

New Approaches to Insulin Therapy in Combination

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Type 2

CORE

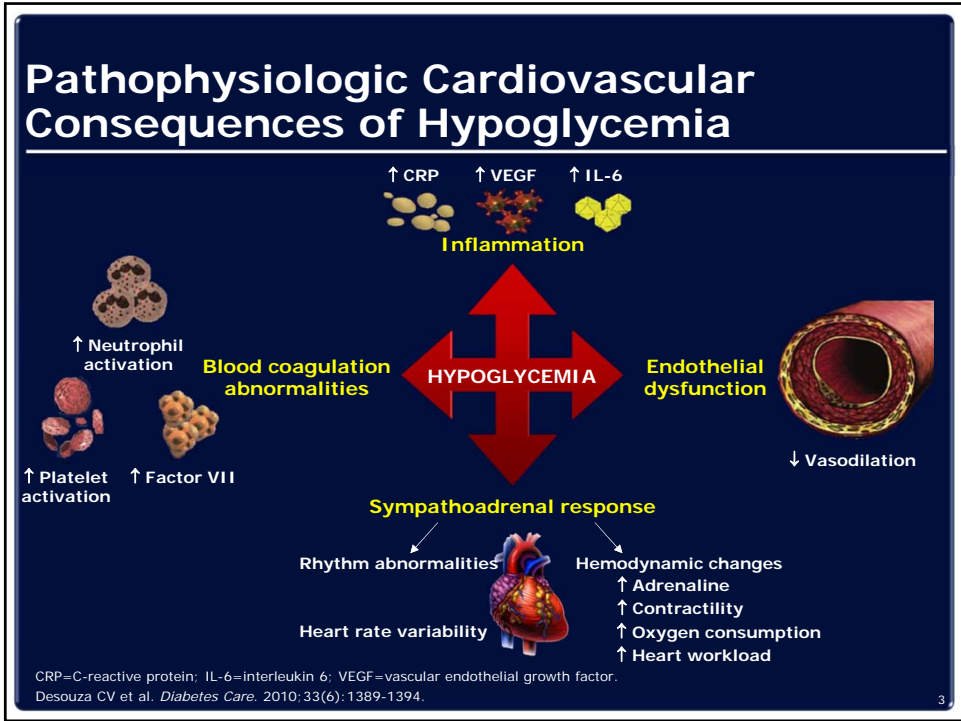
Long-Term Benefits of Glycemic Control for Microvascular Complications

- Long-term benefits persist after intervention
 - Type 1 (EDIC): intensive treatment reduces risk of microvascular complications for at least 8 years beyond therapy
 - Type 2 (UKPDS): tight glycemic control reduces risk of microvascular effects—even 10 years after treatment
- Long-term benefits not seen consistently
 - No reduction of microvascular complications* in Veterans Affairs Diabetes Trial (VADT) intensive arm
- Results suggest a “metabolic memory” (“legacy”) effect

*Except for conversion from normo- to micro- or macroalbuminuria

EDIC=Epidemiology of Diabetes Interventions and Complications;
UKPDS=United Kingdom Prospective Diabetes Study

Martin CL, et al. *Diabetes Care*. 2006;29(2):340-344.
Holman RR, et al. *N Engl J Med*. 2008;359(15):1577-1589.
Writing Team for DCCT/EDIC Research Group. *JAMA*. 2003;290(16):2159-2167.
Del Prato S, et al. *Diabetologia*. 2009;52(7):1219-1226

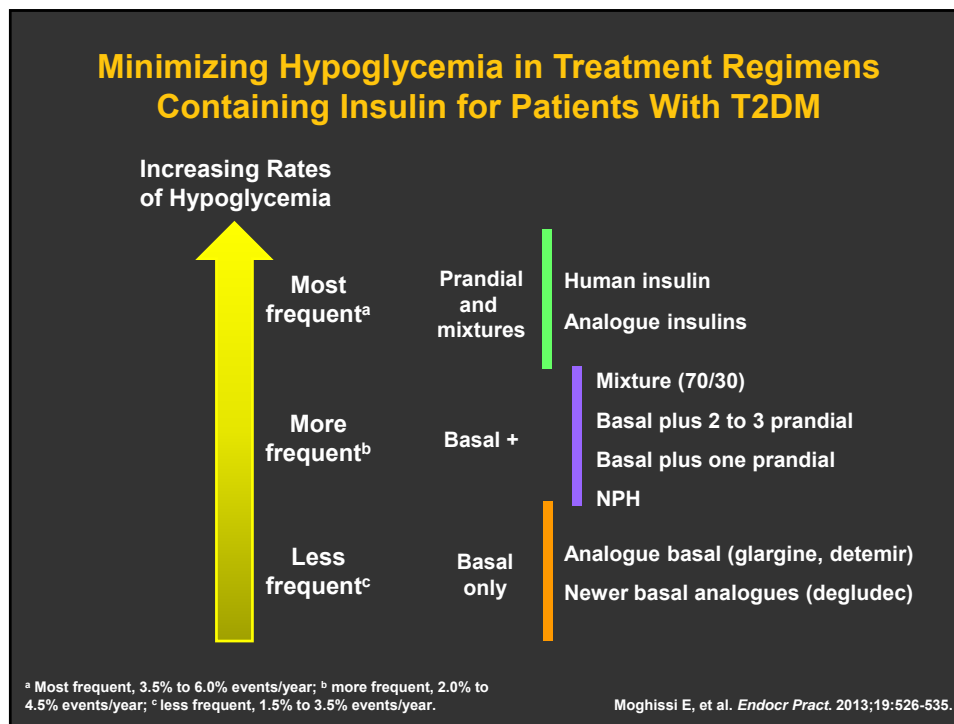


The Quest for a Better Basal Insulin...

