XX Congresso Nazionale AMD

Razionali e Benefici dell'Aggiunta del GLP-1 RA Short-Acting all'Insulina Basale

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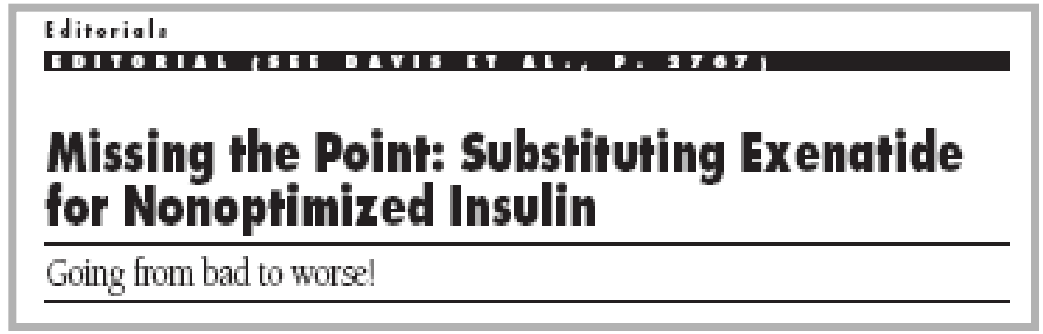
Sezione di Medicina Interna, Endocrinologia e Metabolismo,
Università degli Studi di Perugia.

Genova, 15 Maggio 2015

An Initial Call to Action !

"……. Efforts should be directed to explore the potential role of GLP-1 receptor agonists in combination ***with*** **insulin ……"**


Editorials

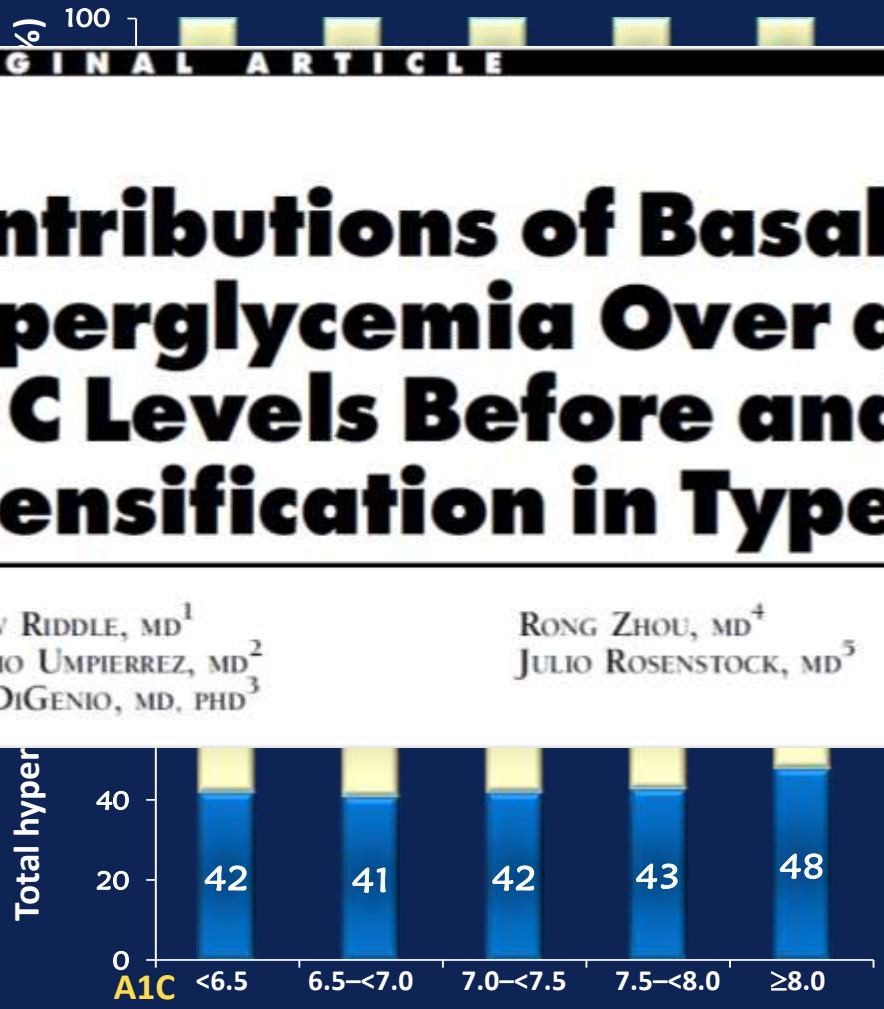
EDITORIAL (SEE DAVIS ET AL., P. 2707)

Missing the Point: Substituting Exenatide for Nonoptimized Insulin

Going from bad to worse!

Rosenstock J and Fonseca V, Diabetes Care 2007

Addressing FPG and PPG Contributions by A1C Level



ORIGINAL ARTICLE

Contributions of Basal and Postprandial Hyperglycemia Over a Wide Range of A1C Levels Before and After Treatment Intensification in Type 2 Diabetes

MATTHEW RIDDLE, MD[1]
GUILLERMO UMPIERREZ, MD[2]
ANDRES DIGENIO, MD, PHD[3]
RONG ZHOU, MD[4]
JULIO ROSENSTOCK, MD[5]

glucose profiles from 290 patients with type 2 diabetes who were treated with diet therapy with or without oral antihy-

Postprandial Increments Persist Following Titration of Basal Insulin

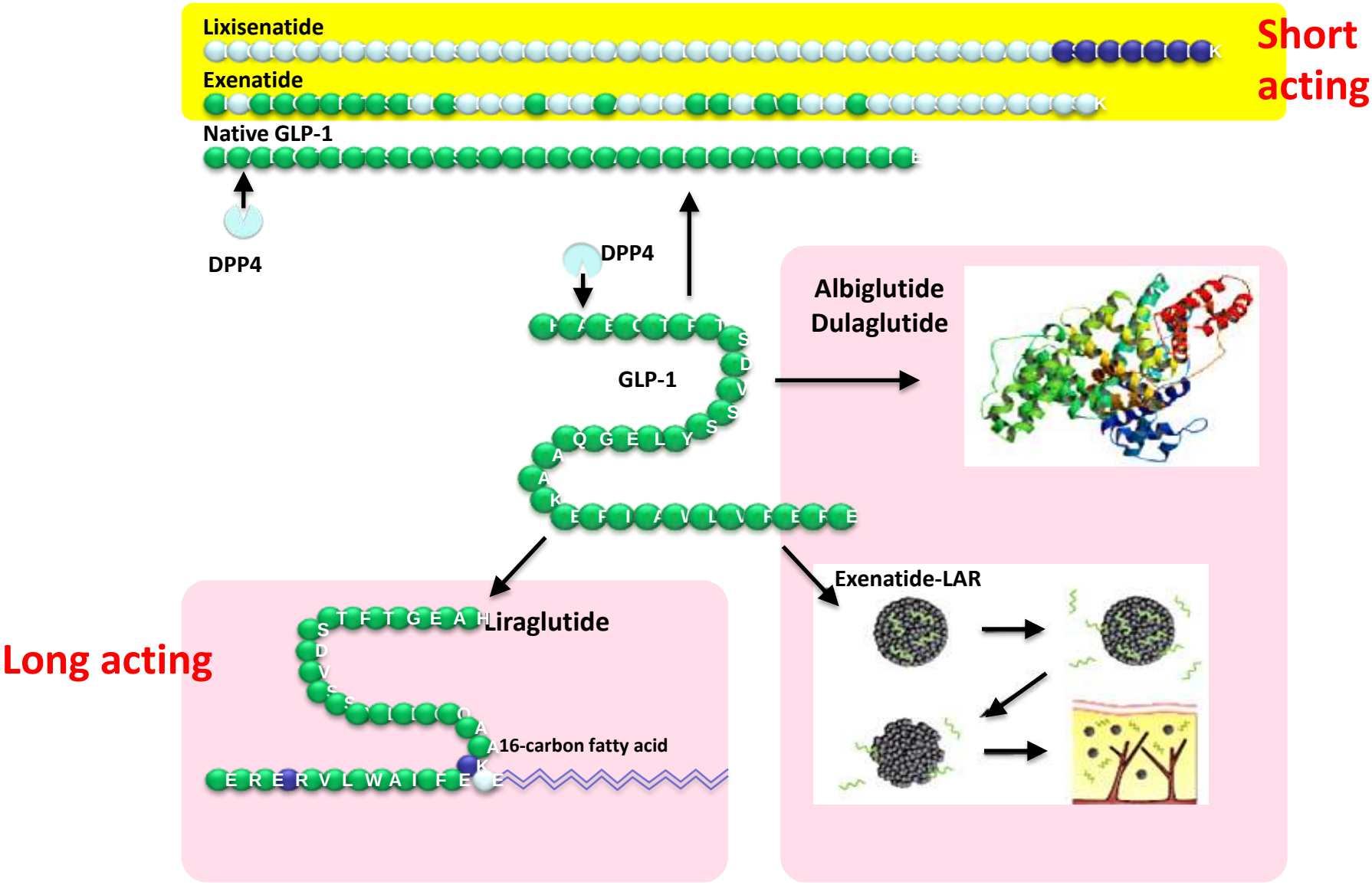
Courtesy of J. Rosenstock

GLP-1 RAs in Combination with Basal Insulin: the Rationale

An attractive therapeutic option as both components may address complementary targets and underlying mechanisms without hypoglycemia and weight gain associated with intensification of the insulin regimen.

Do All GLP-1 Receptor Agonists Interact Equally with Basal Insulin ?

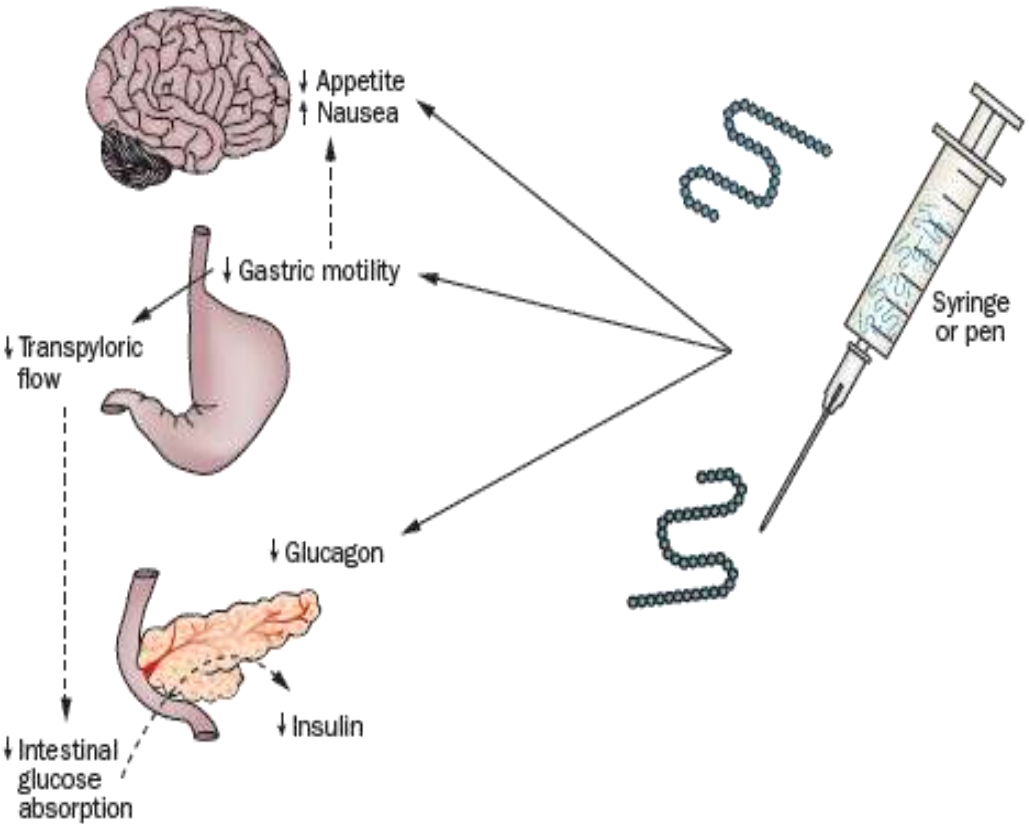
GLP-1 Receptor Agonists: Structures and Pharmacokinetics



