# Innovations in GLP-1 Receptor Agonist Therapy: Individualized Treatment Strategies to Overcome Barriers and Reduce Cardiometabolic Risk in Type 2 Diabetes Mellitus

Supported by an educational grant
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- During the panel discussion, please use the question cards located on each table.
- Complete and return a CME Evaluation Form at the conclusion of the symposium.

# Welcome
# and
# Opening Remarks

**John B. Buse, MD, PhD**
**Verne S. Caviness Distinguished Professor**
**Director, Diabetes Care Center**
**Chief, Division of Endocrinology**
**Executive Associate Dean, Clinical Research**
**University of North Carolina School of Medicine**
**Chapel Hill, North Carolina**

# Clinical Practice Guidelines for Managing Patients with Type 2 Diabetes: Where Do Incretins Fit into the Treatment Paradigm?

John B. Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Director, Diabetes Care Center
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# Glycemic Control Algorithm

## LIFESTYLE MODIFICATION
*(Including Medically Assisted Weight Loss)*

### ENTRY A1c < 7.5%

**MONOTHERAPY***

- Metformin ✓
- GLP-1 RA ✓
- DPP4-i ✓
- AG-i ✓
- SGLT-2 ** ⚠
- TZD ⚠
- SU/GLN ⚠

If A1c > 6.5% in 3 months add second drug (Dual Therapy)

### ENTRY A1c ≥ 7.5%

**DUAL THERAPY***

MET or other first-line agent +

- GLP-1 RA ✓
- DPP4-i ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- Colesevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

If not at goal in 3 months proceed to triple therapy

**TRIPLE THERAPY***

MET or other first-line agent + 2ND LINE AGENT

- GLP-1 RA ✓
- TZD ⚠
- ** SGLT-2 ⚠
- Basal insulin ⚠
- DPP4-i ✓
- Colesevelam ✓
- Bromocriptine QR ✓
- AG-i ✓
- SU/GLN ⚠

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

### ENTRY A1c > 9.0%

| NO SYMPTOMS | SYMPTOMS |
|---|---|
| DUAL THERAPY OR TRIPLE THERAPY | INSULIN ± OTHER AGENTS |

ADD OR INTENSIFY INSULIN

* Order of medications listed are a suggested hierarchy of usage

** Based upon phase 3 clinical trials data

**LEGEND**

✓ = Few adverse events or possible benefits

⚠ = Use with caution

PROGRESSION OF DISEASE

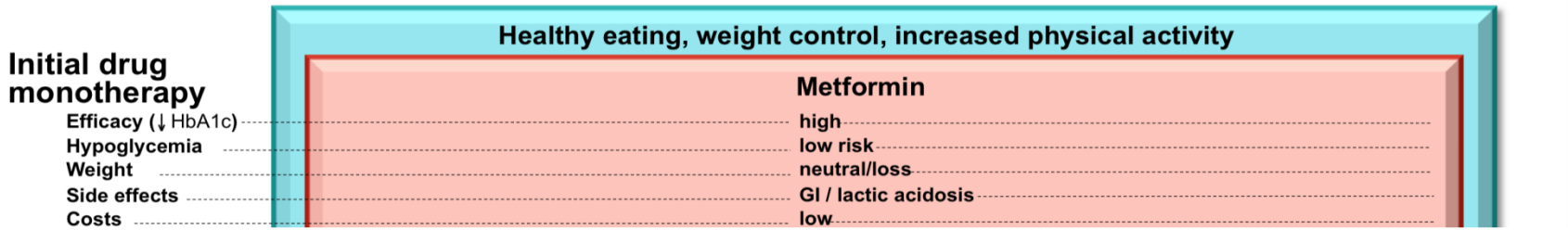



**Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations**

Inzucchi et al. Diabetes Care 2012;35:1364–79.

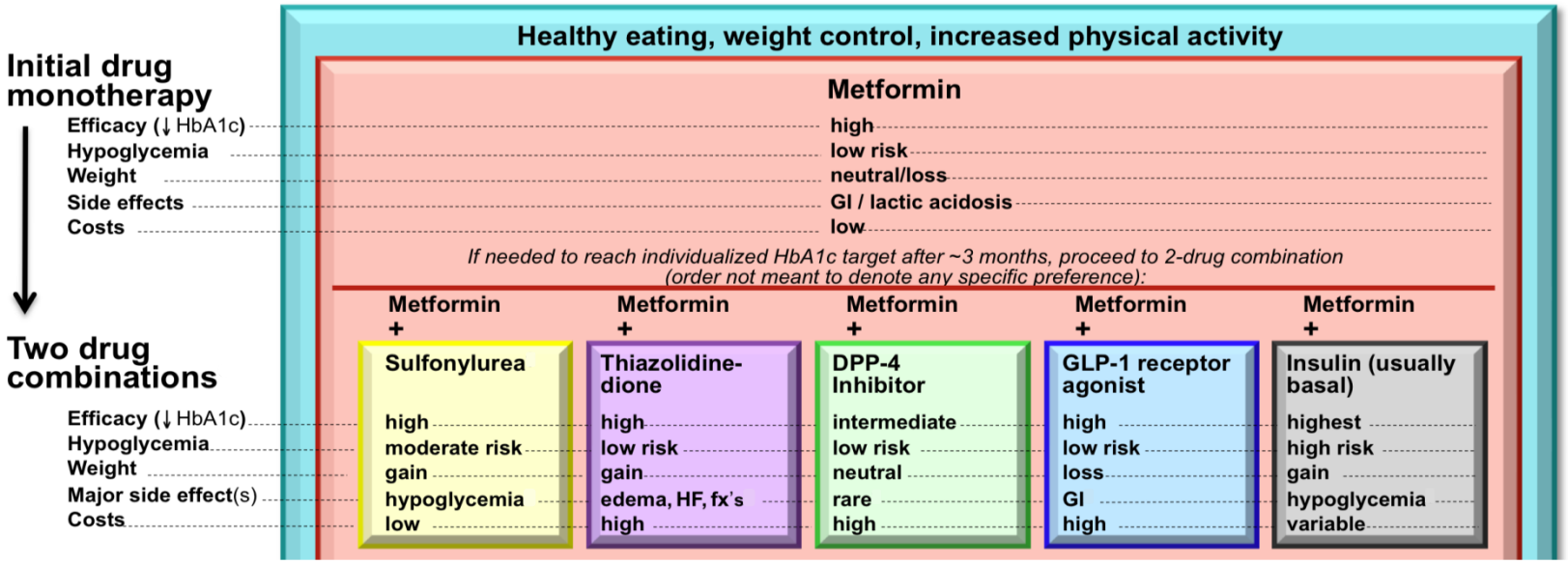
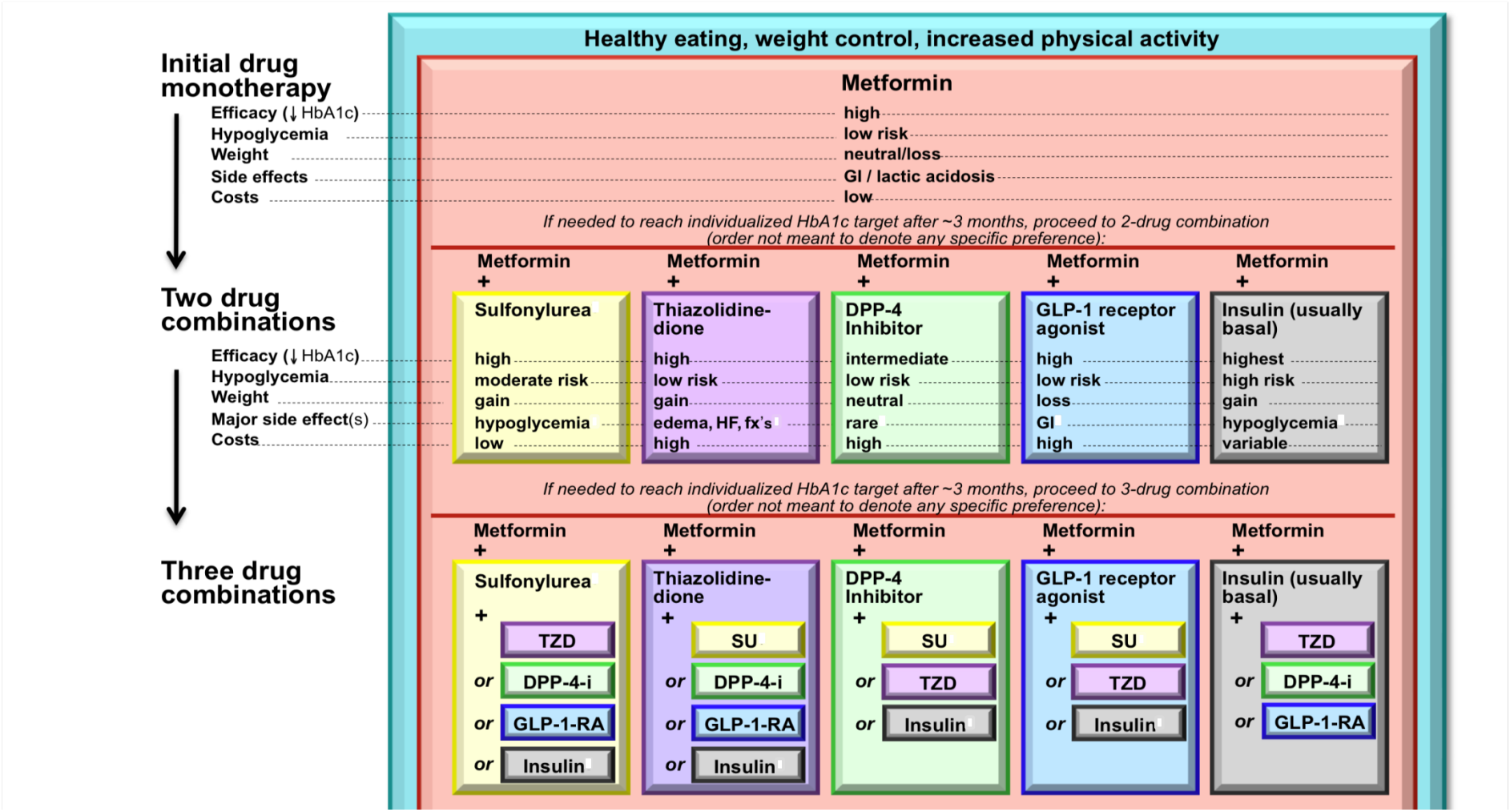



**Figure 2. T2DM Antihyperglycemic Therapy: General Recommendations**

Inzucchi et al. Diabetes Care 2012;35:1364–79.

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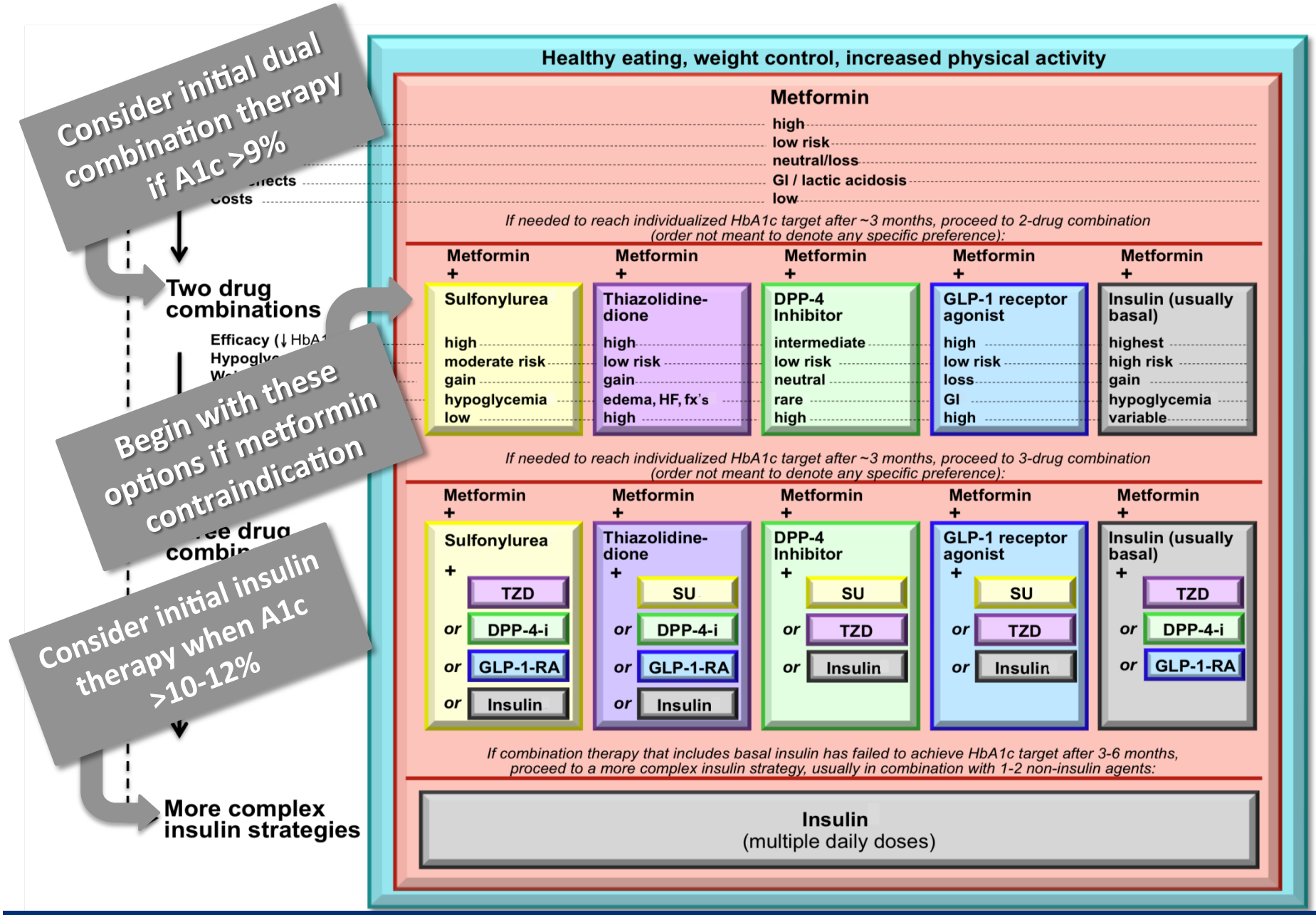


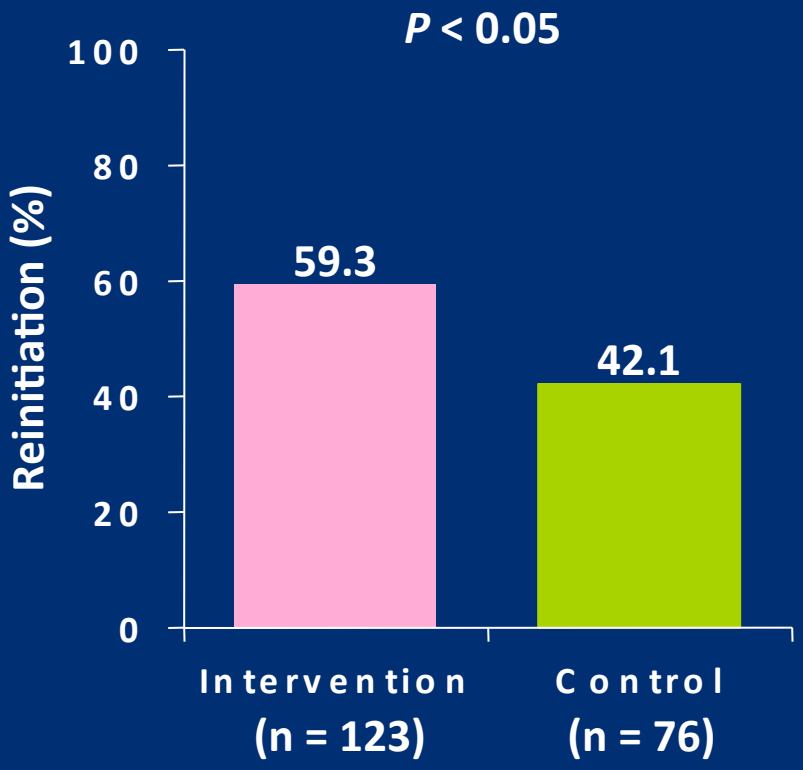

Inzucchi et al. Diabetes Care 2012;35:1364–79.

# Optimizing Outcomes for Patients With Chronic Diseases

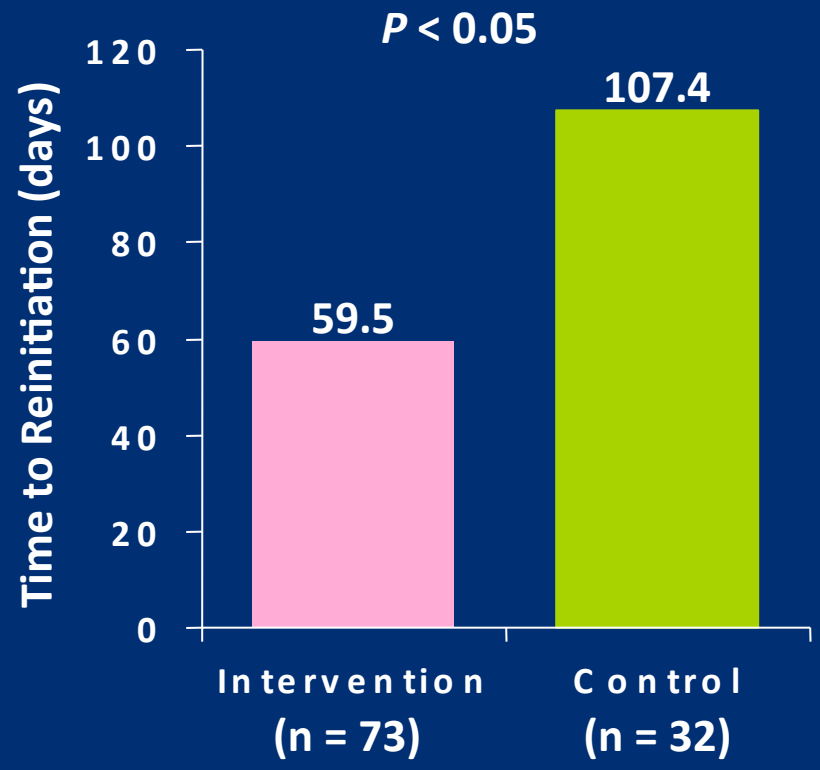
- Medication adherence rates in chronic care: 50%
  - Must have engaged, informed, motivated patient
  - Shared decision-making in a setting of mutual respect, open communication, cultural/ socioeconomic sensitivity
  - Leverage opportunities to change/improve lifestyle behaviors

# Communication* Intervention Improves Medication Use

## Higher Rate of Medication Reinitiation



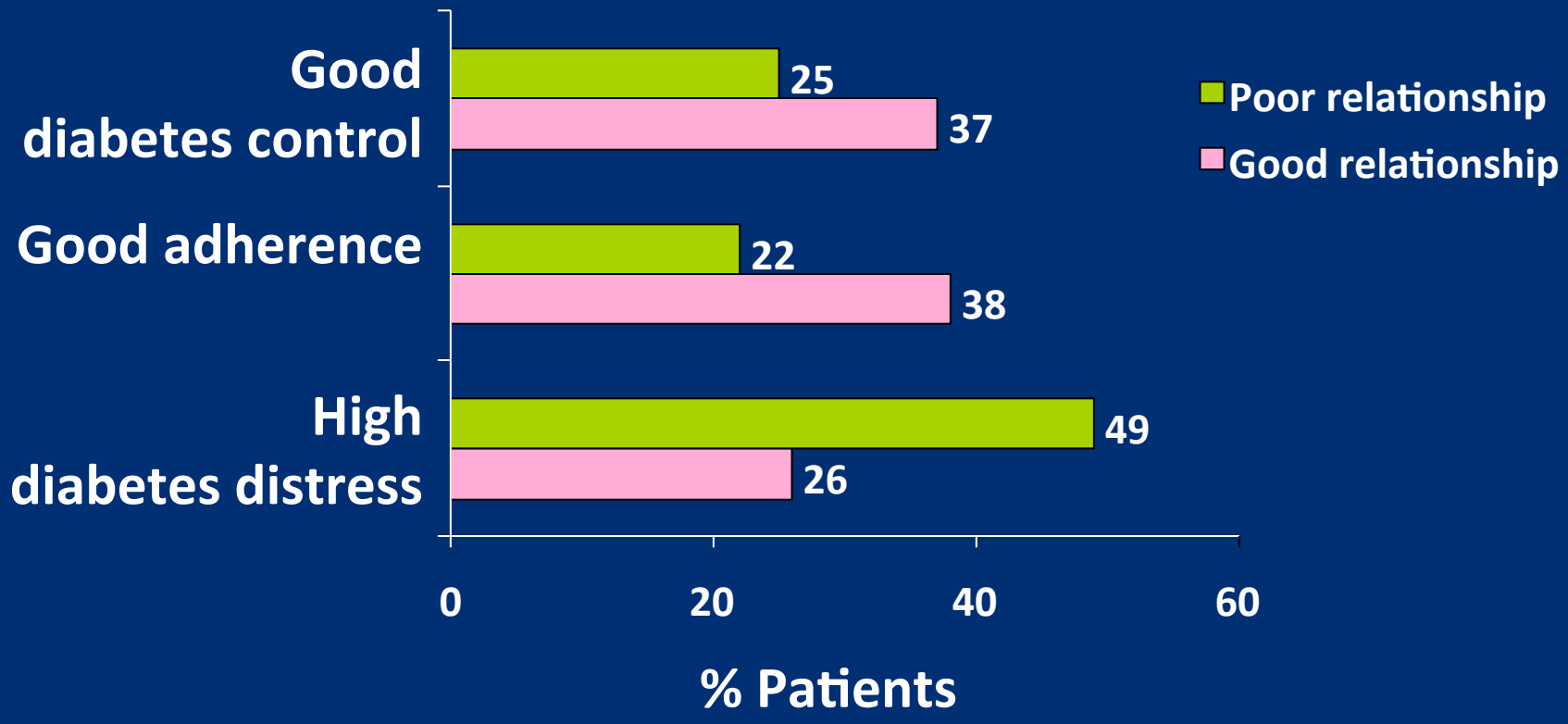

## Shorter Time to Medication Reinitiation




*Care managers trained in behavior change, patient readiness to change, motivational interviewing, and active listening

Lawrence et al. Dis Manag. 2008;11:141-4.

# Relationship With Provider Predicts Diabetes Outcomes




Peyrot et al. Diabetes Care. 2005;28:2673-79.

# Factors Affecting Patient Adherence to Diabetes Medications

| Patient Belief/Concern | Odds Ratio for Poor Adherence | Confidence Interval |
|---|---|---|
| Feeling medicines are hard to take | 14.0 | 4.4–44.6 |
| Belief that they have diabetes only when sugar is high | 7.4 | 2–27.2 |
| No need to take medicine when glucose level was normal | 3.5 | 0.9–13.7 |
| Worry about side effects | 3.3 | 1.3–8.7 |
| Lack of self-confidence in controlling diabetes | 2.8 | 1.1–7.1 |

Mann et al. J Behav Med. 2009;32:278–84.