Insulin Initiation and Optimization in Type 2 DM

Key Factors Assessing Insulin Strategies

- Absolute A1c Reduction !
- Insulin Titration and Doses !
- Amount of Hypoglycemia !
- Degree of Complexity
- Weight Gain



Combining Insulin With Other Diabetes Agents

- **Sulfonylurea, Metformin, Pioglitazone, Rosiglitazone**
 - Bedtime glargine or NPH in combination with 1 or 2 of these OAs was effective in achieving target glycemic levels; glargine had fewer episodes of nocturnal hypoglycemia
 - In combination with metformin, weight gain is contained
- **GLP-1 and Pramlintide**
 - addition to insulin-based therapy associated with reductions in A1C, weight, and insulin requirements
 - Prandial Control
 - Additional injections
- **DPP-4 Inhibitors- modest effect but ? Less hypoglycemia**
- **SGLT-2 Inhibitors**
- **Other drugs- Colesevalam, Bromocriptine, Acarbose**

Riddle M. *Diabetes Care.* 2003;26:3080-3086; Raskin P et al. *Diabetes Care.* 2005;28:260-265; Riddle M. *Diabetes Care.* 2009;32:1577-1582; Hollander PA. *Diabetes Care.* 2003;26:784-790; Yoon NM. *Clin Ther.* 2009;31:1511-1523

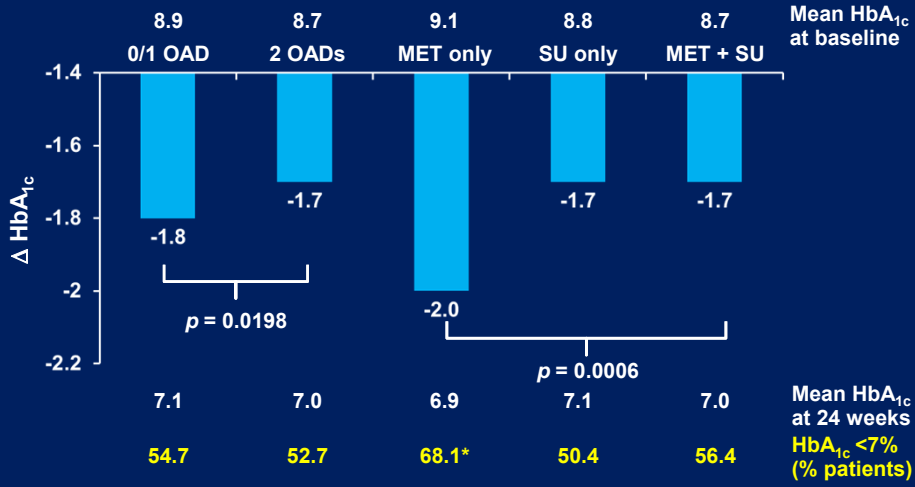
Combining Insulin Therapy With Metformin Minimizes Weight Gain

	Yki-Järvinen ¹		Avilés-Santa ²		Bergenstal ³	
	Insulin	Insulin + Metformin	Insulin	Insulin + Metformin	Insulin	Insulin + Metformin
Number of Subjects	24	19	22	21	22	20
Duration of Study (months)	12	12	6	6	4	4
Insulin Dosage at End (U/day)	24	36	120	92	136	99
A1C at End (%)	7.9	7.2	7.5	6.5	7.0	7.1
Weight Gain (kg)	4.6	0.9*	3.2	0.5*	0.5	-1.4

* P < 0.01

¹Yki-Järvinen H, et al. *Ann Intern Med.* 1999;130:389-396.
²Avilés-Santa L, et al. *Ann Intern Med.* 1999;131:182-188.
³Bergenstal RM, et al. *Diabetes.* 1998;47(suppl 1):A89. Abstract 347.

Glycemic changes with insulin glargine by baseline OAD use[†]

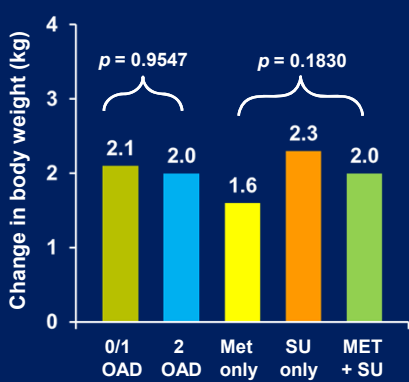
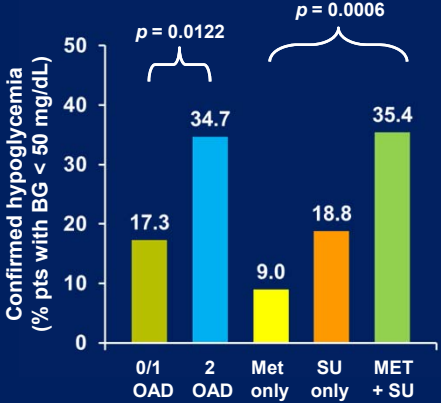


[†] Pooled analysis
 * p = 0.0001 vs all taking SU

Fonseca V, et al. *Diabetes Obes Metab* 2011;13:814-22.

Hypoglycemia and weight with insulin glargine by baseline OAD use: Pooled analysis

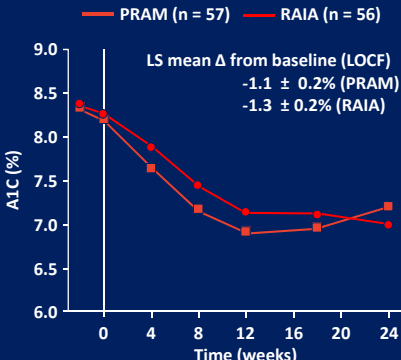
- Significantly lower hypoglycemia in MET only patients
- No significant difference in body weight



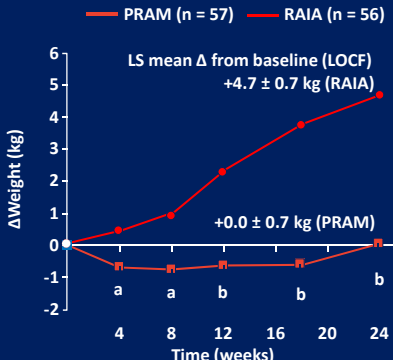
Fonseca V, et al. *Diabetes Obes Metab* 2011;13:814–22.