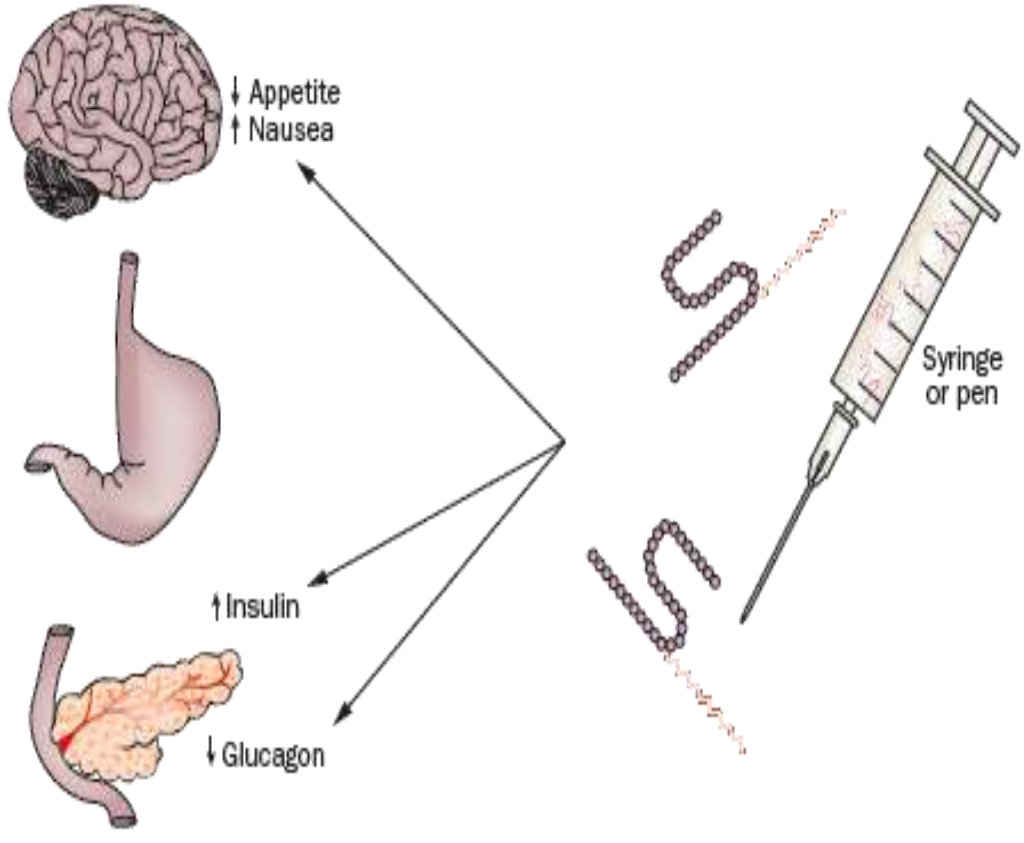
Meier JJ. 2012 Nature Reviews Endocrinology; 8: 728-742

Short- and Long-acting GLP-1 RAs

Short-acting GLP-1 RAs



Long-acting GLP-1 RAs



Meier JJ *Nat Rev Endocrinol* 2012

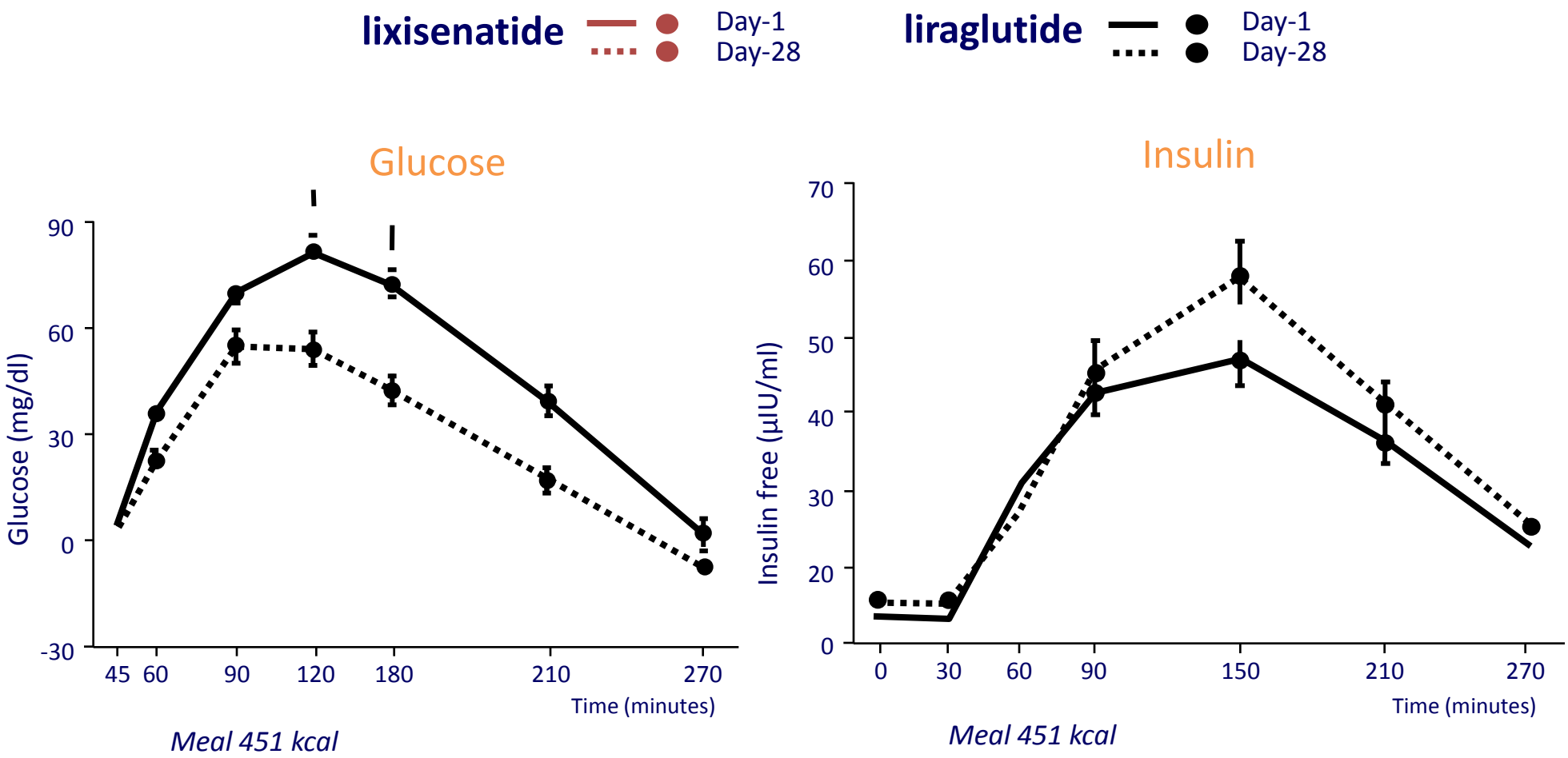
Comparison of Short-Acting versus Long-Acting GLP-1 Receptor Agonists

Parameters	Short acting GLP-1 RAs	Long acting GLP-1 RAs
Compounds	***Exenetide Lixisenatide***	***Albiglutide Dulaglutide Exenatide-LAR Liraglutide***
Half-life	**2-5 h**	**12 h-several days**
Effects		
Fasting blood glucose levels	**Modest reduction**	**Strong reduction**
Postprandial hyperglycemia	**Strong reduction**	**Modest reduction**
Fasting insulin secretion	**Modest stimulation**	**Strong stimulation**
Postprandial insulin secretion	**Reduction**	**Modest stimulation**
Glucagon secretion	**Reduction**	**Reduction**
Gastric empting rate	**Deceleration**	**No effects**
Blood pressure	**Reduction**	**Reduction**
Heart rate	**No effect or small increase**	**Modest increase**
Body weight reduction	**1-5 Kg**	**2-5 Kg**
Induction of nausea	**20–50%, attenuates slowly (weeks to many months)**	**20–40%, attenuates quickly (~4–8 weeks)**

Abbreviations: GLP 1-R, glucagon-like peptide 1 receptor ; LAR, long-acting release.

Meier J Nat. Rev. Endocrinol 8:728-42, 2012

Comparative Effects of Lixisenatide and Liraglutide on Postprandial Glucose Excursions and Insulin Levels



Kapitza C., *et al*. *Diabetes, Obesity and Metabolism* 2013 January 31.