# "Everything else": The Mainstay of Medical Care

**"Dr. [Ted] Kaptchuk [Harvard] describes placebos as not just the traditional sugar pill, but also "everything that surrounds a medical treatment": how caregivers describe the medication, how they administer it, the expectations they have for the medicine, their tone of voice, their strength of eye contact. In short, everything that doctors and nurses do in an interaction with a patient.**

**This is not especially surprising. Healers and shamans have known intuitively about the importance of this interaction since the dawn of time. Before we had developed treatments that could significantly impact the pathology of disease — antibiotics, chemotherapy, stents, organ transplants, transfusions — the 'everything else' was the mainstay of medical care."**

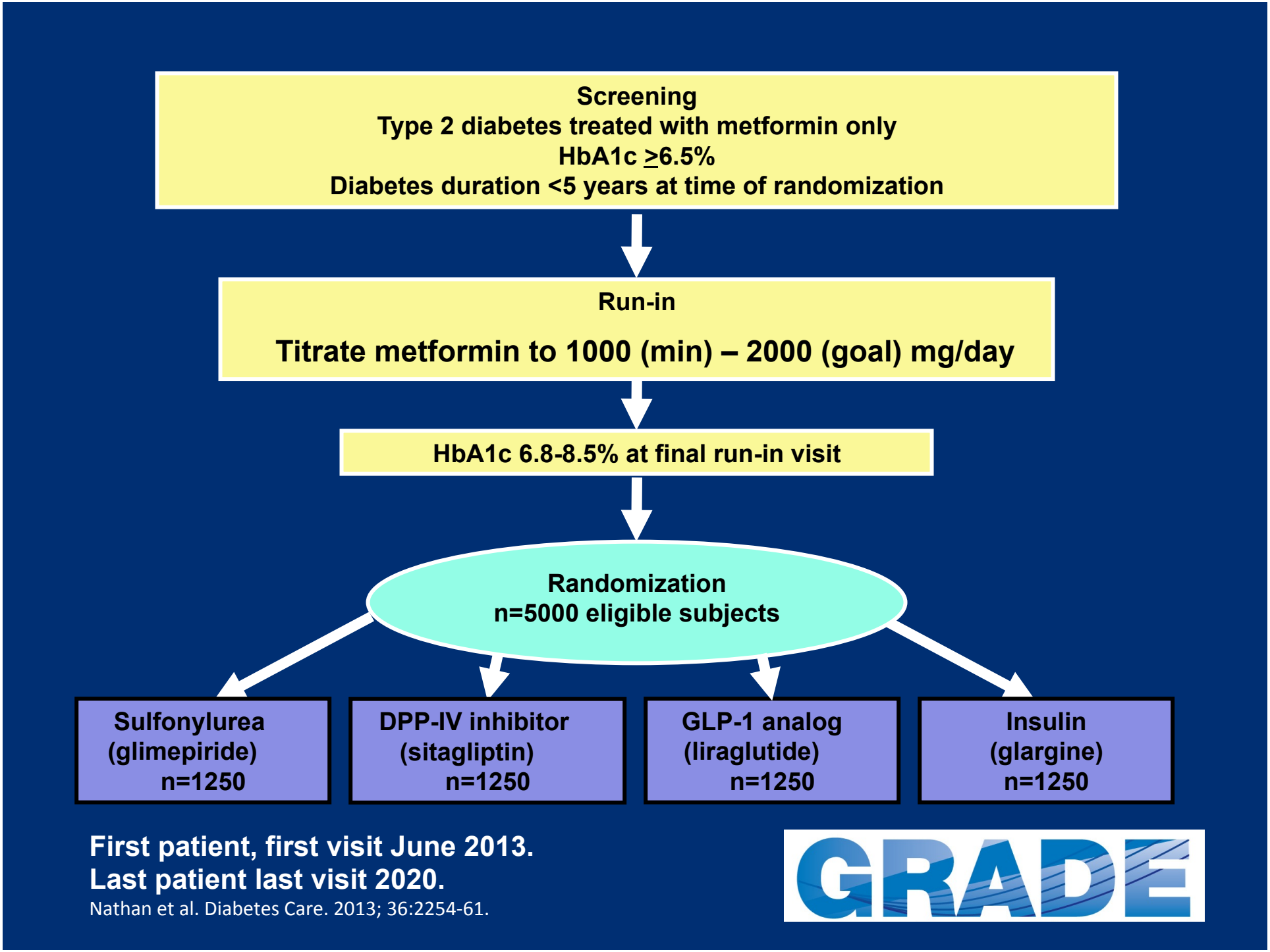
http://well.blogs.nytimes.com/2013/08/15/a-powerful-tool-in-the-doctors-toolkit/?ref=health&_r=0

# Antihyperglycemic Agents in Type 2 Diabetes

| Class | Generic or Brand | A1C Reduction | Usual Dosing (times/day) | Injected or Oral | Severe Hypo-glycemia | Weight Change | Other Safety Concerns (beyond hypoglycemia and weight gain) |
|---|---|---|---|---|---|---|---|
| R, Lispro, Aspart, Glulisine | Brand | 1.5 - 2.5 | 2-4 | Injected | Yes | Gain | Breast Cancer |
| NPH, Glargine, Detemir | Brand | 1.5 - 2.5 | 1 | Injected | Yes | Gain | |
| Glipizide ER, Glimepiride | Generic | 1.5 | 1 | Oral | Yes | Gain | CVD |
| Repaglinide | Brand | 1 - 1.5 | 3 | Oral | Yes | Gain | |
| Nateglinide | Generic | 0.5 - 0.8 | 3 | Oral | Rare | Gain | |
| Metformin | Generic | 1.5 | 1-2 | Oral | No | Neutral | B12 deficiency, lactic acidosis |
| Acarbose, Miglitol | Generic | 0.5 - 0.8 | 3 | Oral | No | Neutral | |
| Pioglitazone | Brand | 0.5 - 1.4 | 1 | Oral | No | Gain | CHF, Bone fx, Bladder Ca |
| Pramlintide | Brand | 0.5 – 0.9 | 3 | Injected | No | Loss | |
| Exenatide | Brand | 0.7 - 1.0 | 2 | Injected | No | Loss | ARF, Pancreatitis, PancCa |
| Liraglutide | Brand | 0.9 - 1.4 | 1 | Injected | No | Loss | ARF, Pancreatitis, MTC, PancCa |
| Exe- OW, albi-, dula- glutide | Brand | 0.9 - 1.6 | Every 7d | Injected | No | Loss | ARF, Pancreatitis, MTC, PancCa |
| Sita-, saxa-, lina-, alo- gliptin | Brand | 0.6 - 0.8 | 1 | Oral | No | Neutral | Pancreatitis, PancCa |
| Colesevelam | Brand | ~0.5 | 1-2 | Oral | No | Neutral | Hypertriglyceridemia |
| Bromocriptine QR | Brand | ~0.6 | 1 | Oral | No | Neutral | Various in PI |
| Cana-, dapa-, empa- gliflozin | Brand | 0.6 – 1.2 | 1 | Oral | No | Loss | LDL, ARF, Genital infections, K |

ARF=acute renal failure; MTC=medullary thyroid carcinoma

Adapted from: Nathan et al. Diabetes Care. 2009; 32:193-203. ADA. Diabetes Care. 2010;33:S11-S61. Buse et al. In: Williams Textbook of Endocrinology, 12th ed . 2012. Individual agents prescribing information.




**First patient, first visit June 2013.**
**Last patient last visit 2020.**

Nathan et al. Diabetes Care. 2013; 36:2254-61.

GRADE

# GLP-1 Receptor Agonists: Similarities and Differences


## Richard Pratley, M.D.

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# Outline

- Structure of GLP-1 receptor agonists
- PK/PD of GLP-1 receptor agonists
- Glycemic efficacy of GLP-1 receptor agonists
- Weight loss, blood pressure, lipids
- Safety and tolerability

# Incretin Therapies to Treat T2DM

**Incretin effect is impaired in Type 2 diabetes**

**Natural GLP-1 has extremely short half-life**

**Add GLP-1 analogues with longer half-life:**

**Injectables**

**Exendin-4 Based:**

- Exenatide
- Exenatide QW
- Lixisenatide*
- Langlenatide*

**Human GLP-1:**

- Liraglutide
- Albiglutide
- Dulaglutide
- Semaglutide*

**Block DPP-4, the enzyme that degrades GLP-1:**

**Oral agents**

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
- Vildagliptin*

*Not FDA approved

Adapted from Drucker. Curr Pharm Des. 2001;7:1399-412. Drucker. Mol Endocrinol. 2003;17:161-71.

# Exenatide and Lixisenatide*

## GLP-1


## Exenatide


- 39 a.a. ~53% homology to human GLP-1
- Similar binding affinity at GLP-1 receptor
- DPP-4 resistant
- Half-life ~ 2.1 hours

## Lixisenatide*

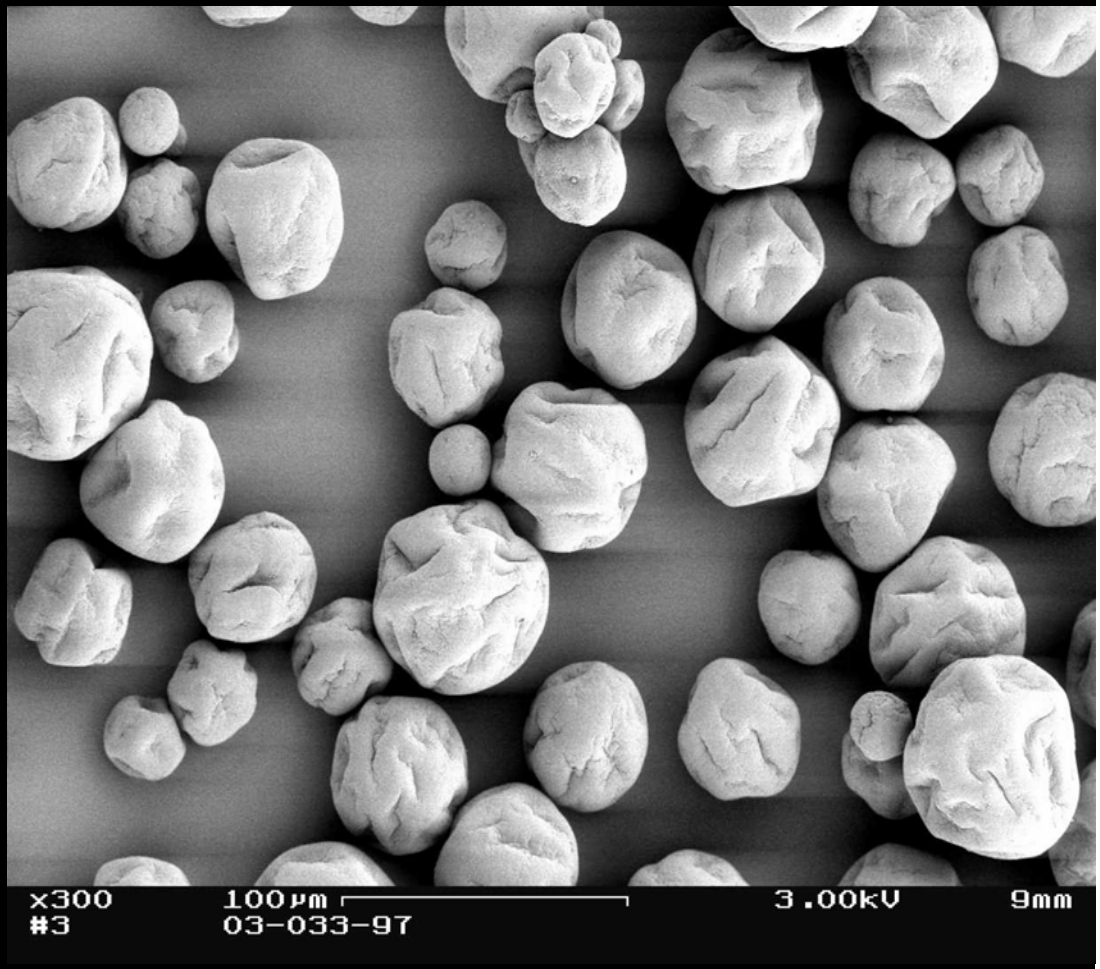

- 44 a.a. <50% homology to human GLP-1
- 1 proline has been deleted and 6 lysines have been added
- DPP-4 resistant
- Half-life ~ 3-4 hour

Meier. Nature Rev Endocrinol. 2012;8:728-42.

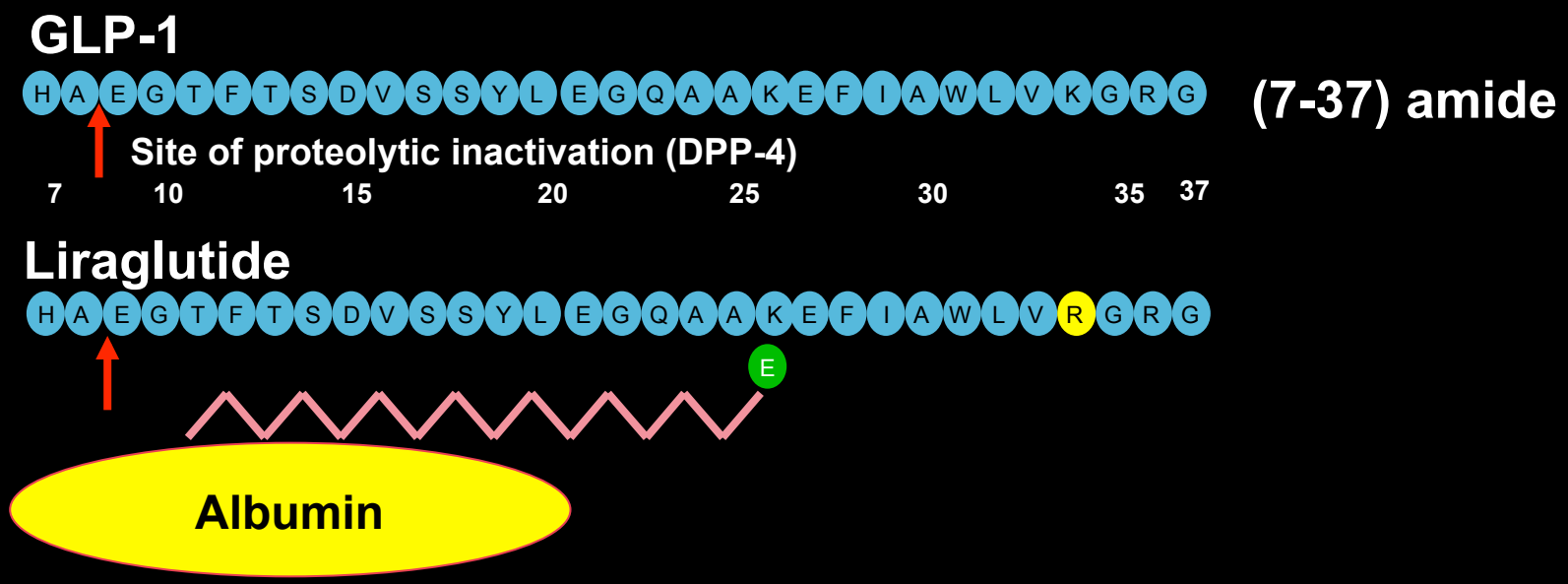
*Not FDA approved

# Exenatide Once Weekly

- Polymer-based microspheres
- Degrade slowly, gradually releasing the drug at a carefully controlled rate.
- Half-life ~ 7-14 d



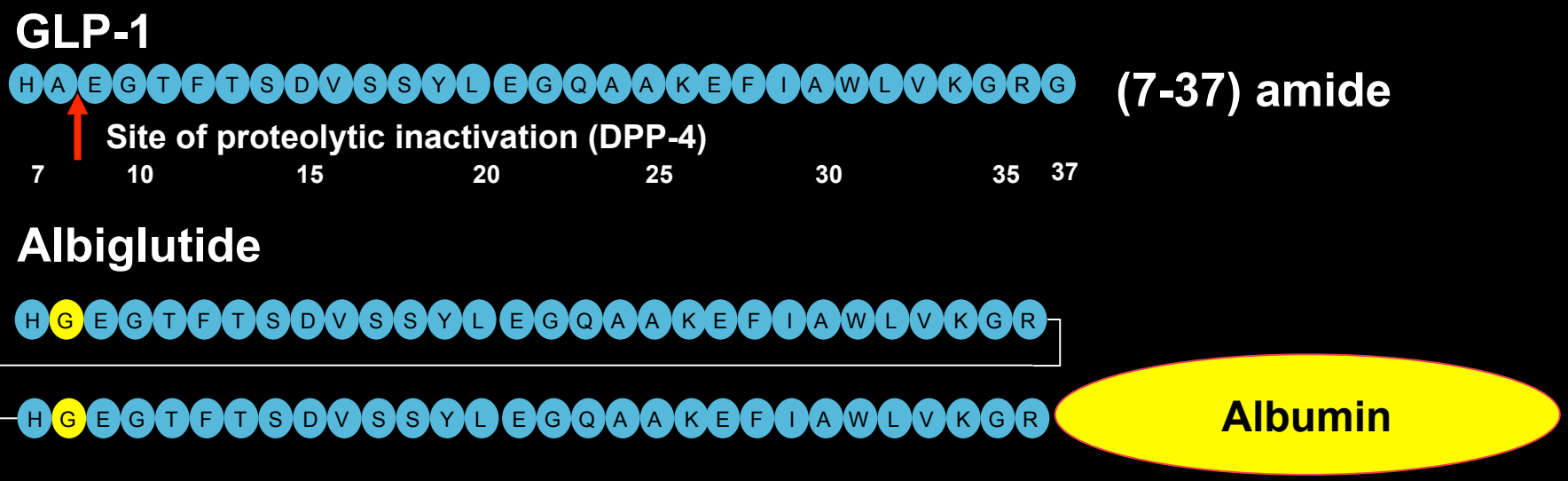
# Liraglutide




- ~97% homology to human GLP-1
- C-16 fatty acid
- Self-association into heptamers
- Noncovalent binding to albumin
- Half-life ~ 13 hours

Knudsen et al. J Med Chem 2000; 43: 1664–69.

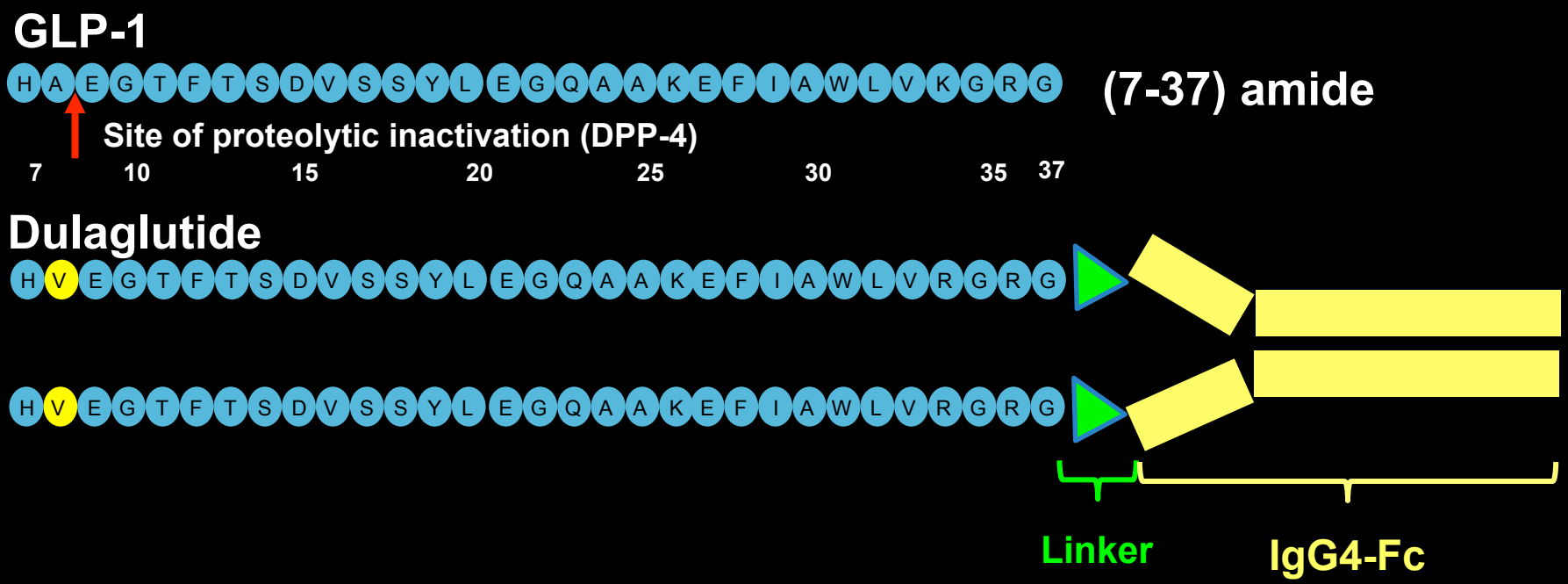
# Albiglutide




- 2 GLP-1 molecules in tandem
- Covalently bound to albumin
- DPP-4 resistant
- Half-life ~ 5 days

Drucker et al. Lancet. 2006;368:1696-1705. Bush et al. Diabetes Obesity Metabolism. 2009;11:498-505.

# Dulaglutide




- Modified GLP-1 covalently bound to IgG4-Fc
- DPP-4 resistant
- Half-life ~ 4 days

Meier. Nature Rev Endocrinol, 2012;8:728-42.

# Short-acting vs. Long-acting GLP-1 RAs: Pharmacokinetic Differences

Increasing protraction

| Category | Agent | Half-life | $T_{max}$ |
|---|---|---|---|
| Short-acting GLP-1 RAs | Exenatide BID[1] | 2.4 hours | 2 hours |
| | Lixisenatide* OD[2] | 2.7–4.3 hours | 1.25–2.25 hours |
| Long-acting GLP-1 RAs | Liraglutide OD[3] | 13 hours | 8–12 hours |
| | Dulaglutide OW[4] | 90 hours | 24–48 hours |
| | Albiglutide OW[5] | 5 days | 3–5 days |
| | Exenatide OW[6] | 7–14 days | 6–7 weeks |

*Not FDA approved

Tmax, time to reach maximum concentration; OD, once a day

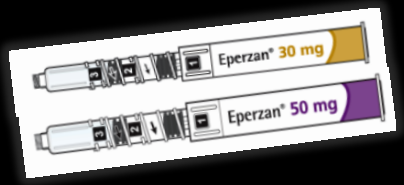
1. Byetta. Summary of Product Characteristics; 2. Lyxumia. Summary of Product Characteristics; 3. Victoza. Summary of Product Characteristics; 4. Barrington et al. Diabetes Obes Metab 2011;13:434–438; 5. Eperzan. Summary of Product Characteristics. 6. Fineman et al. Clin Pharmacokinet 2011;50:65–74

# GLP-1 RA Administration and Devices


## Exenatide BID

2 pre-filled pens (5 µg and 10 µg)[1]

Needle (29-31 gauge) needs attaching prior to use[1]




## Albiglutide

2 pre-filled pens; 30 mg (gold pen) or 50 mg (purple pen)[3]

Needs reconstitution

Needle needs attaching prior to use[3]


## Liraglutide

1 pre-filled pen; each delivers 0.6, 1.2, and 1.8 mg[2]

≥32-gauge needle needs attaching prior to use[2]


## Lixisenatide*

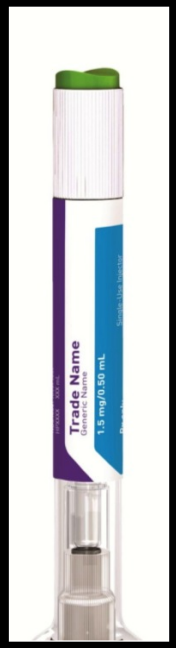
2 pre-filled pens; each dose contains 10 µg (green pen) or 20 µg (purple pen)[4]

Needle (29-32 gauge) needs attaching prior to use[4]

## Exenatide QW

Powder and syringe; needs reconstitution[5]

23-gauge needle needs attaching prior to use[5]




## Dulaglutide

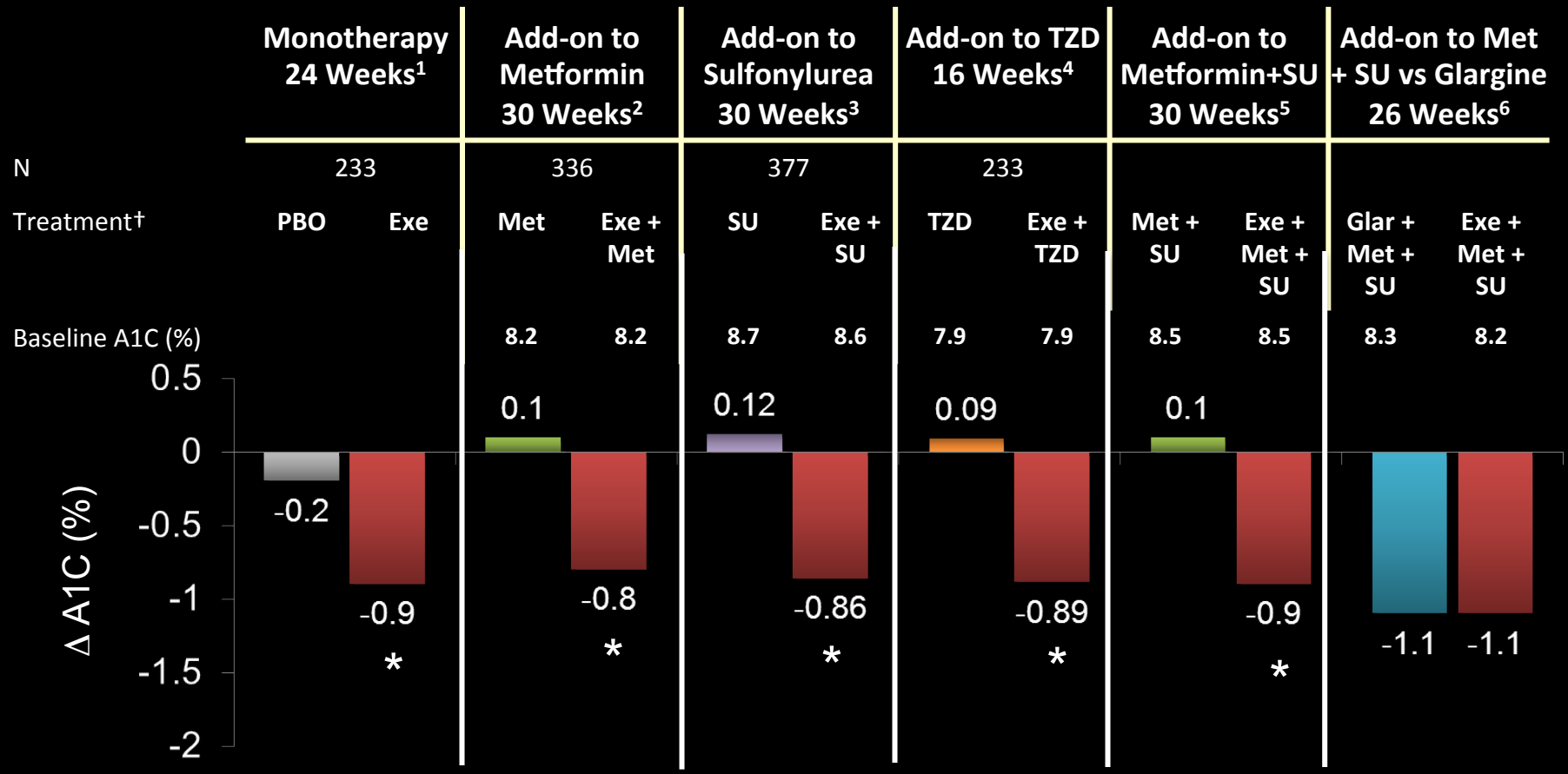
Automatic Injection

Hidden needle

*Not FDA approved

1. BYETTA Prescribing Information.
2. Victoza Summary of Product Characteristics.
3. Eperzan Summary of Product Characteristics.
4. Lyxumia Summary of Product Characteristics.
5. BYDUREON Prescribing Information.