Use of Mealtime Pramlintide vs Mealtime Prandial Rapid-Acting Insulin Analogue With Basal Insulin Analogue ± MET ± SU ± TZD in T2DM

Efficacy

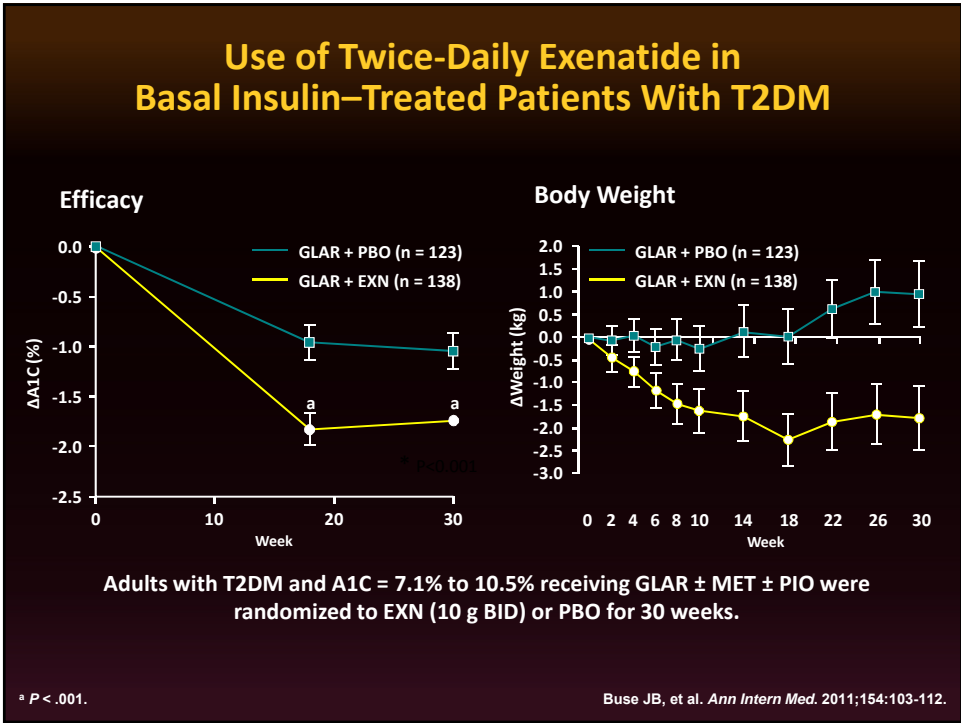
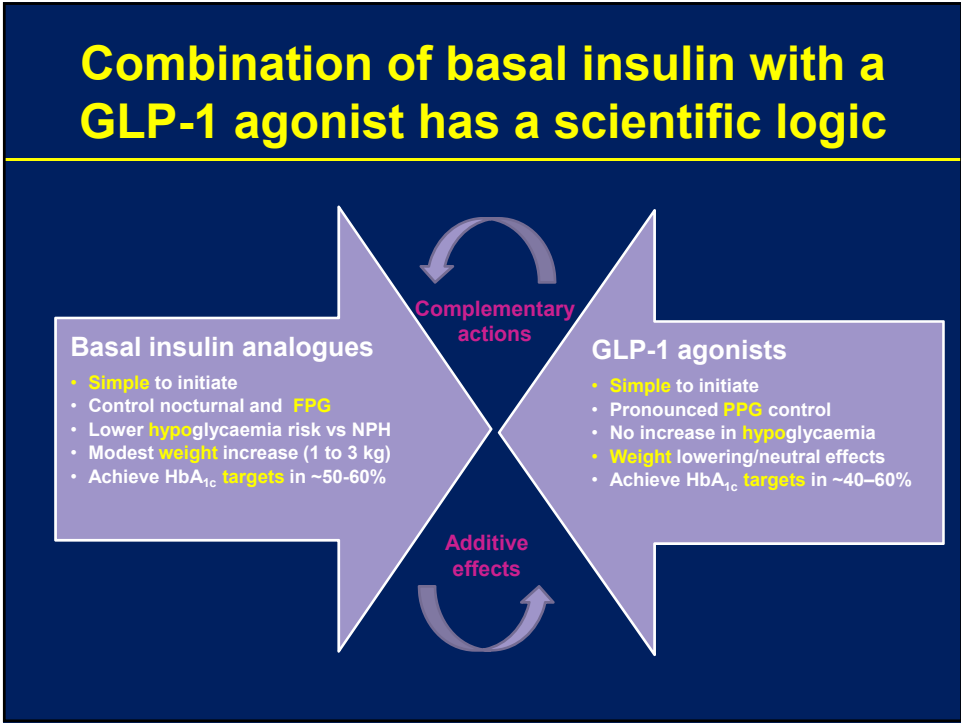