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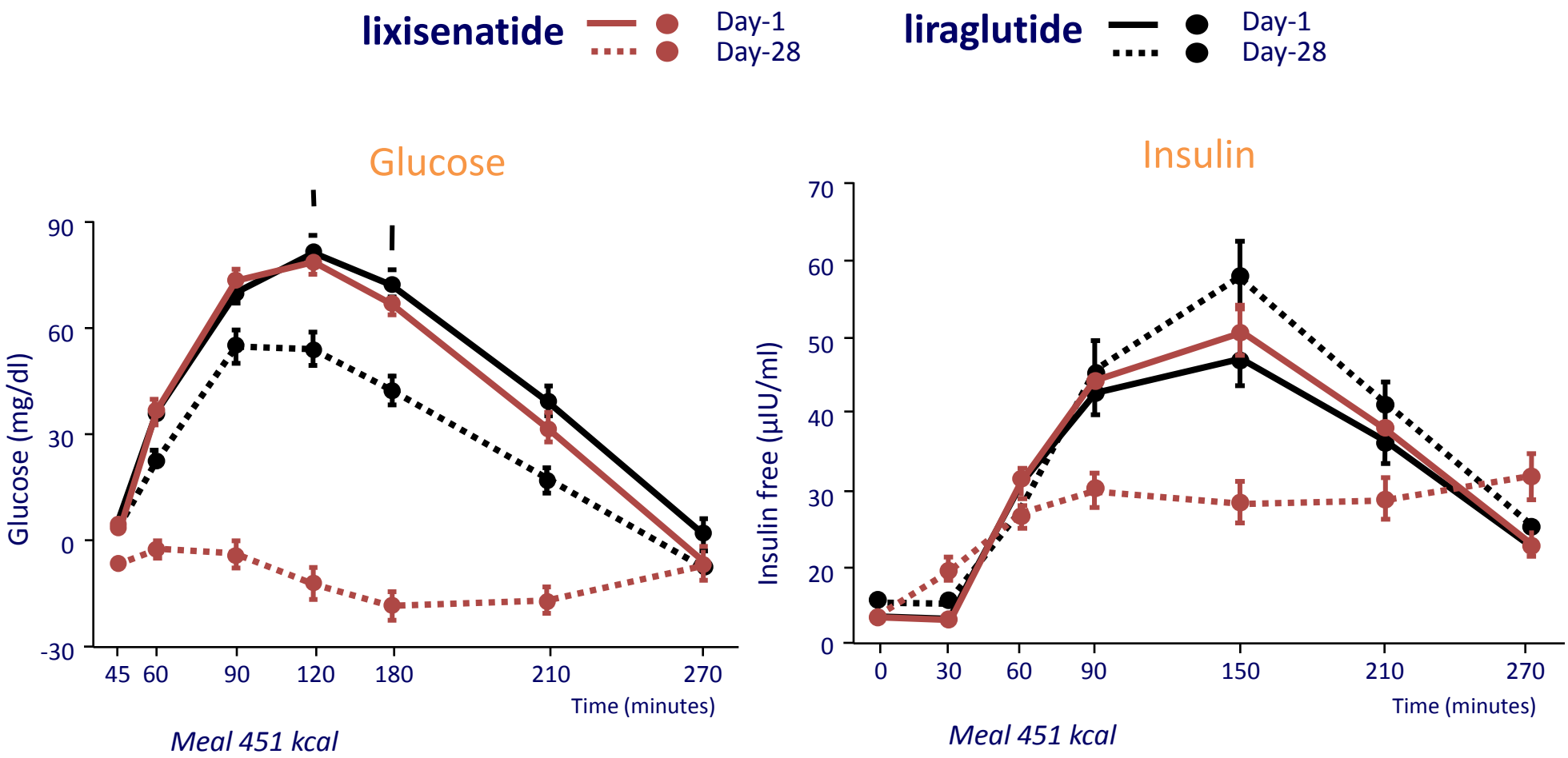
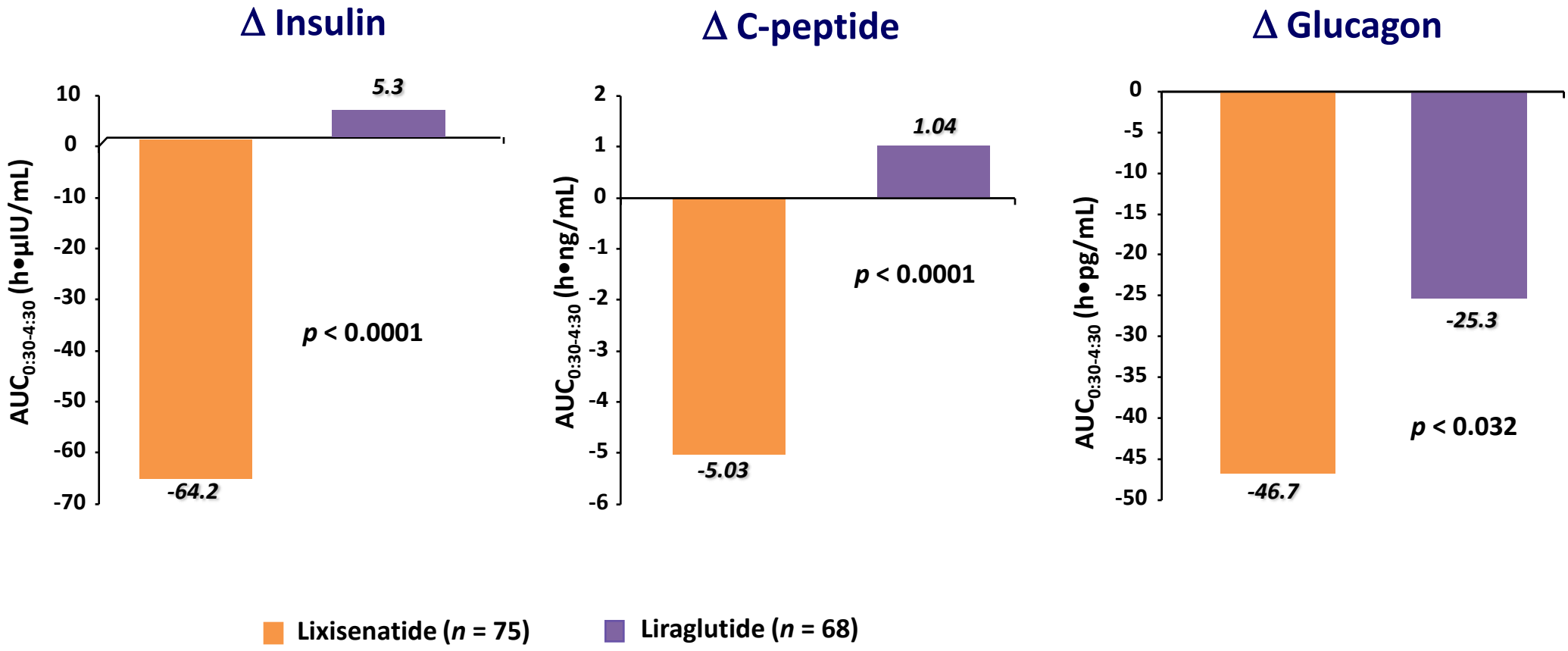


Kapitza C., *et al*. *Diabetes, Obesity and Metabolism* 2013 January 31.

Relative Effects of Lixisenatide and Liraglutide on postprandial Insulin, C-peptide and Glucagon Levels

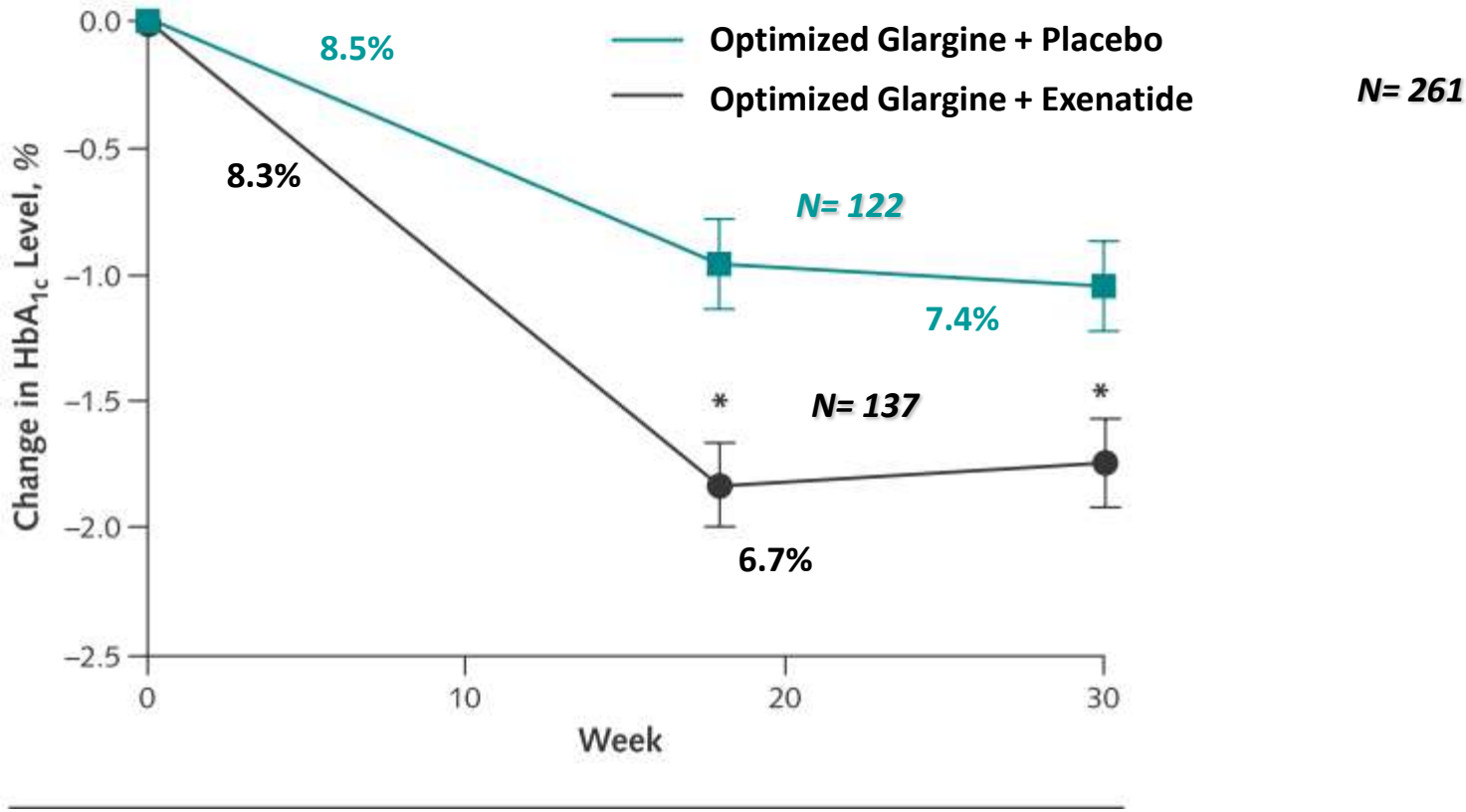


Data shown are changes from baseline in each parameter at 28 days

Kapitza C, *et al*. *Diabetes Obes Metab 15:642-9, 2013*

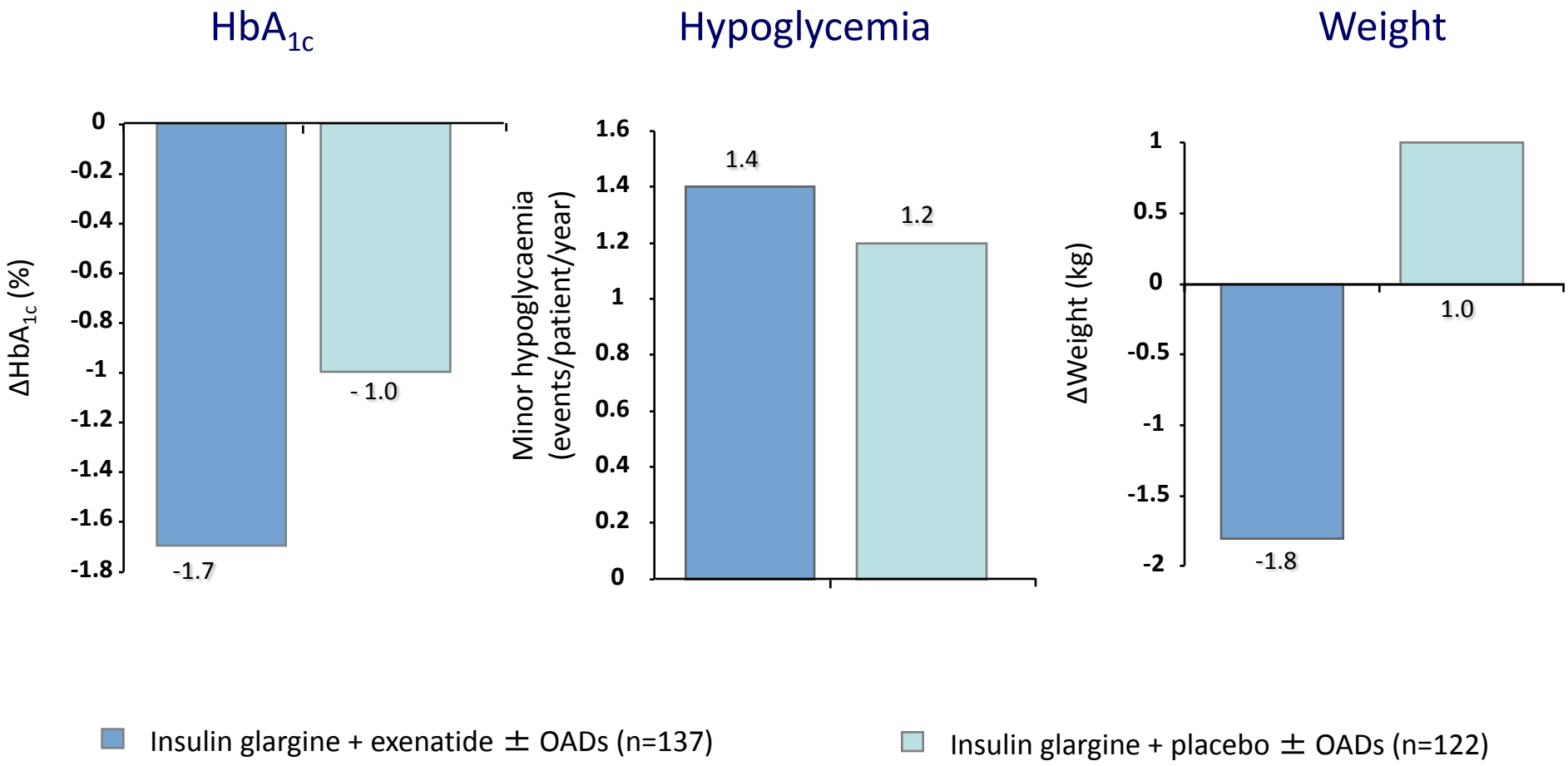
Use of Twice-Daily Exenatide in Basal Insulin–Treated Patients with Type 2 Diabetes

