# The new era of GLP-1RA treatment for T2DM patients

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**정 창 희**

# Today's topics

- Overview of GLP-1RA physiology
- GLP-1RAs' similarities and differences
- Dulaglutide molecule design & True Simplicity Pen device
- Highlights of AWARD trials
- Real world cases

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- **Overview of GLP-1RA physiology**
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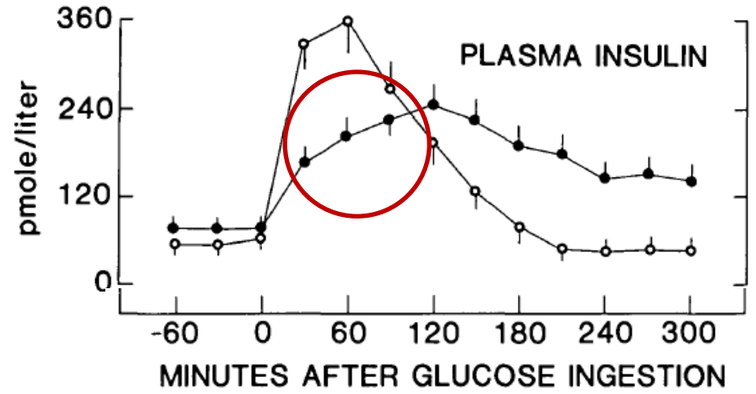
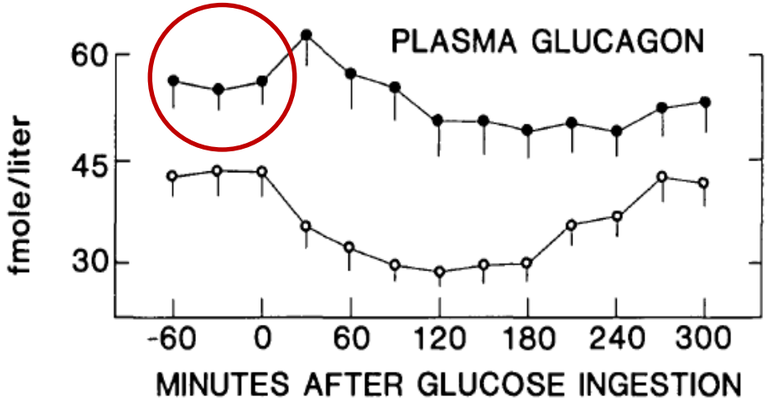
# Insulin and Glucagon Are Dysregulated in Type 2 Diabetes




**Insulin**

Delayed and reduced

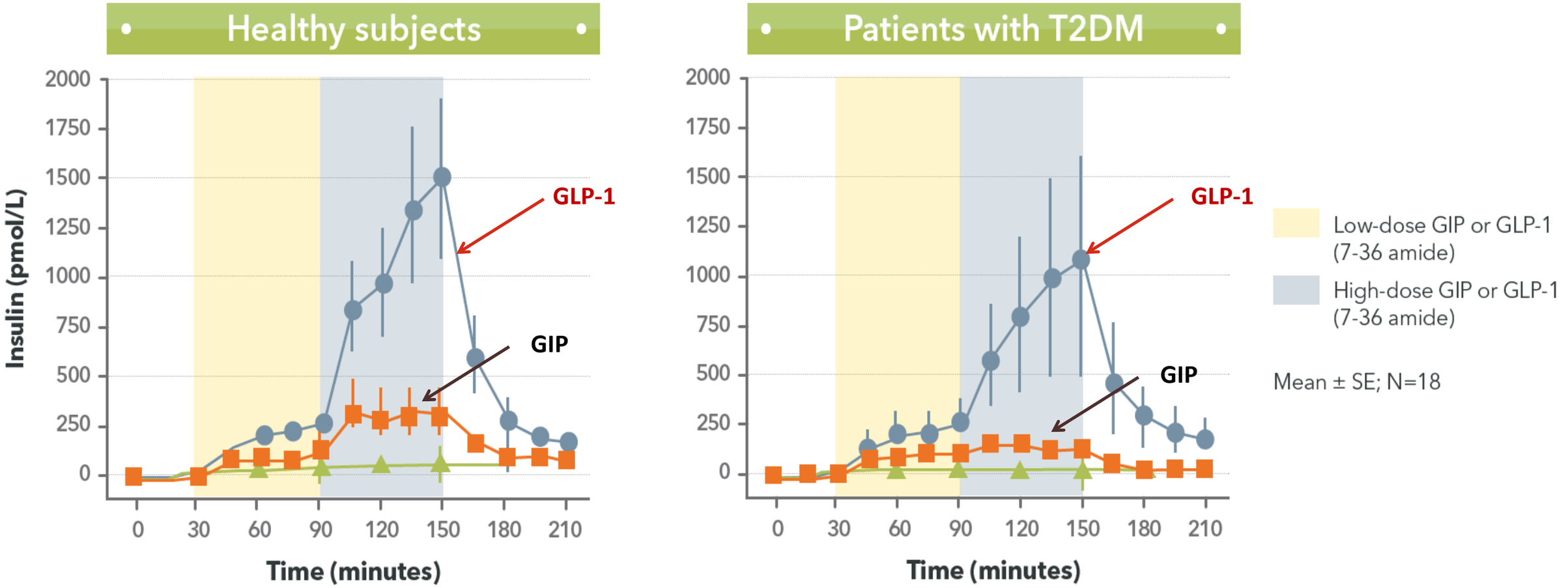



**Glucagon**

High and not suppressed

Diabetes 1990;39:1381-90.

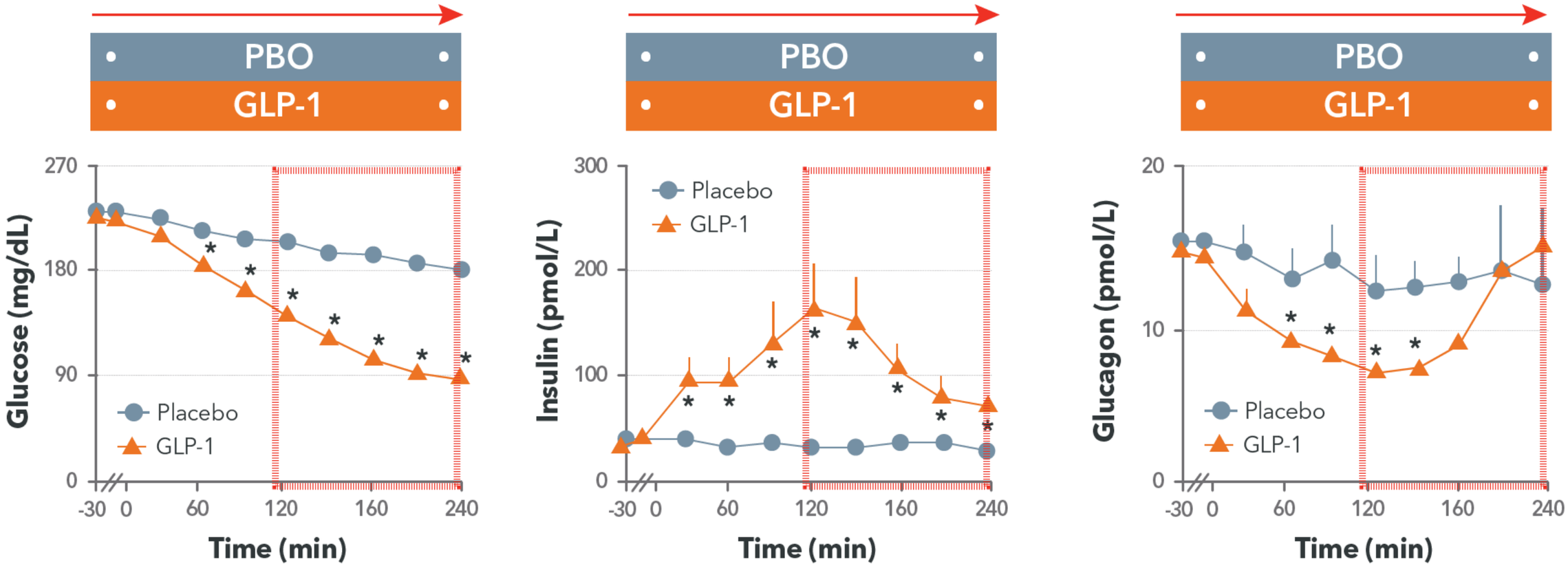
# GLP-1 is a more potent insulin secretagogue than GIP in healthy subjects and patients with T2DM




Nauck MA et al. J Clin Invest. 1993; 91: 301-307.

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

**Fasting State**




N = 10; Mean (SE); *P<0.05

Nauck MA, et al. Diabetologia 1993;36:741-744.

# Circulating GLP-1 Has Many Beneficial Effects

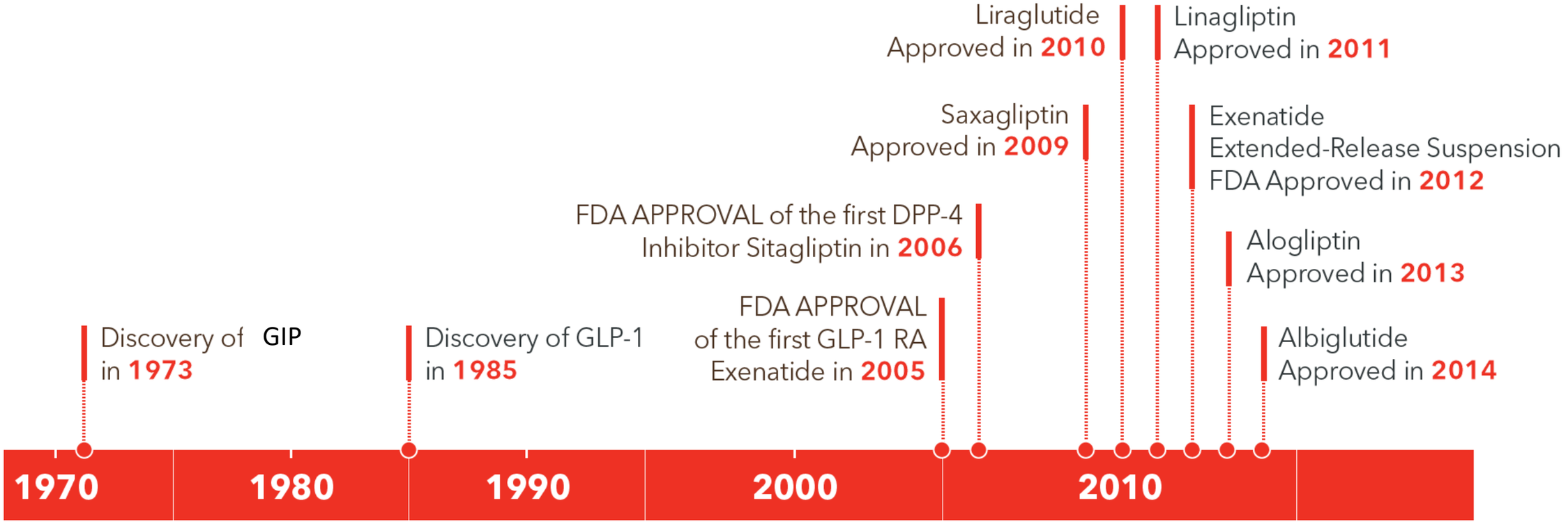
- ↑ Insulin secretion to maintain glucose homeostasis
- ↓ Glucagon secretion
- ↓ Glycemia ↓ PPG ↓ FPG ↓ HbA1c
- ↓ Gastric emptying
- ↑ Satiety due to delayed gastric emptying
- ↓ Food ingestion due to effects on brain
- ↑ β-cell number and ↑ β-cell mass (animal studies)

FFG=fasting plasma glucose; HbA1c=glycated hemoglobin ; PPG=postprandial glucose

Ranganath LR, et al. J Clin Pathol. 2008;61:401-409
Angeli FS, et al. J Endocrinol. 2014;221:T17-T30

# **Incretins** : **IN**testinal Se**CRET**ion of **IN**sulin

- Gut-derived factors that potentiate insulin secretion following meal ingestion.
- 2 principal incretins identified to date:



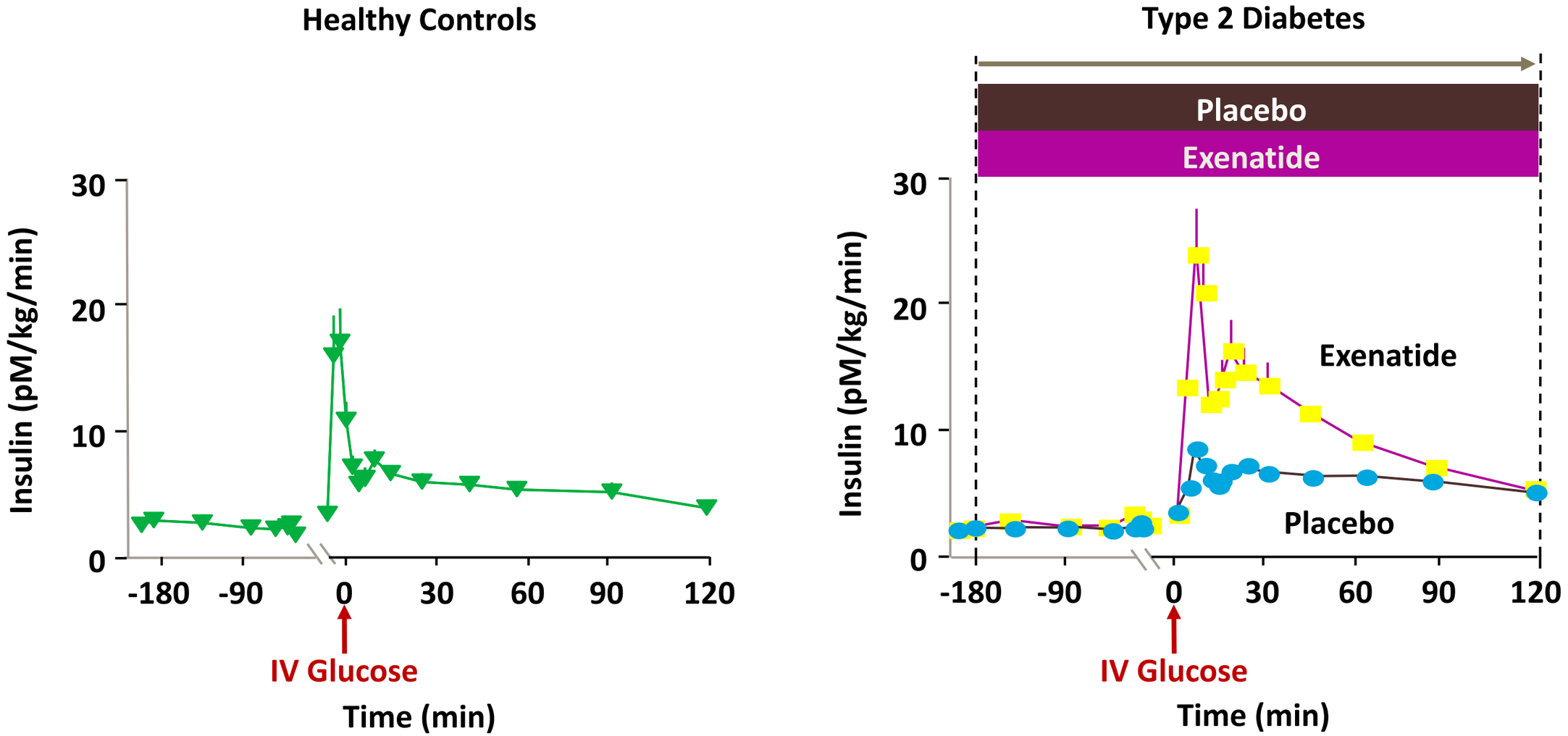

Med Clin N Am 2015;99:107-129.