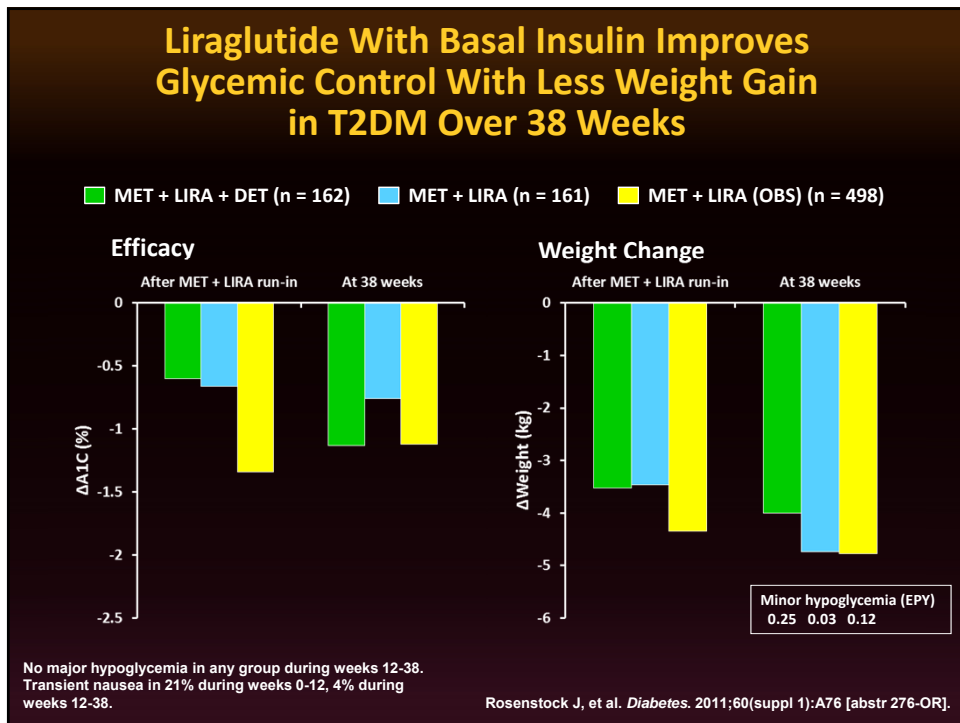
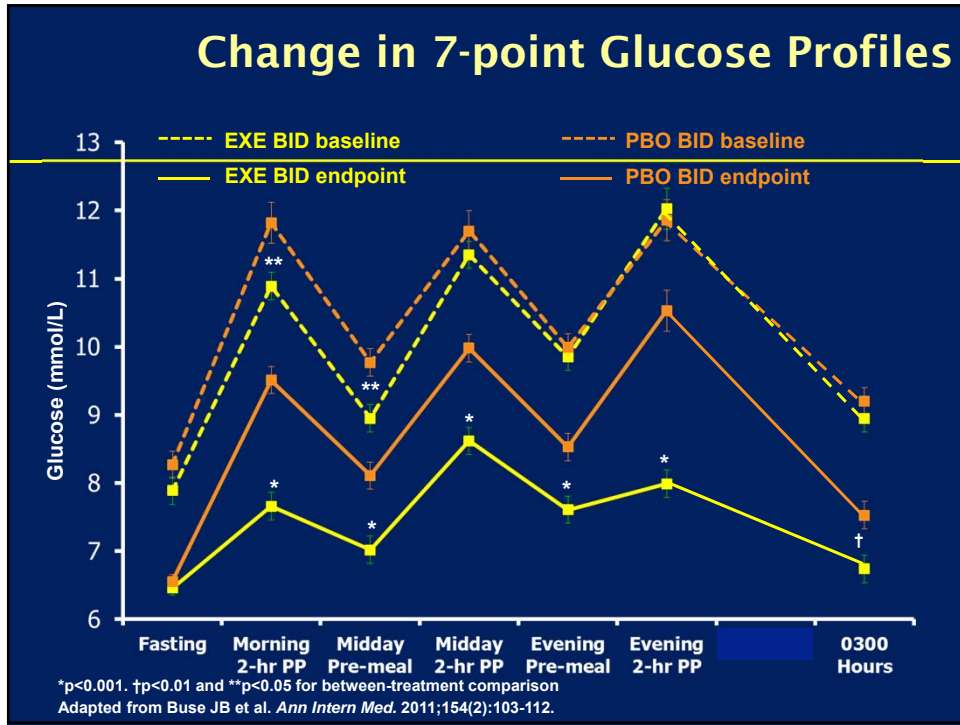
Body Weight

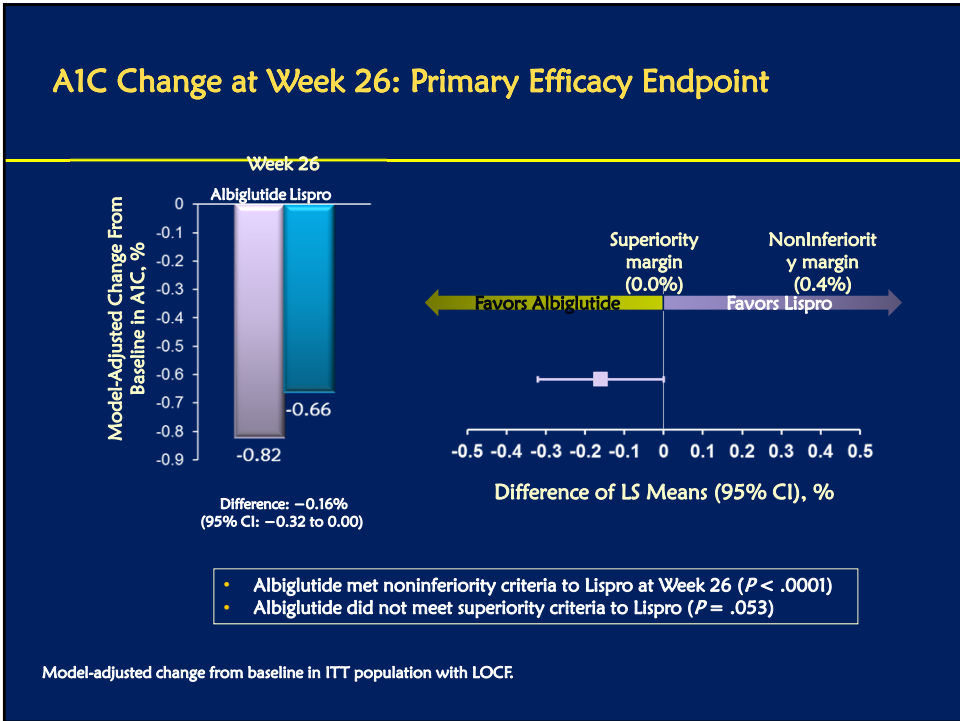
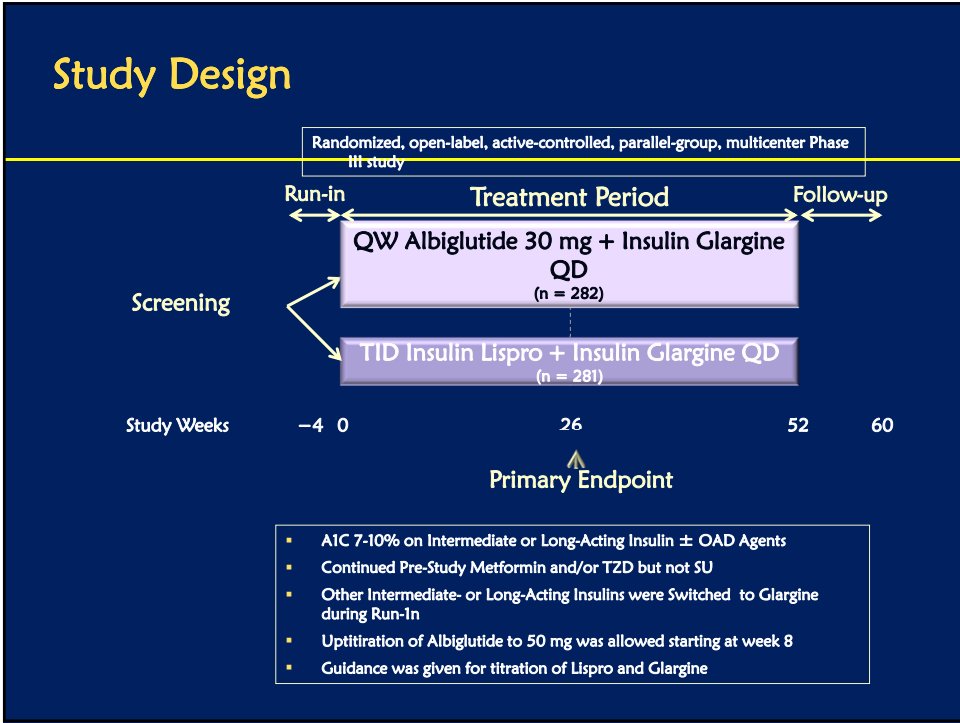