-1.74% vs -1.04% [CI, 1.22%
Difference -0.69% [CI -0.93% to -0.46%]
***P* 0.001**



Buse J B et al. Ann Intern Med 2011;154:103-112

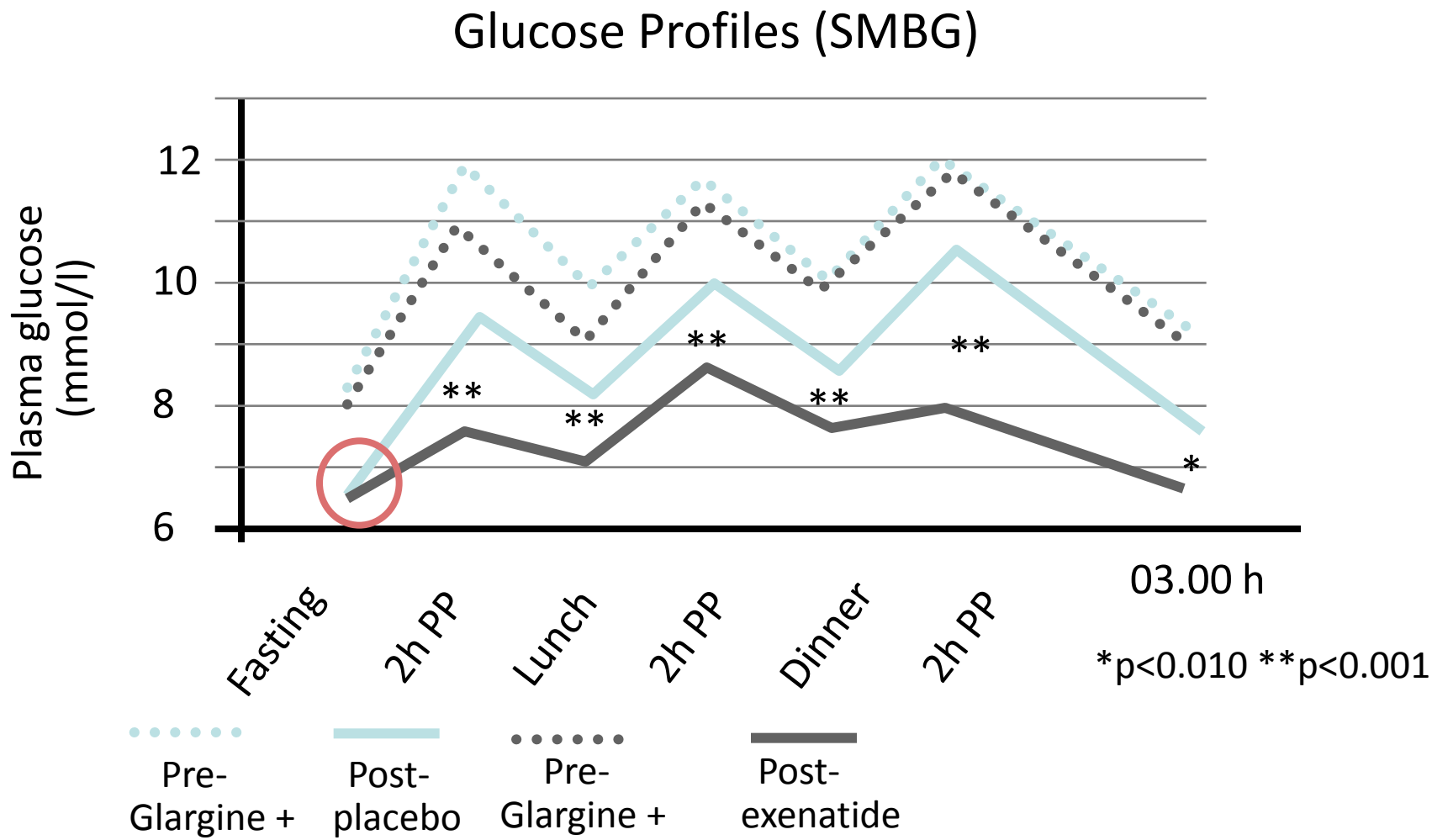
Combination of Insulin Glargine with Exenatide



- Two cases of severe hypoglycemia in the placebo group

Buse J, *et al*. *Ann Intern Med* 2011;154:103–12.

Twice Daily Exenatide in Combination with Insulin Glargine : Changes in PG Profiles after 30 weeks

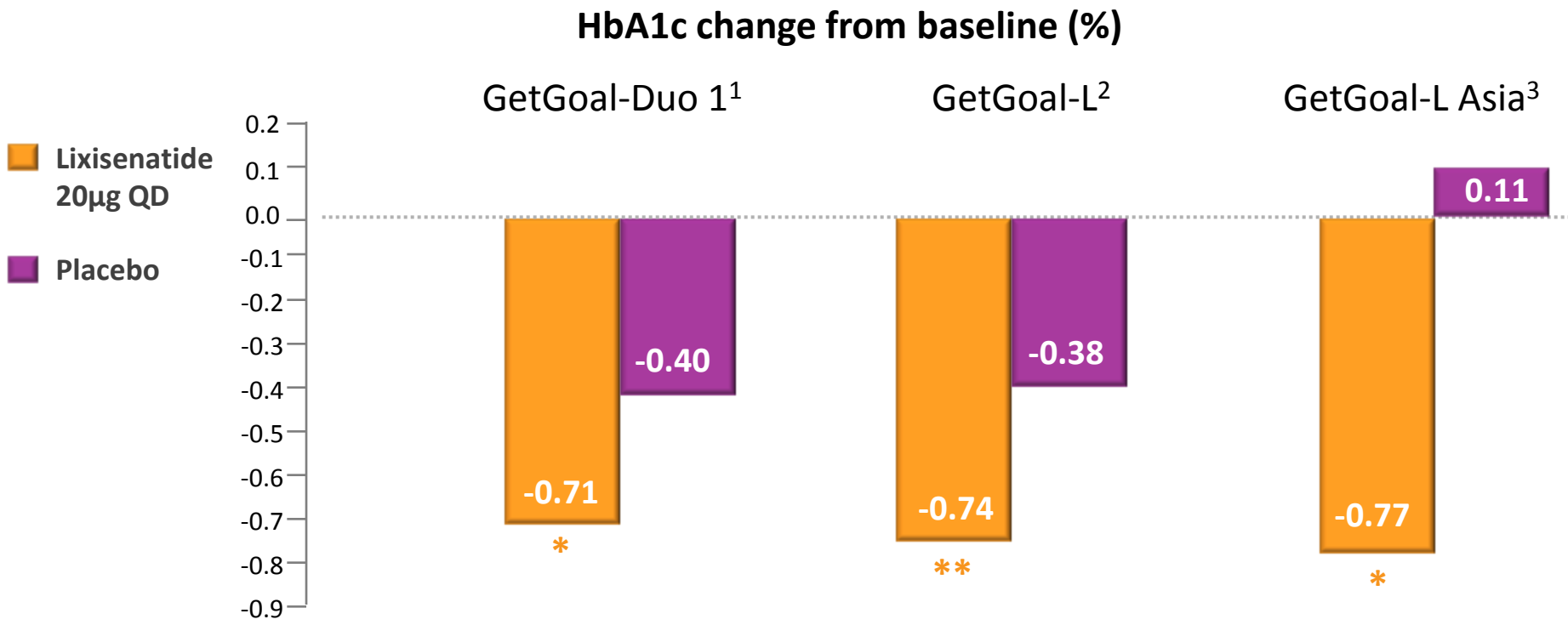


Buse JB, *et al*. Ann Intern Med 2011;154:103–112.

Lixisenatide GetGoal clinical trial programme

Study	Objectives	# of pts	ClinicalTrials.gov Identifier
GetGoal-Mono	**Efficacy and safety of monotherapy (1- or 2-step dose increase)**	**361**	**NCT00688701**
GetGoal-Mono Japan	**Safety and efficacy of monotherapy in Asian patients (1- or 2-step dose increase)**	**69**	**NCT00905255**
GetGoal-M	**Efficacy and safety in combination with MET**	**680**	**NCT00712673**
GetGoal-M-Asia	**Efficacy and safety in combination with MET (± SU)**	**391**	**NCT01169779**
GetGoal-F1	**Efficacy and safety in combination with MET (1 or 2-step dose increase)**	**482**	**NCT00763451**
GetGoal-S	**Efficacy and safety in combination with SU (± MET)**	**859**	**NCT00713830**
GetGoal-P	**Efficacy and safety in combination with pioglitazone (± MET)**	**484**	**NCT00763815**
GetGoal-X	**Efficacy and safety head-to-head vs exenatide (± MET)**	**634**	**NCT00707031**
GetGoal-L	**Efficacy and safety in combination with basal insulin (± MET)**	**496**	**NCT00715624**
GetGoal-L Asia	**Efficacy and safety in combination with basal insulin (± SU)**	**311**	**NCT00866658**
GetGoal-Duo 1	**Efficacy and safety in combination with insulin glargine + MET (± TZDs)**	**446**	**NCT00975286**
GetGoal-Duo 2	***Efficacy and safety in combination with insulin glargine in comparison with glulisine (QD or TID) ± MET***	***855 In progress***	***NCT01768559***

Lixisenatide Added to Background Insulin: Change in HbA1c at Week 24 (primary endpoint)



**p<0.0001 vs placebo; **p<0.001 vs placebo;†following 12 week run-in period; MET, metformin; SU, sulphonylurea; TZD, thiazolidinedione; QD, once daily*

*p<0.0001 vs placebo; **p<0.001 vs placebo;†following 12 week run-in period;
MET: metformin; SU: sulphonylurea; TZD: thiazolidinedione; QD: once daily.

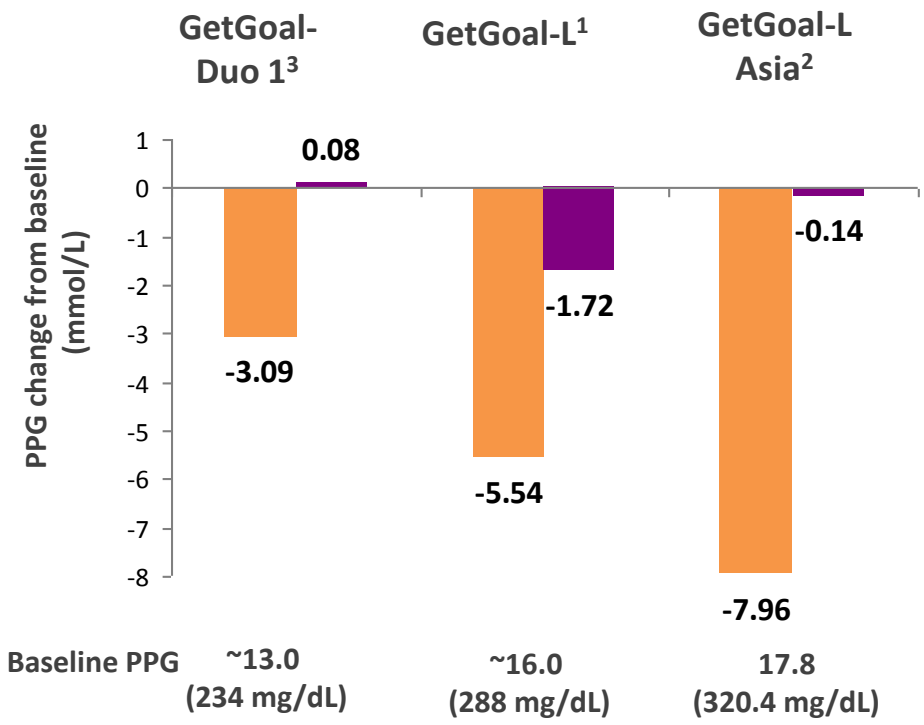
1. Riddle MC, et al. *Diabetes Care*. 2013;36:2497–2503;
2. Riddle MC, et al. *Diabetes Care*. 2013;36:2489–2496;
3. Seino Y, et al. *Diabetes Obes Metab*. 2012;14:910–917.