# The Beginning

- **Exenatide**
  - Synthetic version of salivary protein found in the Gila monster
  - More than 50% amino acid sequence identity with human GLP-1
    - Binds to known human GLP-1 receptors on beta cells (in vitro)
    - Resistant to DPP-IV inactivation


Adapted from Nielsen LL, et al. Regul Pept 2004;117:77-88.
Adapted from Kolterman OG, et al. Am J Health-Syst Pharm 2005;62:173-181.

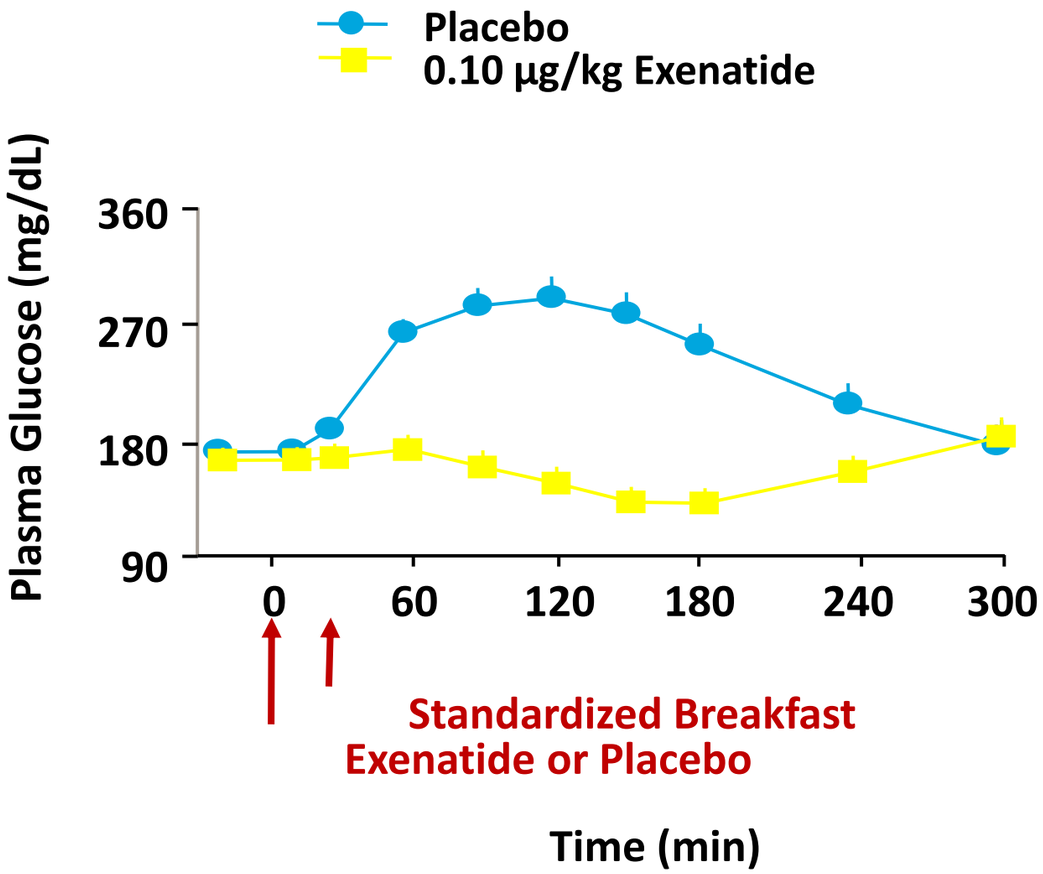
# Exenatide Restored First-Phase Insulin Response

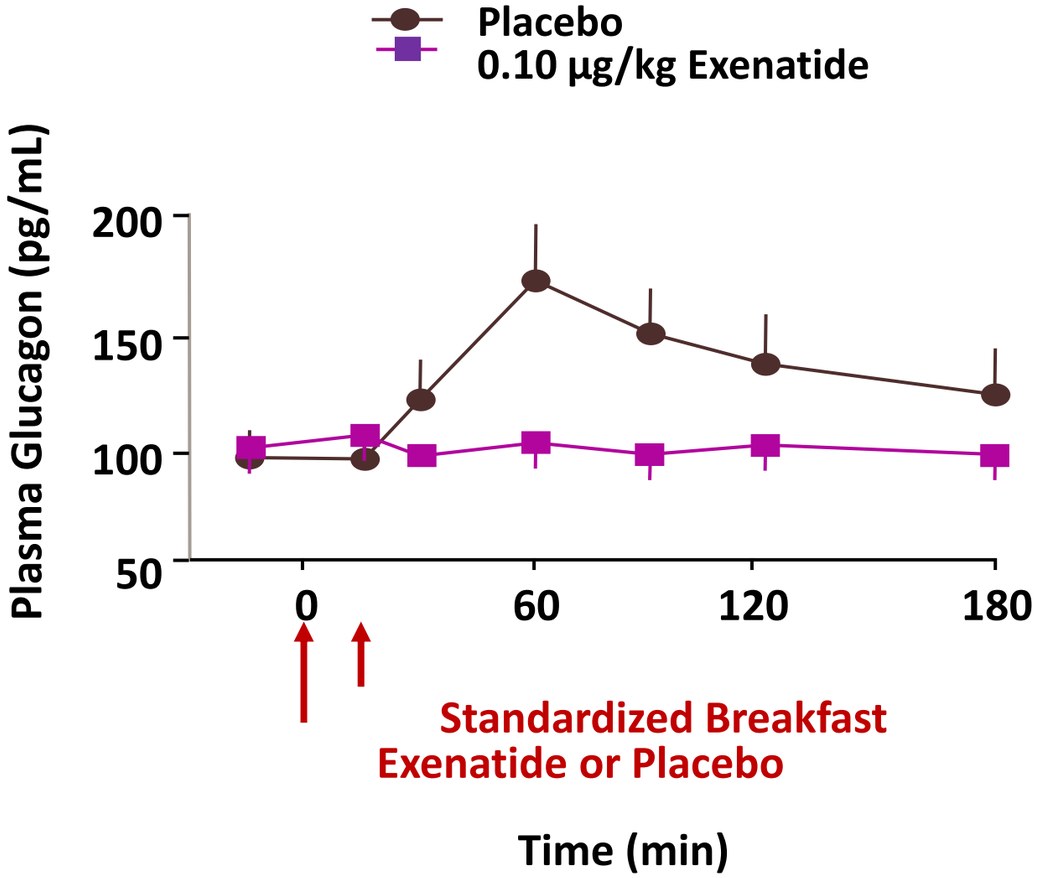



Evaluable; N = 25; Mean (SE)

Fehse F, et al. J Clin Endocrinol Metab 2005;90(11):5991-5997.

# Exenatide Suppressed Postprandial Glucose and Glucagon in Type 2 Diabetes




N = 20; Mean (SE)

Data from Kolterman OG, et al. J Clin Endocrinol Metab 2003;88:3082-3089.

# Incretin Therapies to Treat T2DM

**Incretin effect is impaired in T2DM.**
**Natural GLP-1 has extremely short half-life.**

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

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

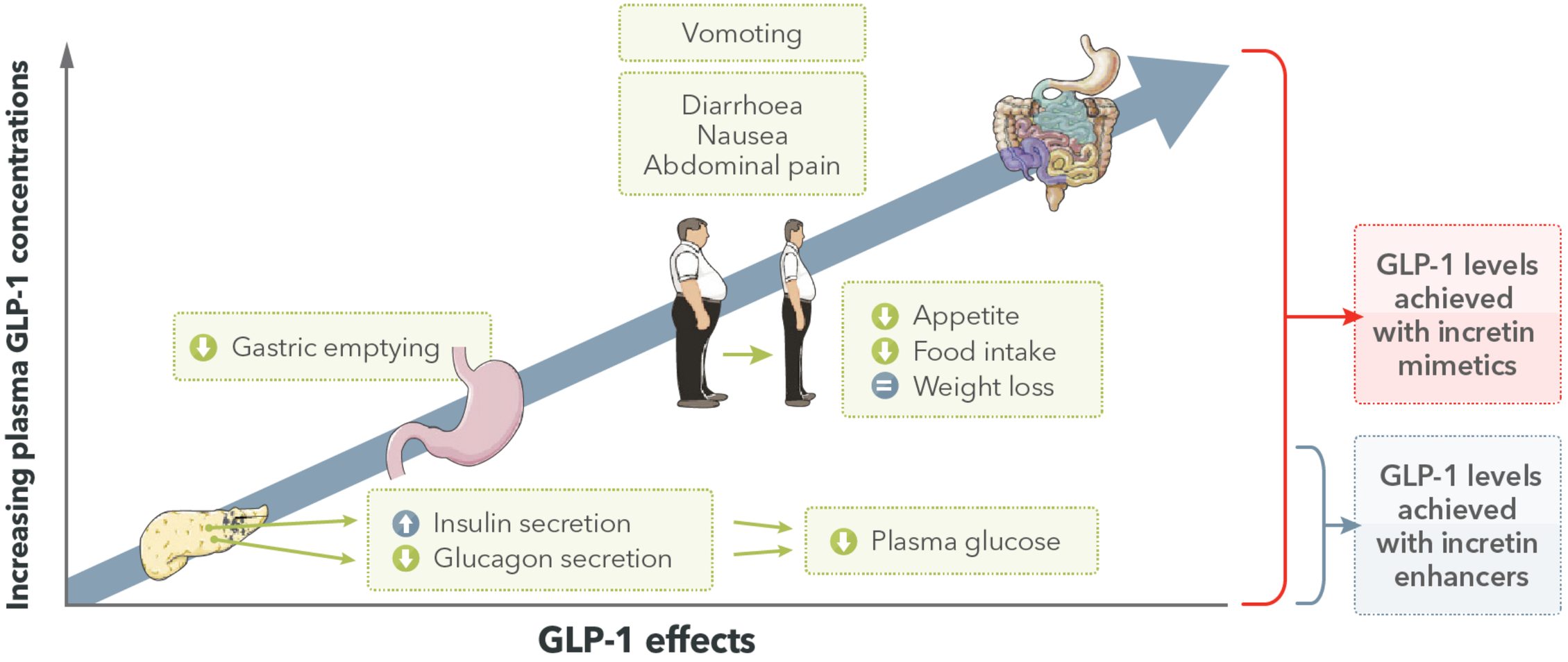
**Exendin-4 based:**
- Exenatide
- Exenatide QW
- Lixisenatide

**Human GLP-1 based:**
- Liraglutide
- Albiglutide
- Dulaglutide
- Semaglutide

- Exendin-4: a naturally DPP-4 resistant GLP-1 analogs

Curr Pharm Des 2001;7:1399
Mol Endocrinol 2003;17:161

# Dose-Response Relationships for the Effects of GLP-1




Trends Mol Med 2008;14:161-68.

# Currently Available GLP-1 RAs

| Drug | Dosing frequency | EMA approval status | US FDA approval status | Phase 3 clinical trial program |
|---|---|---|---|---|
| Exenatide | Twice daily | Approved 20 November 2006 | Approved 28 April 2005 | AMIGO |
| Liraglutide | Daily | Approved 30 June 2009 | Approved 25 January 2010 | LEAD |
| Exenatide | Weekly | Approved 17 June 2011 | Approved 26 January 2012 | DURATION |
| Lixisenatide | Daily | Approved 1 February 2013 | Approved 28 July 2016 | GetGoal |
| Albiglutide | Weekly | Approved 23 January 2014 | Approved 15 April 2014 | HARMONY |
| Dulaglutide | Weekly | Approved 21 November 2014 | Approved 18 September 2014 | AWARD |

European Medicines Agency website,
US FDA website.

# Today's topics

- Overview of GLP-1RA physiology
- **GLP-1RAs' similarities and differences**
- Dulaglutide molecule design & True Simplicity Pen device
- Highlights of AWARD trials
- Real world cases

# GLP-1 RA Pharmacokinetic Profile

Increasing half-life

| | GLP-1 RA | Half-life | Tmax |
|---|---|---|---|
| **Short-acting GLP-1 RA** | **Exenatide BID[1]** | 2.4 hours | 2 hours |
| | **Lixisenatide OD[2]** | 3 hours | 1.0-3.5 hours |
| **Long-acting GLP-1 RA** | **Liraglutide OD[3]** | 13 hours | 8-12 hours |
| | **Semaglutide OW[4,5]** | 6.5-7.5 days | 1-1.5 days |
| | **Dulaglutide OW[6]** | 3.75 days | 1-2 days |
| | **Albiglutide OW[7]** | ~ 5 days | 3-5 days |
| | **Exenatide OW[8]** | 7-14 days | 6-7 weeks |

BID=twice daily, OD=once daily, OW=once weekly, Tmax=time to reach maximum concentration


1. Byetta, Summary of Product Characteristics
2. Lyxumia. Summary of Product Characteristics
3. Victoza, Summary of Product Characteristics
4. Diabetes. 2014;63(S1):A260
5. J Clin Pharm. 2015;55:497-504.
6. Diabetes Obes Metab. 2011;13:434-438.
7. Tanzeum. Prescribing information
8. Clin Pharmacokinet. 2011;50:65-74.