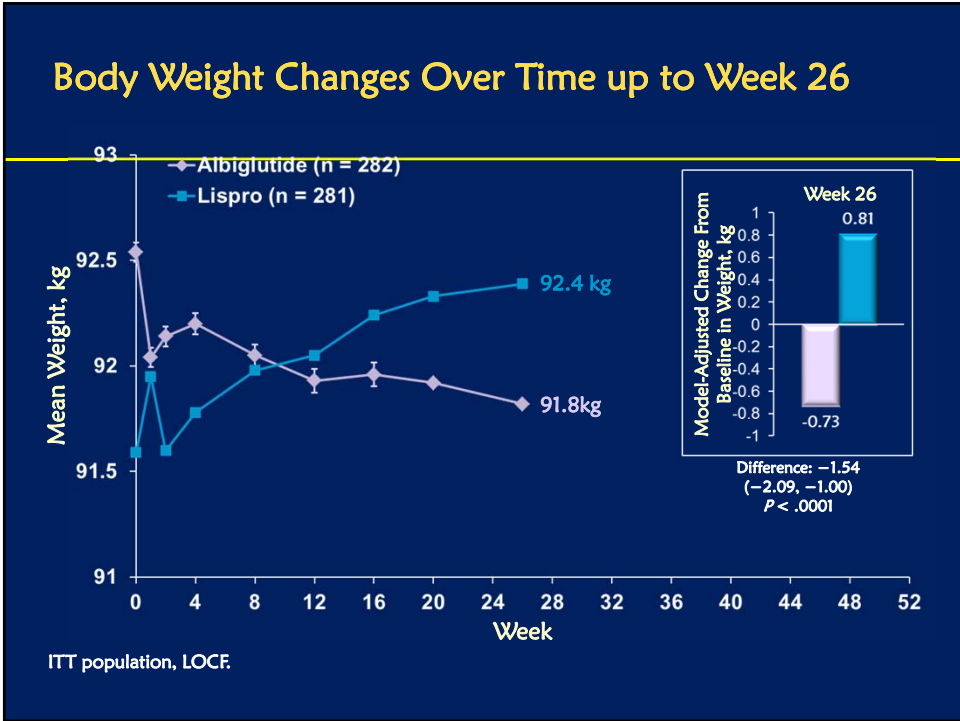
N = 113; PRAM (n = 57), RAIA (n = 56). Randomized, parallel-group trial. ^a P < .01; ^b P < .001.

Riddle M, et al. *Diabetes Care*. 2009;32:1577-1582.









- ### Co-formulations of *Investigational* GLP-1 Receptor Agonist Plus Basal Insulin in Type 2 DM: Ongoing Studies
- Dual Action of Liraglutide and Insulin Degludec in Type 2 Diabetes: A Trial Comparing the Efficacy and Safety of Insulin Degludec/Liraglutide, Insulin Degludec and Liraglutide in Subjects With Type 2 Diabetes (DUAL™ I) - NCT01336023
 - A Trial Comparing the Efficacy and Safety of Insulin Degludec/Liraglutide and Insulin Degludec in Subjects With Type 2 Diabetes (DUAL™ II) - NCT01392573
 - Efficacy and Safety of Insulin Glargine/Lixisenatide Fixed Combination Versus Insulin Glargine Alone on Top of Metformin in Type 2 Diabetic Patients – NCT01476475
- <http://clinicaltrials.gov/show/NCT01336023>
<http://clinicaltrials.gov/show/NCT01476475>

IDegLira*, A Fixed Ratio Combination in Patients with T2DM: Results of a Large, Randomized, Phase 3 Trial