# A1c Reductions with Exenatide BID



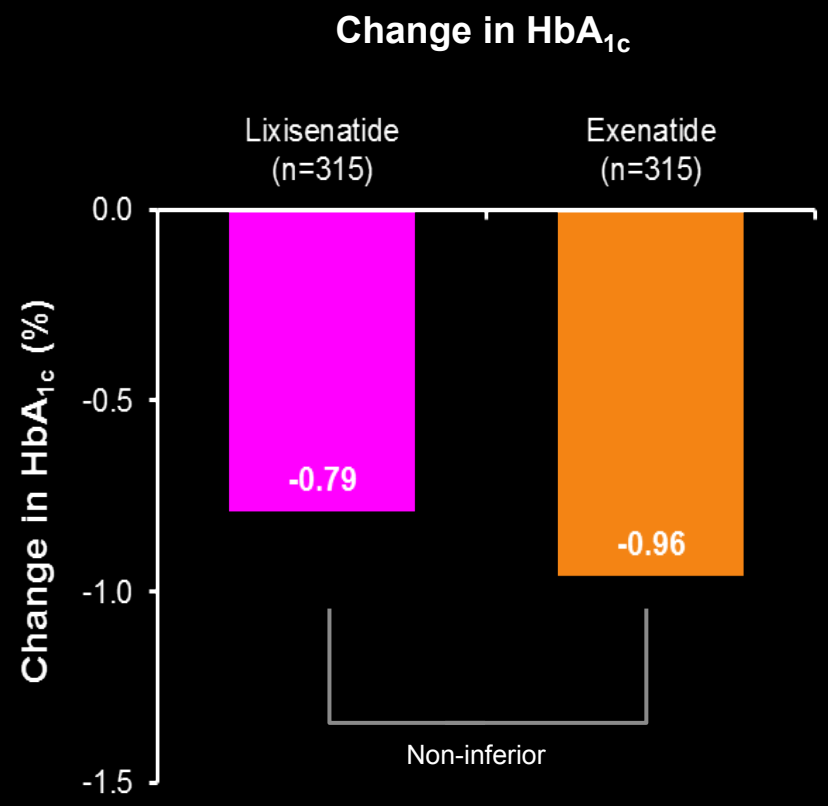

*$P$<0.001 vs comparator.

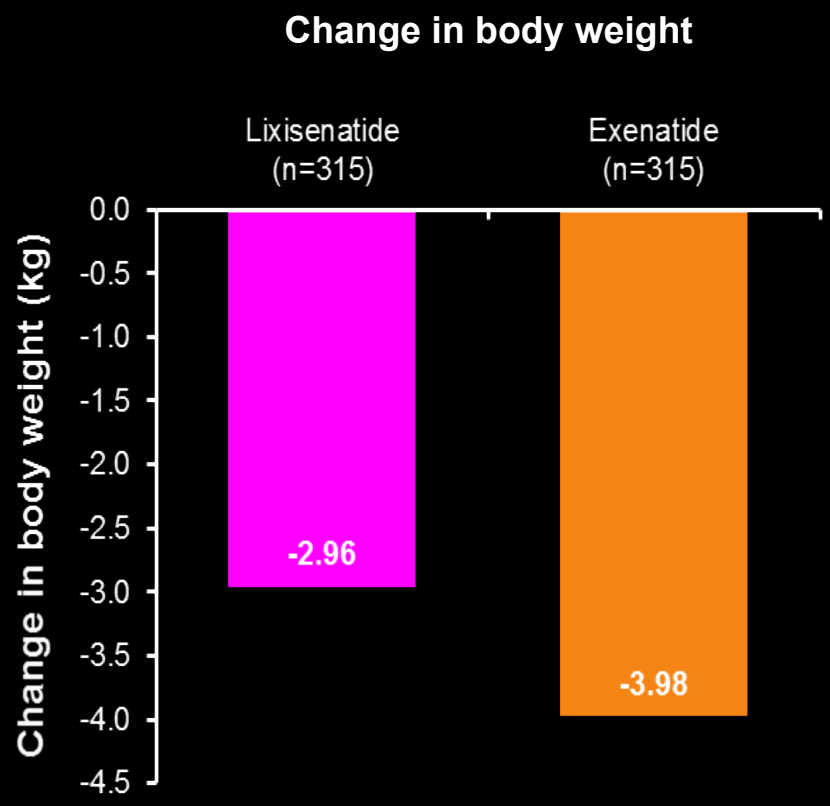
†All exenatide dosages shown are 10 µg BID.

1. Moretto et al. Clin Ther. 2008;30:1448-1460. 2. DeFronzo et al. Diabetes Care. 2005;28:1092-1100. 3. Buse et al. Diabetes Care. 2004;27:2628-2635. 4. Zinman et al. Ann Intern Med. 2007;146:477-485. 5. Kendall et al. Diabetes Care. 2005;28:1083-1091. 6. Heine et al. Ann Intern Med. 2005;143:559-569.

# Lixisenatide* vs. Exenatide : HbA1c and Body Weight over 24 weeks - GetGoal-X

add-on to metformin

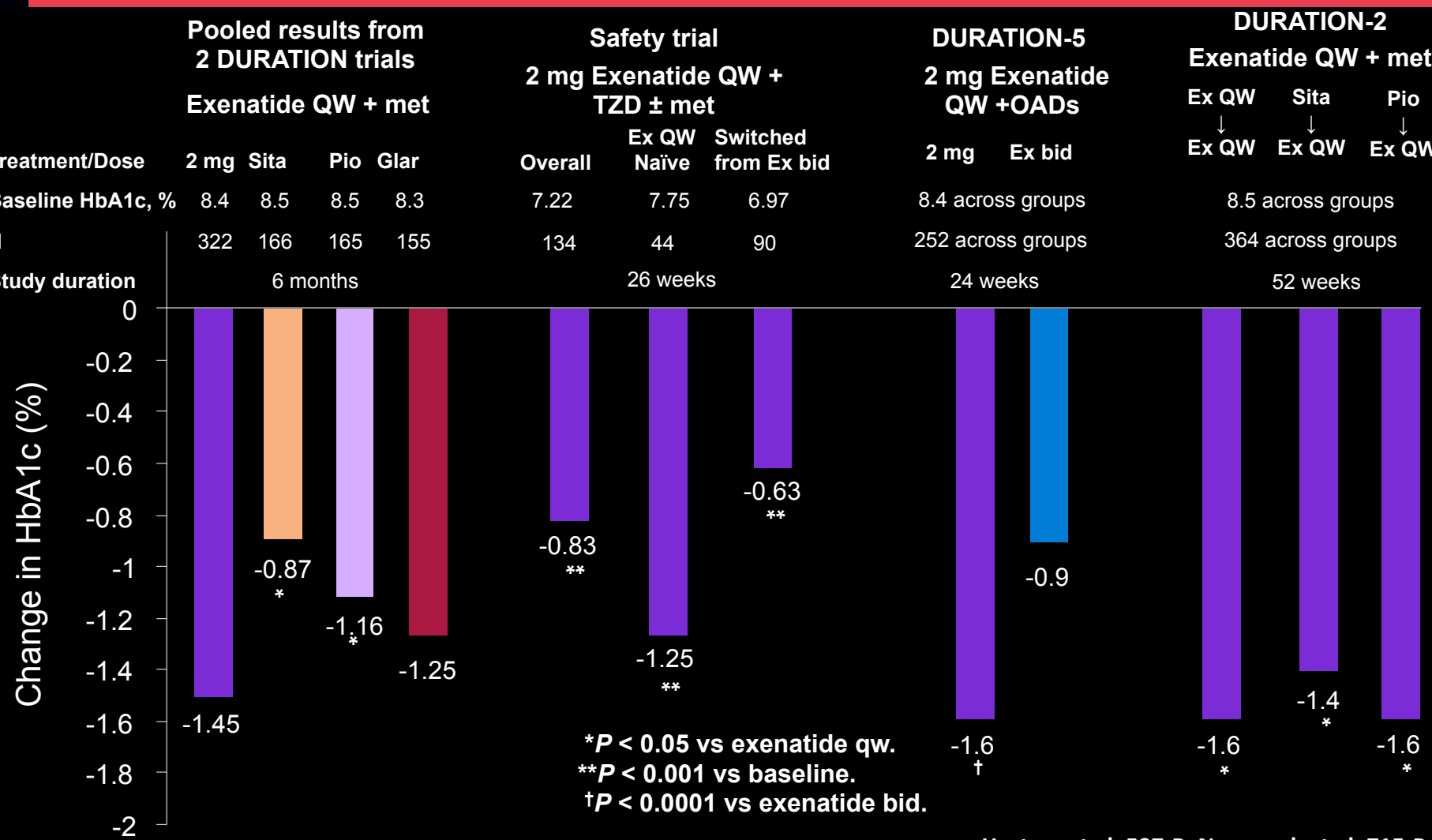



*Not FDA approved

Rosenstock et al. Diabetes Care 2013;36:2945–51

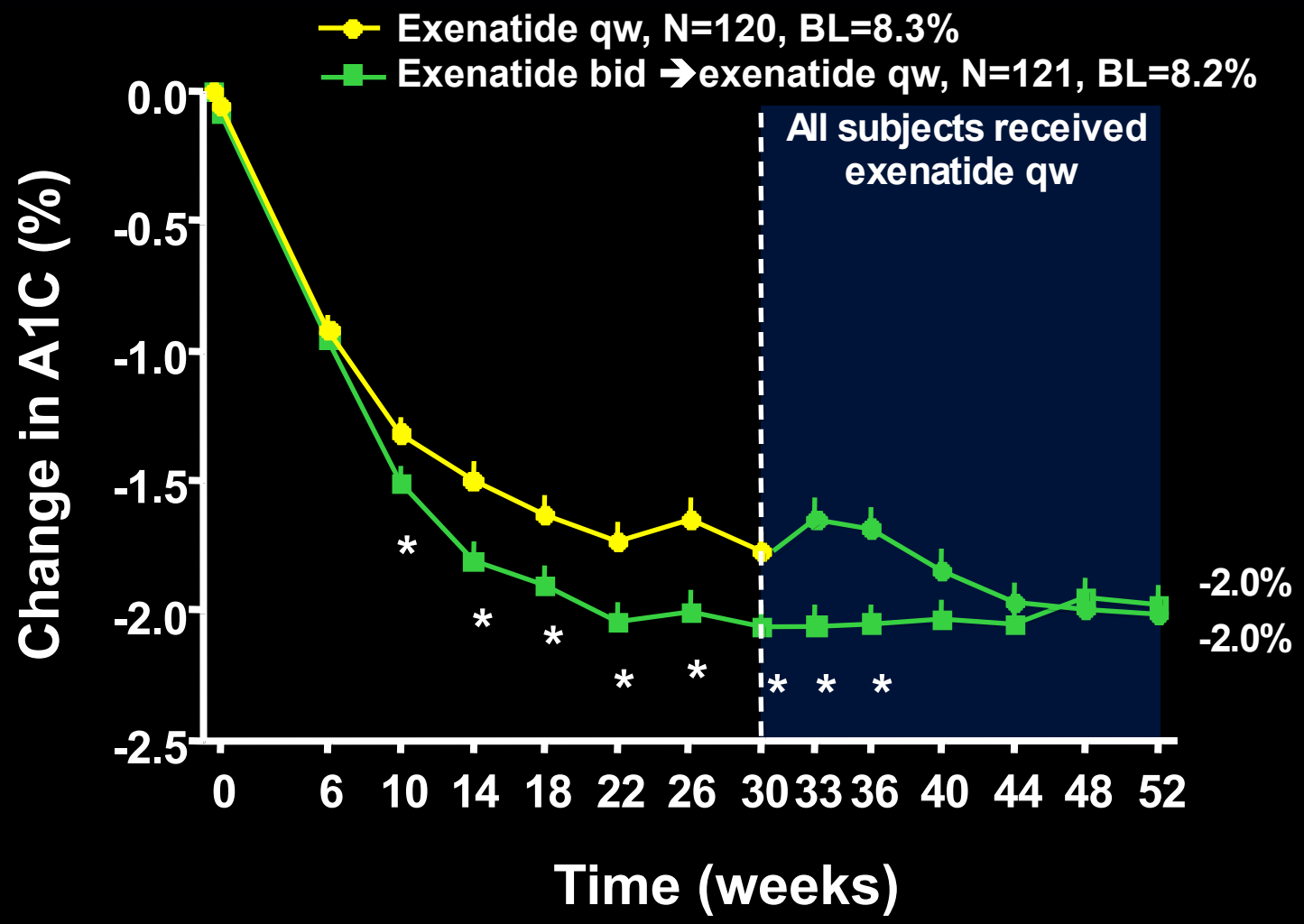
# A1c Reductions with Exenatide Once Weekly




§ Study was 52 weeks in duration, with crossover at 26 weeks. Numbers reported are change from baseline.

Horton et al. 597-P; Norwood et al. 715-P; Blevins et al; 8-LB; Wysham et al. 594-P.

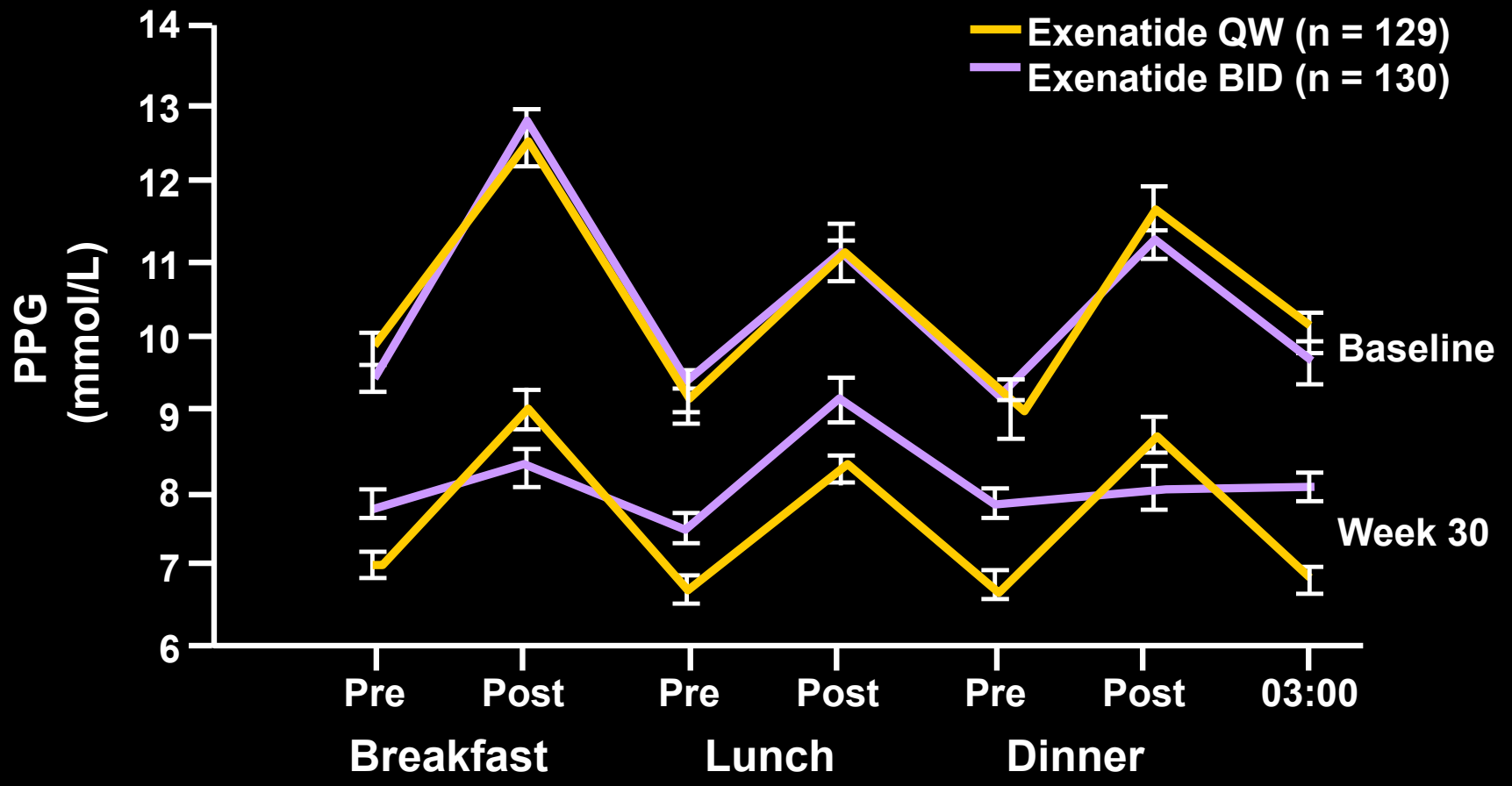
# Exenatide QW vs Exenatide BID: A1C




**52-week Evaluable Population (N=241). LS Mean (SE). **P*<.05 between groups. BL=baseline.**

Buse et al. Presented at ADA, 68th Scientific Sessions; 2008.

# Effects of Exenatide BID vs Exenatide QW on PPG

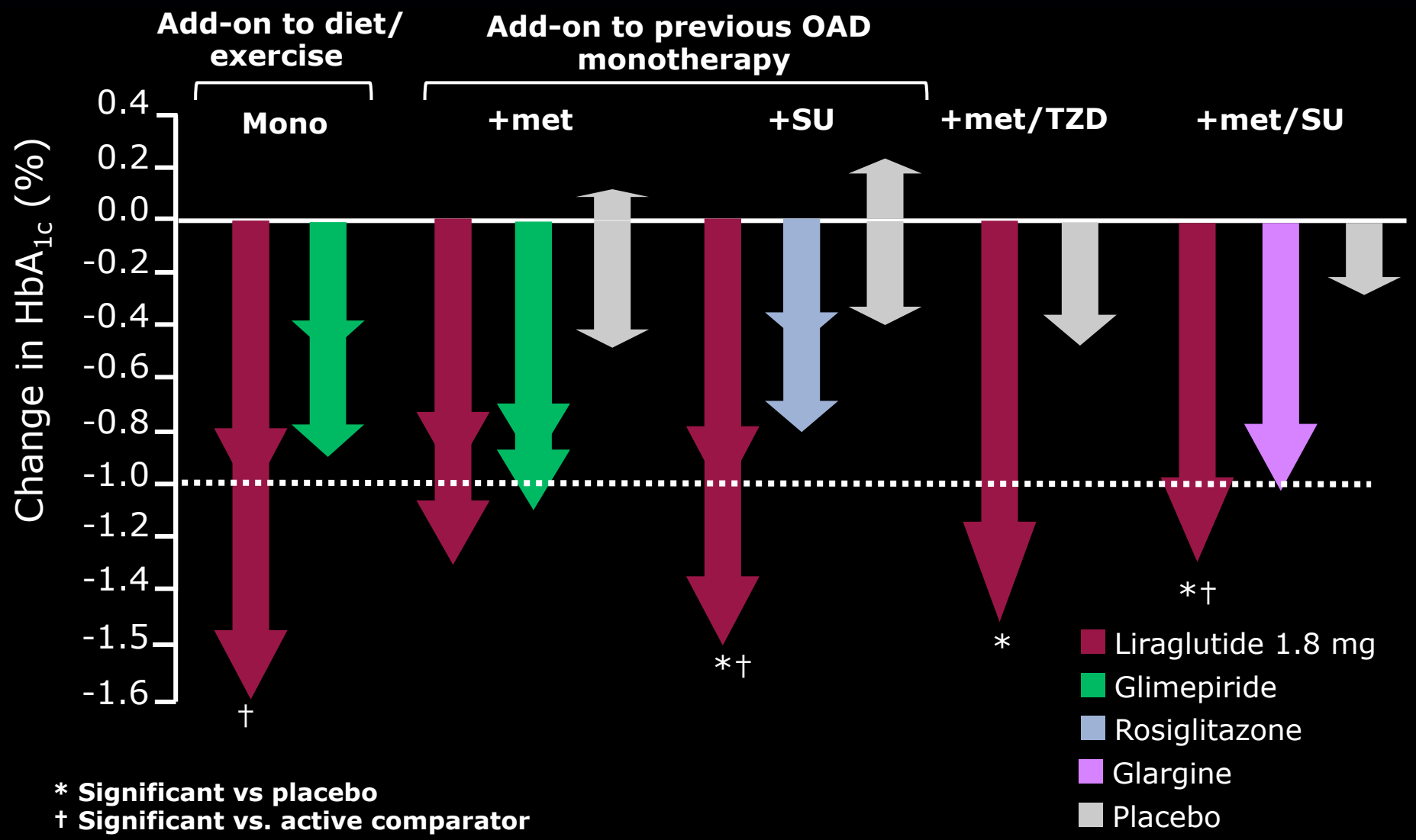



Data presented are means ± SE
PPG taken from SMBG profile

Drucker et al. Lancet 2008;372:1240-50

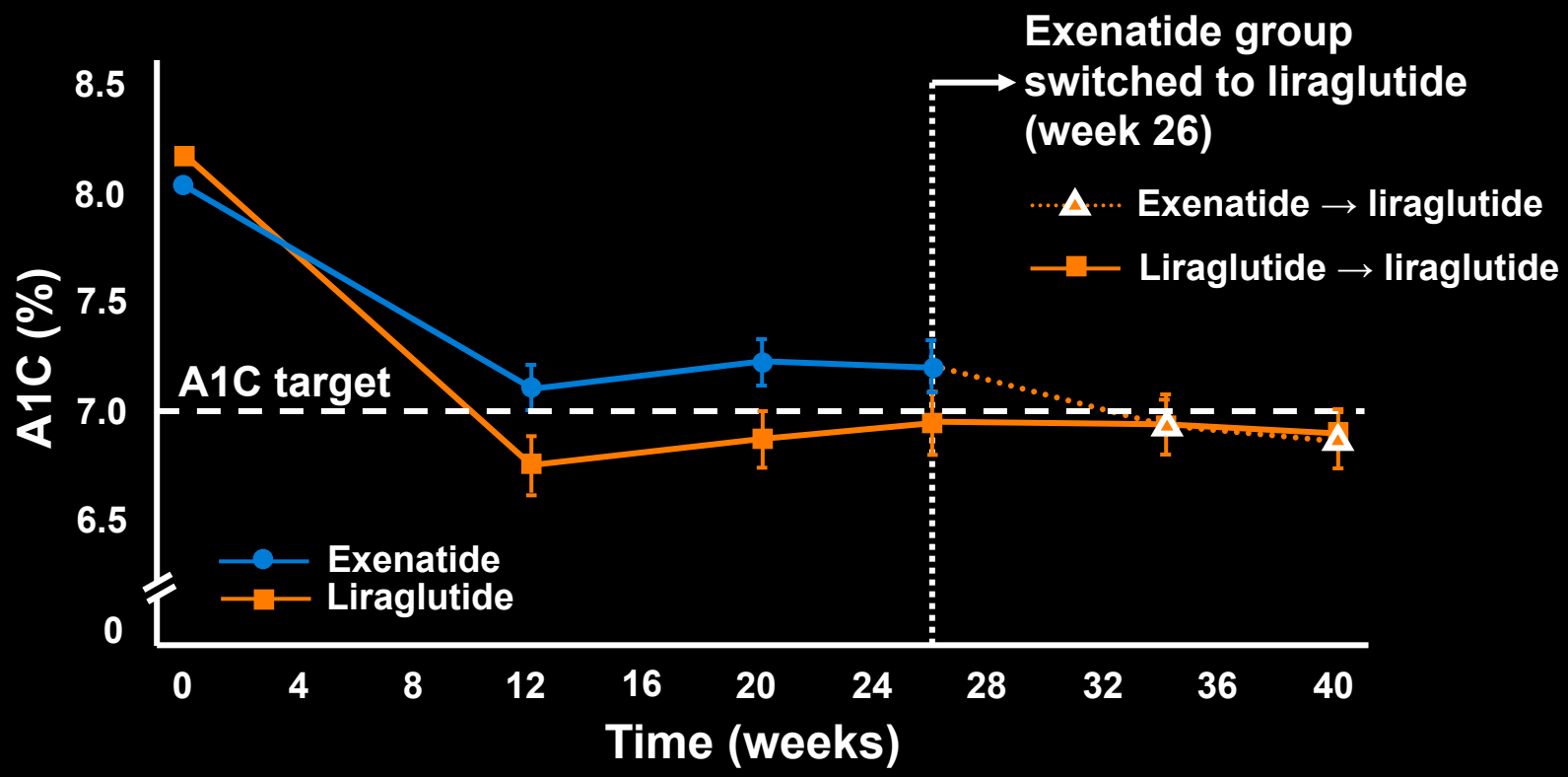
PPG = post-prandial plasma glucose
SMBG = self-monitored blood glucose