Lixisenatide Added to Background Insulin: Secondary Endpoints

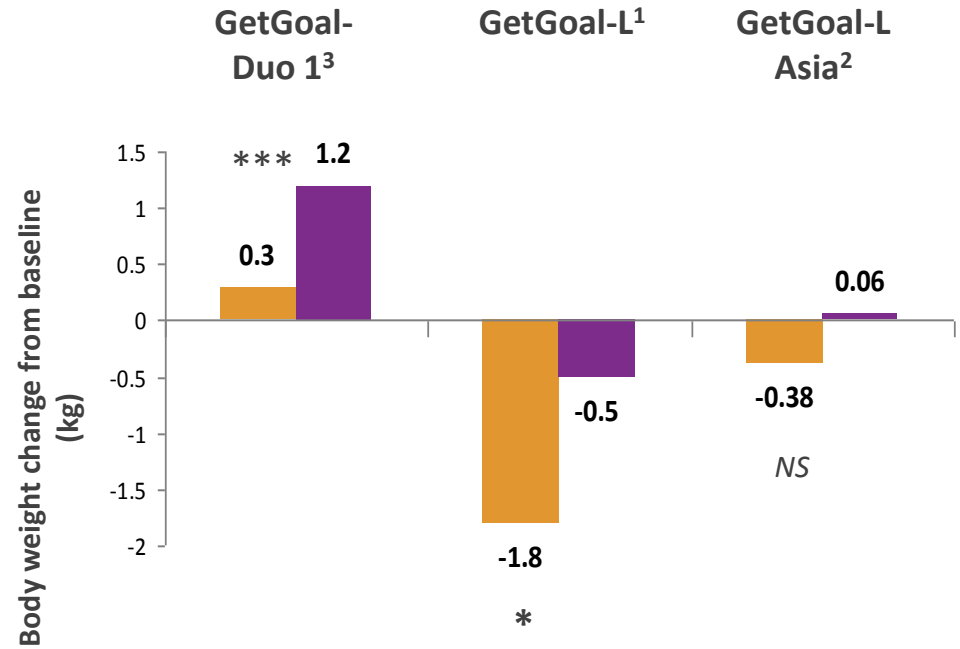
Lixisenatide 20µg QD

Placebo

Change in 2-hr PPG



Change in Body Weight



*P<0.0001 versus placebo; **P<0.001 versus placebo; ***P < 0.01; *NS* = not significant; MET, metformin; SU, sulfonylurea; TZD, thiazolidinedione; QD, once daily

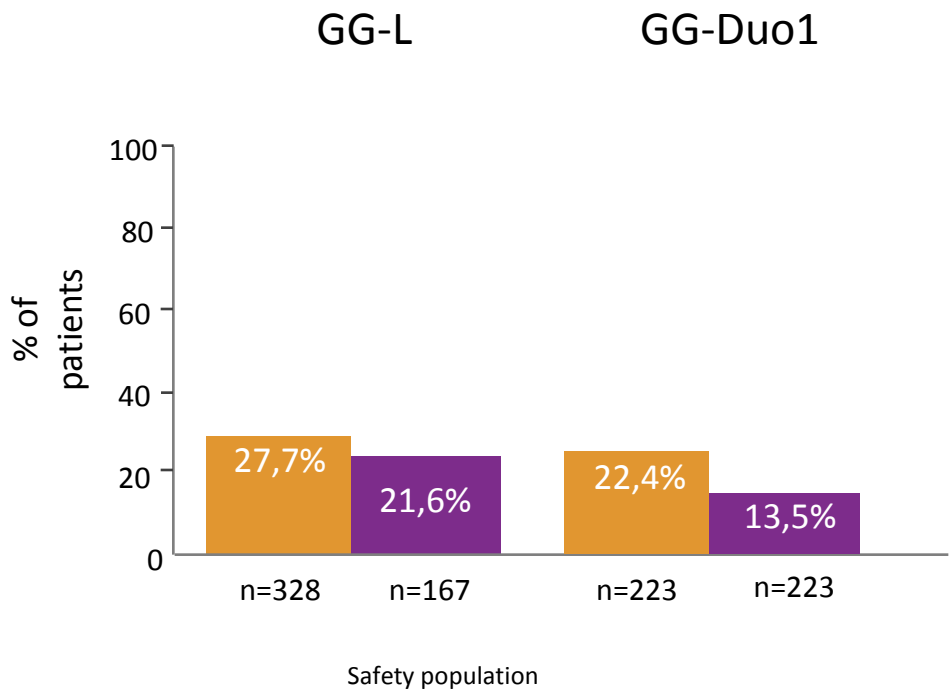
1. Riddle MC, *et al*. *Diabetes Care* 2013;36:2489–96. 2. Seino Y, *et al*. *Diabetes Obes Metab* 2012;14:910–7.
3. Riddle MC, *et al*. *Diabetes Care* 2013;36:2497–503.

Lixisenatide Added to Background Insulin: Hypoglycemia

Lixisenatide 20µg QD

Placebo

Symptomatic hypoglycemia

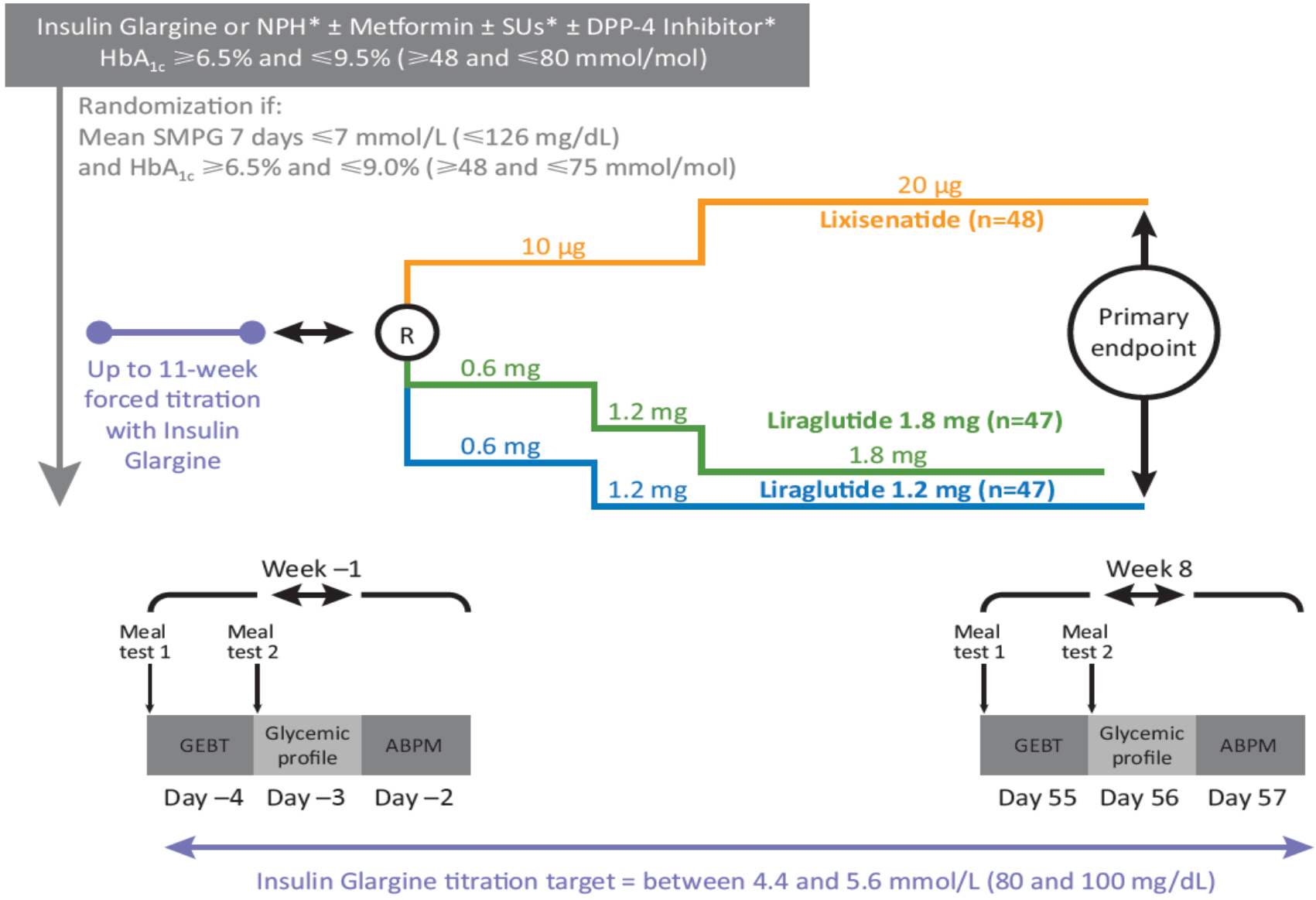


Severe hypoglycemia

Symptomatic documented hypoglycemia o 3.3 mmol/L (60 mg/dL)