Key Results with IDegLira vs. IDeg or Lira Alone

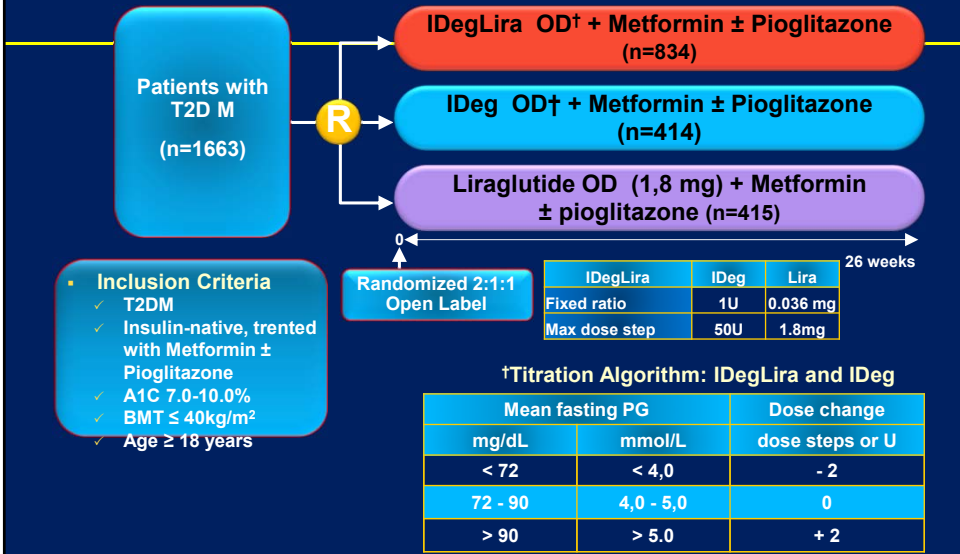
	IDegLira vs. IDeg Estimate [95% CI]	P-value	IDegLira vs. Lira Estimate [95% CI]	P-value
A1C change (%-points)	-0.47 [-0.58; -0.36]	<0.0001	-0.64 [-0.75; -0.53]	<0.0001
FPG change (mg/dL)	-3.1 [-7.4; 1.2]	NS	-31.8 [-36.1; -27.5]	<0.0001
Weight change (kg)	-2.22 [-2.64; -1.80]	<0.0001	2.44 [2.02; 2.86]	<0.0001

The primary endpoint, A1C, decreased by 1.9% from 8.3% to 6.4% with IDegLira. This decrease was greater than with IDeg (-1.4% to 6.9%) or Lira (-1.3% to 7.0%)

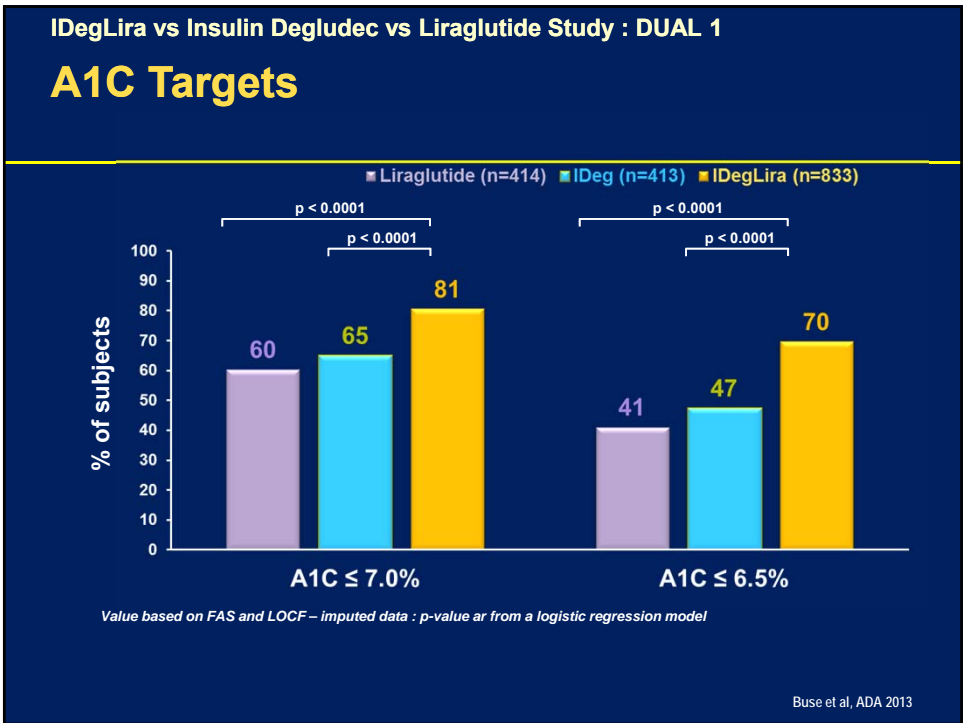
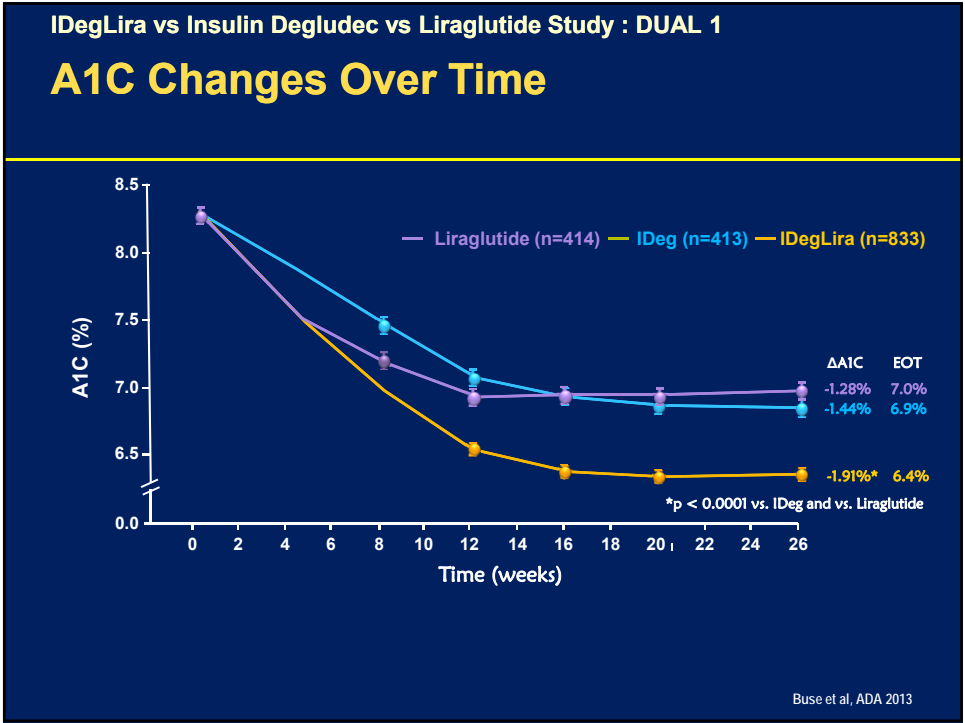
*Not FDA approved
Buse JB et al ADA 2013, 65 OR