# A1c Reductions with Liraglutide




*** Significant vs placebo**
**† Significant vs. active comparator**

# LEAD 6 - Liraglutide vs Exenatide: A1c

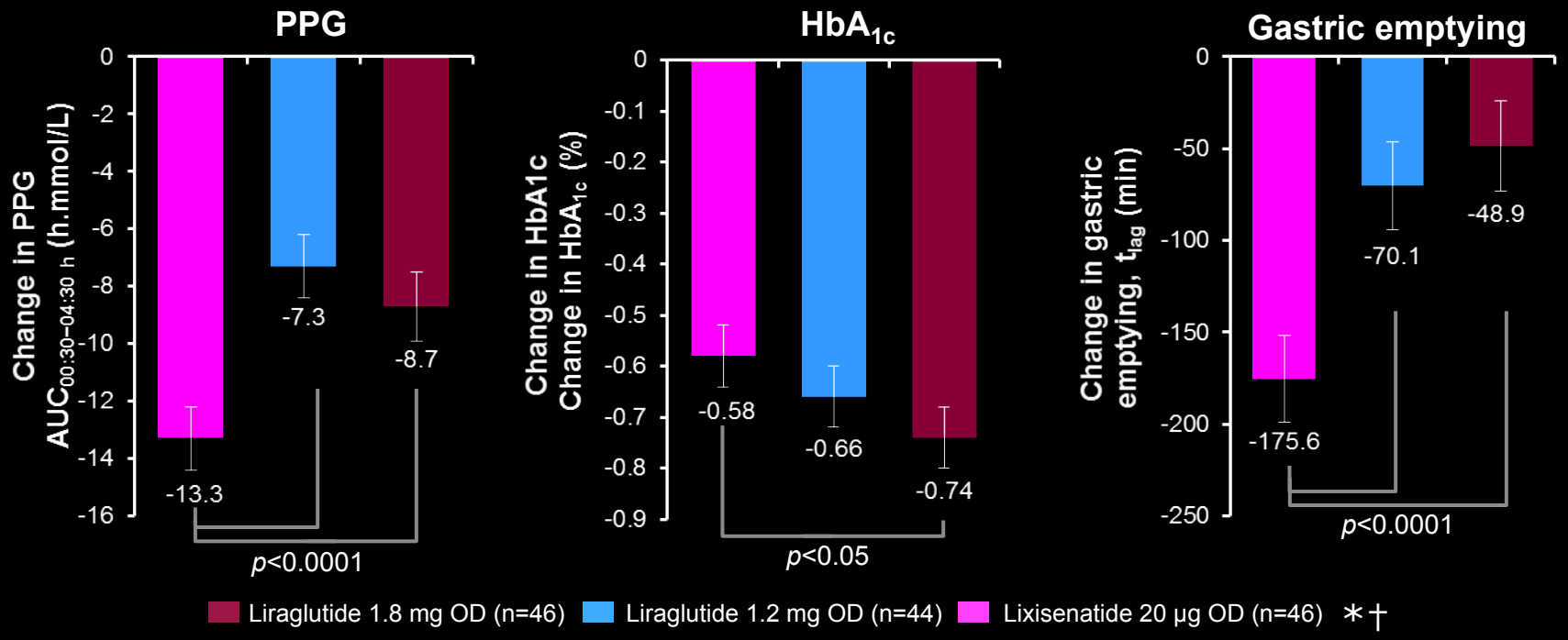



- Randomized 26-wk trial followed by nonrandomized 14-wk extension (N = 386)
- All patients treated with 1.8 mg liraglutide after week 26

Buse et al. Diabetes Care. 2010;33:1300-3.

# Lixisenatide* vs. Liraglutide: Postprandial Glucose, HbA1c and Gastric Emptying

8-week study, background glargine insuln



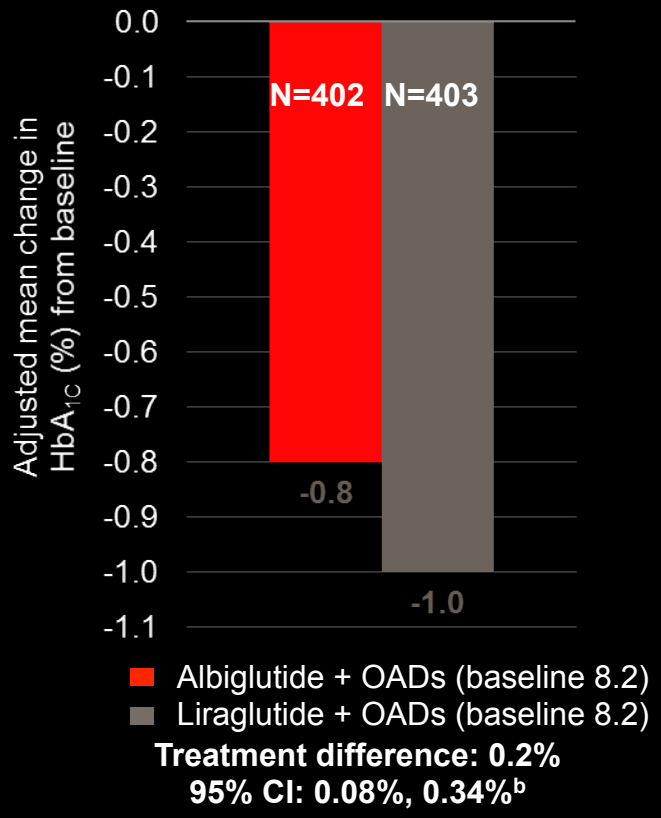

Data are LS mean change (SE)
AUC, area under the curve; HbA1c, glycosylated haemoglobin; LS, least squared; OD, once daily; PPG, postprandial glucose

*Not FDA approved

Meier et al. Diabetes 2014; 63(Suppl. 1): A262 (Abstract 1017-P)

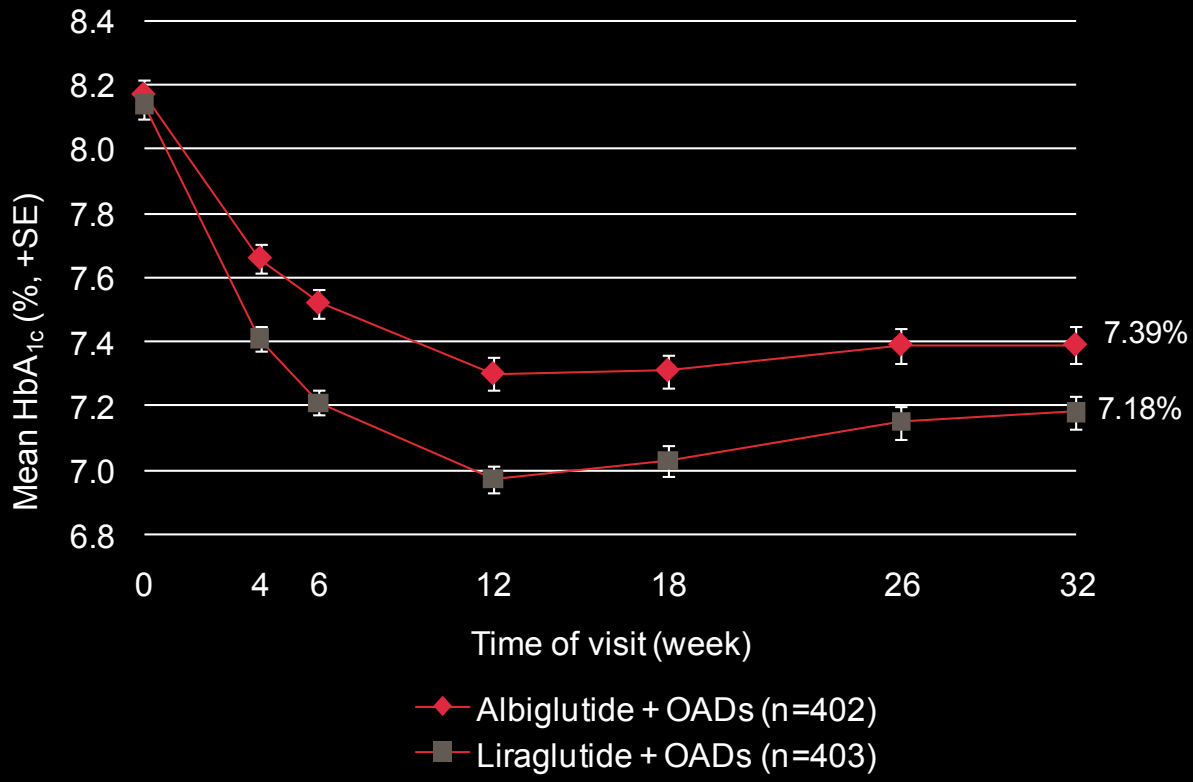
# Albiglutide vs. Liraglutide: Change in $HbA_{1c}$

## Primary endpoint: Week 32[1,2]




**Treatment difference: 0.2%**
**95% CI: 0.08%, 0.34%[b]**

## Secondary Endpoint: Mean $HbA_{1c}$ up to Week 32[3]

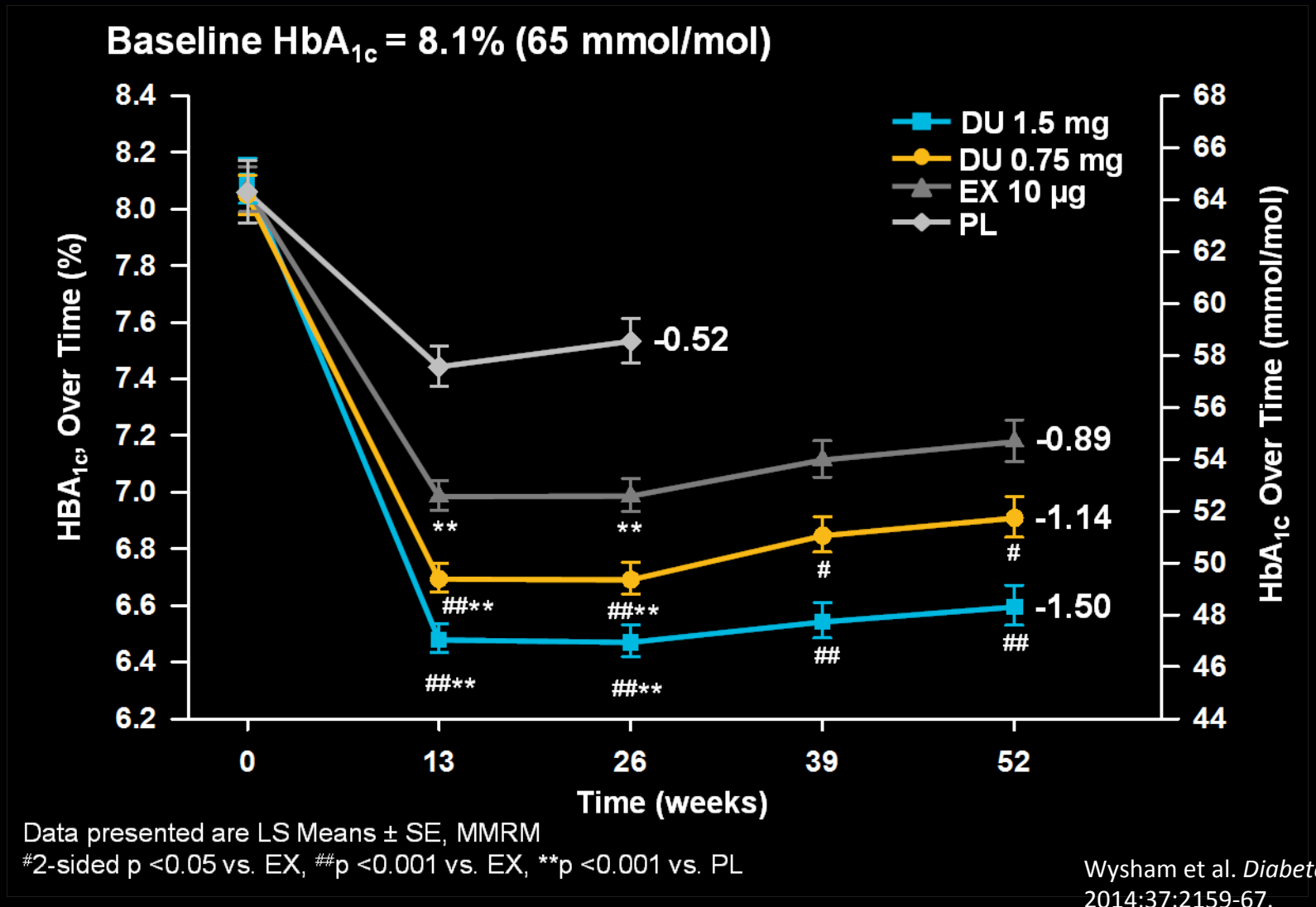



SE = standard error.

[a]ITT population. LOCF was used to impute missing data. Data post-onset of rescue therapy are treated as missing. At 32 weeks, primary efficacy data were imputed for 31% and 24% of individuals randomized to albiglutide and liraglutide, respectively; [b]**Did not meet the non-inferiority margin of 0.3%, treatment difference was statistically significant in favor of liraglutide.**


1. Pratley et al. *The Lancet Diabetes & Endocrinology.* 2014;2:289-97.

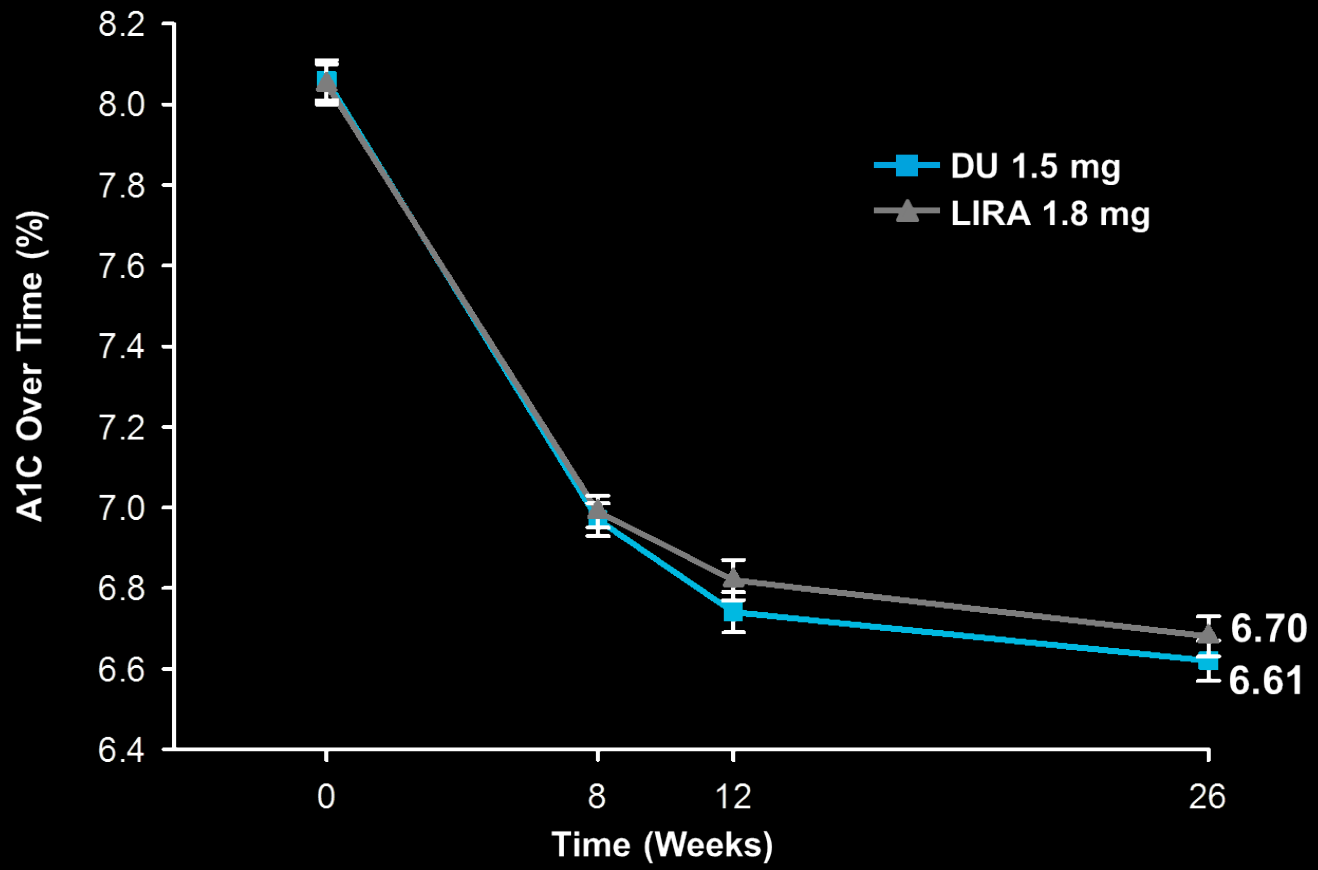
# Dulaglutide vs. Exenatide: $A_{1c}$




Wysham et al. *Diabetes Care* 2014;37:2159-67.

# Dulaglutide vs. Liraglutide: A1C

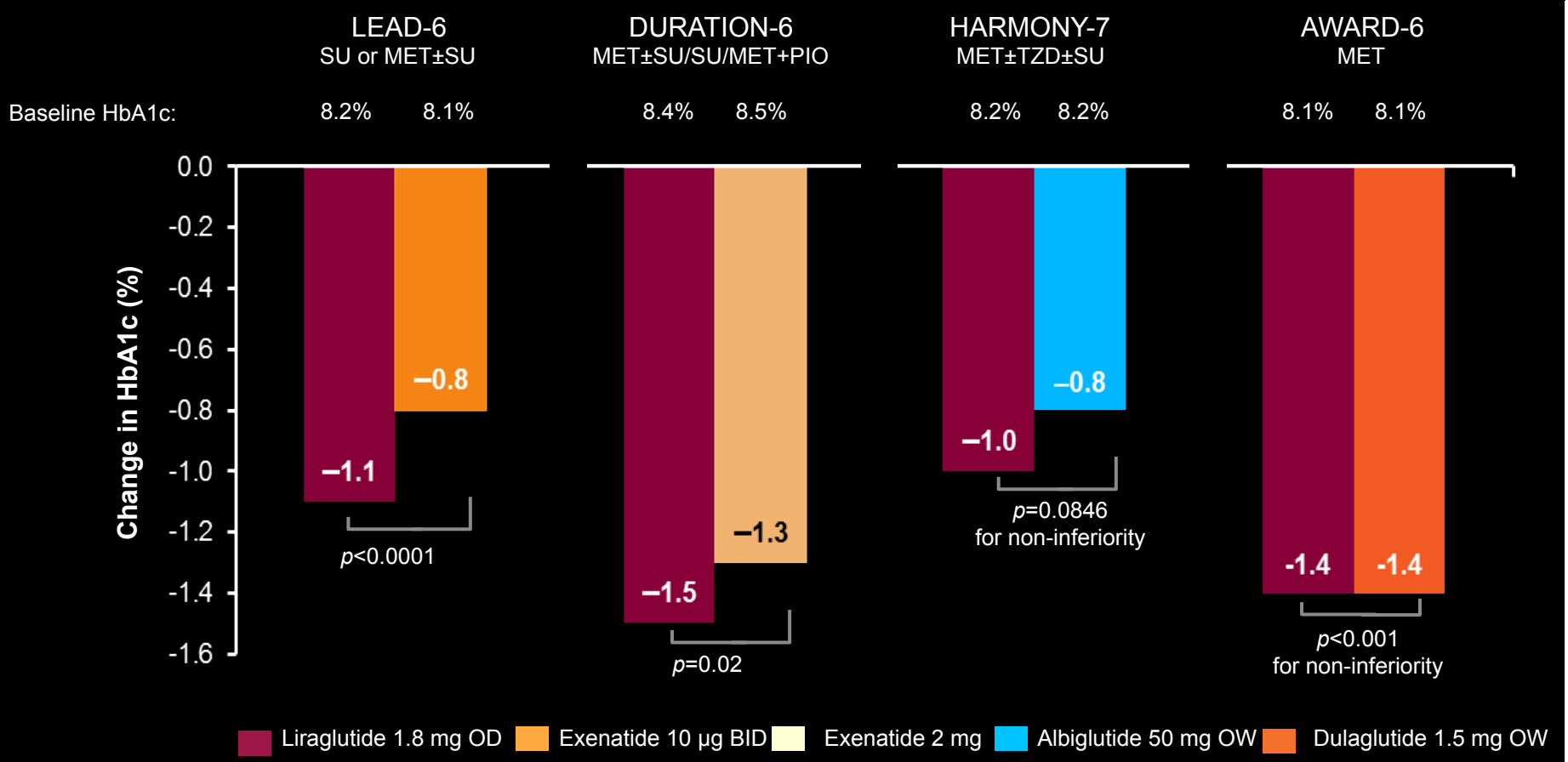
**Baseline A1C = 8.1%**




**D**ata presented are LS means ± SE; ITT, MMRM analysis

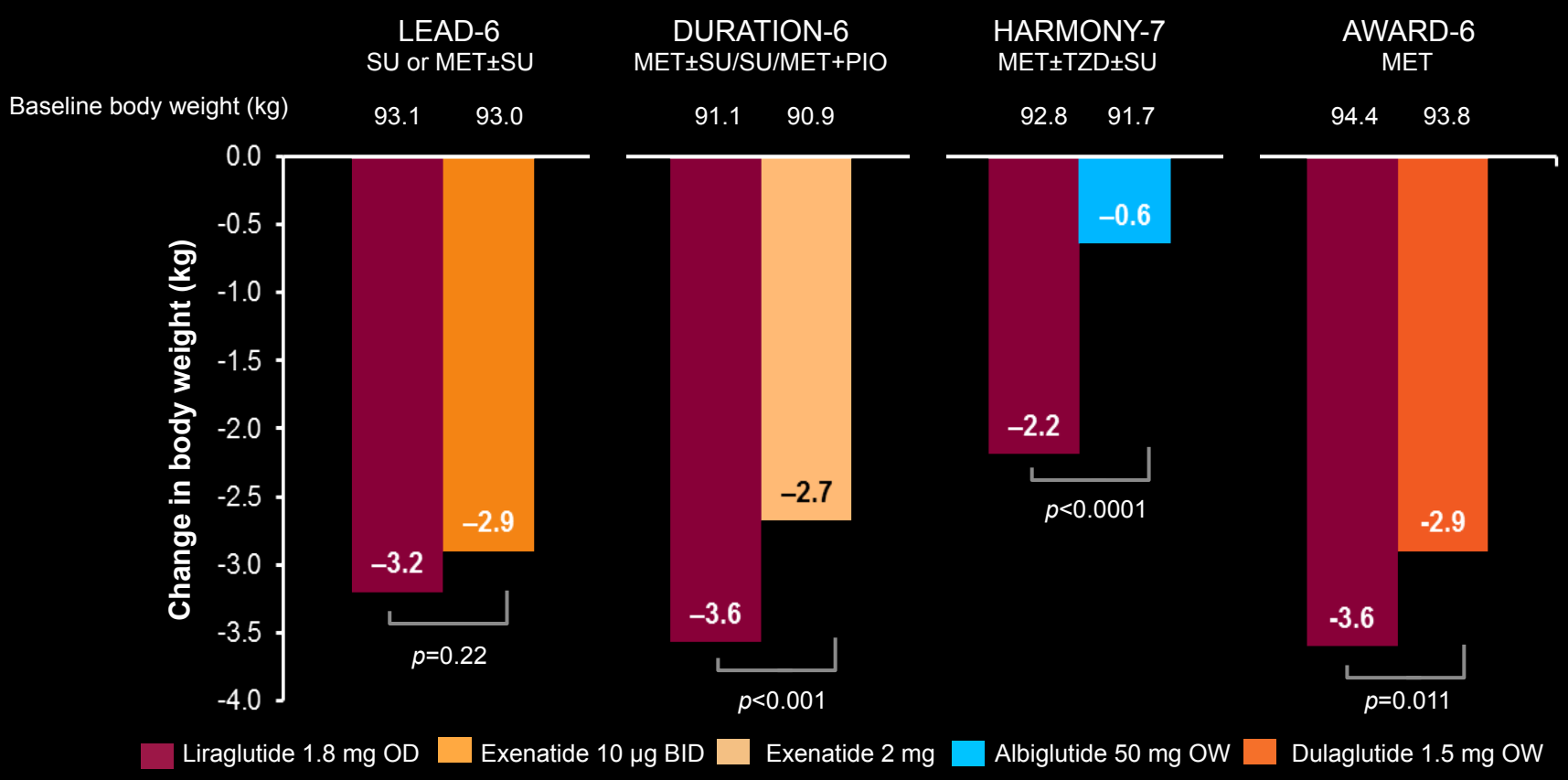
Dungan et al. Presented at: American Diabetes Association's 74th Scientific Sessions June 13 - 17, 2014; San Francisco, CA.110-LB.