# Short-Acting GLP-1 RA vs. Long-Acting GLP-1 RA

**Short-acting GLP-1 RAs (exenatide BID, lixisenatide*)**

**Long-acting GLP-1 RAs (liraglutide, exenatide QW, albiglutide, dulaglutide)**

**Similarities**

**Differences**

Diabetes Obes Metab. 2016;18:317-332.

# Short-Acting GLP-1 RA vs. Long-Acting GLP-1 RA

1. Chemical Structure
2. Glycaemic Measurements
3. Effects on Weight
4. Cardiovascular Measurement
5. Safety and Tolerability

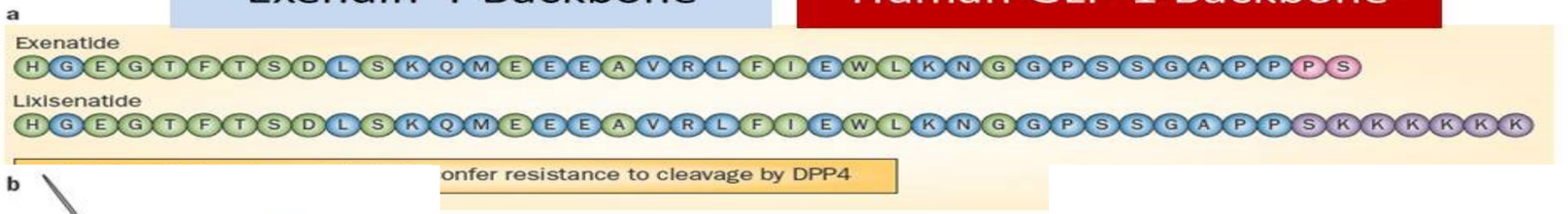
# Chemical Structure

Exendin-4 Backbone

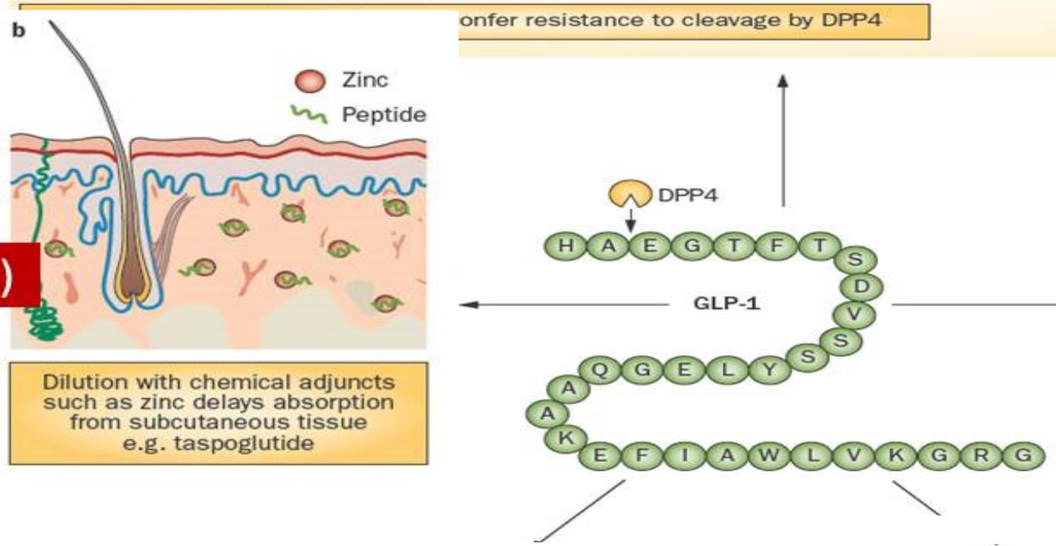
Human GLP-1 Backbone

Exenatide (53%)

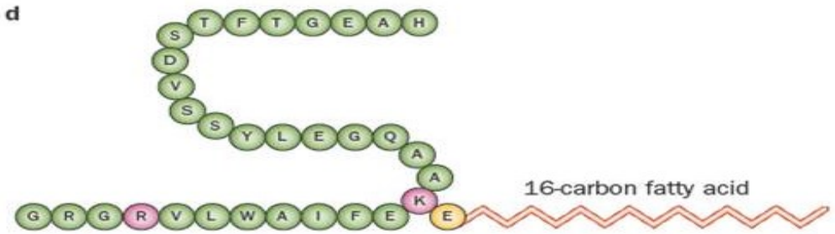
Lixisenatide (50%)




Taspoglutide (93%)

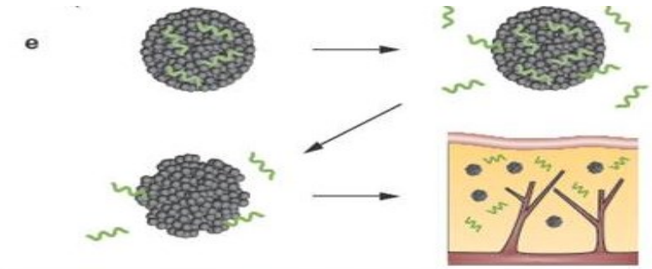



Albiglutide (95%), Dulaglutide (90%)




Liraglutide (97%)

Attachment of fatty acid side chains confers noncovalent albumin binding e.g. liraglutide




Exenatide LAR (53%)

Nat. Rev. Endocrinol. 2012;8:728-742.

# Glycaemic Measurements

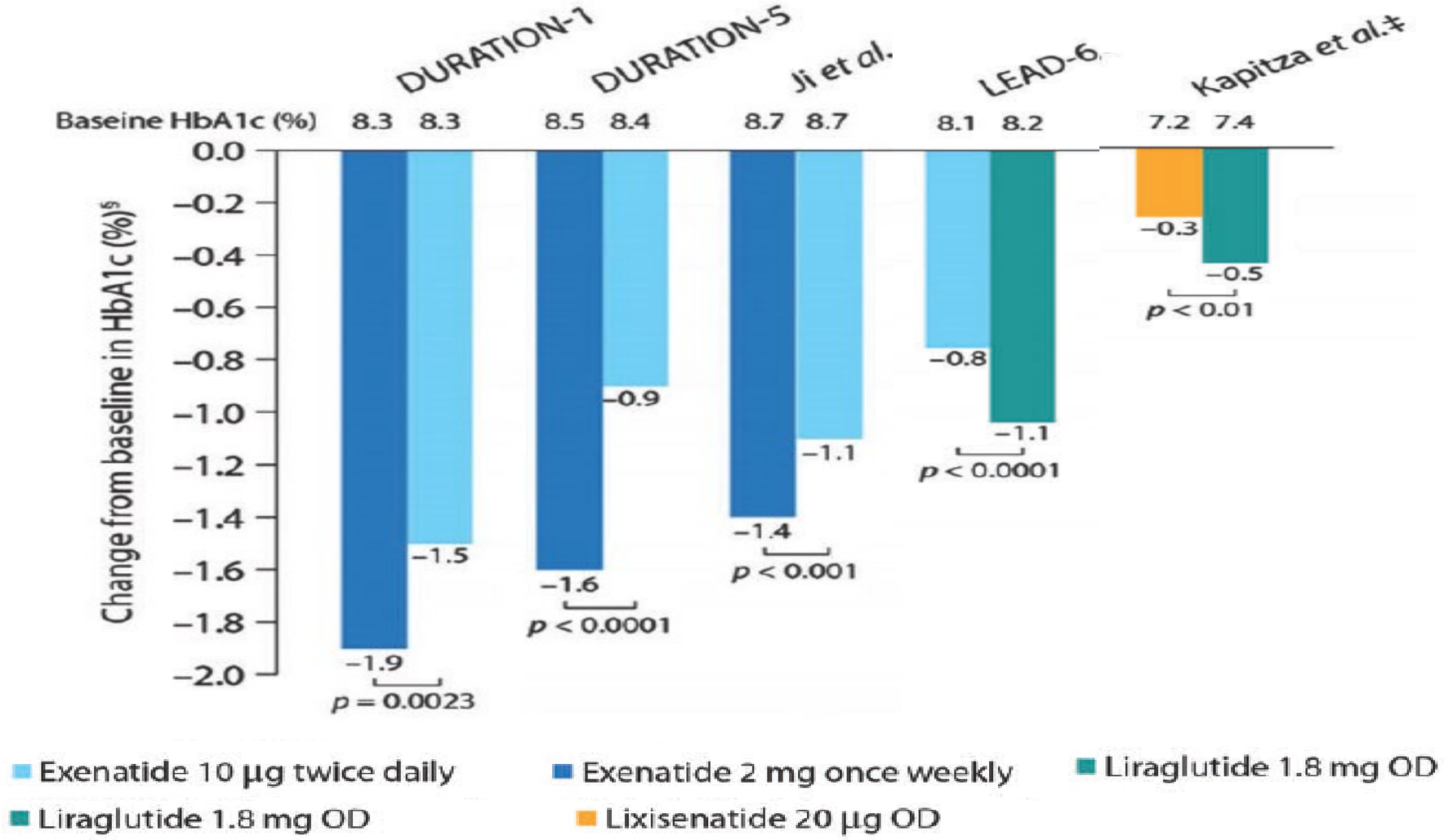
| | |
|---|---|
| **Exenatide BID vs. Exenatide QW** | **DURATION-1 DURAION-5 Ji et al.** |
| Exenatide QW vs. Liraglutide QD | DURAION-6 |
| **Exenatide BID vs. Liraglutide QD** | **LEAD-6** |
| Exenatide BID vs. Lixisenatide QD | GetGoal-X |
| Albiglutide QW vs. Liraglutide QD | HARMONY7 |
| Dulaglutide QW vs. Liraglutide QD | AWARD-6 |
| **Lixisenatide QD vs. Liraglutide QD** | **Kapitza et al.** |

Phase 3 study

Phase 2 study

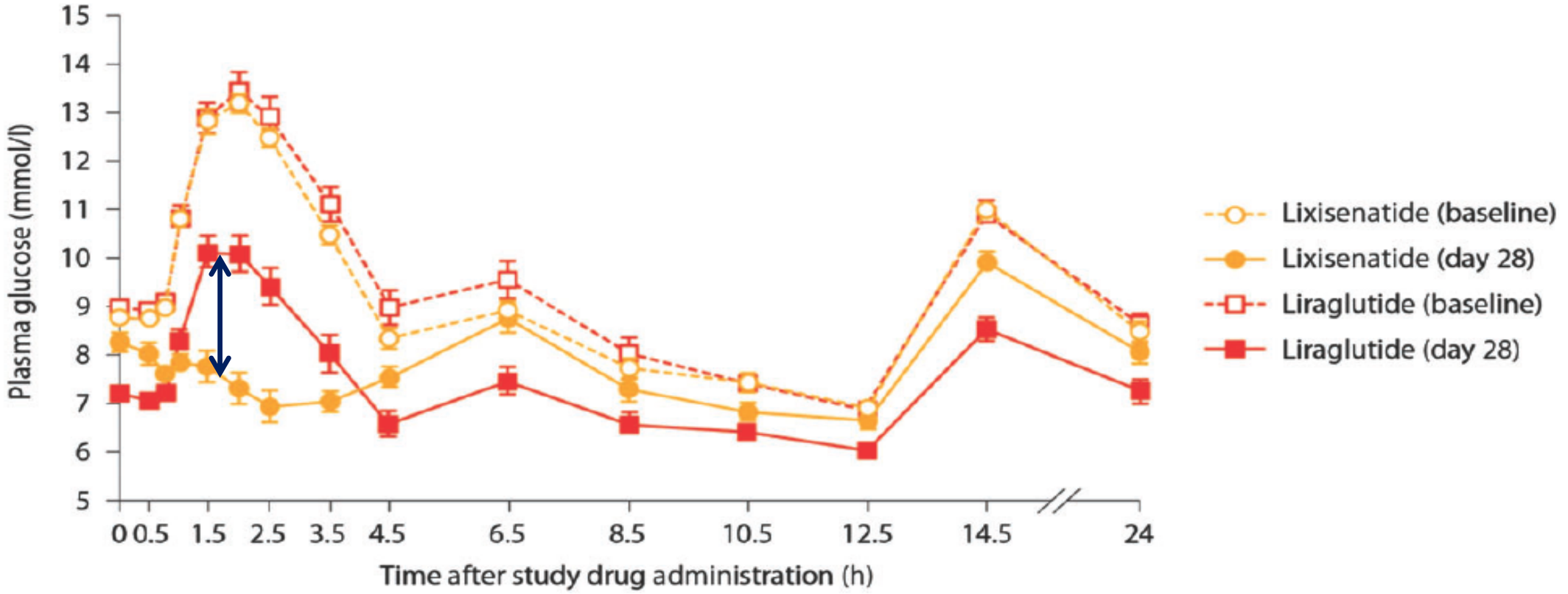
Short vs. Long

# Glycaemic Measurements: HbA1c




Diabetes, Obesity and Metabolism. 2016;18:317-332.