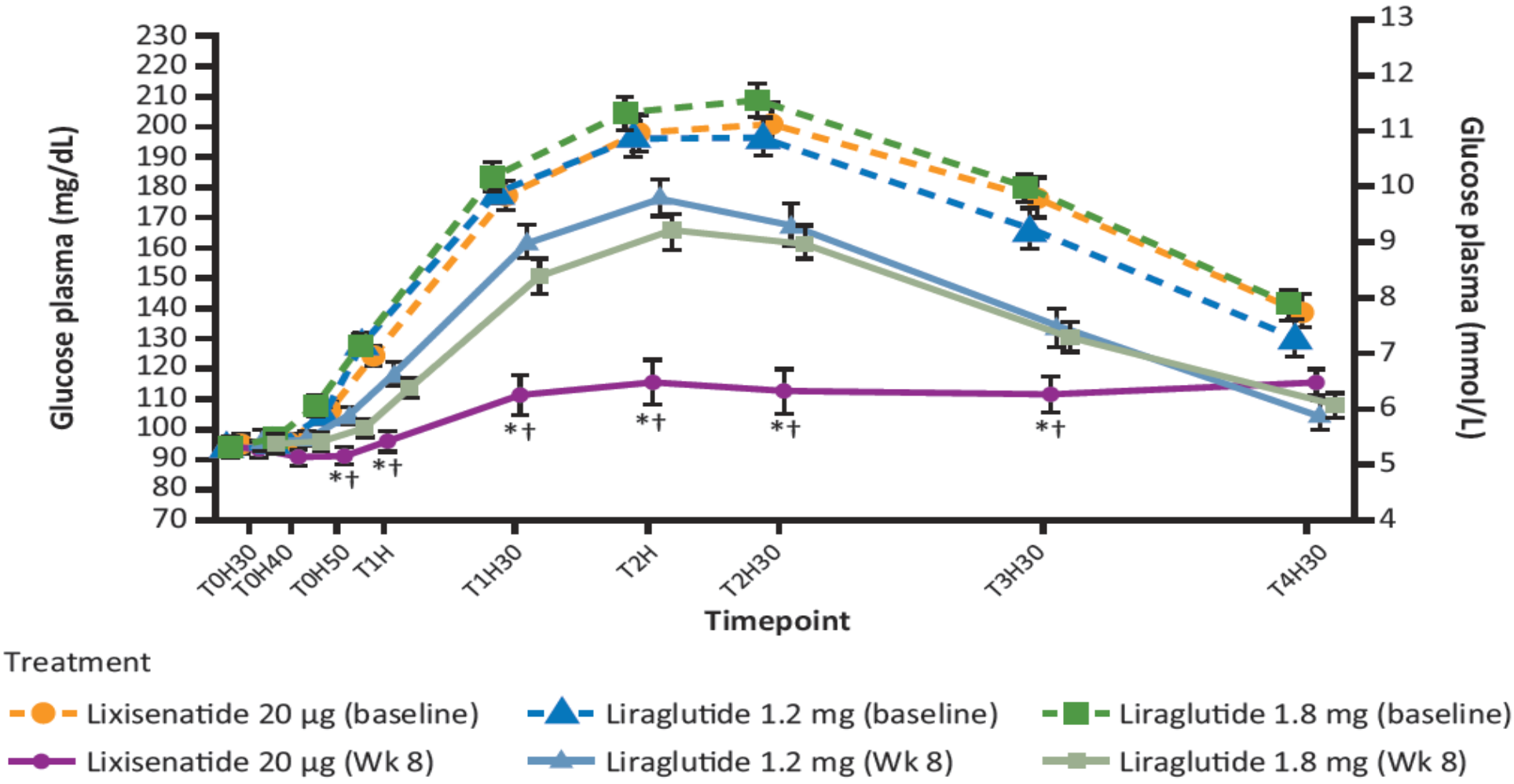
Riddle M. et al. Diabetes Care 2013; DOI: 10.2337/dc12-2454; Riddle M. et al. Diabetes care 2013; DOI: 10.2337/dc12-2462.

Lixisenatide vs Liraglutide on top of basal insulin



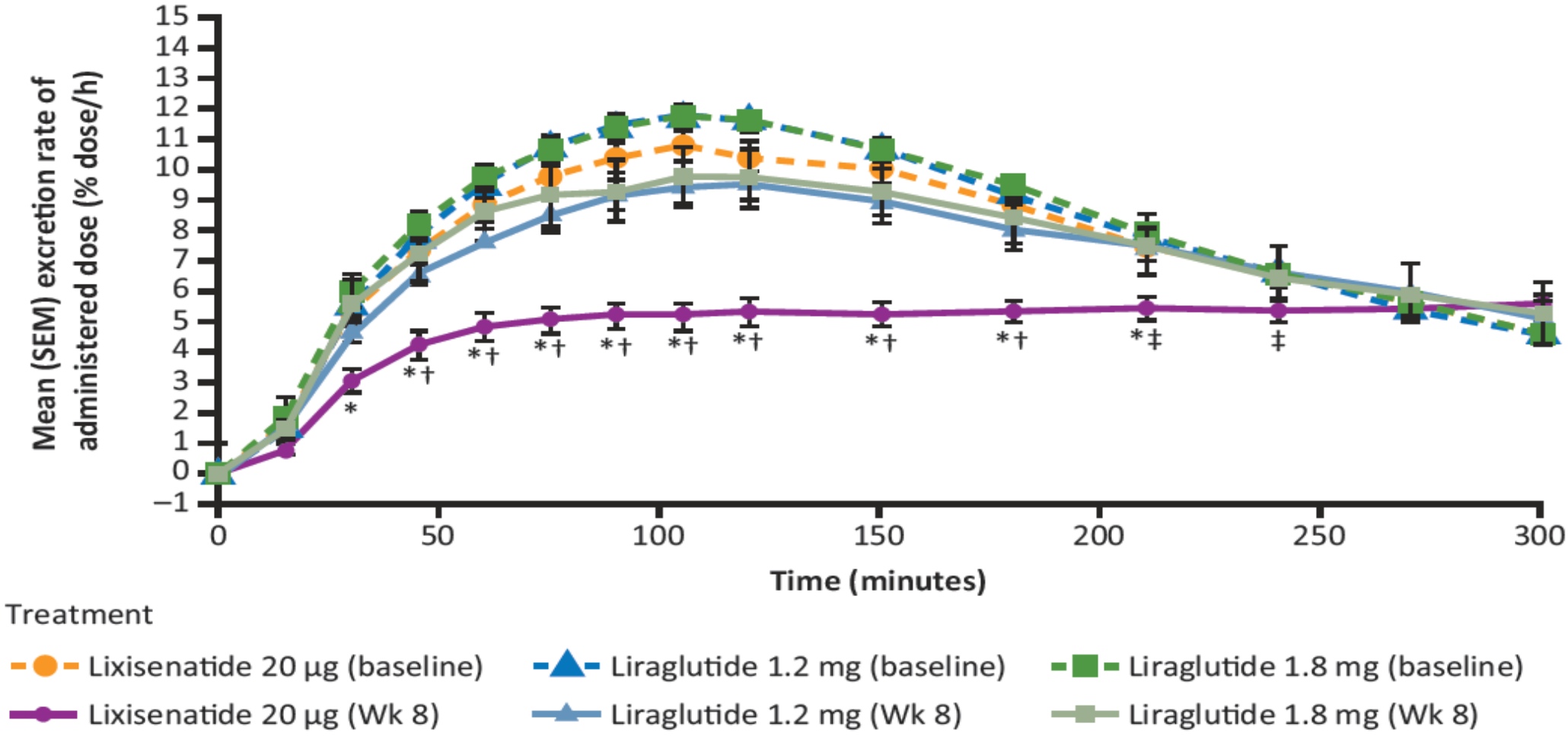
Meier JJ et al, Diabetes Care 2015

Lixisenatide vs Liraglutide on Top of Basal Insulin: Postprandial Glucose Levels



Meier JJ et al, Diabetes Care 2015

Lixisenatide vs Liraglutide on Top of Basal Insulin: Gastric Empting

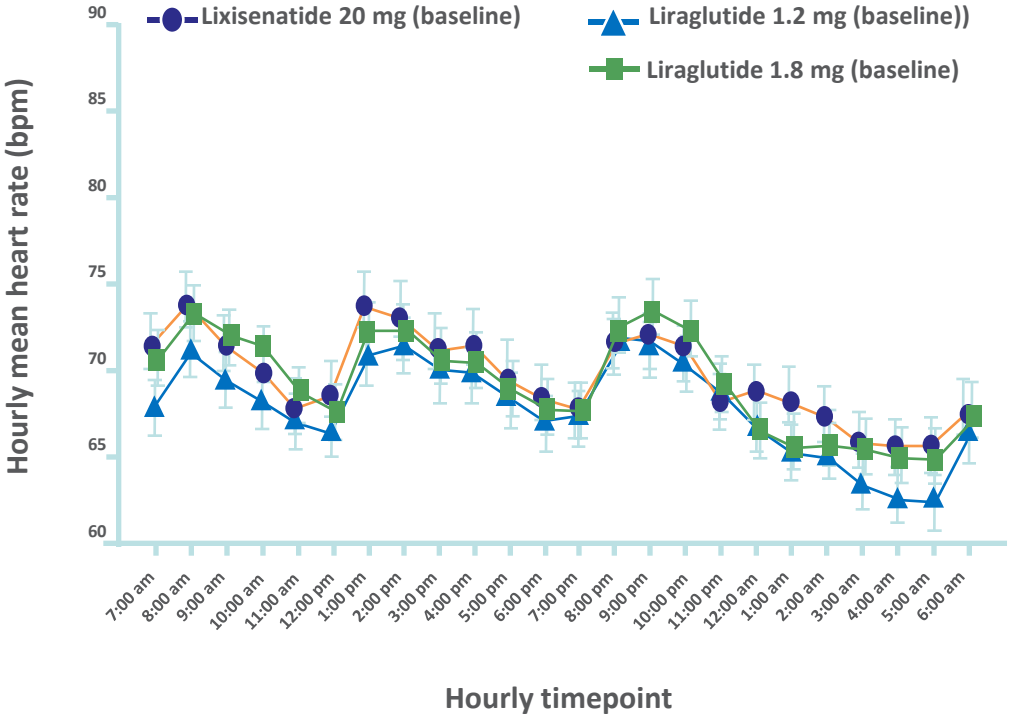


Meier JJ et al, Diabetes Care 2015

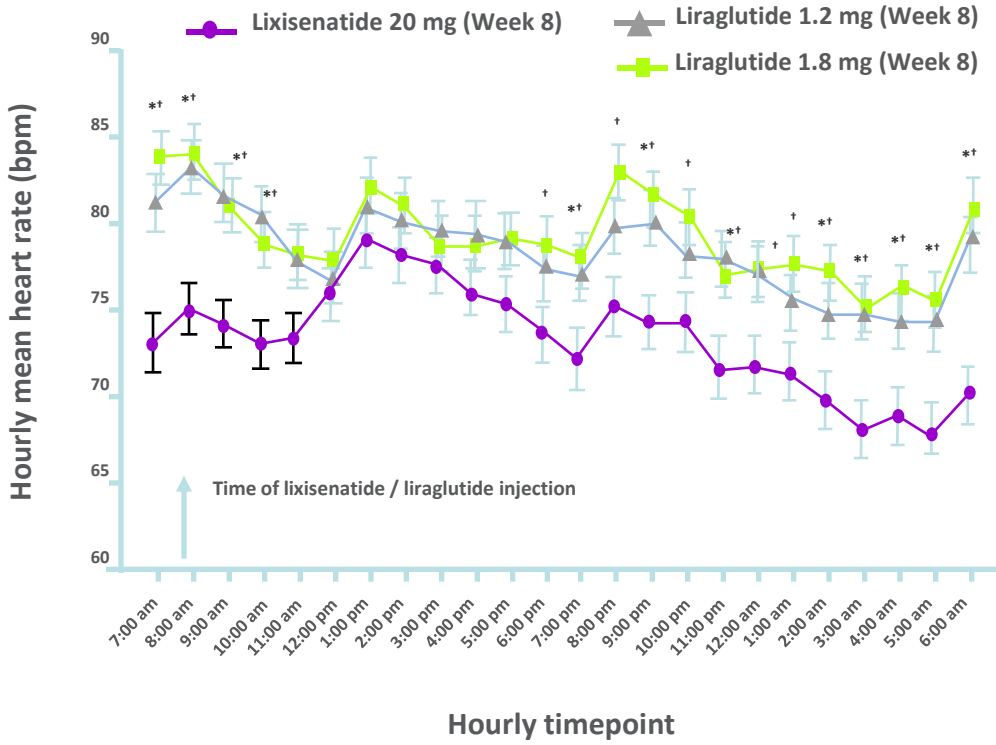
Lixisenatide vs Liraglutide on Top of Basal Insulin: Heart Rate

- Increases in HR were significantly greater with liraglutide 1.2 and 1.8 mg than with lixisenatide (9.3 and 9.2 bpm vs 3.3 bpm, respectively; P<0.0001)

Baseline



Week 8



Statistical tests compared treatment arms at each timepoint at Week 8.
bpm, beats per minute.
*P<0.05 for liraglutide 1.2 mg vs lixisenatide 20 µg; †P<0.05 for liraglutide 1.8 mg vs lixisenatide 20 µg
.