# Comparisons of Long-Acting GLP-1 RAs: Change in HbA1c




Buse et al. Lancet 2009;374:39–47 (LEAD-6); Buse et al. Lancet 2013;381:117–124 (DURATION-6); Clinicaltrials.gov (NCT01029886) (DURATION-6); Pratley et al. Lancet Diabetes Endocrinol 2014; 2:289-97 (HARMONY-7); Dungan et al. Lancet 2014. pii: S0140-6736(14)60976-4 (AWARD-6)

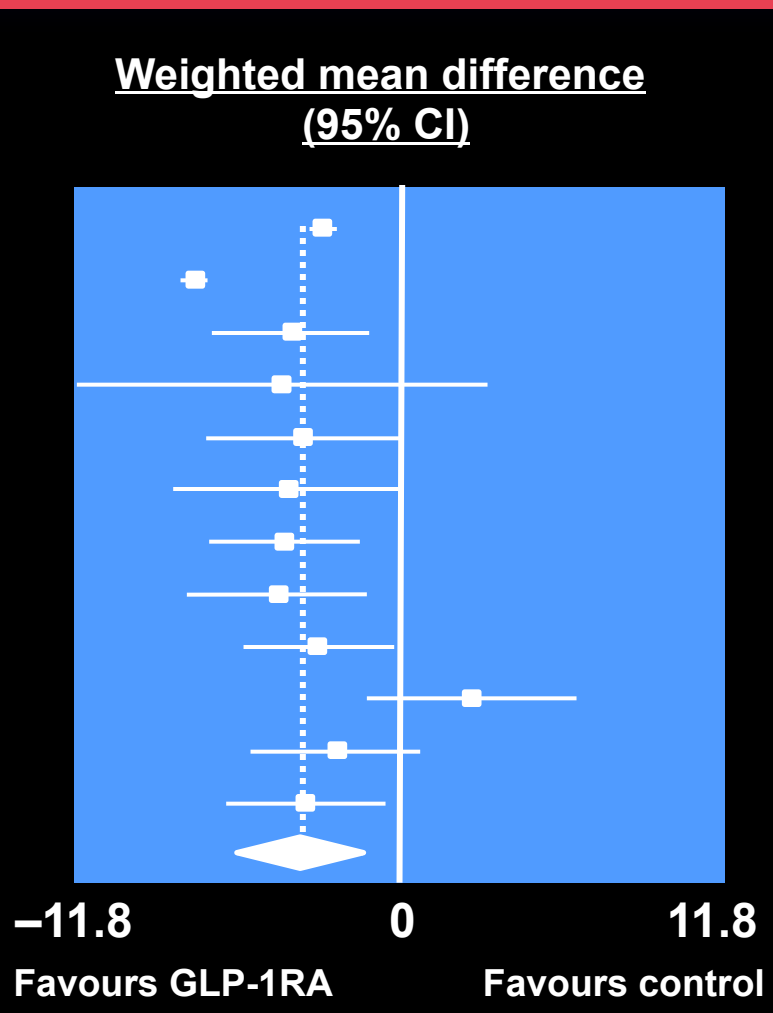
# Comparisons of Long-Acting GLP-1 RAs: Change in Body Weight




Buse et al. Lancet 2009;374:39–47 (LEAD-6); Buse et al. Lancet 2013;381:117–124 (DURATION-6); Clinicaltrials.gov (NCT01029886) (DURATION-6); Pratley et al. Lancet Diabetes Endocrinol 2014; 2:289-97 (HARMONY-7); Dungan et al. Lancet 2014. pii: S0140-6736(14)60976-4 (AWARD-6)

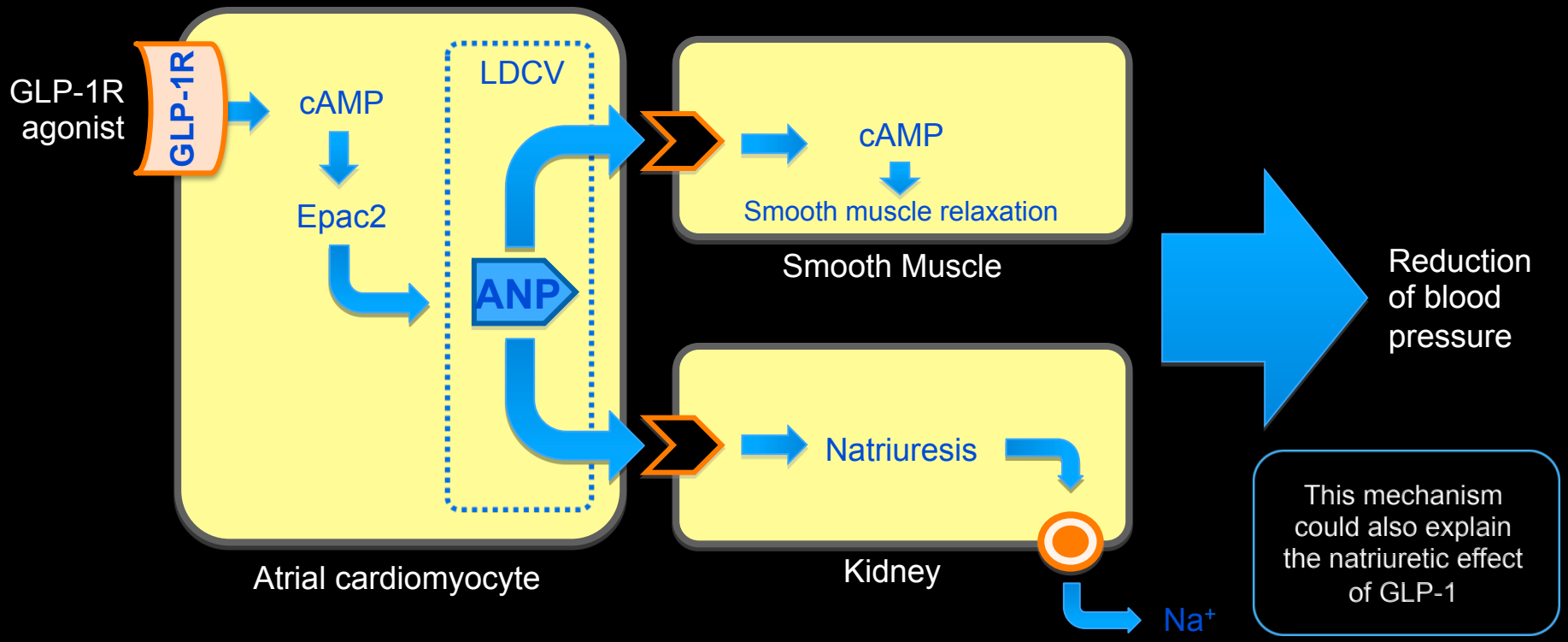
# GLP-1 RAs Lower Blood Pressure Compared to Controls

| Trial | No. of patients | |
|---|---|---|
| | GLP-1RA | Control |
| Astrup 2010 | 82 | 78 |
| Apovian 2010 | 96 | 98 |
| Bergensthal 2010 | 160 | 166 |
| Bunck 2009 | 36 | 33 |
| Davies 2009 | 118 | 117 |
| Moretto 2008 | 78 | 77 |
| Garber 2009 | 217 | 21 |
| Zinman 2009 | 178 | 177 |
| Kendall 2005 | 241 | 247 |
| Buse 2004 | 129 | 123 |
| Diamant 2010 | 233 | 223 |
| Heine 2005 | 282 | 267 |
| Overall; $p<0.01$ | | |




Adapted from Vilsbøll et al. *Br Med J.* 2012;344:d7771.

# GLP-1R Activation Promotes Secretion of ANP and Reduces BP in Rodents




LDCV=large dense core vesicle; ANP=atrial natriuretic peptide

Kim *et al. Nature Medicine*. 2013;19:567-575 doi:10.1038/nm.3128

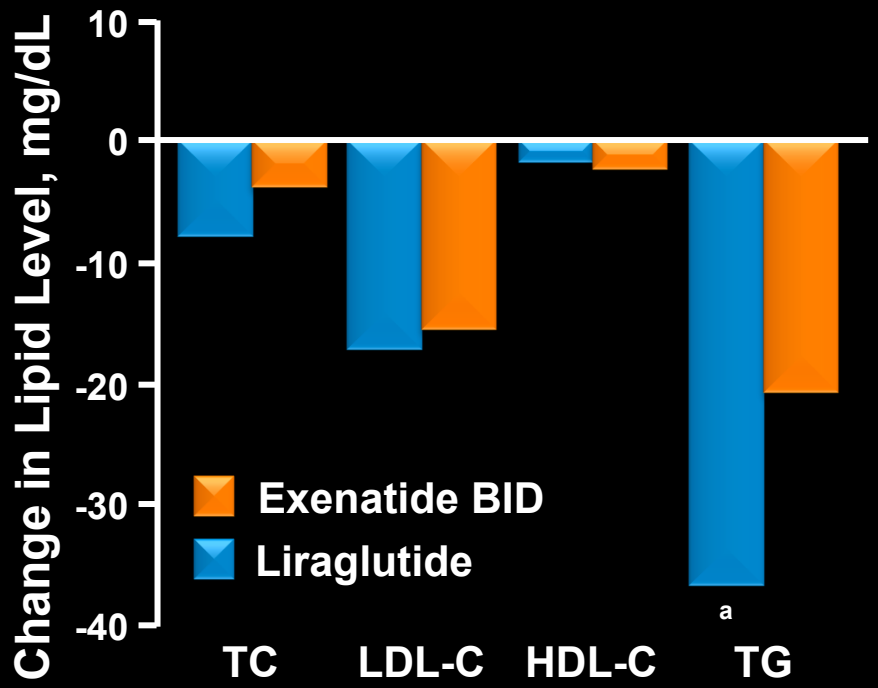
# GLP-1 RAs Increase Heart Rate

| | Exenatide 10 µg BID[7,9] | Exenatide 2 mg OW[8] | Liraglutide 1.2 mg OD[4-7] | Liraglutide 1.8 mg OD[4-7] |
|---|---|---|---|---|
| Increase in heart rate (bpm) | 1–2 | 4 | 2–4 | 2–4 |

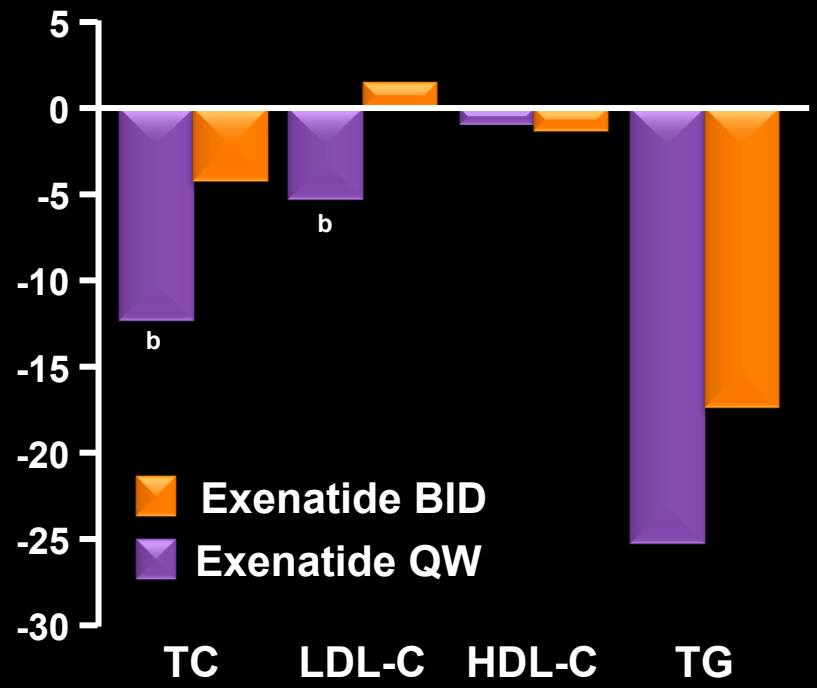
- A resting heart rate increase of 10 bpm has been positively correlated with CV and all-cause mortality[1]
- Small but statistically significant increases in heart rate have been observed with liraglutide and exenatide OW[2–8]
- The mechanism responsible for the small increase in heart rate observed with GLP-1RAs has not been fully elucidated

1. Jensen et al. Heart 2013; 99:882-887; 2. Victoza®. Prescribing Information. Novo Nordisk, April 2013; 3. BYDUREON™. Prescribing Information. Amylin Pharmaceuticals, Inc., 2012; 4. Marre et al. Diabet Med. 2009;26:268-278; 5. Nauck et al. Diabetes Care. 2009;32:84-90; 6. Zinman et al. Diabetes Care. 2009;32:1224-1230; 7. Buse et al. Lancet. 2009;374:39-47; 8. Diamant et al. Lancet. 2010;375:2234-2243; 9. Gill et al. Cardiovasc Diabetol. 2010;9:6.

# Effects of GLP-1 RAs on Lipid Profiles




LEAD-6, 26 Weeks[1]




DURATION-1, 30 Weeks[2]

[a]*P*<0.05 vs exenatide BID; [b]Signifcant difference vs exenatide BID based on CIs.


1. Buse J, et al. *Lancet*. 2009;374:39-47.
   N=464 patients with inadequately controlled T2DM on maximally tolerated doses of metformin, sulfonylurea, or both.
2. Drucker DJ, et al. *Lancet*. 2008;372:1240-1250.
   N=295 patients with T2DM who were naive to drug therapy, or on 1 or more oral antidiabetic agents.

# Cardiovascular Safety: Exenatide BID and Liraglutide[a]

| Agent | Evidence |
|---|---|
| EXN BID | **Meta-analysis of clinical trial data[1]**<br>▪ No increased risk of CV events vs pooled comparators<br>**Retrospective analysis of health claims database[2]**<br>▪ Lower CV event risk in EXN BID group vs non-EXN BID group<br>▪ More patients with CV risk factors in EXN BID group |
| LIRA | **US FDA analyses of clinical trial data[3]**<br>▪ No excess risk of CV events vs comparators (active or PBO)<br>**LEADER trial[4]**<br>▪ Long term CV safety trial<br>▪ August 2010 to January 2016 |

[a] EXN QW CV outcomes trial is also underway.[5]

1. Shen et al. ADA 69th Scientific Sessions; 366-OR; 2. Best JH, et al. ADA 70th Scientific Sessions; 712-P; 3. Update on FDA Advisory Committee meeting. http://www.novonordisk.com/include/asp/exe_news_attachment.pdf?sAttachmentGUID=1c87137d-806f-41bc-832a-e5a74aa86164;
4. LEADER trial. http://www.clinicaltrials.gov/ct2/results?term=NCT01179048;
5. EXSCEL trial. http://www.clinicaltrials.gov/ct2/results?term=NCT01144338.

# Ongoing Cardiovascular Outcomes Trials of GLP-1 RAs

| Trial | Agent | Patients (N) | Duration (y) | Patient-Years | Estimated Completion |
|---|---|---|---|---|---|
| REWIND (NCT01394952 ) | Dulaglutide | 9622 | 6.5 | 62543 | 2019 |
| EXSCEL (NCT01144338) | Exenatide QW | 9500 | 5.5 | 52250 | 2017 |
| LEADER (NCT01179048) | Liraglutide | 9340 | 5 | 46705 | 2016 |
| ELIXA (NCT01147250) | Lixisenatide* | 6000 | 3.9 | 23400 | 2014 |
| SUSTAIN 6 (NCT01720446) | Semaglutide* | 3260 | 2.8 | 9128 | 2016 |

*Not FDA approved

National Institutes of Health website. http://www.clinicaltrials.gov. Accessed May 2, 2014; Petrie JR. *Cardiovasc Diabetol*. 2013;12:130.

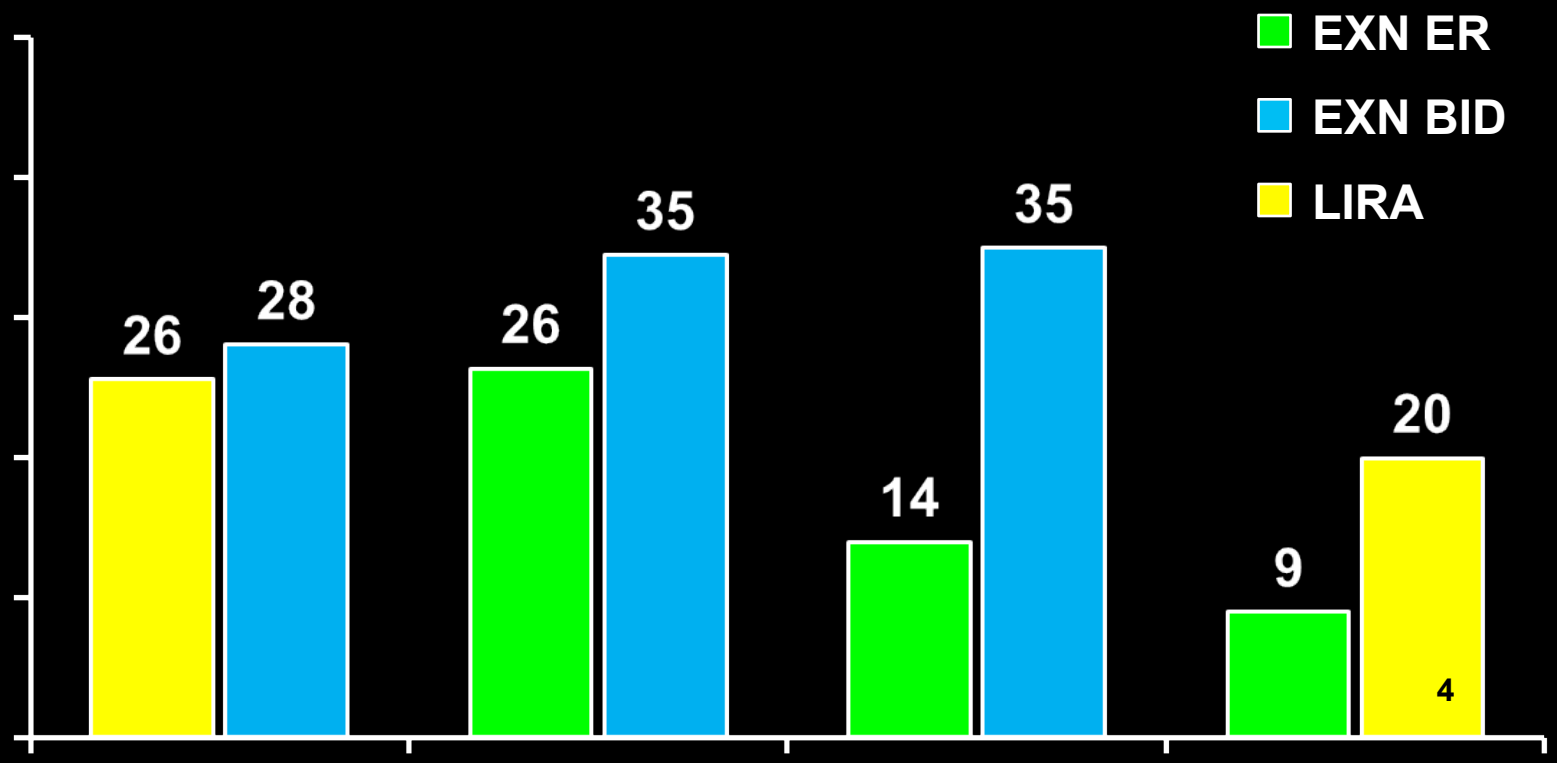
# Recommendations for GLP-1 RA Use in CKD

| Precautions[1-4] | Albiglutide | Exenatide BID | Liraglutide | Exenatide QW |
|---|---|---|---|---|
| Renal impairment | Use with caution | Use with caution<br>Should not be used with severe renal impairment (CrCl <30 mL/min) or ESRD | Use with caution | Use with caution<br>Should not be used with severe renal impairment (CrCl <30 mL/min) or ESRD |

## Recommendations

- Use with caution in patients with renal impairment or renal transplantation, especially when initiating or escalating doses
- Hypovolemia due to nausea/vomiting may worsen renal function

# Nausea Is a Commonly Reported Side Effect of GLP-1 RAs




**1.** Buse et al. Lancet. 2009; 374: 39-47.
2. Drucker et al. Lancet. 2008;372:1240-1250.
3. Blevins et al. J Clin Endocrinol Metab. 2011;96:1301-1310.
4. Buse et al. EASD 47th Annual Meeting. 2011;75.

# Safety and Tolerability of GLP-1 Agonists

- Generally well tolerated
- Rates of hypoglycemia are low when used as monotherapy
- Rates of nausea are variable – appear related to peaks of GLP-1 effect
  - Exenatide BID, Lixisenatide* > Liraglutide > Exenatide QW, Albiglutide
- Pancreatitis has been reported with GLP-1 agonists
  - FDA and EMA have extensively reviewed data
- Rates of antibody formation are variable between GLP-1 agonists
  - Related to GLP-1 homology, injection site reactions infrequent

*Not FDA approved

# Safety and Tolerability of GLP-1 Agonists (2)

- C-cell hyperplasia and neoplasia have been reported with high doses of long-acting GLP-1 analogs in mice and rats, not in primates
  - Humans have few if any GLP-1 receptors on their C-cells and they do not respond to GLP-1
  - GLP-1 agonists do not increase calcitonin in humans in clinical trials
  - No increased risk of C-cell tumors in clinical trials
- Liraglutide is associated with an increase in heart rate
- In clinical trials there does not appear to be a CVD signal, but numbers are small
- Outcomes studies are ongoing

# Summary: GLP-1 RAs

- Mimic effects of GLP-1; pharmacologic GLP-1 levels
- Effective lowering of A1c
  - Long-acting GLP-1 RAs may be more effective (FPG and PPG)
- Weight loss similar among many members of the class
  - Reduction is lower with albiglutide
- Injection (twice daily to once weekly)
- Generally well-tolerated
- Rates of hypoglycemia are low (as monotherapy and with metformin)
- Nausea significant – especially shorter acting
- No cardiovascular disease risk signal; outcomes studies are ongoing

# T2DM Therapy from the Patients' Perspective: The Role of GLP-1 Receptor Agonists in Overcoming Common Patient Treatment Barriers

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DOI 10.1007/s40271-014-0057-0

SYSTEMATIC REVIEW

# The Patient Perspective of Diabetes Care: A Systematic Review of Stated Preference Research

**Lill-Brith von Arx · Trine Kjær**



**Abstract**

*Background* The importance of understanding the perspective of patients towards their own care is increasingly recognized, both in clinical practice and in pharmaceutical drug development. Stated preference methods to assess the preference of patients towards different aspects of diabetes treatment have now been applied for over a decade.

*Objective* Our goal was to examine how stated preference methods are applied in diabetes care, and to evaluate the value of this information in developing the patient perspective in clinical and policy decisions.

*Methods* A systematic review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The information sources were MEDLINE, EMBASE, Biosis, Current Contents, Web of Science, CINAHL, PsycINFO, and EconLit.

*Results* Three contingent valuation studies and 11 discrete choice experiments were retrieved. The majority of studies were conducted from 2009 onwards, but some date back to 1998. The reasons provided for applying the stated preference methods were to help differentiate between products, or to enable inclusion of the patient's perspective in treatment decisions. The main aspects of treatment examined were related to glucose control, adverse events, and drug administration. The majority of patients preferred glucose control over avoiding minor hypoglycemic events. Patient willingness to pay was above $US100/month for glucose control, avoiding immediate health hazards such as nausea, and oral or inhaled drug administration. Preference towards drug administration was highly associated with previous experience with injectable diabetes medicine.

*Conclusions* The ability of a drug to lower glucose levels plays a decisive role in the choice between alternative treatments. Future research should strive to develop questionnaire designs relevant for the decision context of the study. That is, if the aim is to foster shared decision making, in clinical practice or drug development, this should guide the study design. Furthermore, concise reporting of all study dimensions—from the qualitative prework to the analysis stage—is warranted.