# Glycaemic Measurements: FPG vs. PPG
# Lixisenatide QD vs. Liraglutide QD

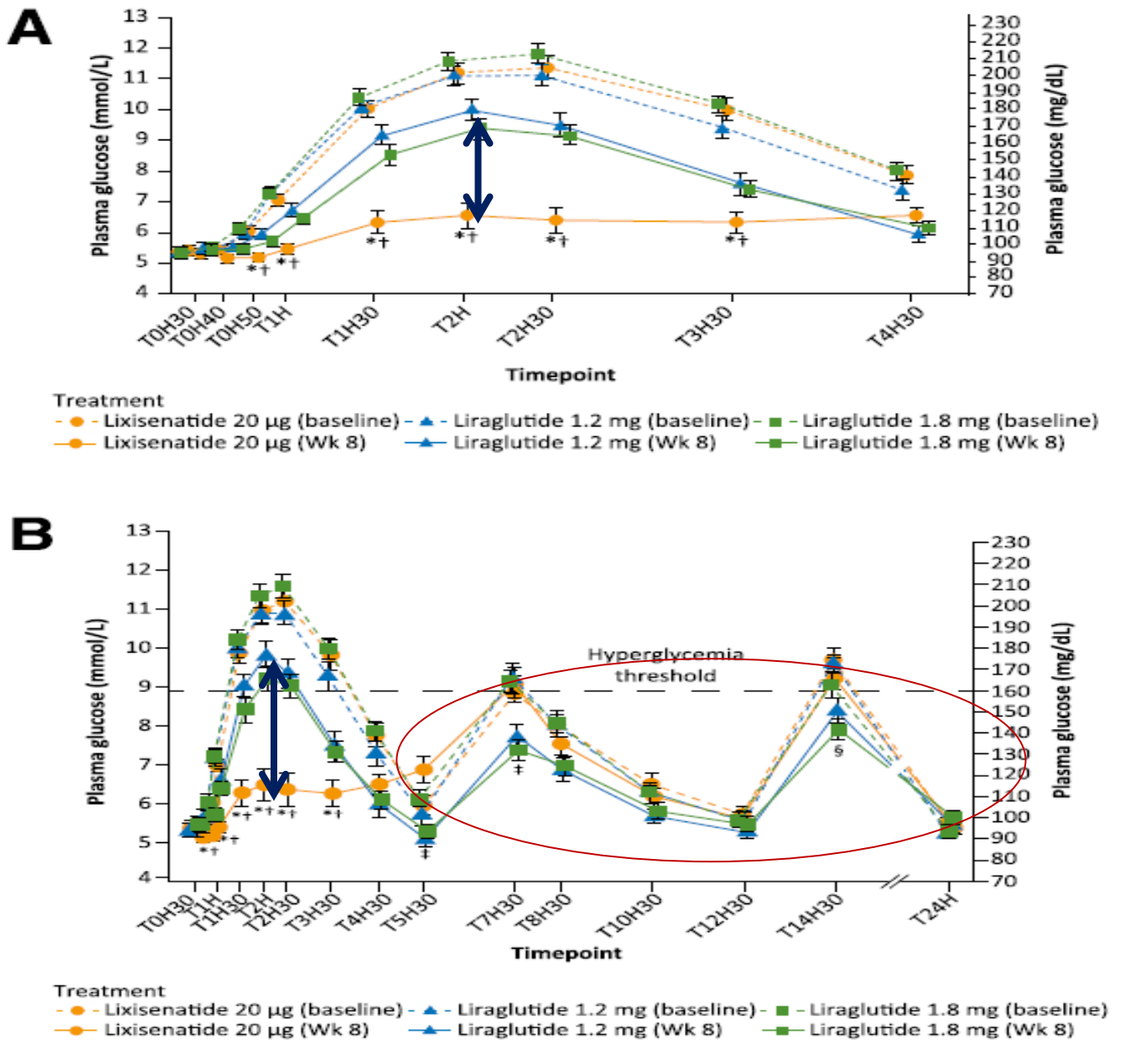



Diabetes, Obesity and Metabolism. 2013;15:642-649.

# Glycaemic Measurements: FPG vs. PPG
# Lixisenatide QD vs. Liraglutide QD

AUC (0.5-4.5 hr)

24 hr Glucose Profile

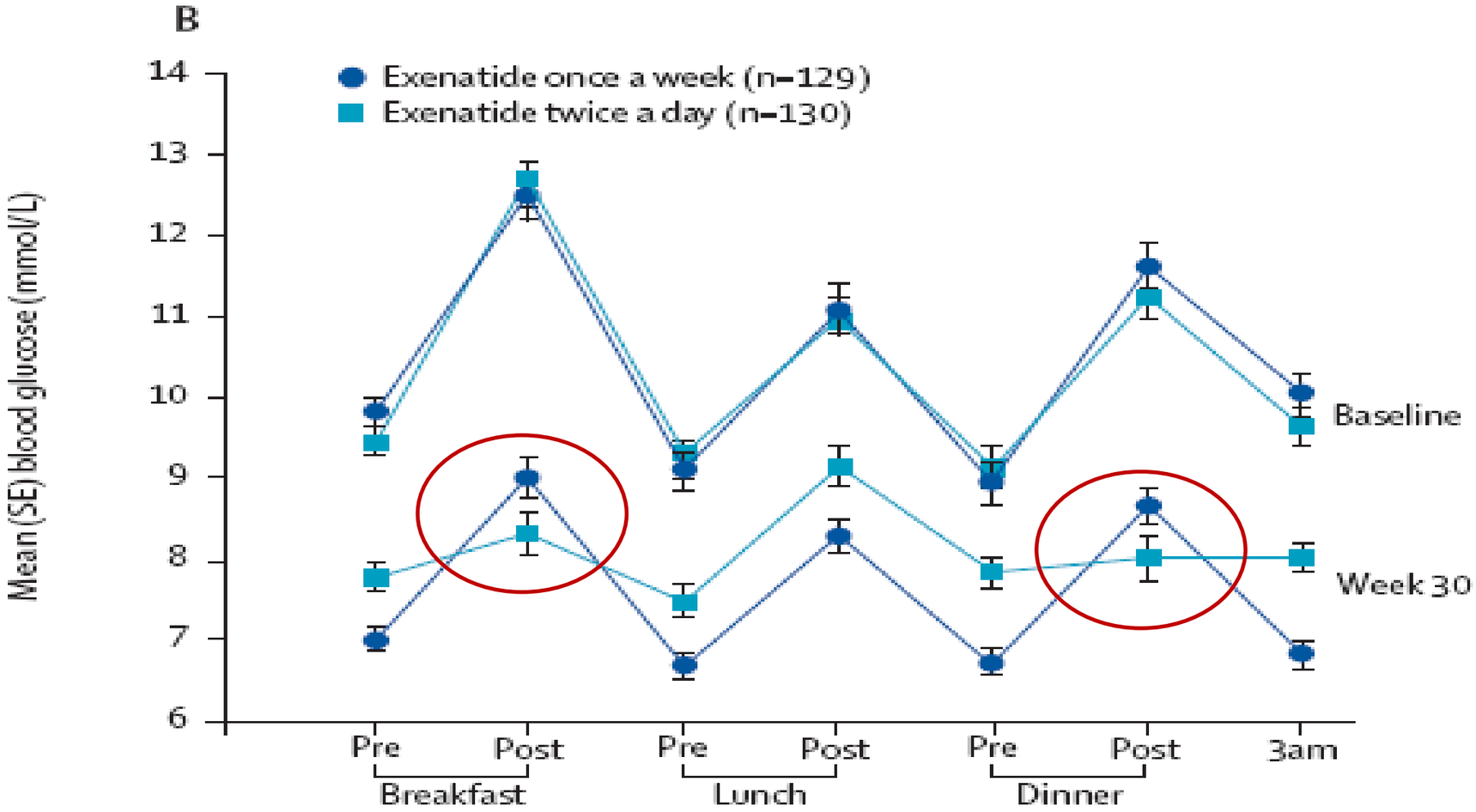






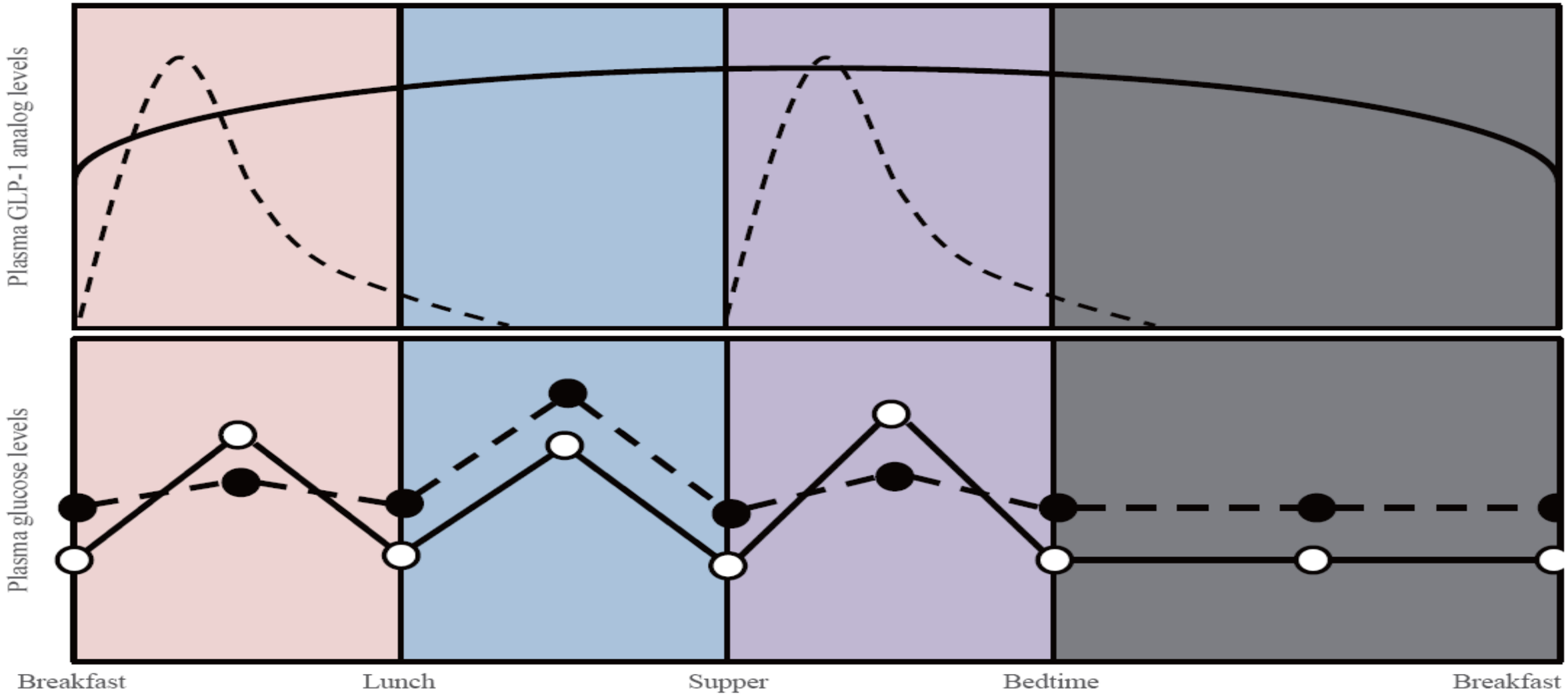
Diabetes Care. 2015;38:1263-1273.

# Glycaemic Measurements: FPG vs. PPG
# Exenatide BID vs. Exenatide QW



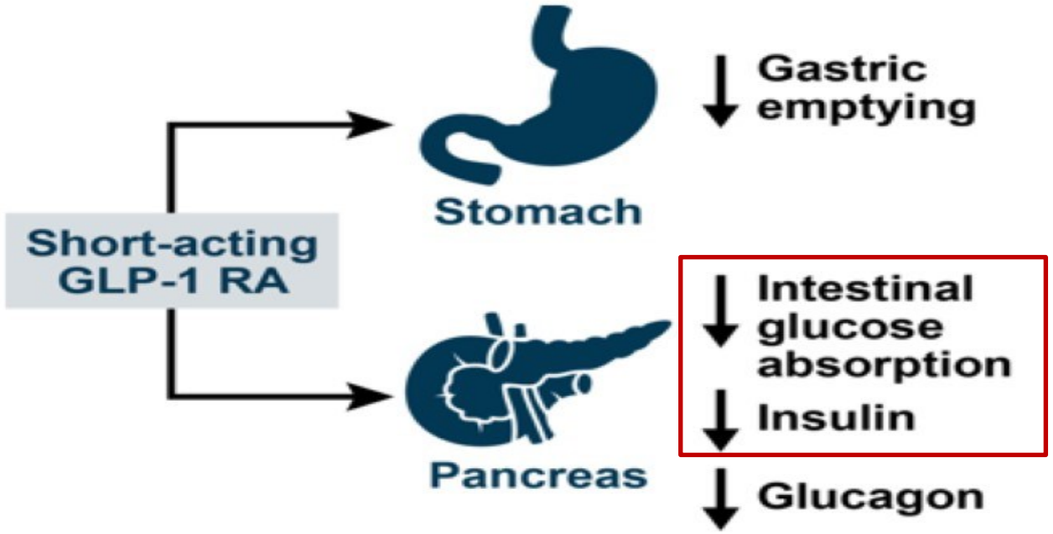

Lancet. 2008;372:1240-50

# Plasma GLP-1 RA Levels and Plasma Glucose Levels with Short- vs. Long-Acting GLP-1 RA




Cho YM. Endocrinol Metab. 2013;28:262-274.

