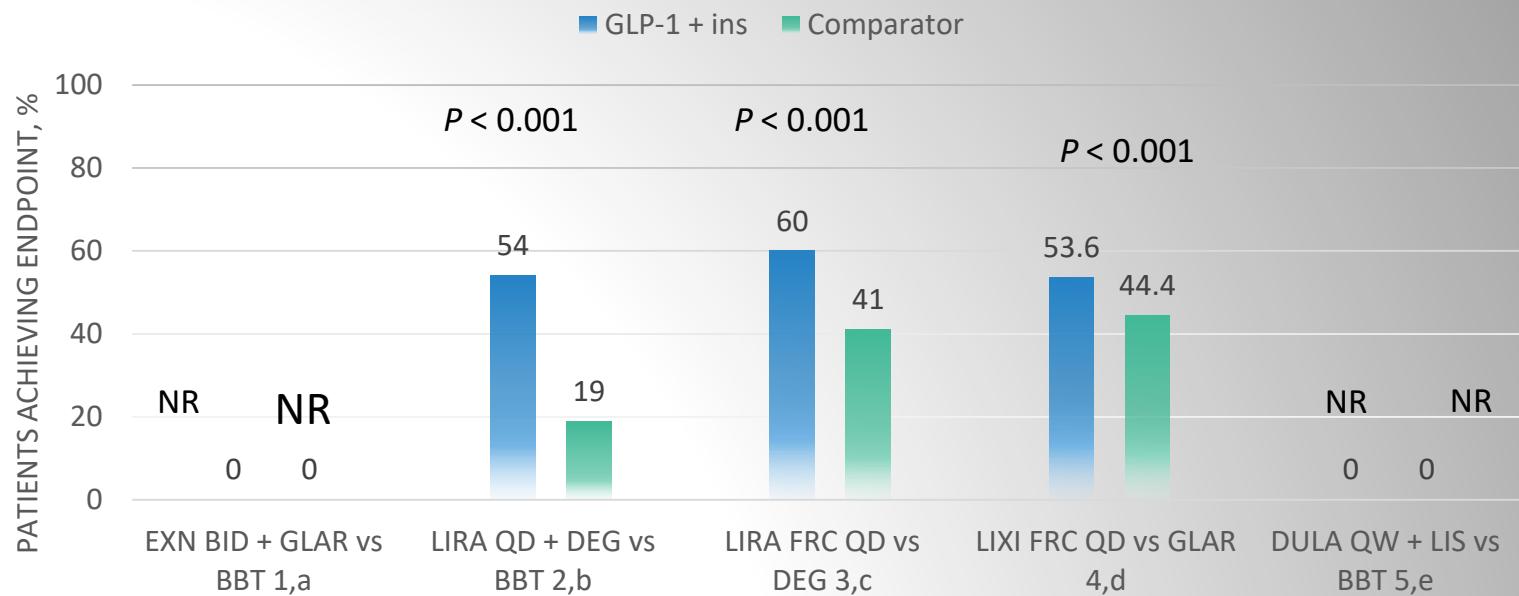


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GLP-1 RA and Insulin: Efficacy Outcomes