**Key Points for Decision Makers**

Recent applications of stated preference methods may inform economic evaluations of medicine adopting a user perspective.

Glucose control is important to patients, and in most cases a higher priority than avoiding minor hypoglycemic events.

Drug administration and the reduction of insulin injections motivate patient preference for inexperienced insulin users.

## 1 Introduction

Diabetes care involves a number of therapeutic challenges affecting health outcomes. For insulin users, one example is the adjustment of insulin therapy to control glucose

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Published online: 02 April 2014

# Patient's Perspective

- Efficacy: Preference for glucose control over avoiding minor hypoglycemic events.
- Route: Preference towards drug administration highly associated with previous experience with injectable diabetes medicine.
- Adverse events: "Avoiding a 3-kg weight gain is important but not superior to avoiding hypoglycemic events."
- Cost: Patient willingness to pay: US $28 - $205/month

**CONCLUSIONS**

- The ability of a drug to lower glucose levels plays a decisive role in the choice between alternative treatments.
- Future research should develop questionnaire designs to foster shared decision making in clinical practice or drug development.

von Arx, Kjær . Patient 2014;7:283-300; Gelhorn et al. Diabetes Obes Metab. 2013;15:802–9.

# Patient Willingness to Pay (WTP) for Pharmaceutical Diabetes Treatment

***Variable overall WTP across studies and Rx domains ($US28 –215 per month)***

WTP among studies of all insulin users:

- $28/mo for having a 2hrPG of 9.4 mmol/L
- $36/mo for having optimal BG 2–6 days/wk

WTP in studies with ~ 50 % insulin users:

- $146/mo for optimal FPG
- $205/mo for a 1% HbA1c reduction

WTP for adverse events:

- Highest ($124 - $220/mo) for avoiding nausea
- $ 45– $94/mo for avoiding hypoglycemia
- $US72 - $94 /mo for avoiding night-time events)
- WTP reported for weight control: $58 – $76/mo

WTP for mode of treatment:

- $86 for meal-independent injections (Prandial exper. $117/None $65)
- Inhaled administration: $62- $215/mo
- Oral drug administration $50–$108/mo

von Arx, Kjær . Patient 2014;7:283-300; Guimaraes et al. Diabetes Technol Ther. 2009;11:567–73; Lloyd et al. Clin Ther. 2011;33:1258–67; Jendle et al . Curr Med Res Opin. 2010;26:917–23.

# Common Barriers to Treatment Adherence

- Weight gain
- Severe hypoglycemia
- Dosing frequency
- Complexity of regimens
- Injection: pain, inconvenience
- Other

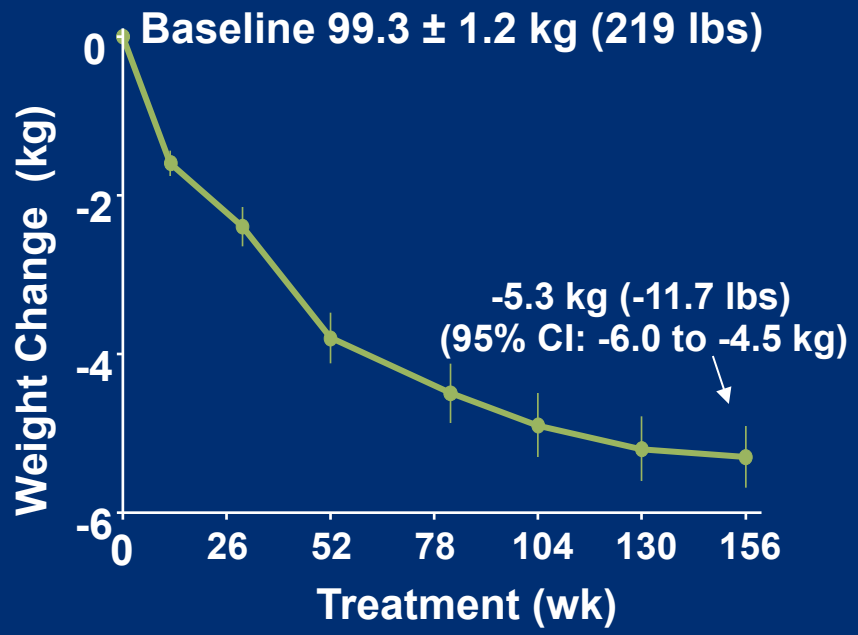
# Role of GLP-1 RAs in Addressing Barriers

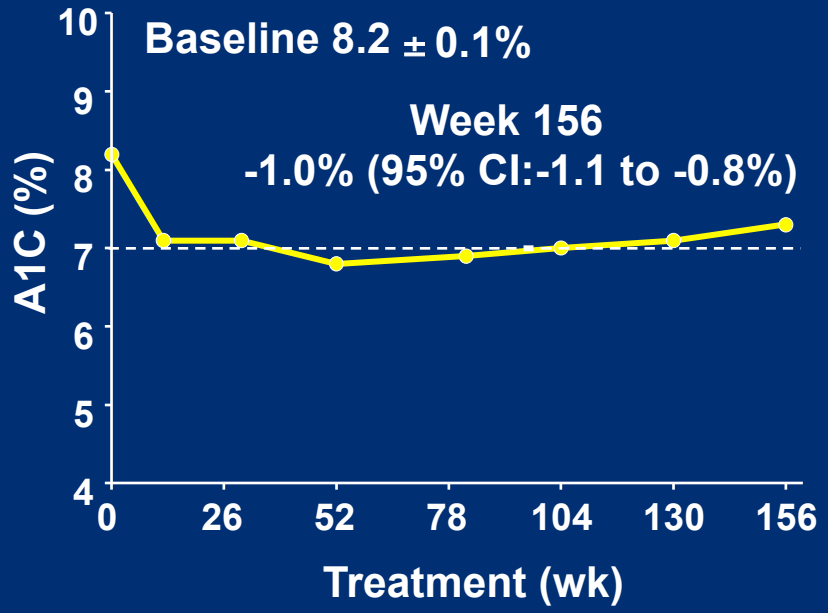
- Weight loss
- Low hypoglycemia risk
- Injection: Improvements in delivery devices
  - BIW, QW, or less frequent injections

**QUESTIONS**

- **Do longer-acting GLP-1 RAs offer adherence advantages?**
- **Adverse effects and patient-reported outcomes with GLP-1 RAs**

# Change in Weight and A1C: Exenatide 3-Yr Data



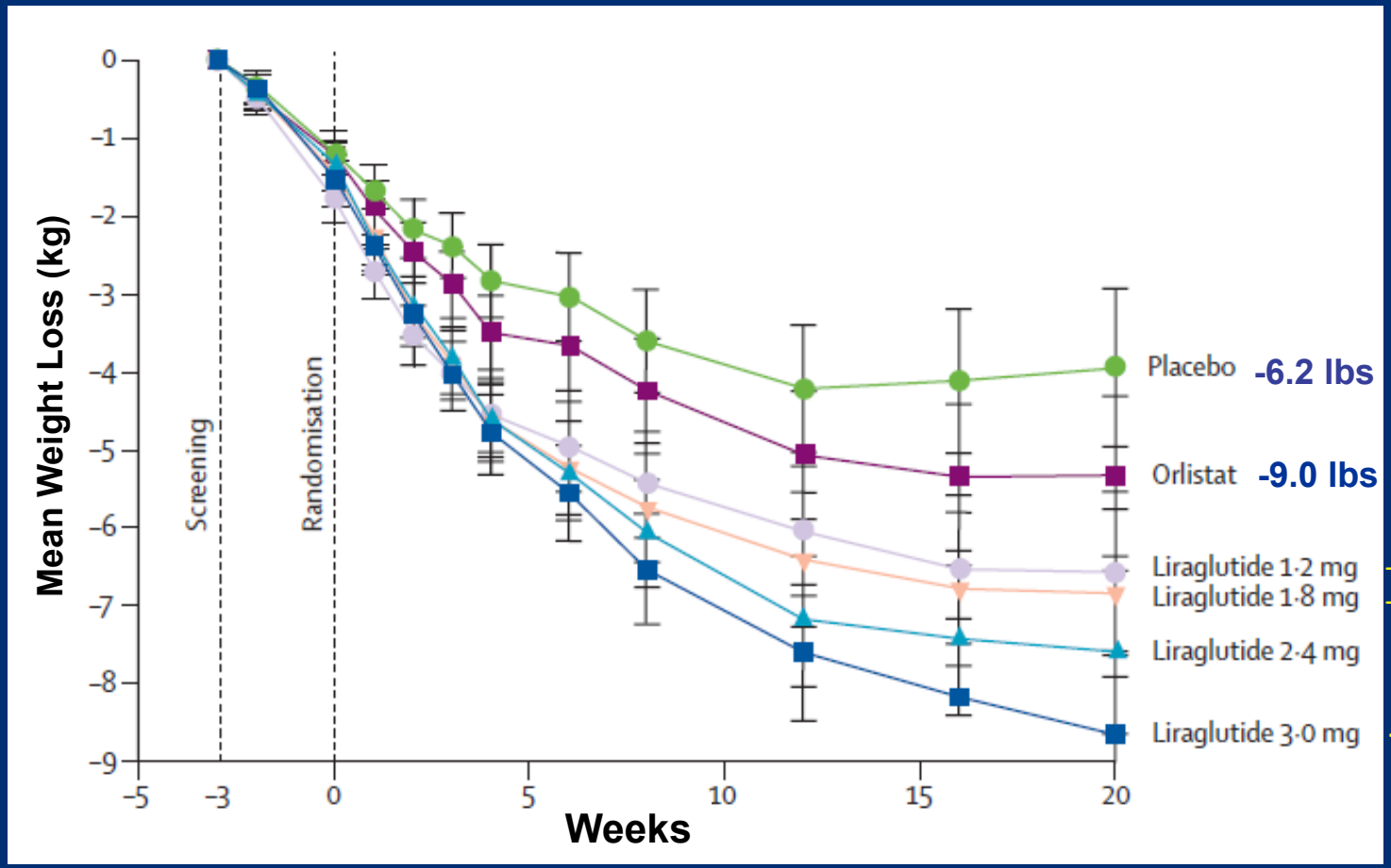




Note: N= 527 eligible, N = 217 completers (primary loss due to patient/provider decision (41%) followed by adverse event (11%)

Klonoff et al. Curr Med Res Opin 2008; 24:275-86.

# Liraglutide for Weight Loss

## *In patients with prediabetes and normal glucose*

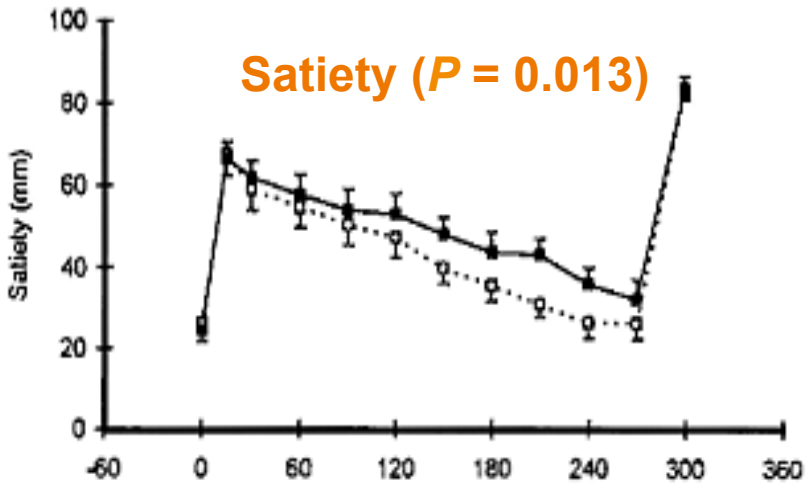


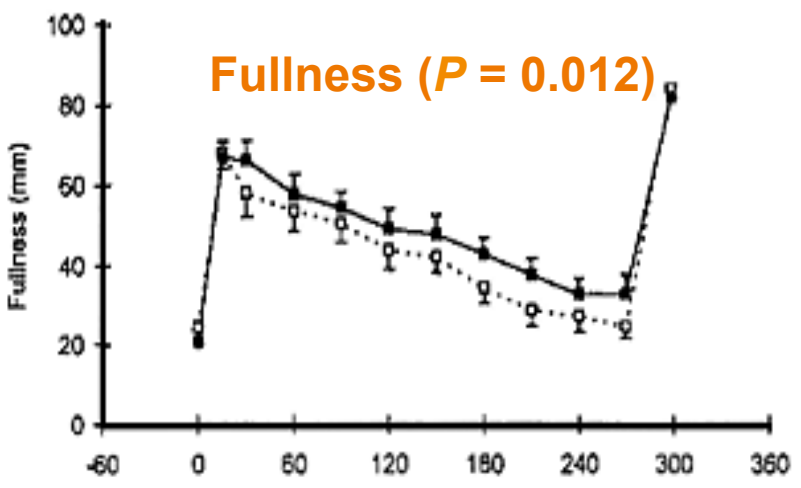

- N=564 divided among 6 cohorts, 500 kcal/day energy deficit diet and physical activity
- Improvement in BP, lower waist circumference, ~90 reduction in prevalence of prediabetes

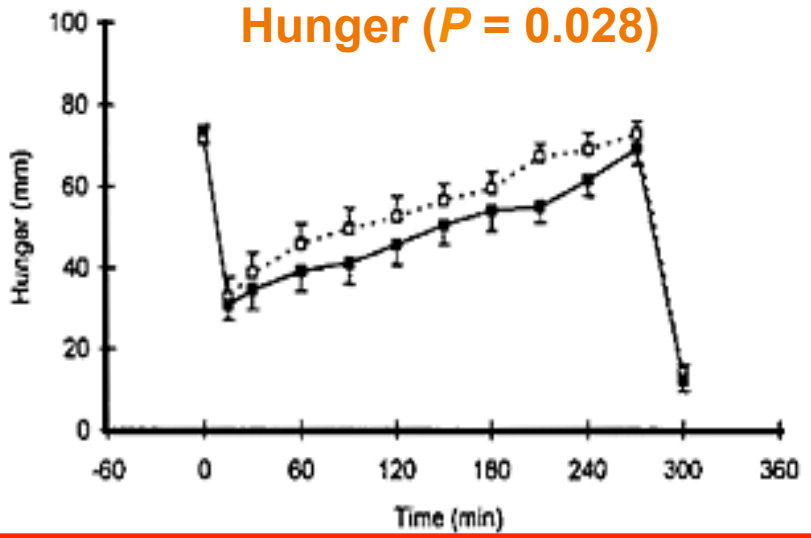
Astrup et al. Lancet 2009; 374:1606-16.

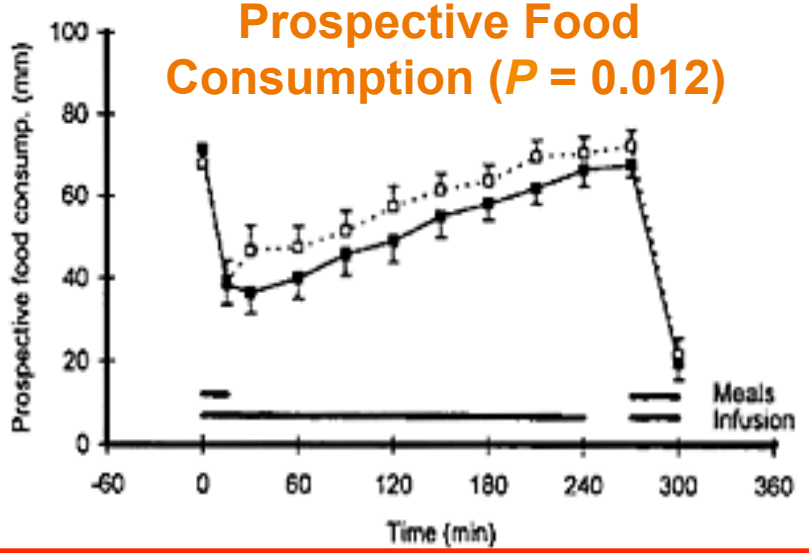
# GLP-1 and Appetite/Satiety

(Healthy Subjects)



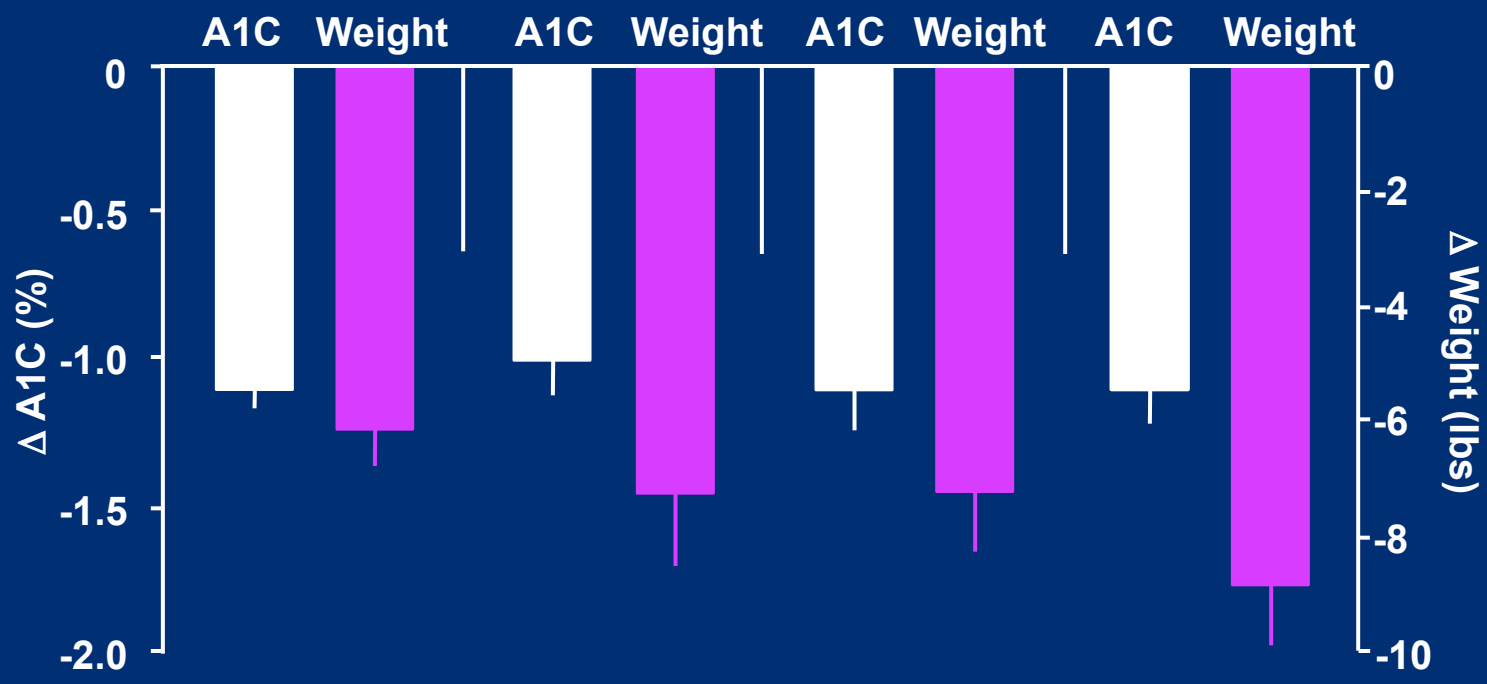




Flint et al. J Clin Invest 1998;101:515–20.

# Dissociation of Nausea From A1C and Weight Loss With Exenatide Use

| Patient Subgroup (Based on Nausea Experience) | None-Minimal | Early | Late | Sustained |
|---|---|---|---|---|
| % of Subjects | 57% | 14% | 13% | 16% |




52-wk completer analysis; N = 547; Mean (SE).

Maggs et al. Diabetes. 2005; 54:485

# Quality of Life Data: Exenatide QW vs. Sitagliptin

| | Exenatide QW | | | | Sitagliptin | | | |
|---|---|---|---|---|---|---|---|---|
| | *n*† | Baseline | Change‡ | 95% CI | *n*† | Baseline | Change‡ | 95% CI |
| IWQOL-Lite | | | | | | | | |
| Total score | 132 | 80.67 | 5.15* (1.04) | 3.11–7.19 | 139 | 80.74 | 4.56* (1.02) | 2.56–6.57 |
| Physical function | 133 | 73.37 | 6.78* (1.35) | 4.11–9.44 | 141 | 73.75 | 5.81* (1.33) | 3.20–8.42 |
| Self-esteem | 133 | 77.81 | 5.88* (1.39) | 3.16–8.61 | 141 | 79.12 | 5.79* (1.36) | 3.11–8.47 |
| Sexual life | 129 | 83.83 | 5.80* (1.61) | 2.64–8.95 | 132 | 82.38 | 5.02* (1.61) | 1.85–8.18 |
| Public distress | 132 | 91.03 | 3.86* (1.17) | 1.56–6.15 | 140 | 90.23 | 2.40* (1.14) | 0.16–4.64 |
| Work | 131 | 89.74 | 2.79* (1.28) | 0.28–5.30 | 139 | 88.95 | 3.02* (1.25) | 0.57–5.47 |
| EQ-5D | | | | | | | | |
| Index score | 129 | 0.77 | 0.04* (0.02) | 0.01–0.08 | 139 | 0.78 | 0.05* (0.02) | 0.02–0.08 |
| Visual analog score | 132 | 74.25 | 4.46* (1.34) | 1.82–7.10 | 139 | 73.10 | 6.04* (1.32) | 3.45–8.64 |
| PGWB | | | | | | | | |
| Global score | 132 | 67.54 | 6.82* (1.00) | 4.85–8.79 | 141 | 69.96 | 6.97* (0.98) | 5.04–8.90 |
| Anxiety | 132 | 66.32 | 8.40* (1.31) | 5.83–10.97 | 141 | 70.35 | 8.20* (1.28) | 5.68–10.71 |
| Depressed mood | 133 | 80.23 | 3.84* (1.33) | 1.22–6.45 | 141 | 81.98 | 3.80* (1.30) | 1.24–6.37 |
| Positive well-being | 133 | 61.92 | 4.65* (1.42) | 1.85–7.44 | 141 | 61.84 | 7.86* (1.39) | 5.12–10.60 |
| Self control | 133 | 75.11 | 5.53* (1.37) | 2.83–8.22 | 141 | 78.71 | 4.30* (1.34) | 1.67–6.94 |
| General health | 133 | 65.39 | 9.46* (1.40) | 6.72–12.21 | 141 | 67.84 | 6.95* (1.37) | 4.26–9.65 |
| Vitality | 133 | 61.20 | 7.46* (1.37) | 4.76–10.16 | 141 | 63.51 | 8.98* (1.35) | 6.33–11.63 |
| DTSQ | | | | | | | | |
| Total score | 121 | 27.99 | 3.96* (0.60) | 2.78–5.15 | 127 | 28.13 | 2.35* (0.59) | 1.19–3.51 |
| Perceived frequency high blood glucose | 121 | 3.84 | −1.63* (0.17) | −1.96 to −1.30 | 127 | 3.94 | −1.30* (0.17) | −1.63 to −0.97 |
| Perceived frequency low blood glucose | 120 | 0.94 | 0.22 (0.15) | −0.07 to 0.51 | 126 | 1.12 | −0.05 (0.15) | −0.33 to 0.24 |

† No. with baseline and postrandomization data. ‡ Least sq. means (SE). *P <0.05 (within Rx group)

Best et al. Diabetes Care 2011;34:314–19.