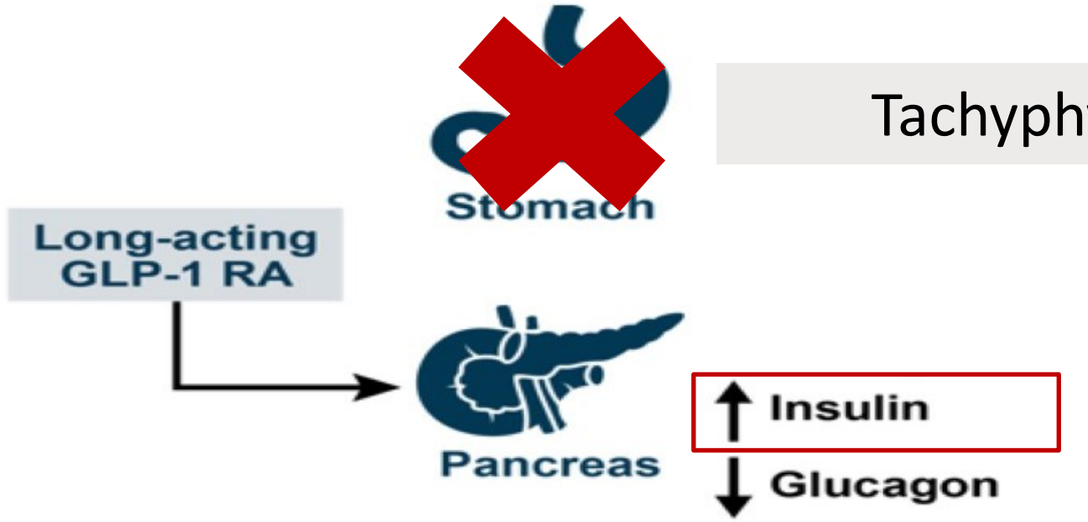
# GLP-1 RA for Prandial Control: Short-Acting GLP-RA




| Short-Acting GLP-1 RAs | Dosing | Glucose Effect |
|---|---|---|
| Exenatide BID | Taken before 2 largest meals of the day | Primarily inhibit gastric emptying to control postprandial glucose excursions |
| Lixisenatide | Taken before breakfast | |

Diabetes, Obesity and Metabolism. 2016;18:317-332.

# GLP-1 RA for Fasting Control: Long-Acting GLP-1 RA

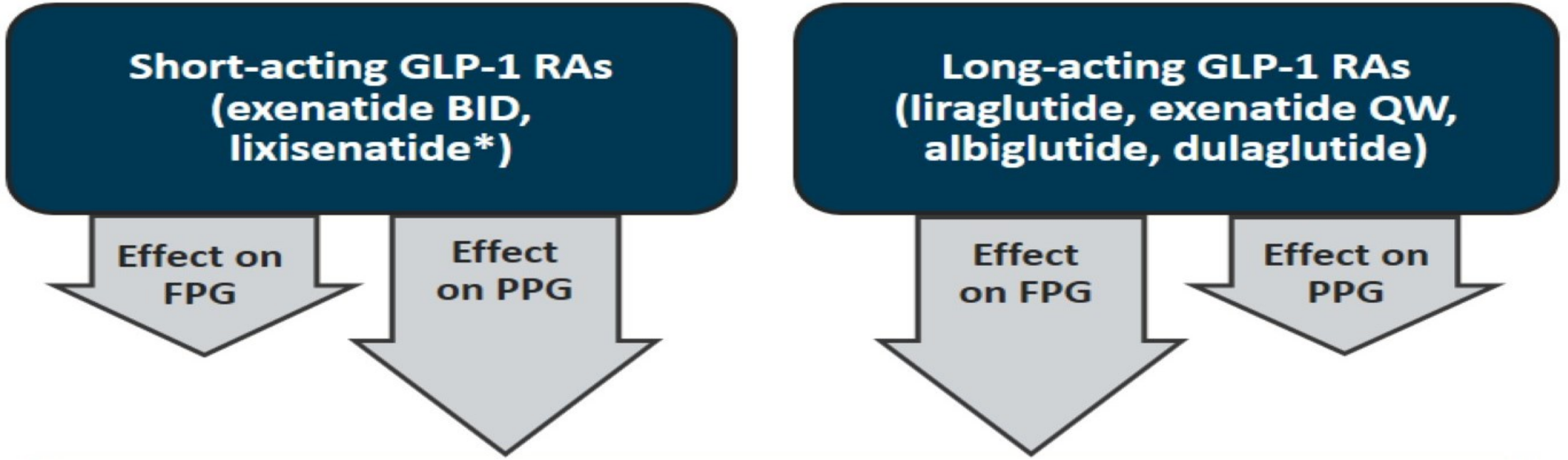



Tachyphylaxis

| Long-Acting GLP-1 RAs | Glucose Effect |
|---|---|
| Liraglutide once daily | Primarily inhibit insulin secretion and decrease glucagon to control fasting glucose |
| Exenatide QW | |
| Dulaglutide QW | |
| Albiglutide QW | |

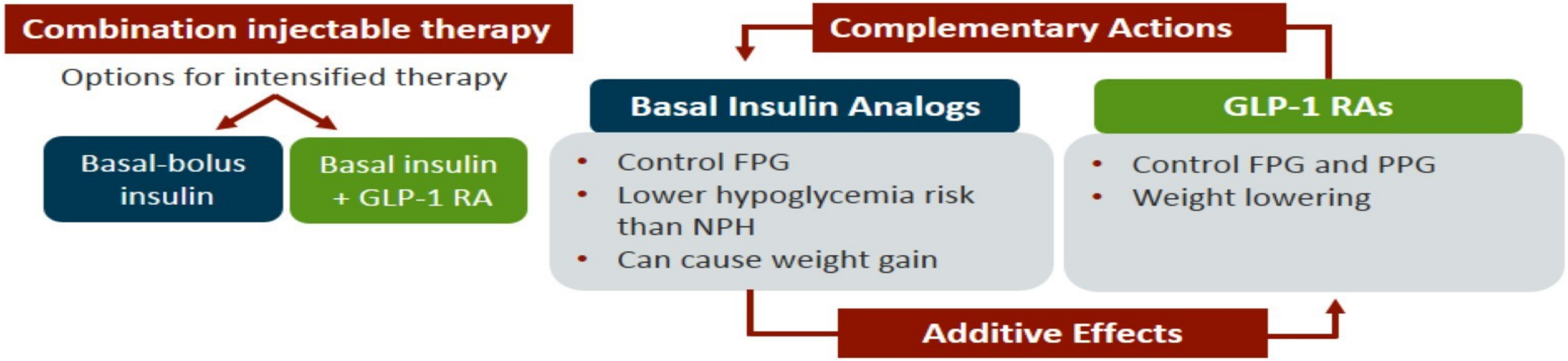
Diabetes, Obesity and Metabolism. 2016;18:317-332.

# Choice of GLP-1 RA Depends on Effect on FPG and PPG




Diabetes, Obesity and Metabolism. 2016;18:317-332.

# GLP-1 RA in Combination with Basal Insulin




Endocr Pract. 2016;22:84-113.
Diabetes Care. 2015;38:140-149.

# Upcoming GLP-1 RAs + Insulin Mixture


**Insulin degludec + liraglutide = Xultophy**

- Convenience of a single injection
- Efficacy proven from DUAL-1 trial & DUAL-2 trial results
- **Premixed form**

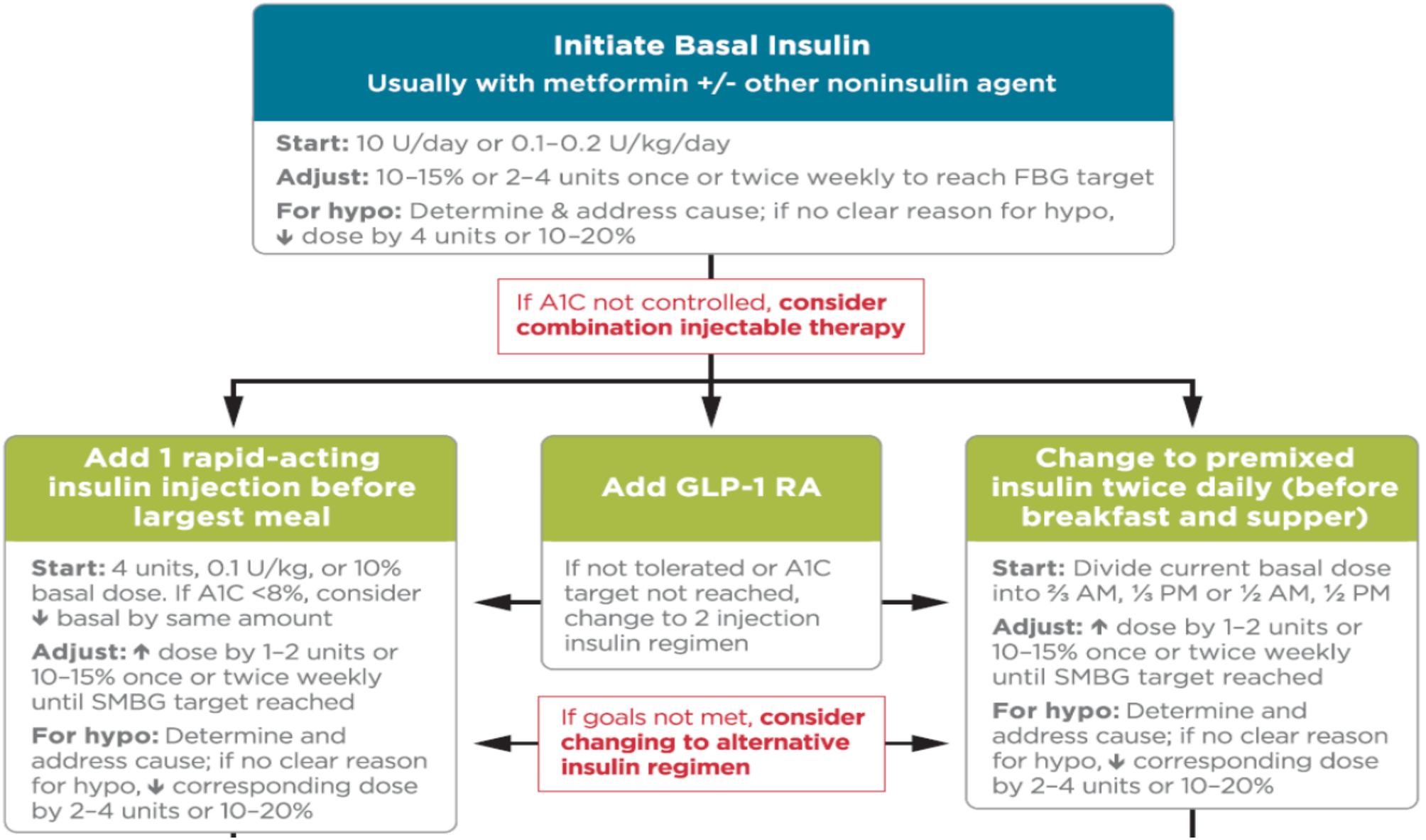
  Xultophy 1cc = 100u IDeg + 3.6 mg LIRA

  → 1 dose step = 1u IDeg + 0.036mg LIRA


**Insulin glargine + lixisenatide = Lixilan**

- Entering phases for industrialization, validation, usability and manufacturing

# 2017 ADA Guideline




Diabetes Care 2017;40:S64-S74

# 2017 AACE Glycemic Control Algorithm

## START BASAL (Long-Acting Insulin)

**A1C < 8%**

**TDD** 0.1–0.2 U/kg

**A1C > 8%**

**TDD** 0.2–0.3 U/kg

**Insulin titration every 2–3 days to reach glycemic goal:**

- Fixed regimen: Increase TDD by 2 U
- Adjustable regimen:
  - **FBG** > 180 mg/dL: add 20% of TDD
  - **FBG** 140–180 mg/dL: add 10% of TDD
  - **FBG** 110–139 mg/dL: add 1 unit
- If hypoglycemia, reduce TDD by:
  - **BG** < 70 mg/dL: 10% – 20%
  - **BG** < 40 mg/dL: 20% – 40%

**Consider discontinuing or reducing sulfonylurea after starting basal insulin (basal analogs preferred to NPH)**

***Glycemic Goal:**

- <7% for most patients with T2D; fasting and premeal BG < 110 mg/dL; absence of hypoglycemia
- A1C and FBG targets may be adjusted based on patient's age, duration of diabetes, presence of comorbidities, diabetic complications, and hypoglycemia risk

**Glycemic Control Not at Goal***

## INTENSIFY (Prandial Control)

**Add GLP-1 RA**

**Or SGLT-2i**
**Or DPP-4i**

**Add Prandial Insulin**

**Basal Plus 1, Plus 2, Plus 3**

- Begin prandial insulin before largest meal
- If not at goal, progress to injections before 2 or 3 meals
- Start: 10% of basal dose or 5 units

**Basal Bolus**

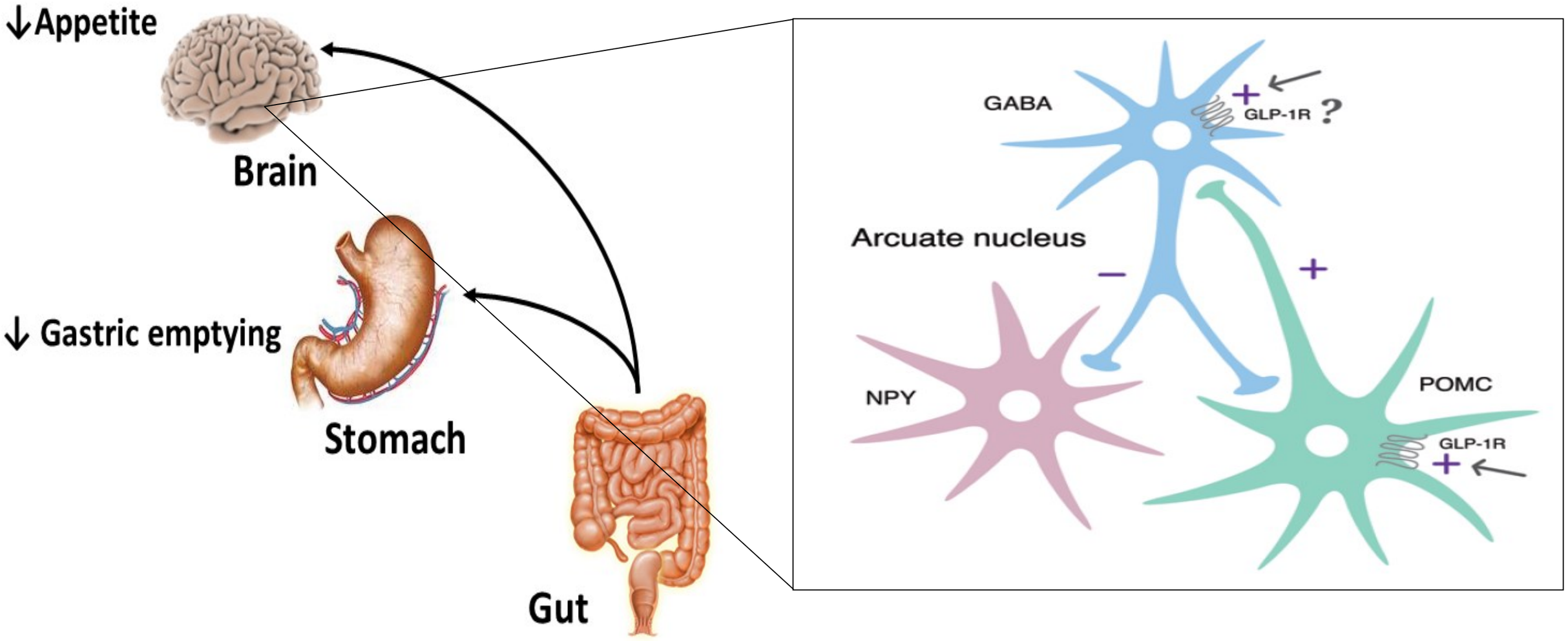
- Begin prandial insulin before each meal
- 50% Basal / 50% Prandial TDD 0.3–0.5 U/kg
- Start: 50% of TDD in three doses before meals