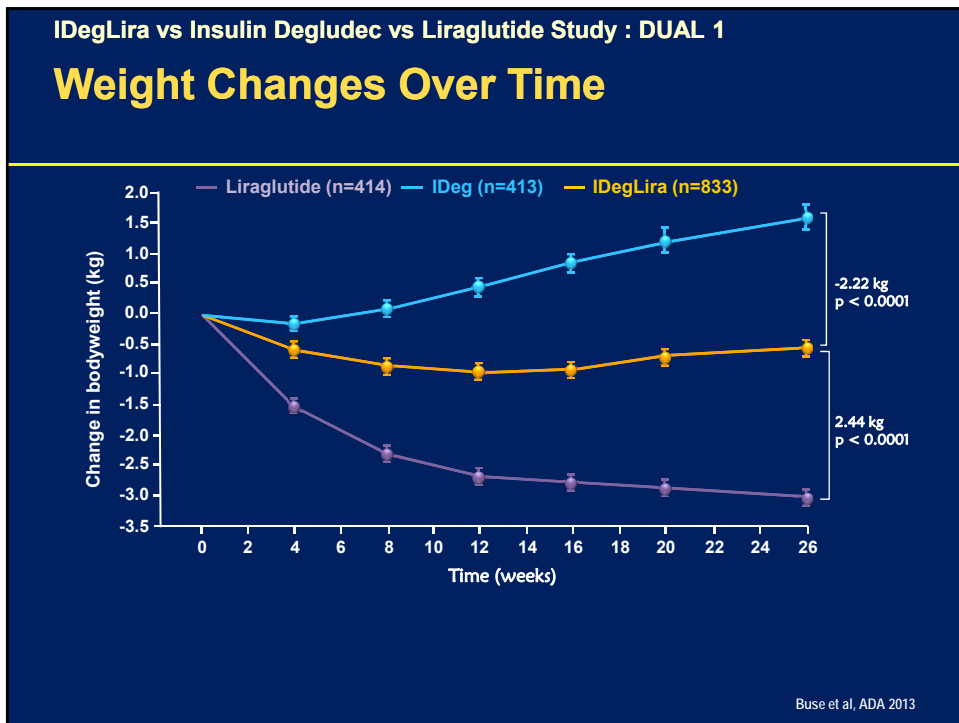
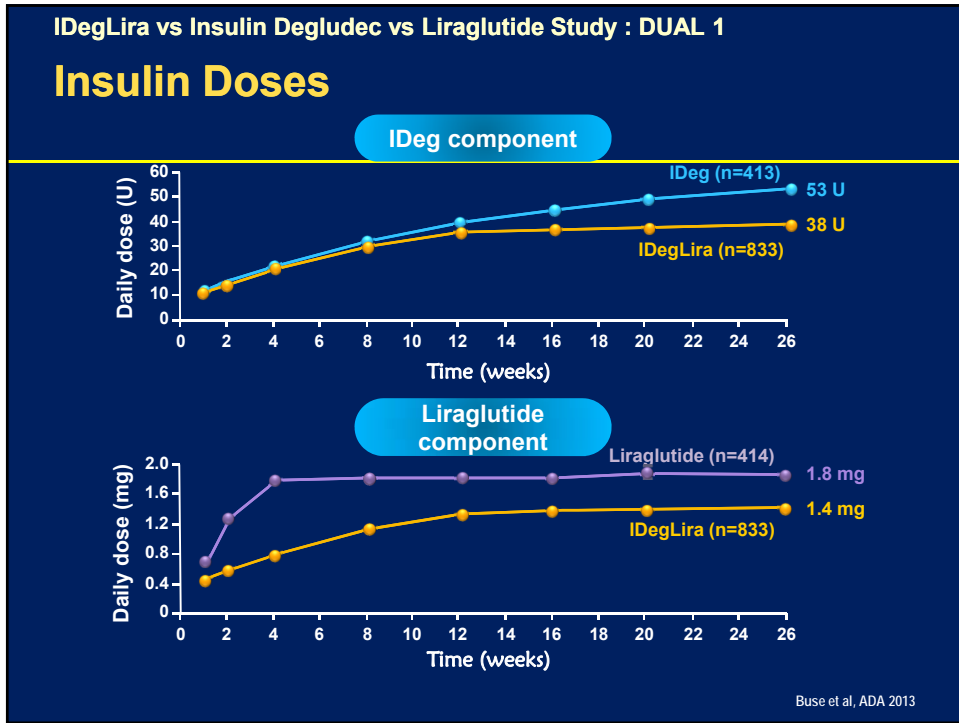
IDegLira vs Insulin Degludec vs Liraglutide Study: DUAL 1

Study Design



Buse et al, ADA 2013





LixiLan vs Glargine Proof of Concept Study in Type 2 DM on Metformin

Study Design and Endpoints

24-week, open-label, 1:1 randomized, active-control, 2-arm, parallel trial

On top of stable dose of Metformin ≥1.5g per day

N = 155

Insulin Glargine titration
(No upper limit fixed)

stratified by screening values of A_{1c} (<8, ≥8%) and BMI (<30, ≥ 30 kg/m²)

N = 155

LixiLan Combination Titration
(maximum dose 60U/30 µg)

Open label treatment period (24 weeks)

▪ T2DM ≥ 1 year

▪ Metformin: stable dose ≥ 1.5 g/day

▪ 7 ≤ A1c ≤ 10%

Primary Endpoint

- ✓ A1c change from baseline (non inferiority; once shown, superiority can be tested)

Secondary Endpoints

- ✓ Glycemic control in relation to a meal
- ✓ 7-point SMPG
- ✓ Body weight
- ✓ Insulin doses
- ✓ FPG
- ✓ Composite endpoints

Safety

- ✓ Hypoglycemia
- ✓ GI Adverse events

LixiLan: Efficacy results

HbA1c changes

	(N= 161)	(N= 162)
Baseline HbA1	8.1%	8.0%
HbA1c (Wk24 LOCF)	6.3%	6.5%
LS mean change	-1.8%	-1.6%