# Quality of Life Data: Exenatide QW vs. Pioglitazone

| | Exenatide QW | | | | Pioglitazone | | | |
|---|---|---|---|---|---|---|---|---|
| | *n*† | Baseline | Change‡ | 95% CI | *n*† | Baseline | Change‡ | 95% CI |
| IWQOL-Lite | | | | | | | | |
| Total score | 132 | 80.67 | 5.15* (1.04) | 3.11–7.19 | 130 | 79.32 | 1.20§ (1.06) | −0.87–3.28 |
| Physical function | 133 | 73.37 | 6.78* (1.35) | 4.11–9.44 | 131 | 73.00 | 2.00§ (1.38) | −0.71–4.71 |
| Self-esteem | 133 | 77.81 | 5.88* (1.39) | 3.16–8.61 | 131 | 76.71 | 3.11 (1.41) | 0.34–5.89 |
| Sexual life | 129 | 83.83 | 5.80* (1.61) | 2.64–8.95 | 127 | 81.59 | 2.41 (1.63) | −0.79–5.60 |
| Public distress | 132 | 91.03 | 3.86* (1.17) | 1.56–6.15 | 130 | 88.53 | −0.63§ (1.18) | −2.96–1.70 |
| Work | 131 | 89.74 | 2.79* (1.28) | 0.28–5.30 | 128 | 87.58 | −1.28§ (1.29) | −3.82–1.26 |
| EQ-5D | | | | | | | | |
| Index score | 129 | 0.77 | 0.04* (0.02) | 0.01–0.08 | 130 | 0.82 | 0.02 (0.02) | −0.01–0.06 |
| Visual analog score | 132 | 74.25 | 4.46* (1.34) | 1.82–7.10 | 130 | 74.85 | 2.54 (1.37) | −0.16–5.24 |
| PGWB | | | | | | | | |
| Global score | 132 | 67.54 | 6.82* (1.00) | 4.85–8.79 | 130 | 71.60 | 4.78* (1.02) | 2.77–6.79 |
| Anxiety | 132 | 66.32 | 8.40* (1.31) | 5.83–10.97 | 130 | 70.85 | 5.10* (1.33) | 2.48–7.73 |
| Depressed mood | 133 | 80.23 | 3.84* (1.33) | 1.22–6.45 | 130 | 84.00 | 3.73* (1.36) | 1.06–6.40 |
| Positive well-being | 133 | 61.92 | 4.65* (1.42) | 1.85–7.44 | 130 | 64.10 | 5.02* (1.45) | 2.17–7.88 |
| Self control | 133 | 75.11 | 5.53* (1.37) | 2.83–8.22 | 130 | 83.33 | 3.68* (1.40) | 0.93–6.43 |
| General health | 133 | 65.39 | 9.46* (1.40) | 6.72–12.21 | 130 | 67.56 | 6.37* (1.43) | 3.56–9.17 |
| Vitality | 133 | 61.20 | 7.46* (1.37) | 4.76–10.16 | 130 | 65.00 | 6.23* (1.41) | 3.46–9.00 |
| DTSQ | | | | | | | | |
| Total score | 121 | 27.99 | 3.96* (0.60) | 2.78–5.15 | 123 | 26.78 | 2.50* (0.61) | 1.31–3.69 |
| Perceived frequency high blood glucose | 121 | 3.84 | −1.63* (0.17) | −1.96 to −1.30 | 123 | 3.56 | −1.28* (0.17) | −1.62 to −0.94 |
| Perceived frequency low blood glucose | 120 | 0.94 | 0.22 (0.15) | −0.07 to 0.51 | 122 | 0.91 | −0.12 (0.15) | −0.42 to 0.17 |

*P < 0.05 (within Rx group). §P <0.05 (vs. exenatide group at wk 26).

Best et al. Diabetes Care 2011;34:314–19.

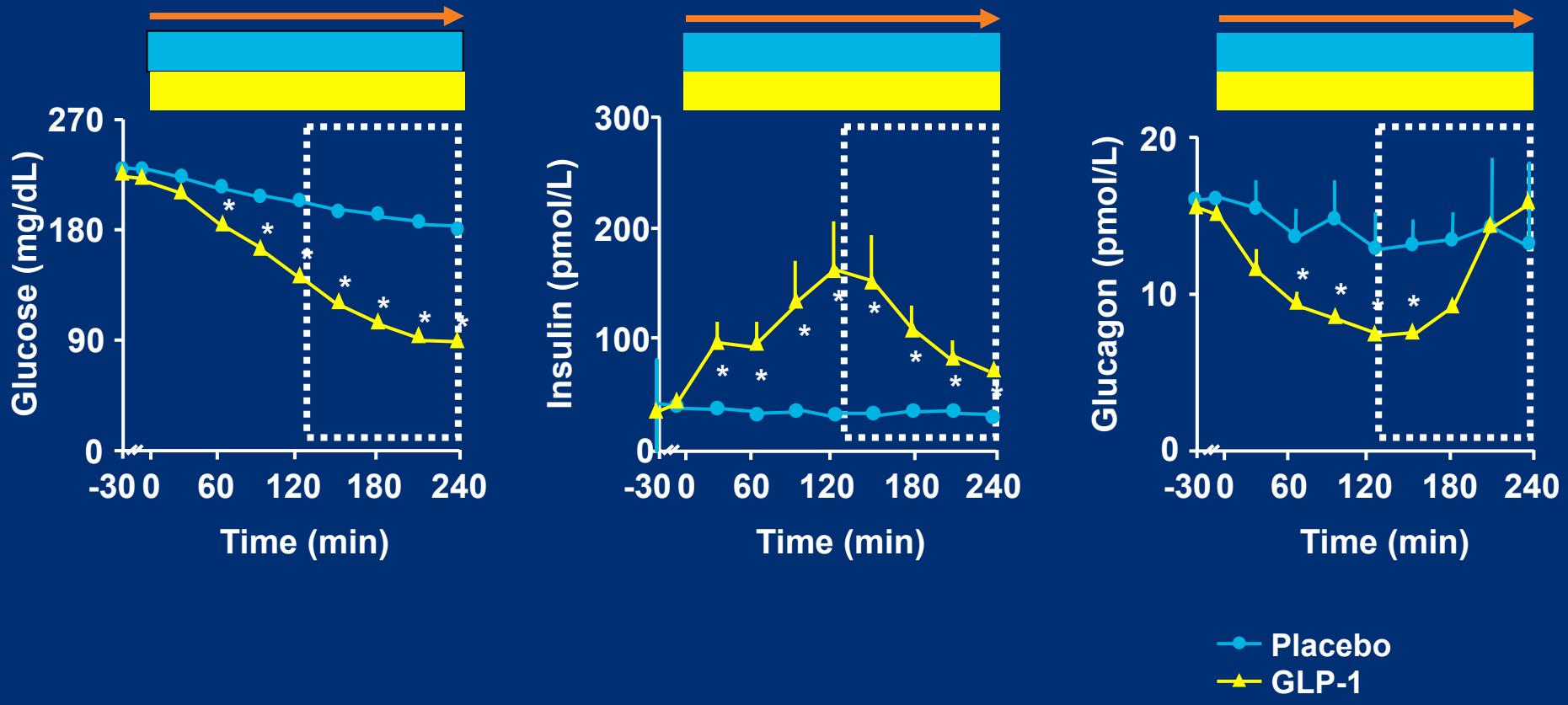
# Role of GLP-1 RAs in Addressing Barriers

- Weight loss
- Low hypoglycemia risk
- Injection: Improvements in delivery devices
  - BIW, QW, or less frequent injections

**QUESTIONS**

- **Do longer-acting GLP-1 RAs offer adherence advantages?**
- **Adverse effects and patient-reported outcomes with GLP-1 RAs**

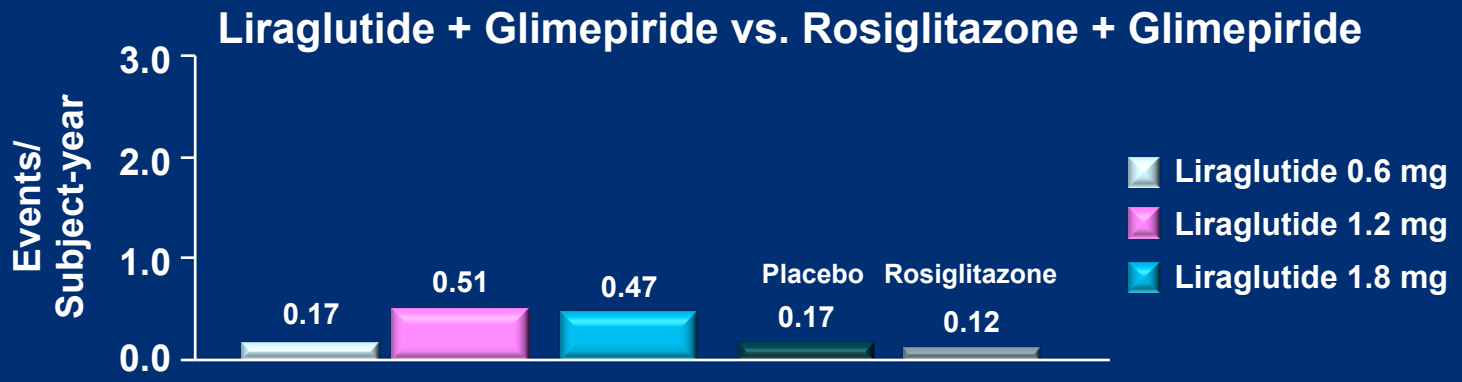
# GLP-1 Effects Are Glucose Dependent in Type 2 Diabetes




N = 10; Mean (SE); *P<0.05
Nauck et al. Diabetologia. 1993;36:741-44

# Rate of Minor Hypoglycemic Events: Liraglutide Trials

**LEAD-1**

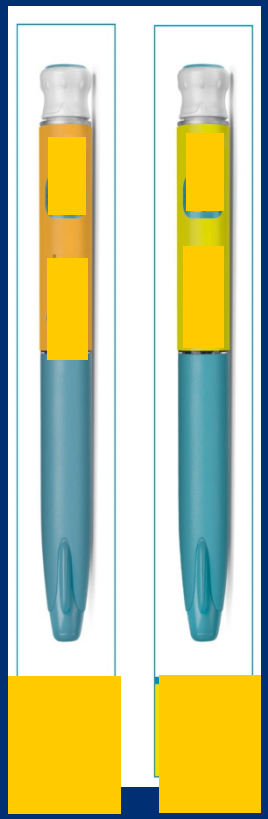



**LEAD-5**


FDA briefing materials —liraglutide (April 2, 2009).
http://www.fda.gov/ohrms/dockets/ac/09/briefing/2009-4422b2-01-FDA.pdf

# Role of GLP-1 RAs in Addressing Barriers

- Weight loss
- Low hypoglycemia risk
- Injection:
  - Improvements in delivery devices
  - BIW, QW, or less frequent injections



## QUESTIONS

- **Do longer-acting GLP-1 RAs offer adherence advantages?**
- **Adverse effects and patient-reported outcomes with GLP-1 RAs**

# Short, Intermediate, and Long-acting GLP-1 RAs

Short acting

- Twice-daily dosage
  - Exenatide
- Once-daily dosage
  - Lixisenatide

Intermediate acting (once-daily dosage)

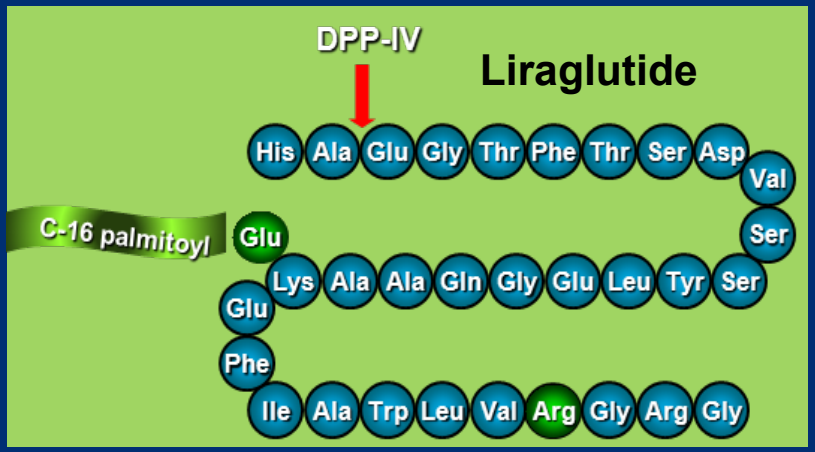
- Liraglutide

Long acting (once-weekly dosage)

- Exenatide LAR
- Albiglutide (GLP1 dimer + human albumin)
- Semaglutide
- Dulaglutide(+Fc fragment)

Fixed ratio combinations

- Liraglutide + degludec
- Lixisenatide + glargine

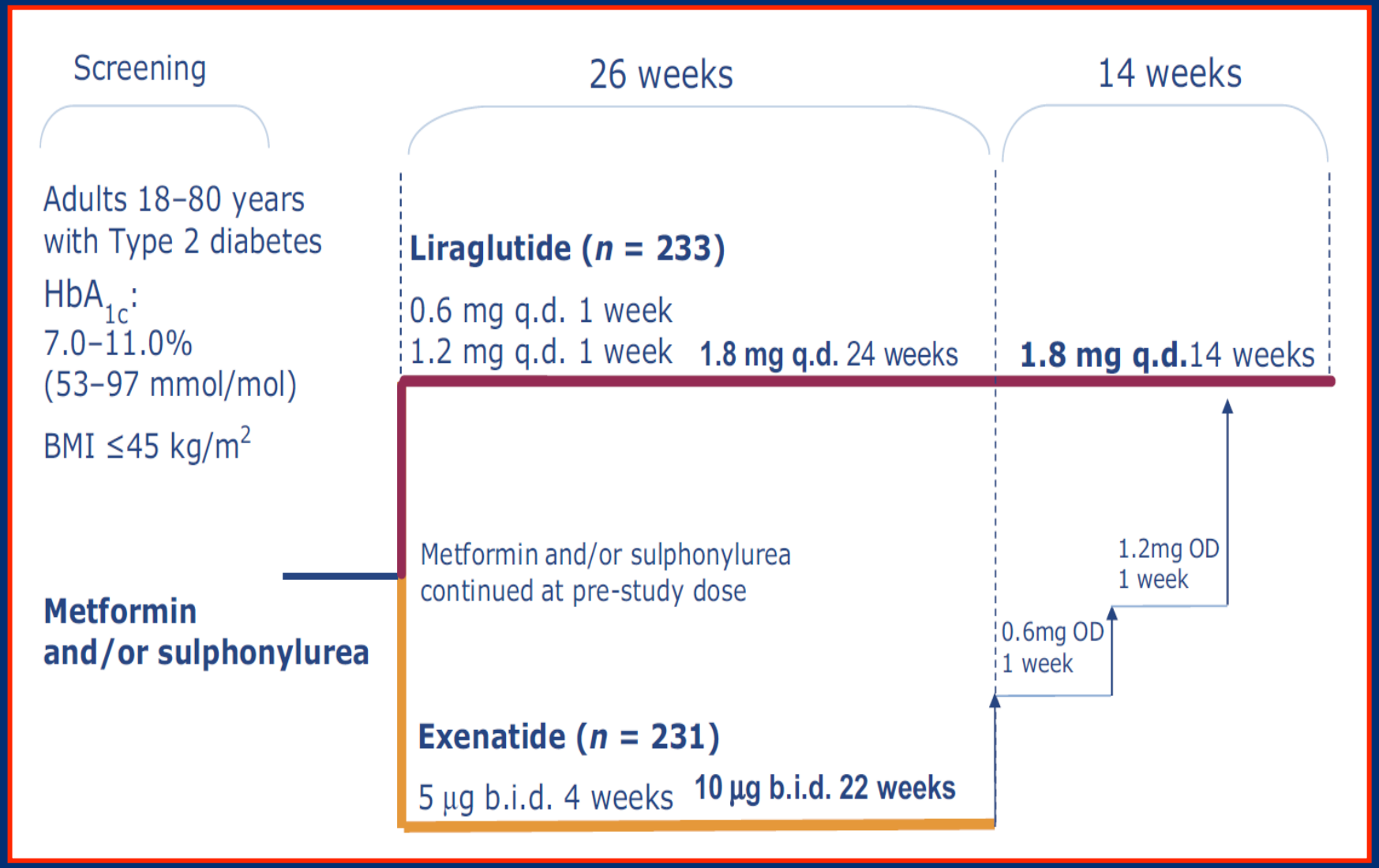

Adapted from Nielsen et al. Regul Pept 2004;117:77-88

# Comparison of Short and Longer-Acting GLP-1 RAs

| | Short-acting | Longer-acting |
|---|---|---|
| Gauge of needle | Thin (31G, 32G) | Thick (23G) for exenatide LAR |
| Injection technique | Simple | Requires manual dexterity for exenatide LAR, injection technique is also simple for liraglutide, titrated with the same pen |
| Injection site reactions | Rare | Common, seldom with liraglutide |
| Gastrointestinal symptoms | More common | Less common |
| Increase in pulse rate | Less common | More common |
| Weight loss | Effective | Effective |
| Improvement in lipid profile | Minimal | Minimal |
| Antibody formation | Relatively high with exenatide | Relatively high with exenatide LAR; low for liraglutide |
| Ability to stop in case of adverse events | Retained | Lost for once-weekly injections |

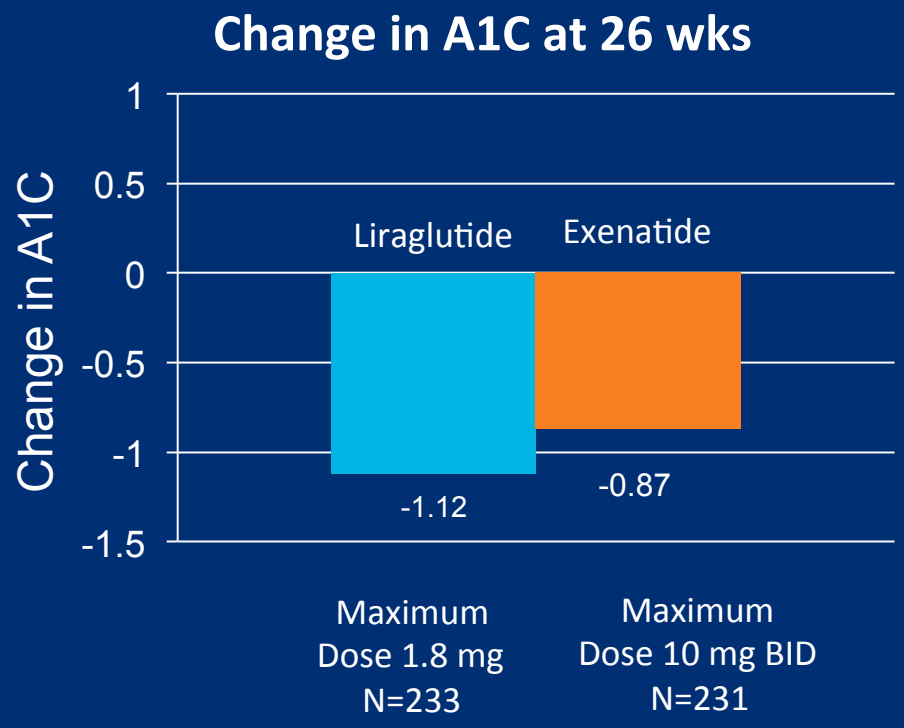
Kalra. Diabetes Ther 2014;5:333–40.

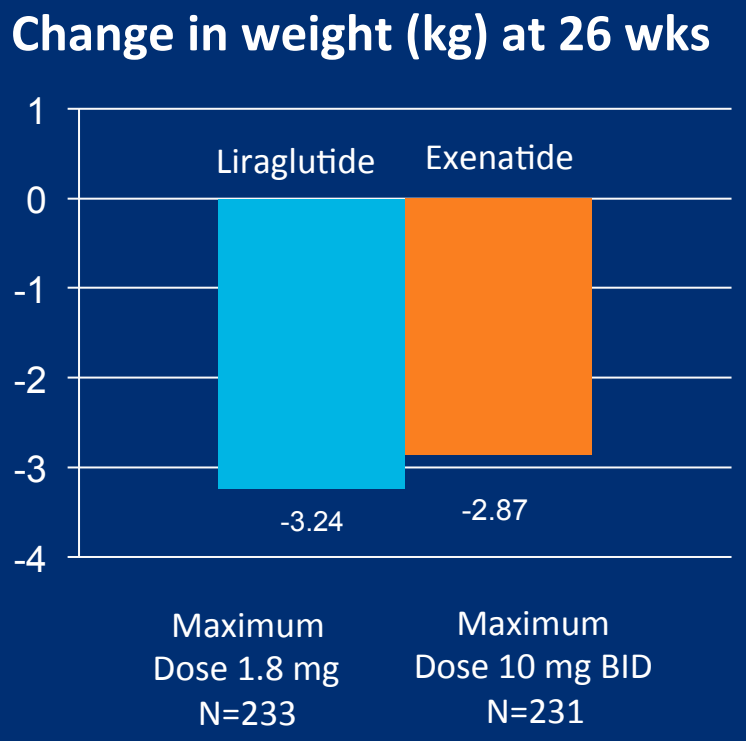
# Study design of Liraglutide Effect and Action in Diabetes 6 (LEAD 6)




Schmidt et al. Diabet Med. 2011;28:715–23.

# LEAD-6: Exenatide vs. Liraglutide

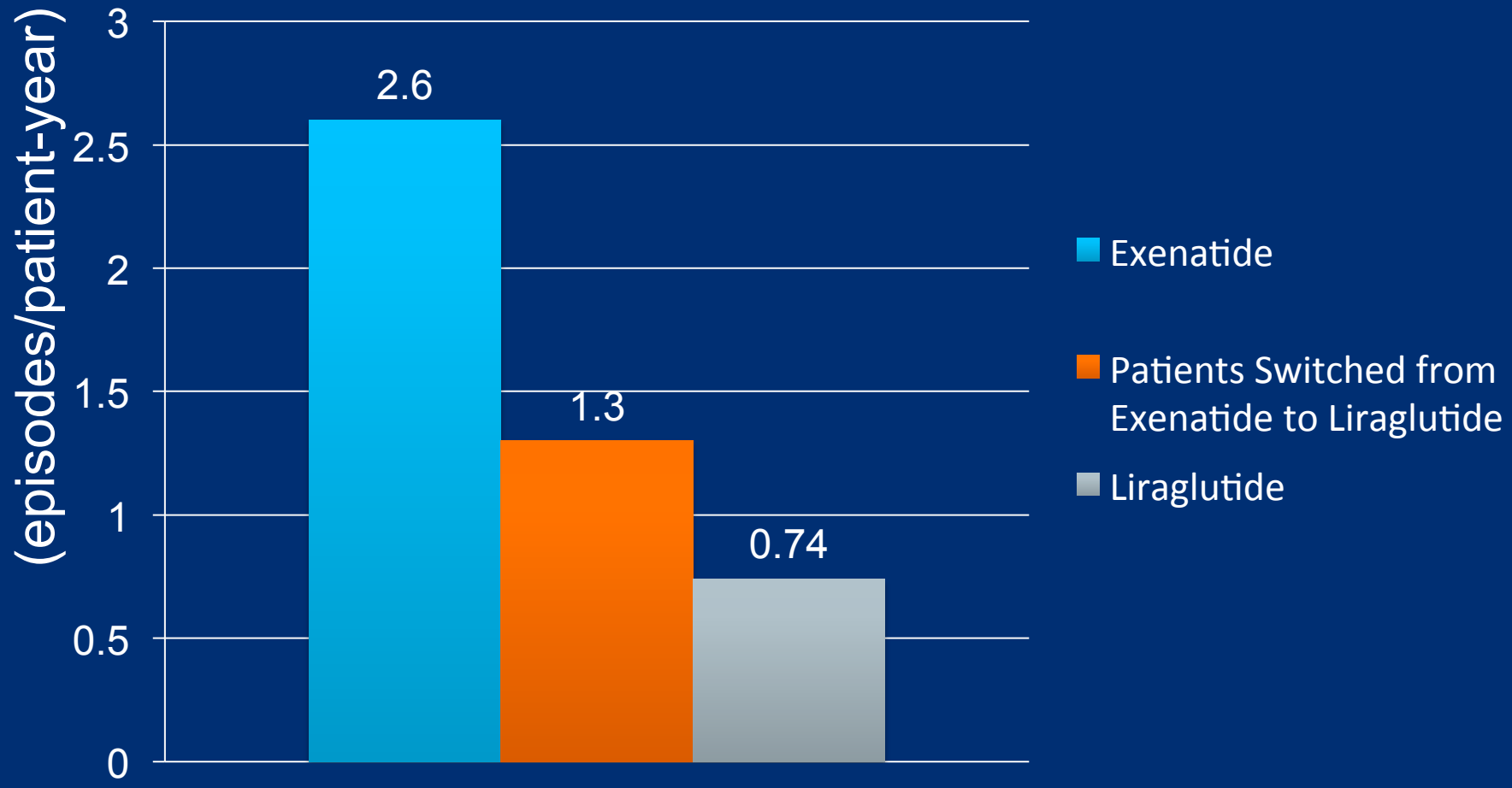



Estimated treatment difference for changes from baseline
Least square mean: -0.33 (95% CI, -0.47 to -0.18) *$P$<.0001.