**Insulin titration every 2–3 days to reach glycemic goal:**

- Increase prandial dose by 10% or 1-2 units if 2-h postprandial or next premeal glucose consistently > 140 mg/dL
- If hypoglycemia, reduce TDD basal and/or prandial insulin by:
  - BG consistently < 70 mg/dL: 10% - 20%
  - Severe hypoglycemia (requiring assistance from another person) or BG < 40 mg/dL: 20% - 40%

 DOI 10.4158/EP161682.CS

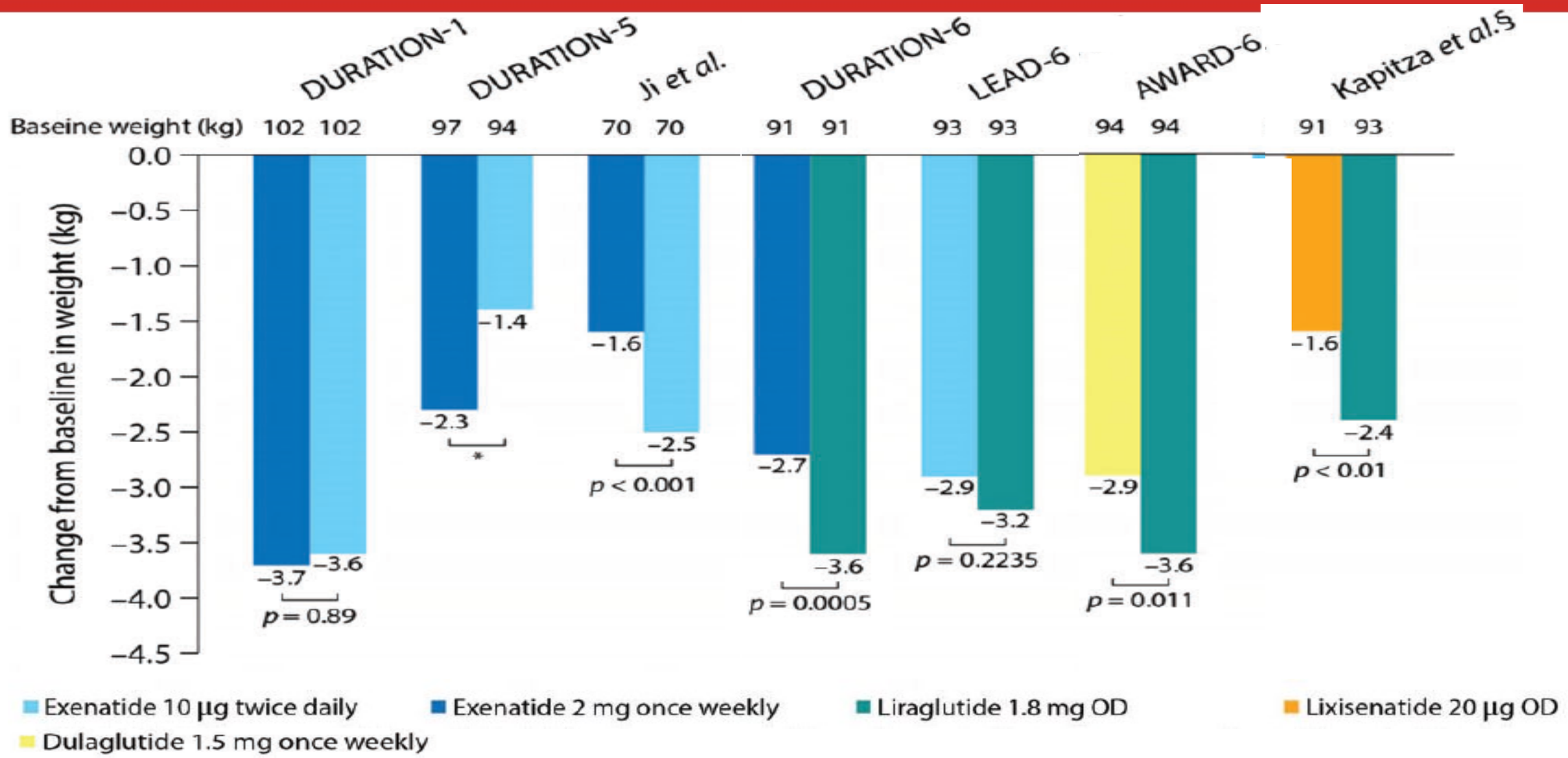
# GLP-1: Its Role in Weight Loss




J Endocrinol. 1997;155:197-200.
Diabetologia. 1992;35:701-711.

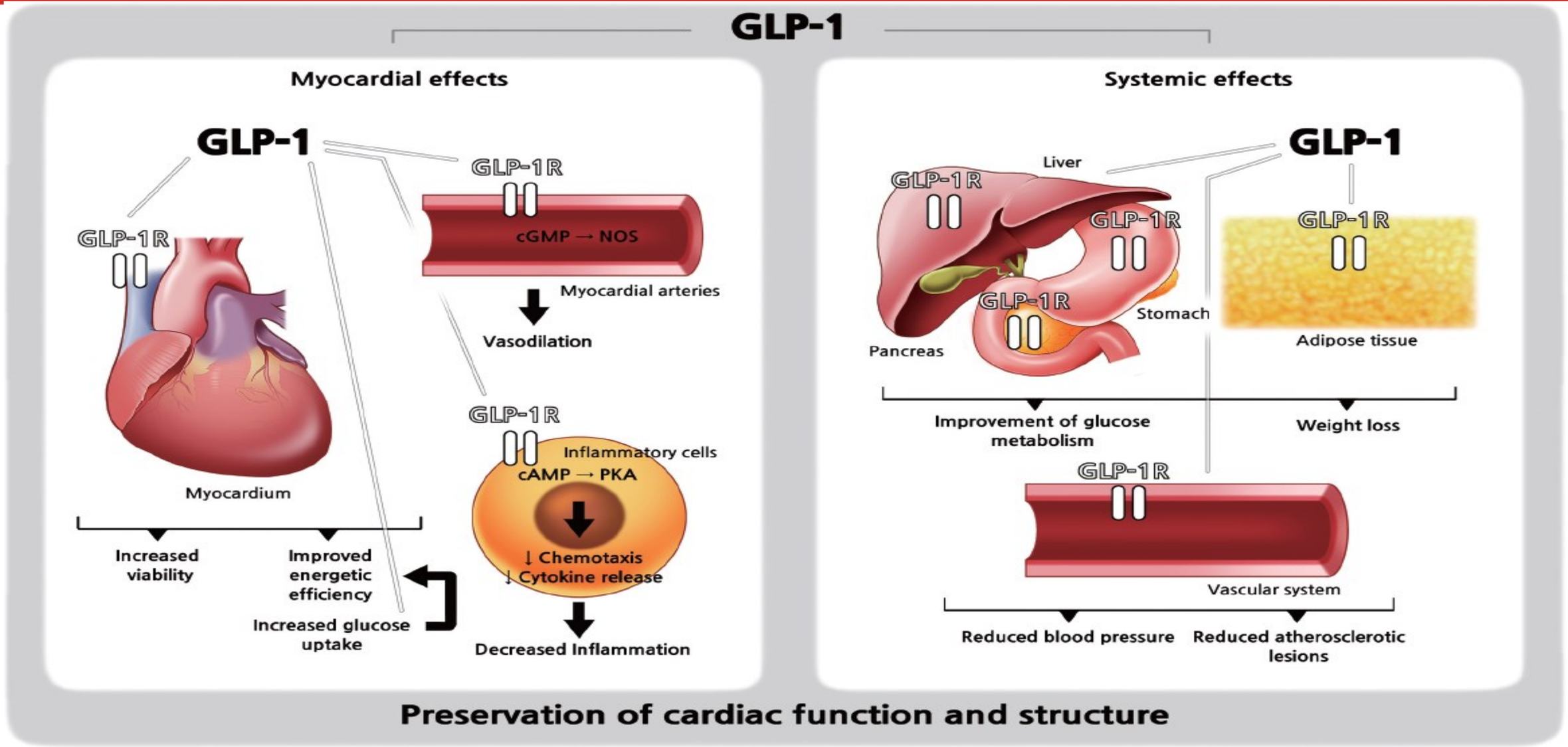
JCI. 2014;124:4473-4488

# Effect on Weight



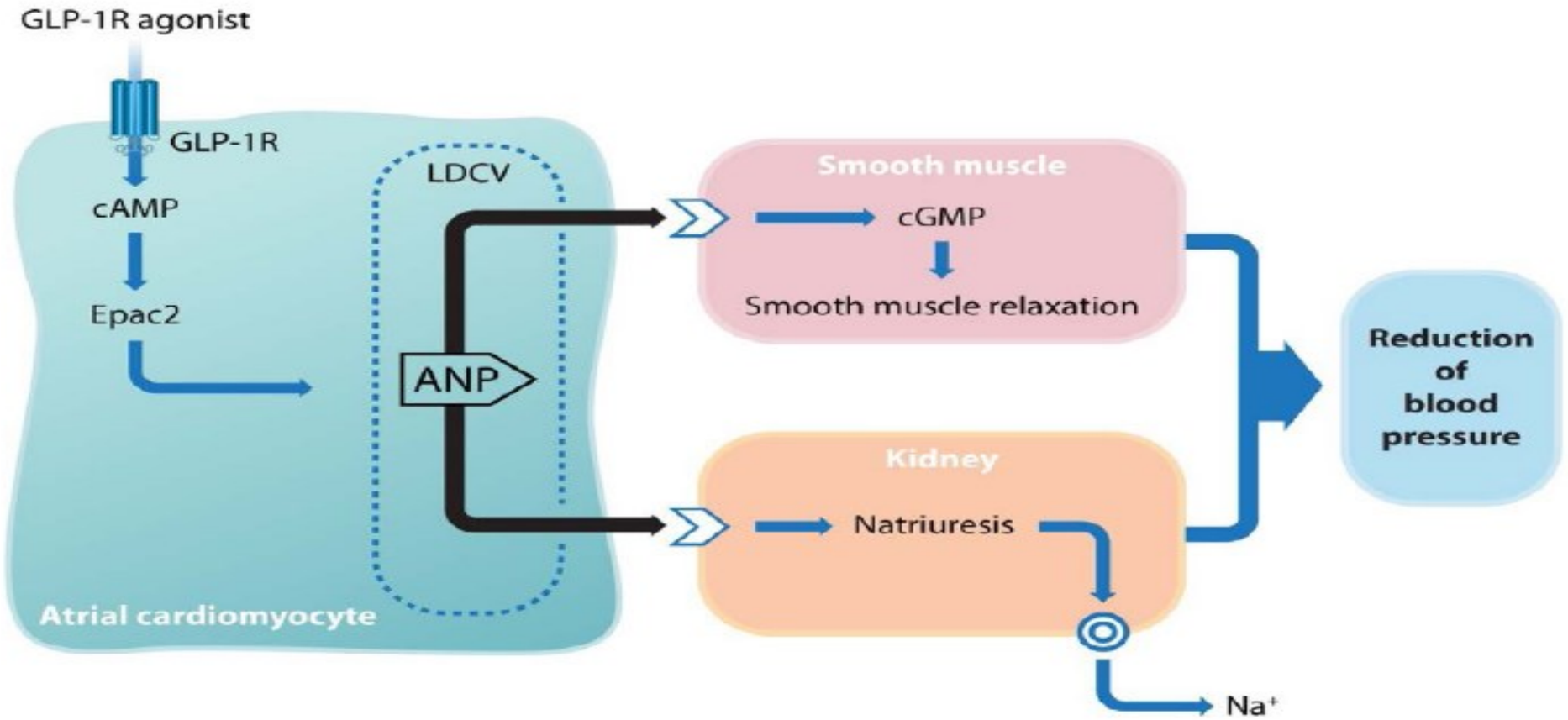

Diabetes, Obesity and Metabolism. 2016;18:317-332.

# Cardiovascular Effects of GLP-1 RA




Kang YM & Jung CH. Endocrinol Metab (Seoul). 2016;31:258-274.

# Cardiovascular Effects of GLP-1 RA: BP Lowering Efffect




Nat Med. 2013;19(5):567-575.