Meier JJ et al, Diabetes Care 2015

Lixisenatide vs Liraglutide on Top of Basal Insulin: Safety findings

	Lixisenatide 20µg (N=48)	Liraglutide 1.2mg (N=47)	Liraglutide 1.8mg (N=47)
Gastrointestinal AEs	17 (35.4%)	21 (44.7%)	22 (46.8%)
Amylase (mean change, week 8)	2.98 ± 4.00	8.01 ± 4.00	5.68 ± 4.13
Lipase (mean change, week 8)	6.97 ± 7.11	21.12 ± 7.16	20.76 ± 7.38
Number (%) of patients experiencing symptomatic hypoglycemia	14 (29.2)	9 (19.1)	10 (21.3)
Number (%) of patients experiencing severe symptomatic hypoglycemia	1 (2.1)	0	0

Lixisenatide resulted in:

- **Fewer reports of gastrointestinal adverse events**
- **Lower increases in levels of pancreatic enzymes (amylase and lipase)**
- **More frequent symptomatic hypoglycemia**

Meier JJ et al, Diabetes Care 2015

Baseline FPG Level Influences the Therapeutic Effects of Lixisenatide

GetGoal-L

FPG at baseline

Group 1
FPG ≤ 6.7 mmol/l
(120 mg/dl)

Group 2
FPG > 6.7 to 8.9 mmol/l

Group 3
FPG ≥ 160 mg/dl
(160 mg/dl)

Basal insulin + lixisenatide
vs
Basal insulin + placebo

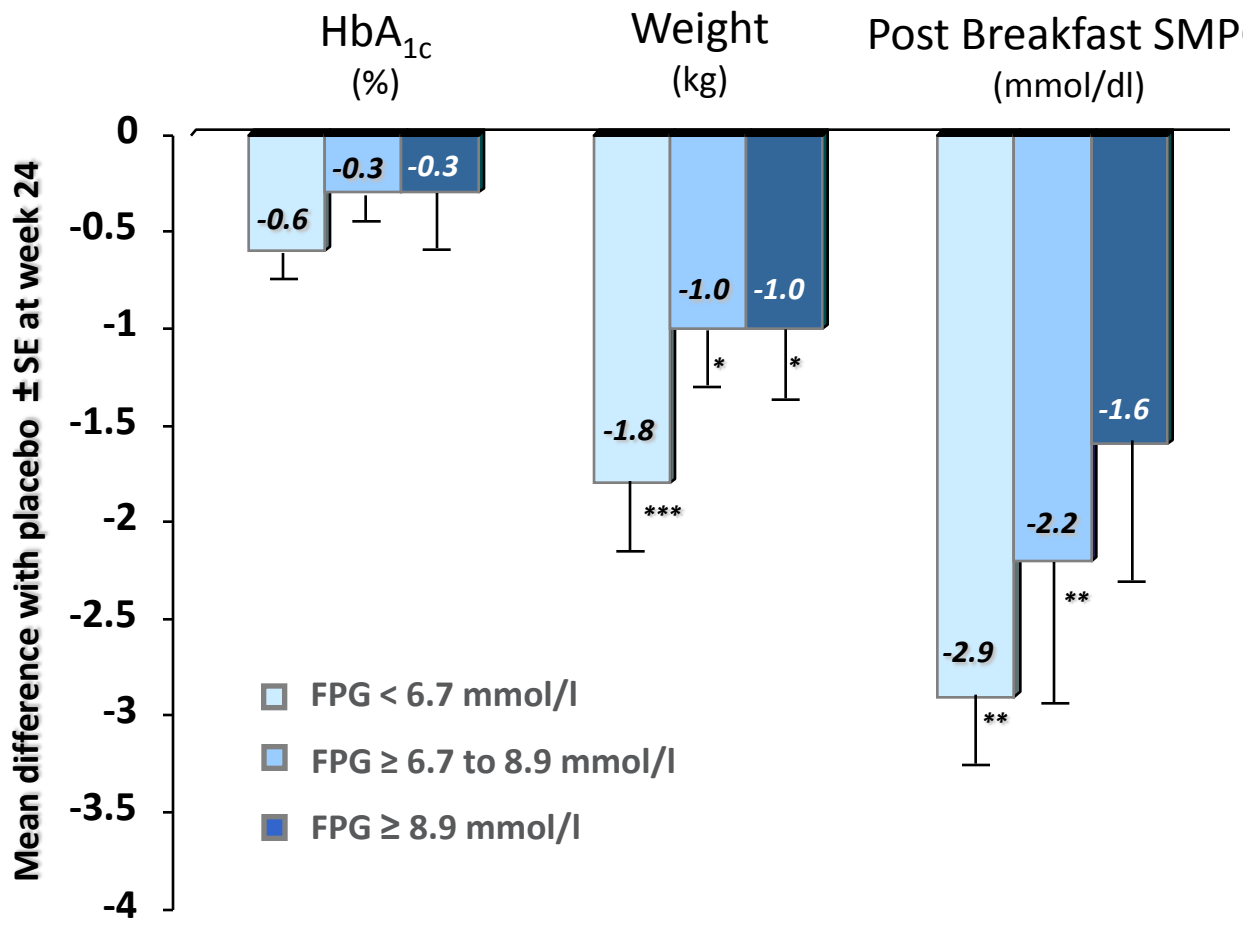
Efficacy measurements

- HbA_{1c}
- Body weight
- 2-hour PPG after a standardized breakfast
- SMPG
- Basal insulin dose

Symptomatic hypoglycaemia

FPG=fasting plasma glucose; HbA_{1c}=glycated haemoglobin; PPG=postprandial plasma glucose; SMPG=self-monitored plasma glucose; mITT=modified intent-to-treat; LOCF=last observation carried forward; LS=least squares; ANCOVA=analysis of covariance.

Baseline FPG Level Influences the Therapeutic Effects of Lixisenatide



Placebo adjusted changes by FPG tertiles

SMPG: Self Monitored Plasma Glucose

* P < 0.05 ** P < 0.01 *** P < 0.001

Vidal J, *et al*. EASD, 2013

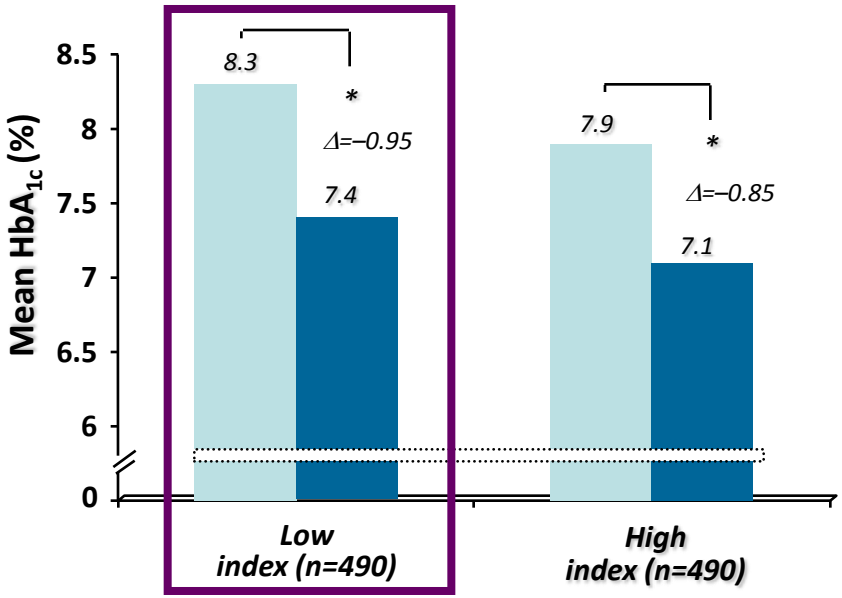
Efficacy of Lixisenatide According to Baseline β-cell Function

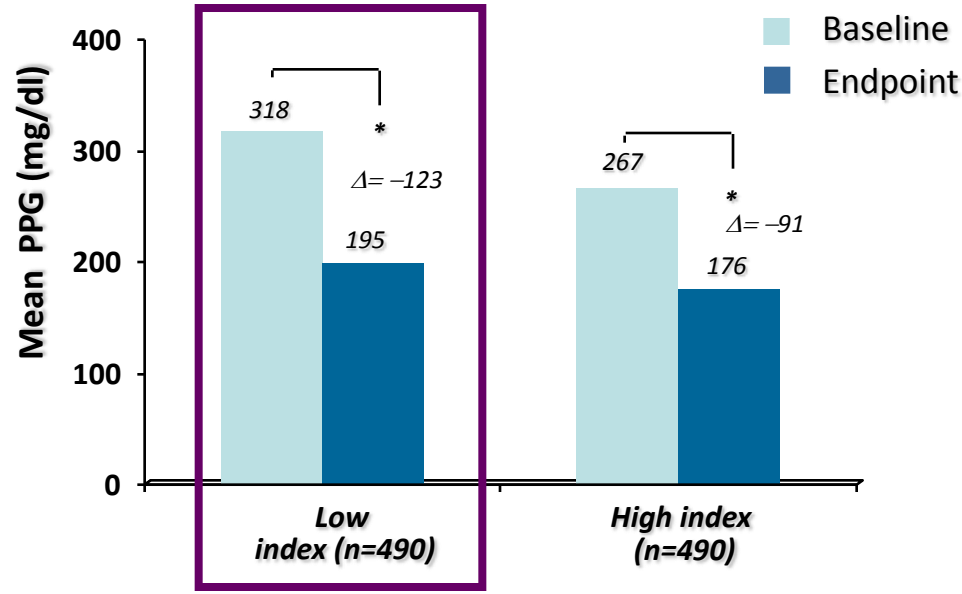
Characteristic	Low HOMA-β index (n=490)	High HOMA-β index (n=490)	*p*-value
Mean age, years (SD)	56.5 (9.7)	54.7 (9.4)	0.0025
Sex, male/female, %	47.8/52.2	41.2/58.8	0.0005
Race (%) Asian Black/African American White Other	 25.1 3.1 68.4 3.5	 9.6 4.5 83.7 2.2	 <0.0001
Mean BMI, kg/m^2 (SD)	29.9 (5.7)	34.9 (6.9)	<0.0001
Mean known diabetes duration, years (SD)	8.7 (6.4)	6.4 (4.9)	<0.0001
Mean duration of OAD therapy, years (SD) Metformin at baseline, % Sulfonylurea at baseline, %	4.7 (4.3) 85.7 32.2	4.1 (4.1) 92.5 16.5	0.0263 0.0007 <0.0001
Mean HbA_{1c}, % (SD)	8.3 (0.9)	7.9 (0.8)	<0.0001
Mean PPG, mg/dL (SD)	318 (74)	267 (68)	<0.0001
Mean FPG, mg/dL (SD)	176 (40)	158 (35)	<0.0001

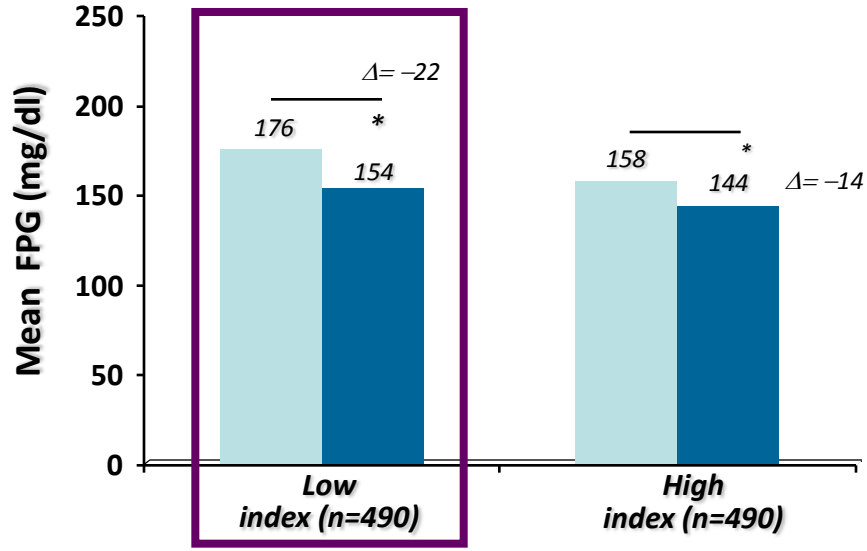
Post hoc analysis data extracted from the intent-to-treat populations of three GetGoal trials: GetGoal-M, GetGoal-S, GetGoal-P