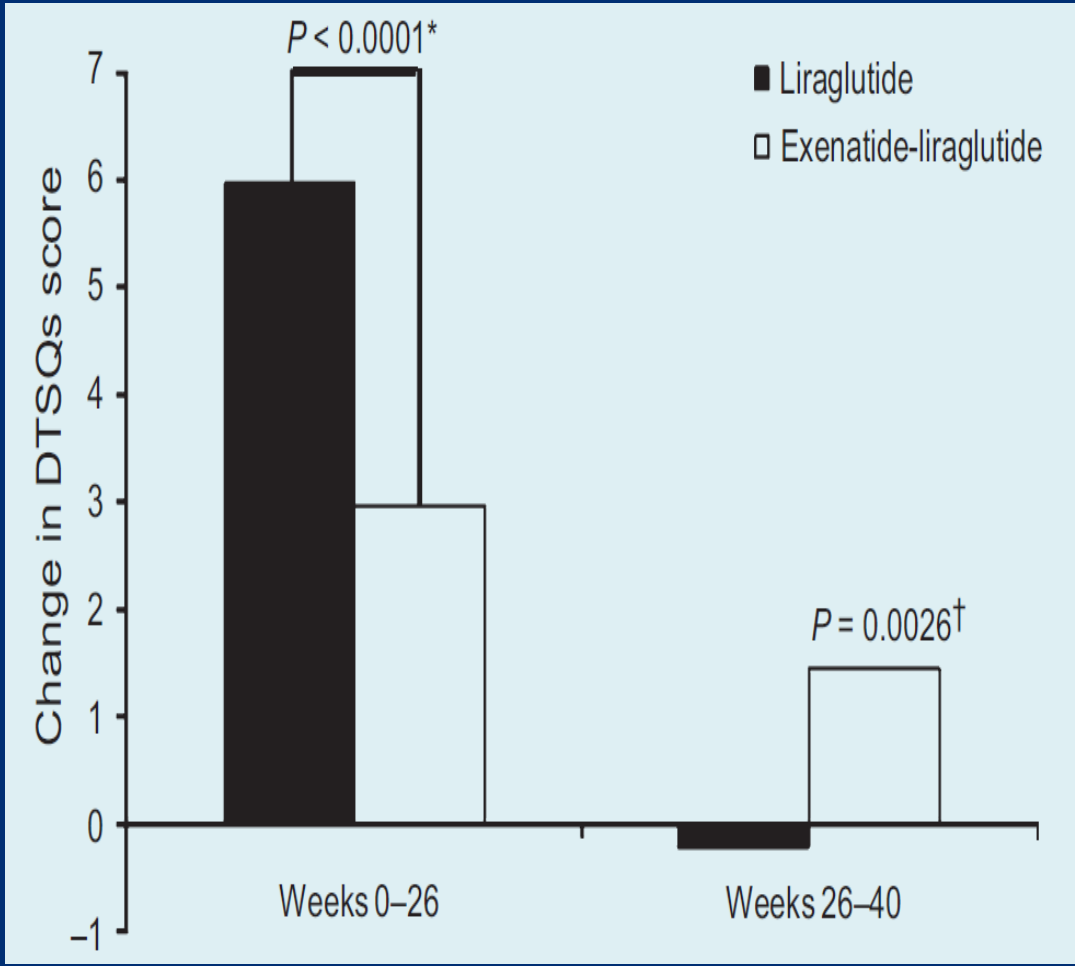
Buse et al. Lancet 2009; 374:39-47.

# Minor Hypoglycemia: Liraglutide vs Exenatide




Buse et al. (Lead-6). Diabetes Care 2010;33:1300–03.

# Diabetes Treatment Satisfaction (DTSQs) : Liraglutide vs Exenatide



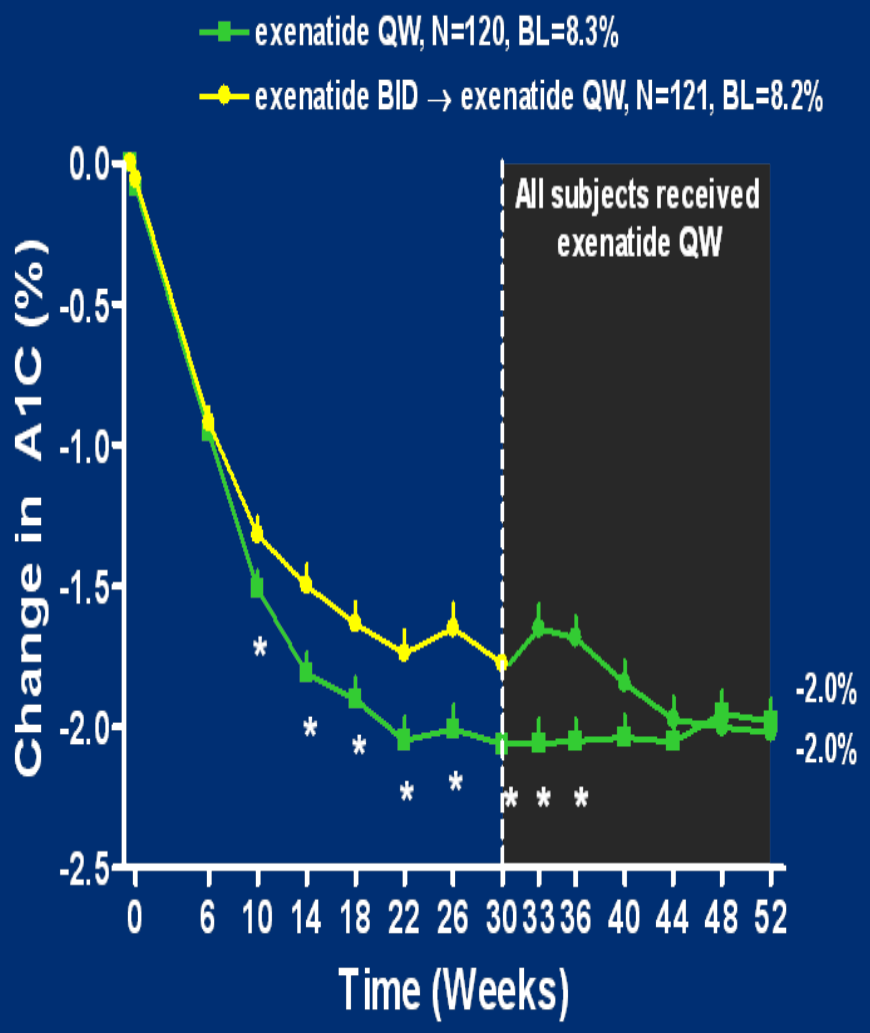

- Lira. 1.8 mg qd or
- Exen. 10 ug bid x 26 wk
- Then Lira.1.8 mg qd x 14 wk

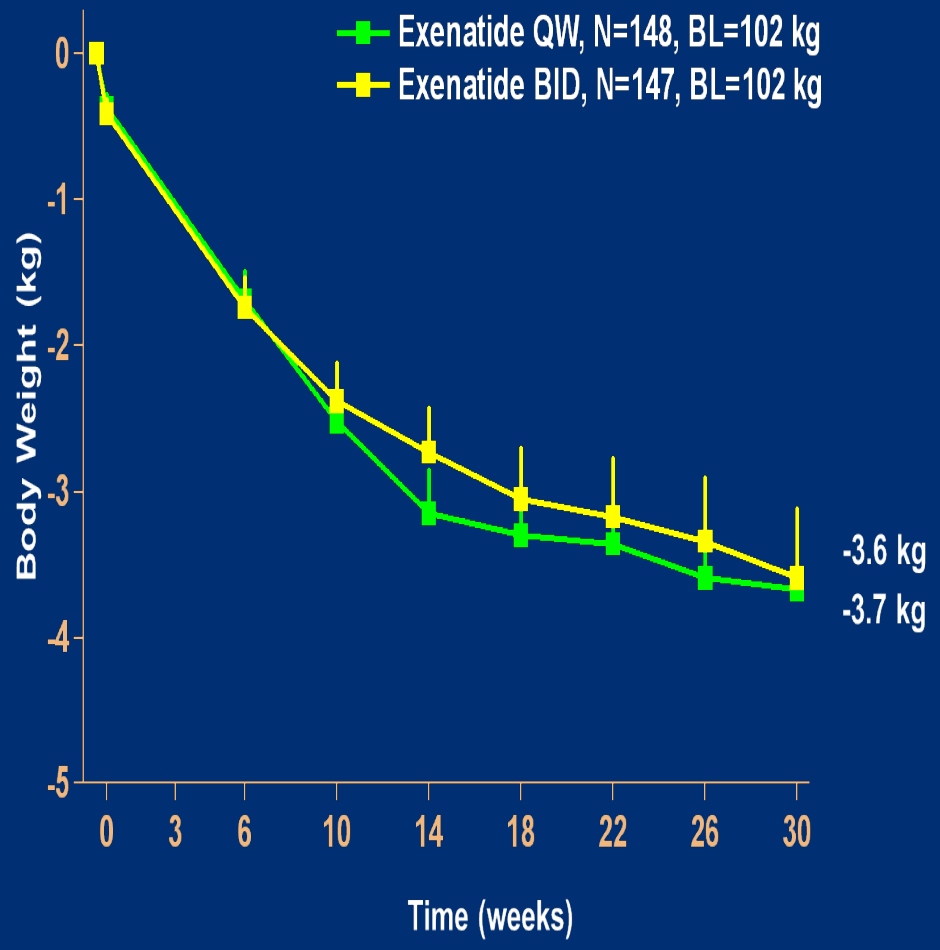
*Lira vs. Exen- change from baseline

+Wk 40 vs. Wk 26: exenatide to liraglutide group.

Schmidt et al. Diabet Med. 2011;28:715–23.

# Exenatide Once Weekly Vs. Exenatide BID




Drucker et al. Lancet. 2008;372:1240-50.

Data are LS mean (SE)

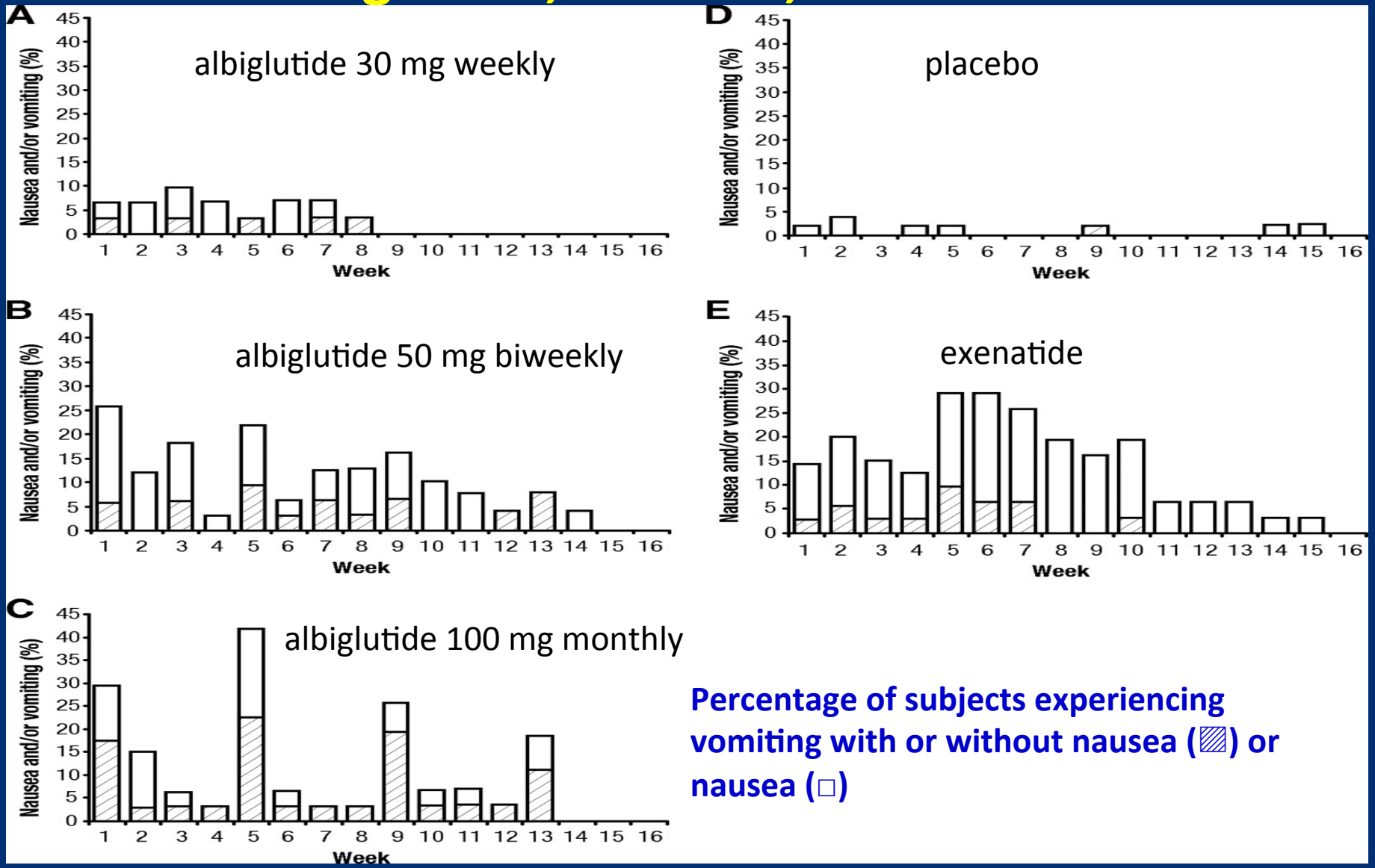
# Albiglutide: Clinical Data

| | Albiglutide + Metformin | Placebo + Metformin | Sitagliptin + Metformin | Glimepiride + Metformin |
|---|---|---|---|---|
| **Body Weight (kg)** | | | | |
| Baseline (mean) | 90 | 92 | 90 | 92 |
| Change at Week 104 [b] | -1.2 | -1.0 | -0.9 | +1.2 |
| Difference from placebo + metformin [b] (95% CI) | -0.2 (-1.1, 0.7) | | | |
| Difference from sitagliptin + metformin [b] (95% CI) | -0.4 (-1.0, 0.3) | | | |
| Difference from glimepiride + metformin [b] (95% CI) | -2.4 (-3.0, -1.7) [c] | | | |

Rosenstock et al. Diabetes Care 2009;32:1880-86

http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/125431s000lbl.pdf

# Time Course of Nausea and Vomiting: Albiglutide, Placebo, Exenatide




**Percentage of subjects experiencing vomiting with or without nausea (▨) or nausea (□)**

Rosenstock et al. Diabetes Care 2009;32:1880-86.

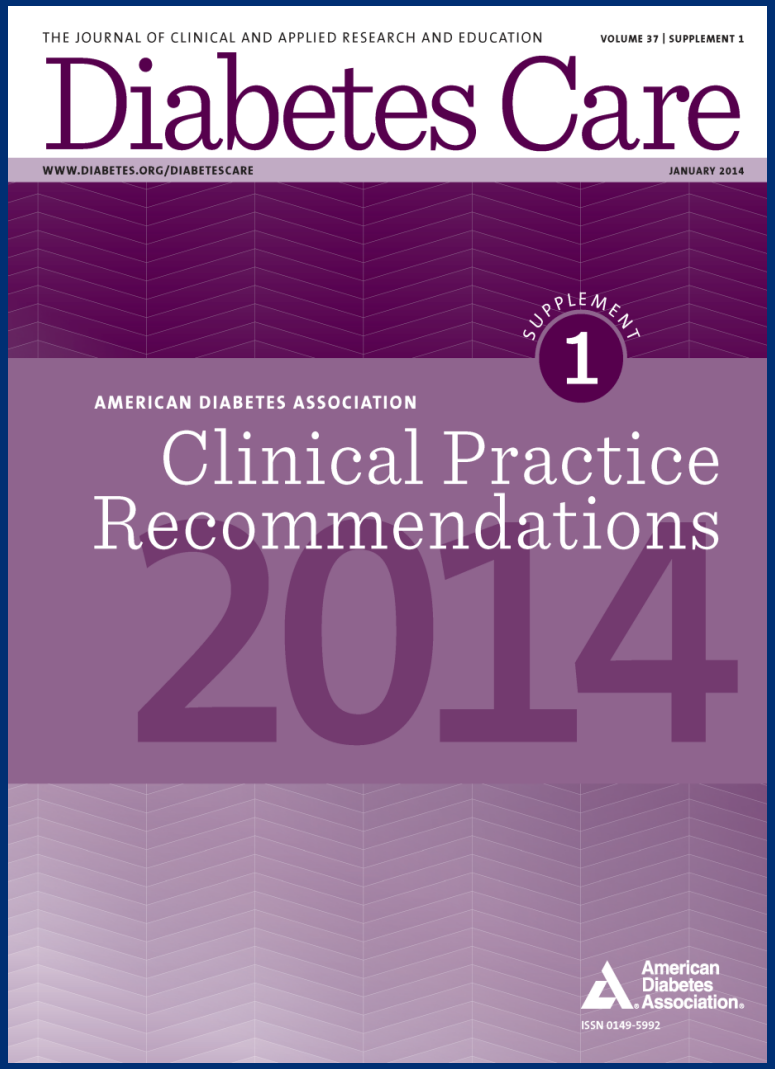
# GLP-1 Analogues: Adverse Effects

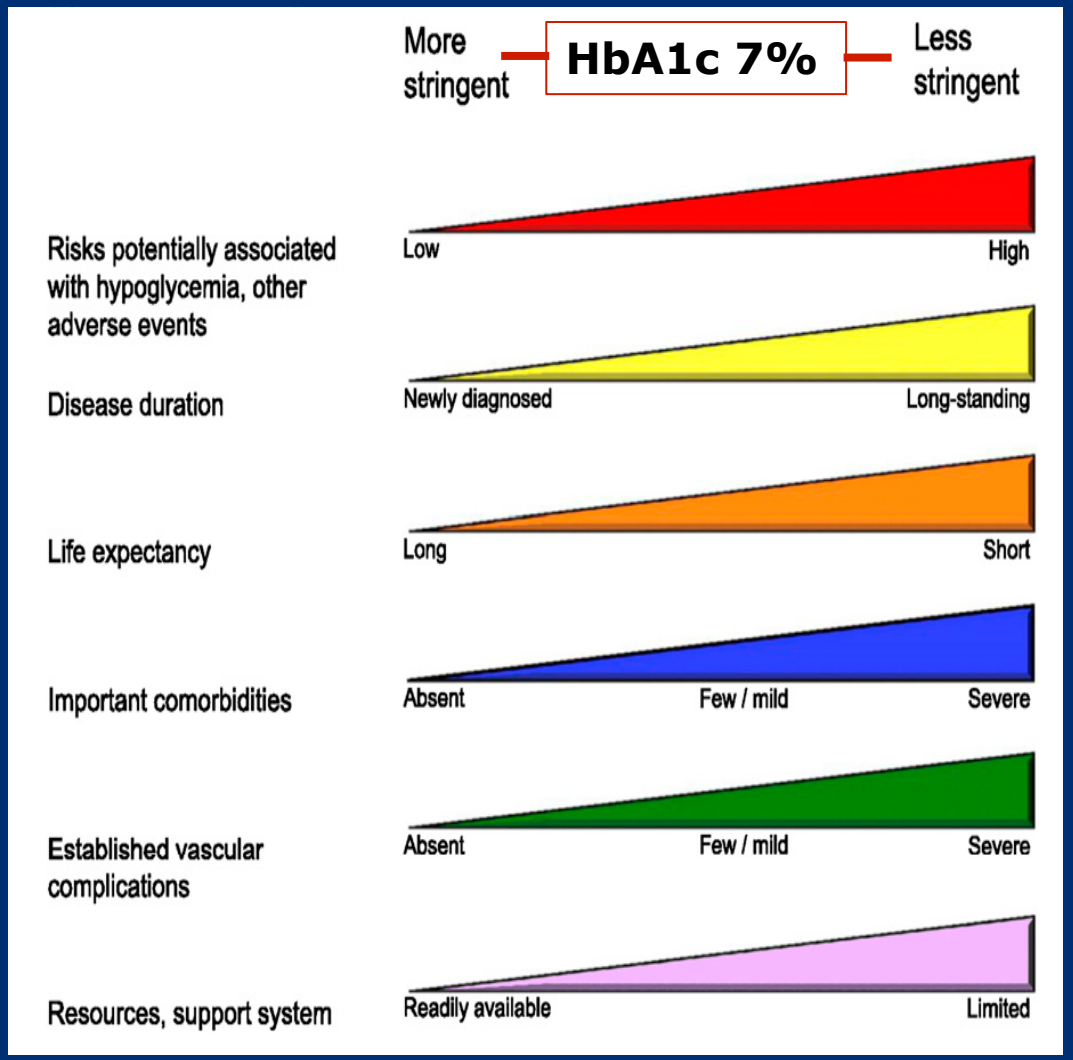
- Gastrointestinal: nausea, vomiting, diarrhea, usually during initiation of therapy[1-4]
  - Mitigated by slow titration of dose to tolerance (5% discontinuations in RCTs)
- Rare acute pancreatitis reported with liraglutide, exenatide[5,6]
  - Causality not established; discontinue drug, do not re-challenge
- Thyroid C-cell tumors in mice, rats associated with increase in plasma calcitonin levels in rodents[7]
  - No documented MTC, pathological calcitonin levels in liraglutide vs control groups in humans
- Renal warning: severe renal impairment (creatinine clearance <30 mL/min), end-stage renal disease[3,4]
  - Also use with caution in patients with renal transplantation

RCT, randomized controlled trial

1. Nauck et al. Diabetes Care. 2009;32:84-90. 2. Garber et al. Lancet. 2009;373:473-481. 3. Byetta (exenatide) injection prescribing information. Princeton, NJ: Bristol-Meyers Squibb; 2013. 4. Victoza (liraglutide) injection prescribing information. Plainsboro, NJ: Novo Nordisk A/S; 2013. 5. Ahmad, Swann . N Engl J Med. 2008;358:1970-71. 6. Dore et al. Curr Med Res Opin. 2009;25:1019-27. 7. Boess et al. J Mol Endocrinol. 2013;50:325-36.

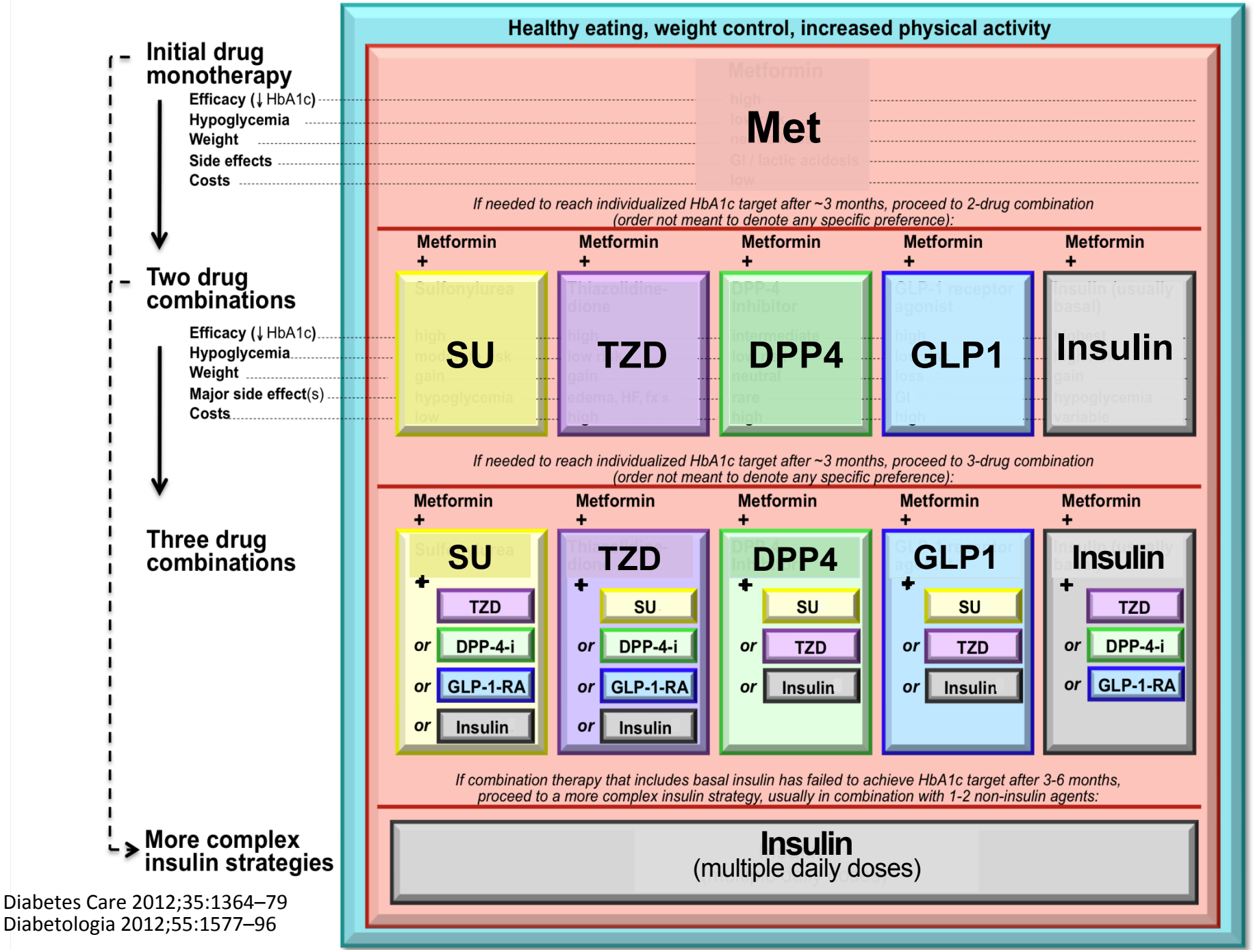
# Approach to Management of Hyperglycemia




American Diabetes Association.

ADA. Diabetes Care 2014;37(suppl.1):S25;
adapted from Ismail-Beigi et al. Ann Intern Med 2011;154:554-59.




Diabetes Care 2012;35:1364–79
Diabetologia 2012;55:1577–96