A1c < 7.0% and no hypoglycemia

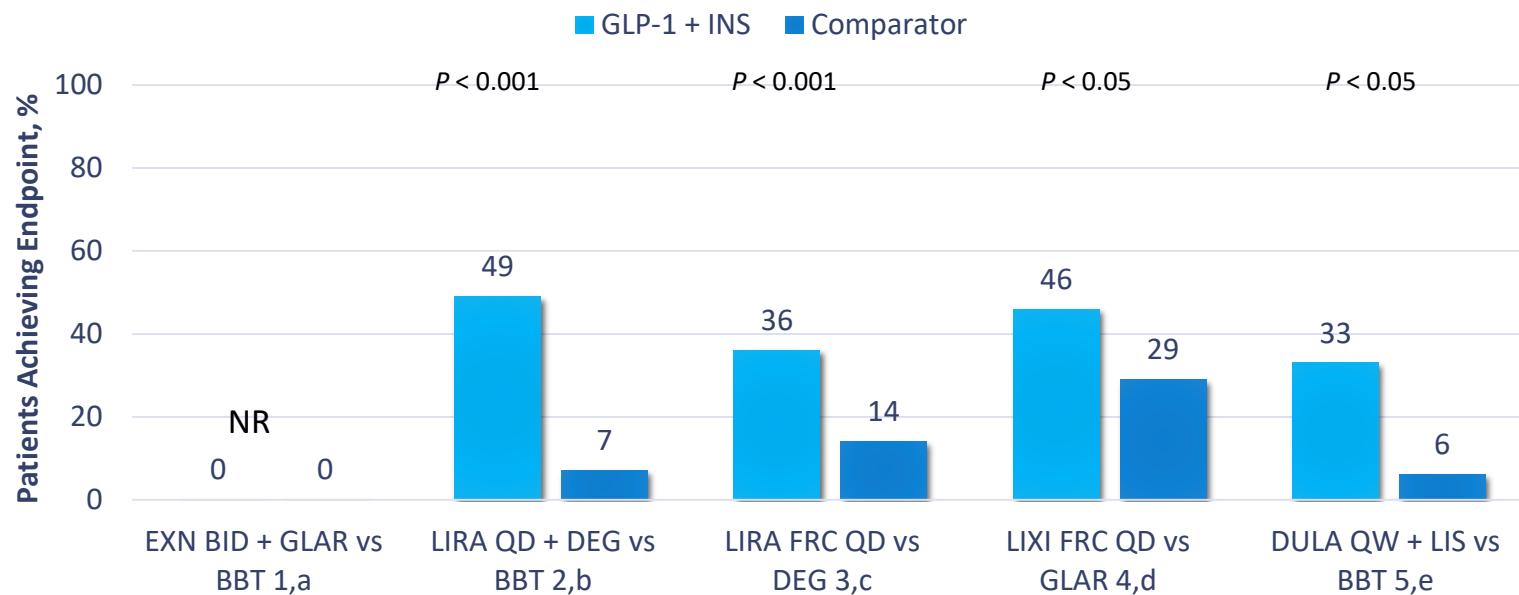


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GLP-1 RA and Insulin: Efficacy Outcomes

A1c < 7.0%, no hypoglycemia, and no weight gain



a. BL A1c 8.5%, BL Wt 89 kg; 30 weeks; b. 26-weeks, BL A1c 7.7%, BL Wt 91-95 kg, BL BMI 32-33 kg/m², age 61 y, diabetes duration 12-13 y; c. 26-weeks BL A1c 8.3%, BL Wt 87 kg; d. 24 weeks, BL A1c 8.0%, BL BMI 32.1 kg/m²; e. DULA 1.5 mg, BL A1c 8.5%, BL Wt 91 kg, 26 wk results.

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Safety Considerations: GLP-1 RAs Used with Insulin

	GLP-1 Approved for Use with Insulin
Contraindications	Not indicated for treatment of DKA ^{a,b,c,d} Personal or family history of MTC ^{a,b,d} , or MEN syndrome type 2 ^{a,b,d} Prior history of hypersensitivity reaction to specific agent or components ^{a,b,c,d}
Warnings and precautions	Hypoglycemia (with SUs or insulin) ^{a,b,c,d} Thyroid C-cell tumors in preclinical studies ^{a,b,d} Discontinue if pancreatitis is suspected ^{a,b,c,d} Hypersensitivity reactions ^{a,b,c,d} Use caution in renal impairment ^{a,b,d} ; reduce dose or monitor renal function in renal impairment ^{b,d} ; do not use exenatide BID in severe renal impairment ^c Pregnancy category C ^{a,b,c,d}
Adverse reaction	Gastrointestinal (mild-severe) ^{a,b,c,d} Allergic reactions (mild-severe) ^{a,b} Neurological (mild-moderate) ^{b,c,d} Respiratory (mild-moderate) ^a Hypoglycemia ^{c,d} Orthopedic (mild-moderate) ^a

Summary

- ✓ Fixed dose combinations of a GLP1-RA and basal insulin have been extensively tested for safety and efficacy.
- ✓ Two FDC have been recently approved by the FDA.
- ✓ Benefits of FDC:
 - Better efficacy than either component given alone
 - Improved fasting and post-prandial glucose levels
 - Lower rates of hypoglycemia and Wt gain than insulin monotherapy
- ✓ Limitations of FDC:
 - Nausea remains problematic
 - Dose titration is required
 - Cost



*"Aprende como si
fueses a vivir
siempre"*

M. Gandhi