LS Mean difference (SE) vs. insulin glargine
95% CI : (-0.312 to -0.037)
P-value = **0.0130**

Body weight changes

LS mean difference vs. Lantus®: -1.44 kg (95%CI: -2.1 to -0.8)

Glucose excursion (standardized meal test)

LS mean difference vs. Lantus®: -3.2 mmol/L (95%CI: -3.9 to -2.6)

Improved HbA1c

Body weight reduction

Reduced postprandial glucose

Lantus®
Combination

Data Presented at ADA meeting 2014

LixiLan: PoC study in T2D

Proof-of-Concept Study of Fixed-Ratio Once-Daily LixiLan in T2D on Metformin

LixiLan

- Robust A1c reduction from 8.1% to 6.3%
- Reduced body weight (-1 kg)
- Less frequent nausea and vomiting compared to what has been reported for the GLP-1 Rapid Acting class
- Low incidence of symptomatic hypoglycemia

⇒ **84%** of patients reached A1c goal <7%

- 68% reached this target with no documented hypoglycemia
- 56% reached it with no weight gain
- 46% with no weight gain and no documented hypoglycemia

1. Mean HbA1c change of 1.8% at week 24 (n=161)
 2. Mean change of body weight from baseline to week 24 (n=161)
 3. Documented symptomatic hypoglycemic events ≤ 70 mg/dL occurred in 21.7% of patients (n=161)

Fluctuation Reduction With Insulin and GLP-1 Added Together (FLAT-SUGAR): Study Design

Add GLP-1 RA to Basal Insulin

EXN, GLAR, MET
 ("Glipulin")
 n = 60

Add RAI to Basal Insulin

RAI, GLAR, MET
 (Basal-bolus insulin)
 n = 60

- **Population:**
 - T2DM > 12 months, A1C 7.5% to 8.5%, aged 40 to 75 years \pm CVD, risk factors
- **Intervention:**
 - AHA/ADA meal plan
 - "Glipulin" vs basal-bolus insulin
 - Maintain A1C 6.7% to 7.3% during trial
- **Length: 6 months**
- **Primary outcome:**
 - Δ CoV using blinded CGM
- **Secondary outcomes:**
 - **Hypoglycemia frequency**
 - Systemic inflammation, oxidative stress
 - Diabetic renal disease
 - Weight gain
 - Cardiac arrhythmias (simultaneous Holter monitoring at 0, 13, and 26 weeks)
 - Drug-induced adverse events
- **Completion date: July 2014**

Phase 4 clinical trial.
 RAI: ASP, GLU, or LIS.

www.clinicaltrials.gov. NCT01524705.

Basal Insulin/GLP-1 RA Coformulated Agent— Results at 26 Weeks

**Coformulation (n = 834) vs
Degludec (n = 414)**

Parameter	Difference (95% CI)	P
ΔA1C, %	-0.47 (-0.58 to -0.36)	< .0001
A1C < 7%, %	81% vs 65%	
A1C ≤ 6.5%, %	70% vs 48%	
ΔFPG, mg/dL	-3.1 (-7.4 to 1.2)	NS
ΔPPG, mg/dL	-8.2 (-11.3 to -5.1)	< .0001
ΔWeight, kg	-2.22 (-2.64 to -1.8)	< .0001
Hypoglycemia ^a	0.68 (0.53 to 0.87)	.0023

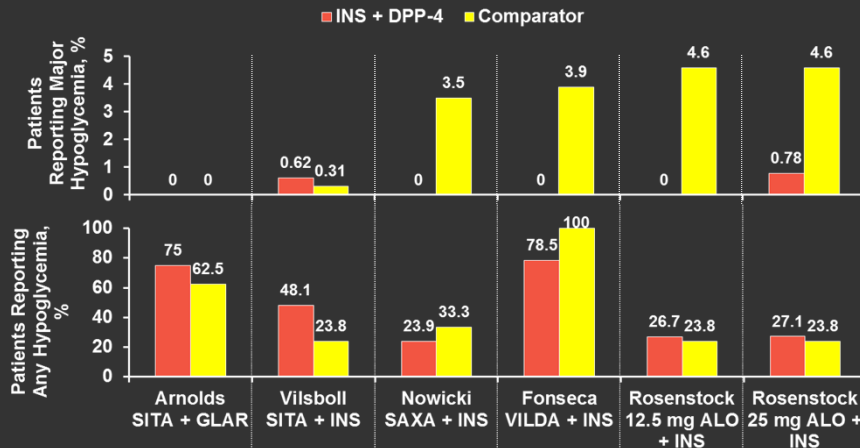
**Coformulation (n = 834) vs
Liraglutide (n = 415)**

Parameter	Difference (95% CI)	P
ΔA1C, %	-0.64 (-0.75 to -0.53)	< .0001
A1C < 7%, %	81% vs 60%	
A1C ≤ 6.5%, %	70% vs 41%	
ΔFPG, mg/dL	-31.8 (-36.1 to -27.5)	< .0001
ΔPPG, mg/dL	-1.1 (-2.0 to 4.2)	NS
ΔWeight, kg	2.44 (2.02 to 2.86)	< .0001
Hypoglycemia ^a	7.61 (5.17 to 11.21)	< .0001
Nausea	8.8% vs 19.7%	
Vomiting	3.9% vs 8.5%	

^a Rate ratio, coformulation vs comparator.
Hypoglycemia, plasma glucose < 56 mg/dL.

Buse JB, et al. *Diabetes*. 2013;62(suppl 1):A16 [abstract 65-OR].

Overall and Severe Hypoglycemia With DPP-4 Inhibitors in Combination With Insulin in T2DM—Systematic Review



A1C improved by 0.5% to 1.9% from baseline to endpoint across studies

6 arms of 5 RCTs published 2007-2011. Major hypoglycemic episodes occurred in 3 patients using INS + DPP-4 and 15 patients using comparator regimens.

Rizos EC, et al. *Curr Vasc Pharmacol*. 2012 Jun 22. [Epub ahead of print].