# GLP-1 RA's Effect on SBP

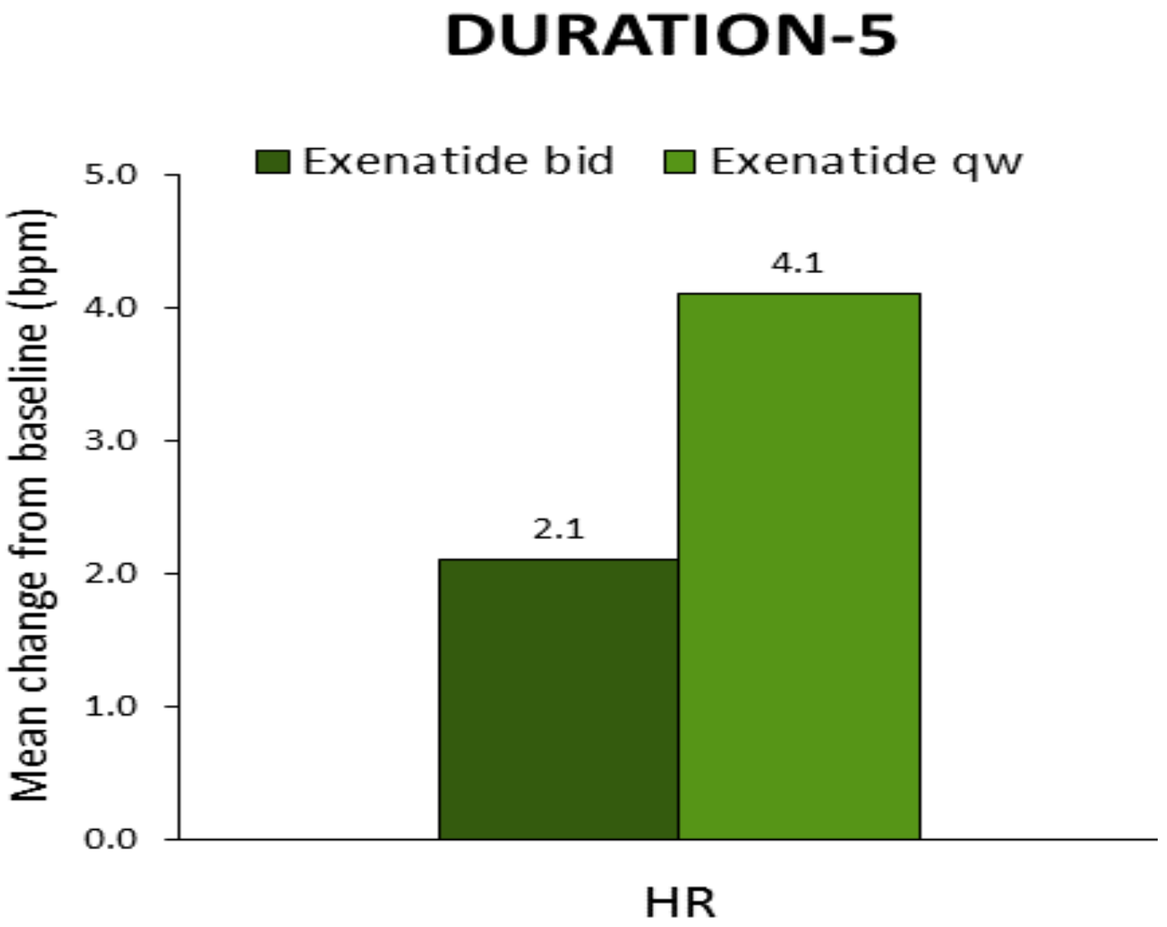
| Study Name | GLP-1 RA | SBP (mmHg) | GLP-1 RA | SBP (mmHg) |
|---|---|---|---|---|
| DURATION-1 | Exenatide BID | -3.4 | Exenatide QW | -4.7 |
| LEAD-6 | Exenatide BID | -2.0 | Liraglutide QD | -2.5 |
| GetGoal-X | Lixisenatide QD | -2.5 | Exenatide BID | -2.9 |
| AWARD-6 | Dulaglutide QW | -3.4 | Liraglutide QD | -2.8 |

Short-Acting

Long-Acting

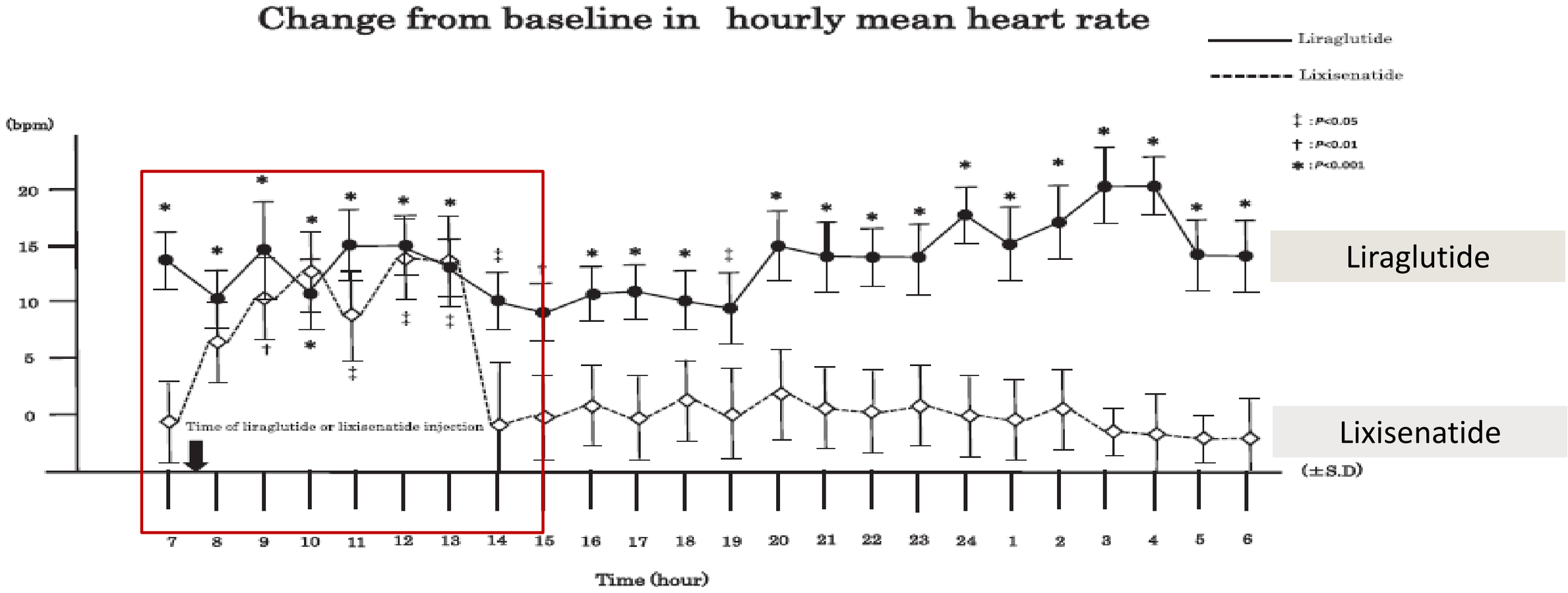
Lancet. 2008;372:1240-1250. Lancet. 2019;374:39-47.
Diabetes Care. 2013;36:2945-2951. Lancet. 2014;384:1349-1357.

# GLP-1 RA's Effect on HR



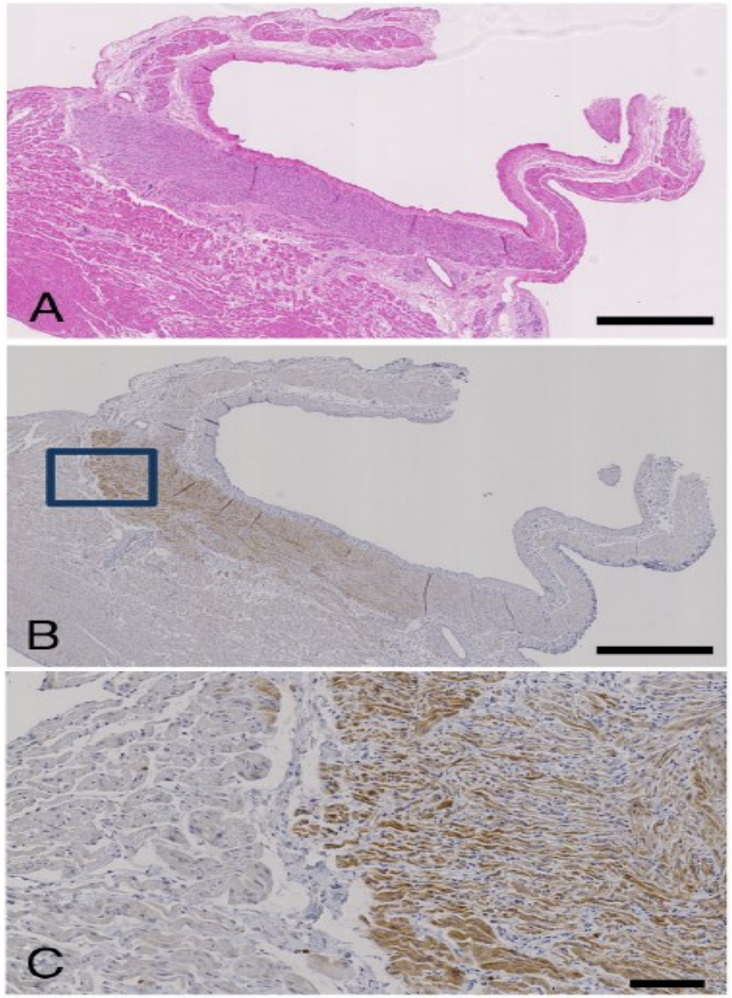

J Clin Endocrinol Metab. 2011;96:1301-1310.

# GLP-1 RA's Effect on HR

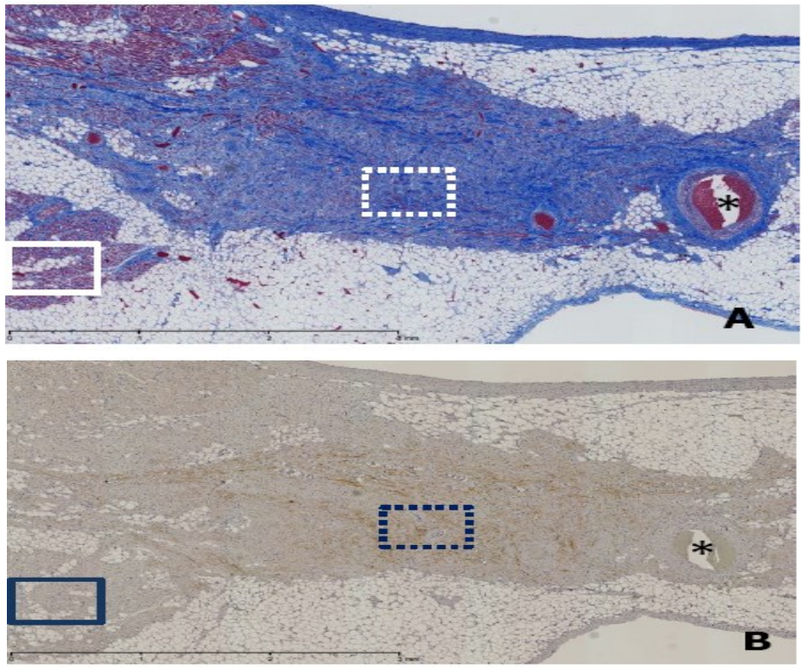



Diabetes Care. 2016;39;e22-e23.