Bonadonna R et al., ADA, 2014

Lixisenatide is Effective Regardless β-cell Function (HOMA-β)







** (p <0.0001)*

Bonadonna R et al., ADA, 2014

The Evaluation of Lixisenatide in Acute Coronary Syndrome

Introduction **-** John McMurray, MD, PhD

8th June, 2015

- *ELIXA Design and Baseline* Eldrin F. Lewis, MD, MPH
- *Results—Part 1* Matthew C. Riddle, MD
- *Results—Part 2* Marc A. Pfeffer, MD, PhD
- *ELIXA in Perspective* Hertzel C. Gerstein, MD, MSc,
- FRCPC *Panel Discussion/Question-and- Answer Period*

..... *the Ideal Partners .....*

Basal insulin therapy

- Simple to initiate
- Controls nocturnal and FPG
- Decreases hepatic glucose production
- Often started when residual endogenous insulin is compromised
- Less hypoglycemia risk
- Weight gain ~1-3 kg
- Achieves A1C targets in ~50-60%

Short-acting GLP-1 RAs Rx

- Simple to use
- Controls PPG and some FPG
- Decreases gastric emptying
- Efficay regardless the presence of residual endogenous insulin
- No increase of hypoglycemia
- Weight loss ~1-3 kg
- Achieves A1C targets in ~40-60%

Complementary and potentially synergistic effects

Combination Option of Basal Insulin and Short Acting GLP-1 receptor agonists in Type 2 DM

"… an obvious approach that theoretically could restore physiology through pharmacology….."


PHARMACOTHERAPY

GLP-1 analogues and insulin: sound the wedding bells?

Michael A. Nauck and Juris J. Meier

The Challenge of Diabetes

Thank you for your attention

GLP-1 RAs in Combination with Basal Insulin: the Rationale

An attractive therapeutic option as both components may address complementary targets and underlying mechanisms without hypoglycemia and weight gain associated with intensification of the insulin regimen.

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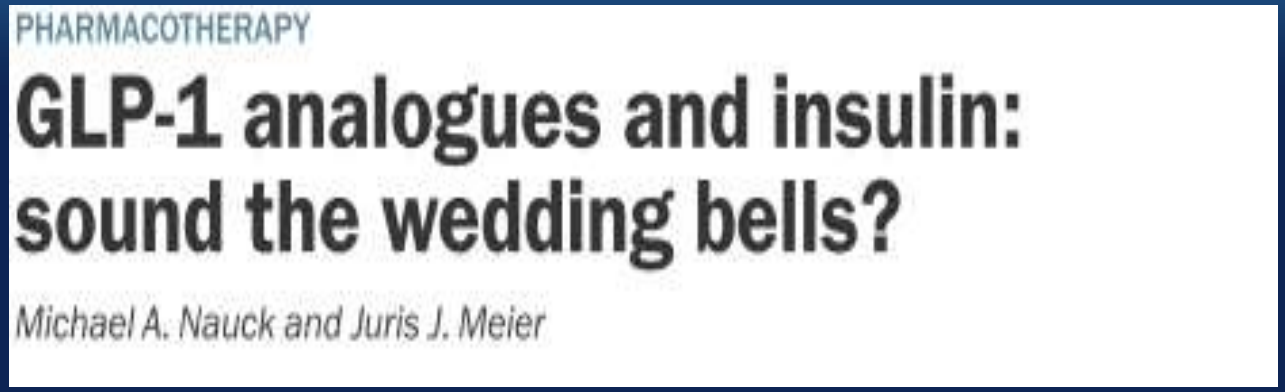
PHARMACOTHERAPY

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Michael A. Nauck and Juris J. Meier

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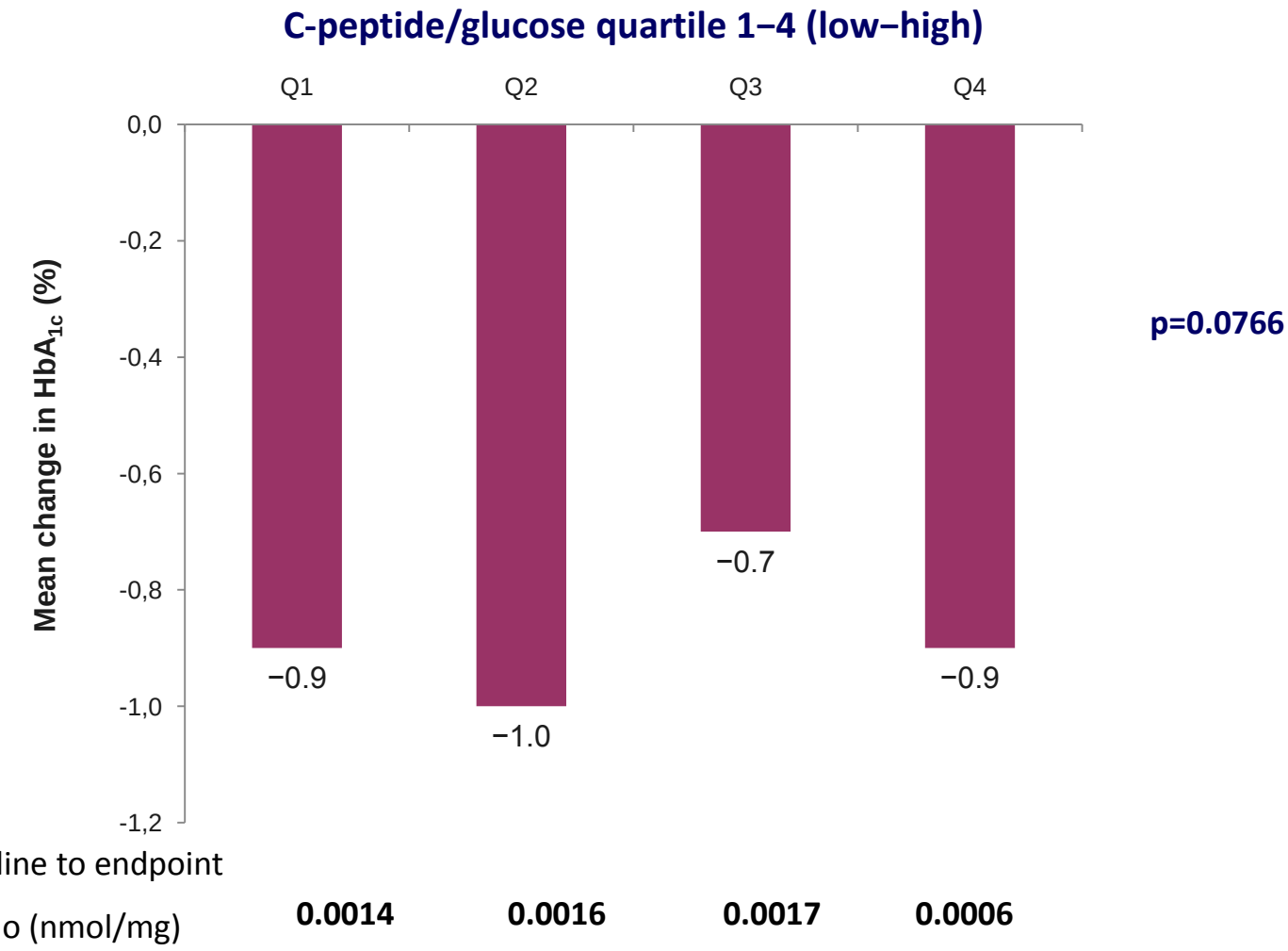
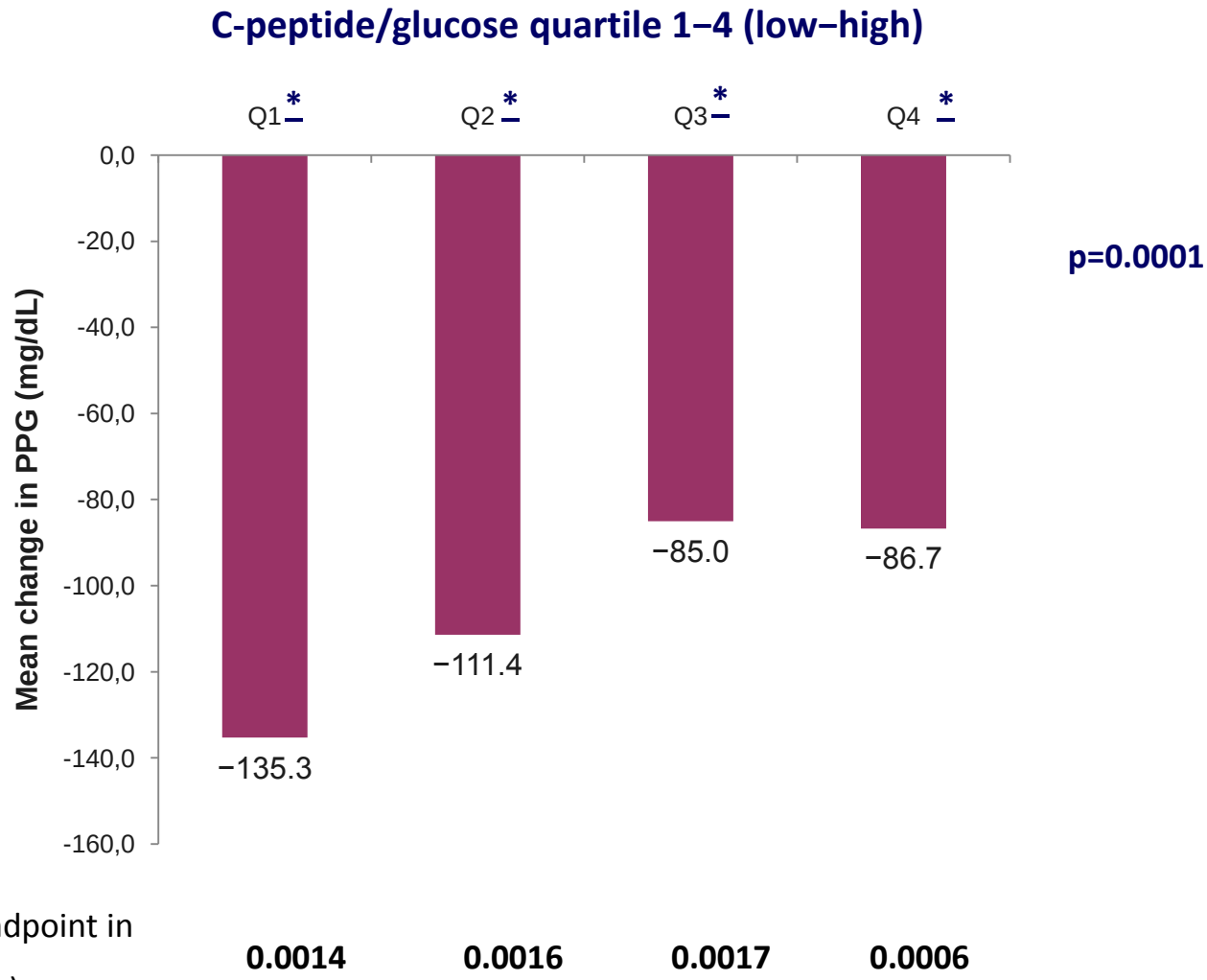
Complementary and potentially synergistic effects

Effects of Lixisenatide on HbA1c in Patients with Different Degrees of β-cell Function



Meier JJ et al., 2013 Diabetologia (EASD abstract)

Effects of Lixisenatide on HbA1c in Patients with Different Degrees of β-cell Function



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