# GLP-1 Receptor in Heart



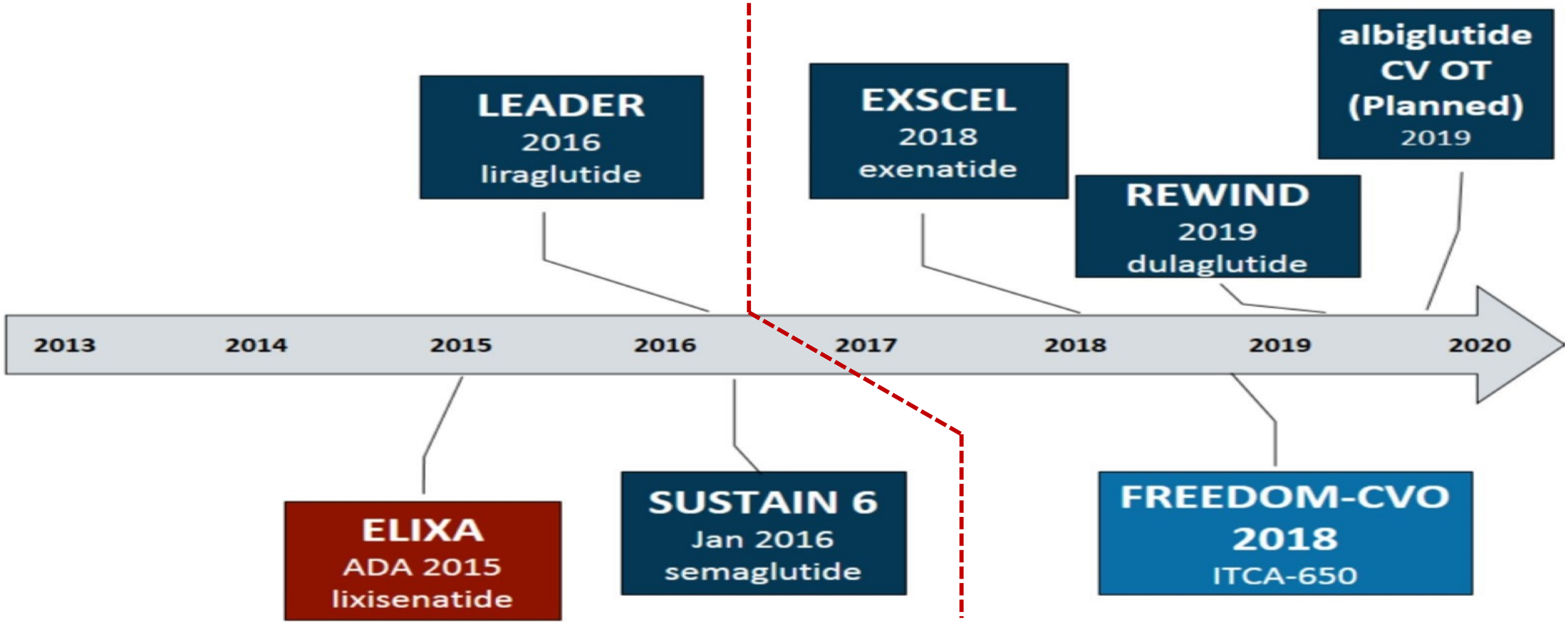

Monkey SA Node




Human SA Node

Endocrinology. 2014;155:1280-90

# GLP-1 RA CV Outcome Trials



# GLP-1 RA CV Outcome Trials

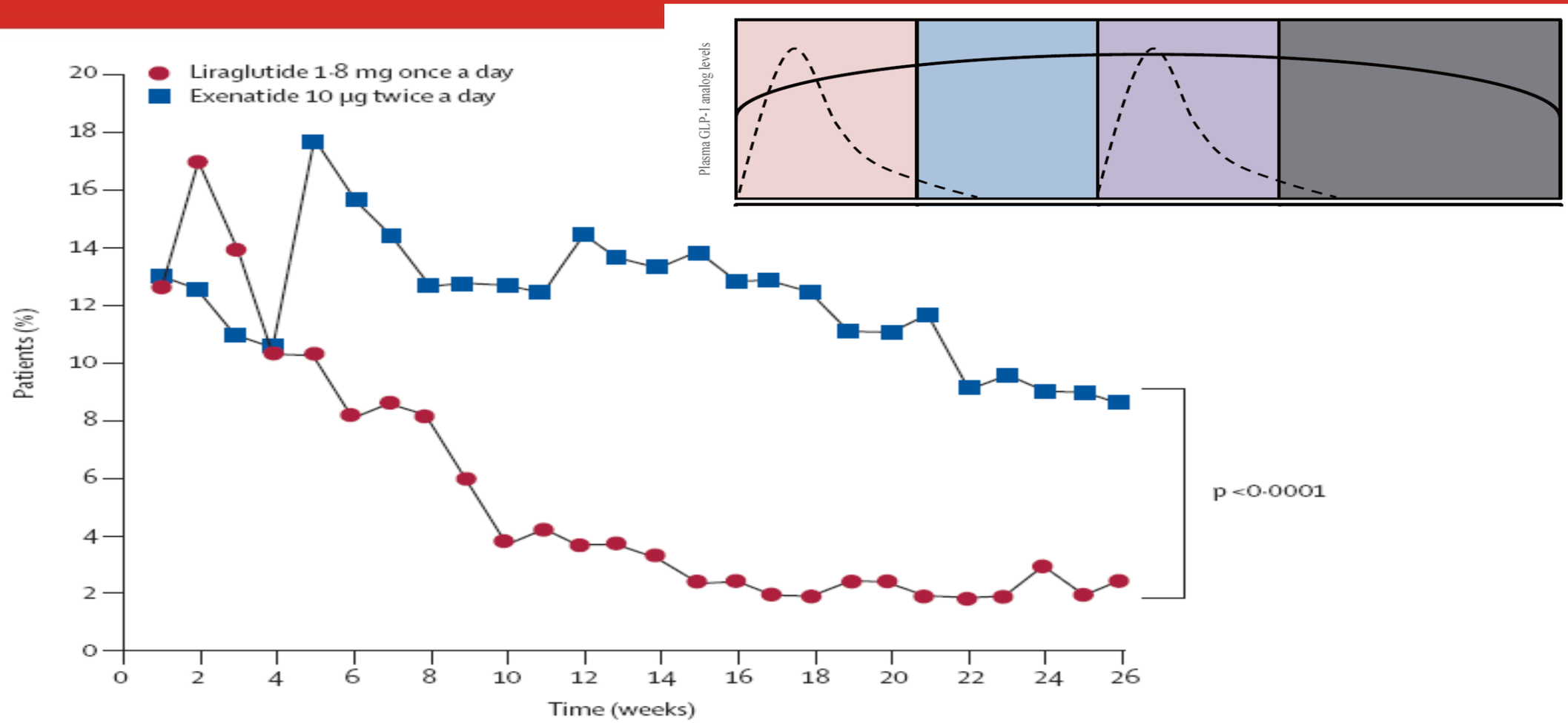
| Study Name | GLP-1 RA | CV Outcome | n | Age | yr | △A1c |
|---|---|---|---|---|---|---|
| ELIXA | Lixisenatide QD | No Benefit | 6,068 | 60.0 | 2.0 | 0.27 |
| LEADER | Liraglutide QD | Benefit | 9,340 | 64.2 | 3.8 | 0.4 |
| SUSTAIN-6 | Semaglutide QW | Benefit | 3,297 | 64.6 | 2.1 | 0.7-1.0 |

Short-Acting

Long-Acting

N Engl J Med. 2015;373:2247-2257.
N Engl J Med. 2016;375:311-322.
N Engl J Med. 2016;375:1834-1844

# GI Adverse Events (LEAD-6)




In general, the **long-acting GLP-1 RAs** seem to exhibit improved GI tolerability, and the incidence of nausea declines over time.

Lancet. 2009;374:39-47.

# Injection Site Reactions

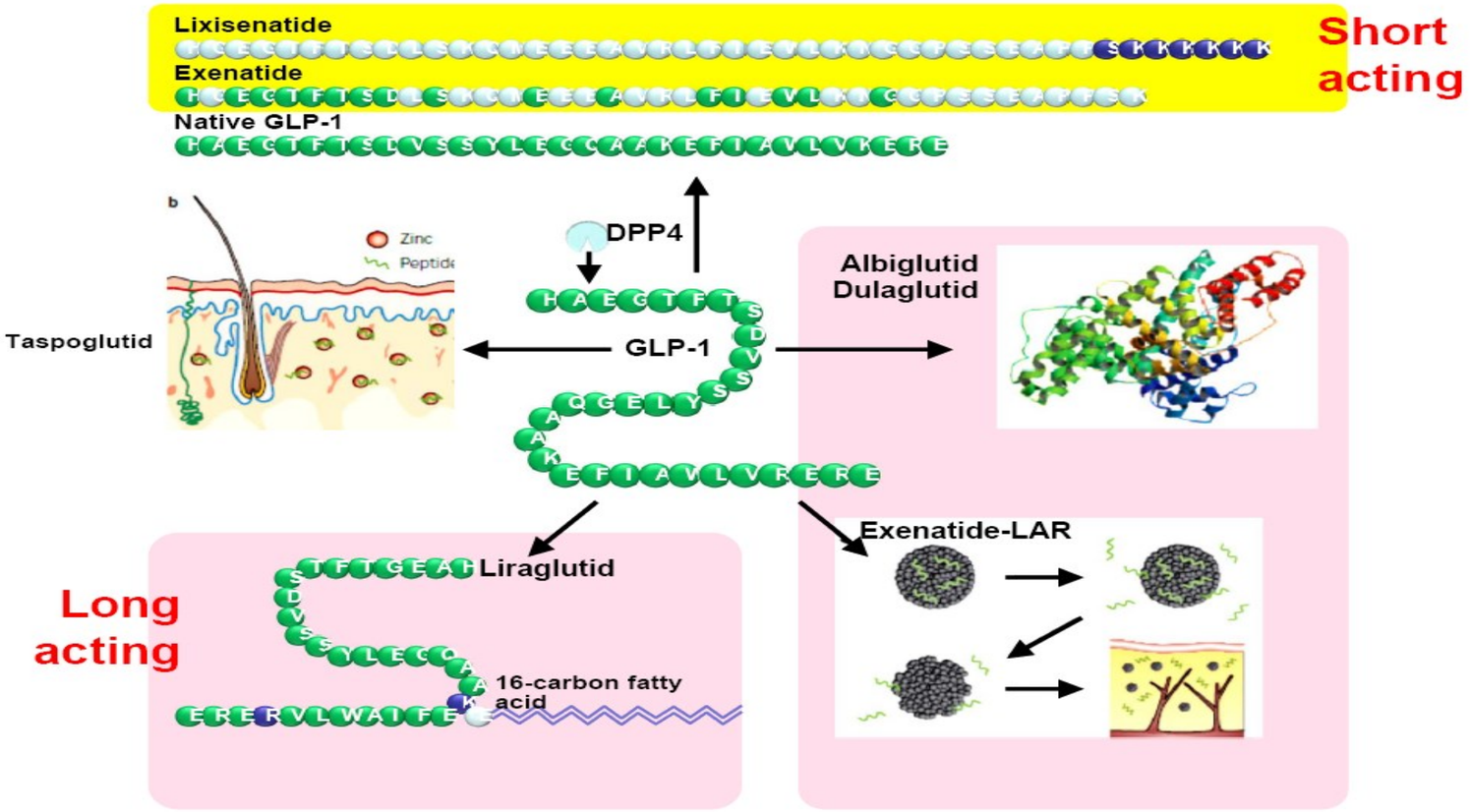
| Adverse reactions | Albiglutide [30] | | Dulaglutide [35] | | | Liraglutide [22] | Exenatide QW [26] | Exenatide BID [17] | |
|---|---|---|---|---|---|---|---|---|---|
| N | Albiglutide N=923, % | Placebo N=468, % | Dulaglutide 0.75 mg N=834, % | Dulaglutide 1.5 mg N=836, % | Placebo N=568, % | Liraglutide N=497, % | Exenatide N=248, % | Exenatide N=963, % | Placebo N=483, % |
| Diarrhea | 13.1 | 10.5 | 8.9 | 12.6 | 6.7 | 17.1 | 10.9 | 13 | 6 |
| Nausea | 11.1 | 9.6 | 12.4 | 21.1 | 5.3 | 28.4 | 11.3 | 44 | 18 |
| Vomiting | 4.2 | 2.6 | 6.0 | 12.7 | 2.3 | 10.9 | NA | 13 | 4 |
| Injection-site reaction or nodules | 10.5 | 2.1 | 0.5 | 0.5 | 0 | NA | 10.5 | NA | NA |

In general, the once-weekly GLP-1 RAs appear to be associated with higher incidence of injection-site reaction than BID or QD.

The exception appears to be dulaglutide once weekly.

Drugs in Context. 2015;4:212283.

# Immunogenicity




- **Antibody formation** was much more common with exenatide or exenatide LAR than with liraglutide, presumably because of **their lesser degree of homology with native human GLP-1.**

- **The immunogenicity** reported in the trials would appear to have **little impact on the efficacy and safety of these GLP-1 RAs.**

Diabetes, Obesity and Metabolism. 2016;18:317-332.

# Summary

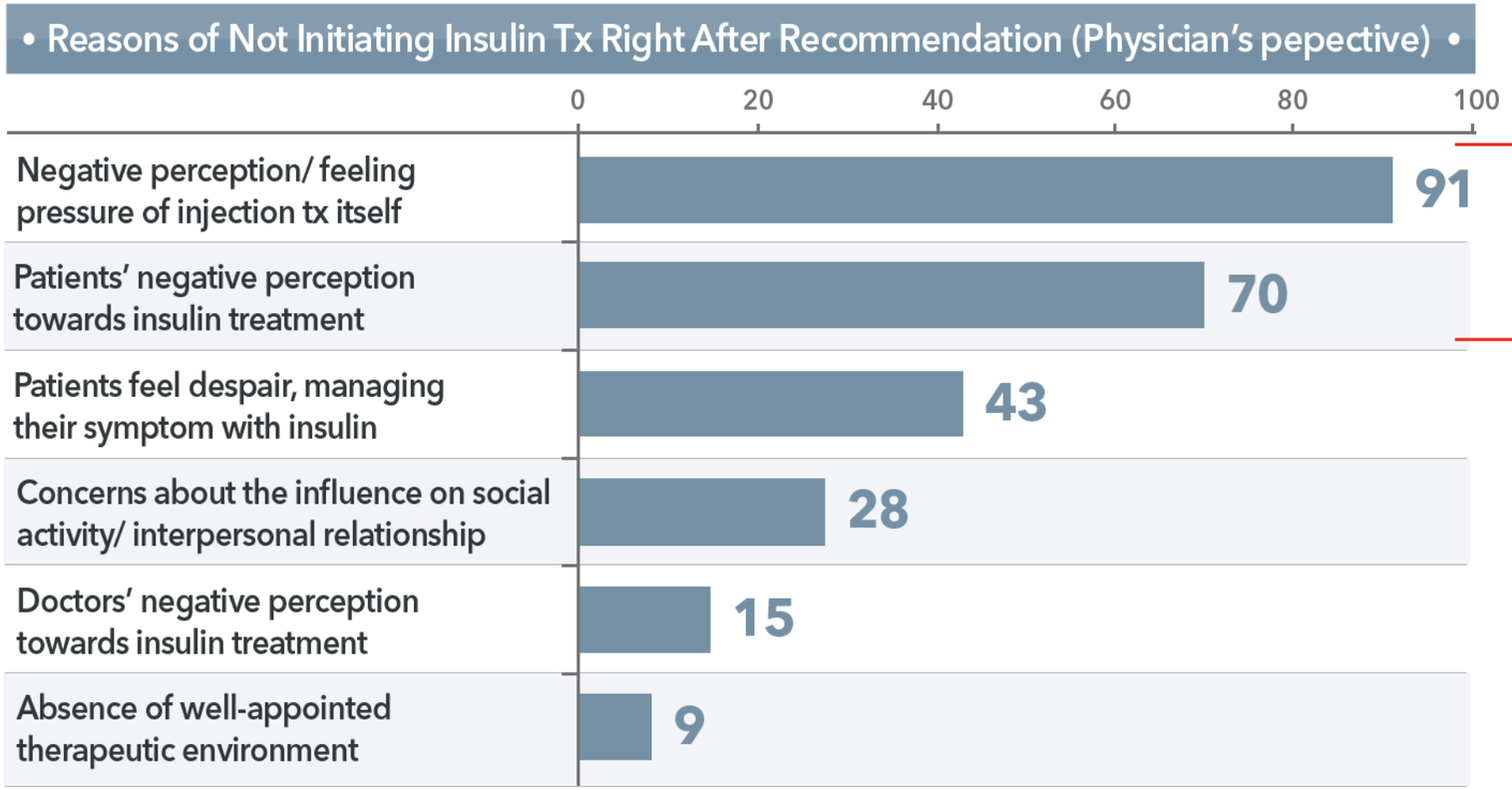
| Parameters | Short-Acting GLP-1 RAs | Long-Acting GLP-1 RAs |
|---|---|---|
| **Compounds** | Exenatide, Lixisenatide | Liraglutide, Albiglutide, Dulaglutide, Exenatide-LAR |
| **Effects** | | |
| **FPG levels** | ↓↓ | ↓↓↓ |
| **PPG levels** | ↓↓↓ | ↓↓ |
| **Fasting Insulin** | ↑↑ | ↑↑↑ |
| **Postprandial Insulin** | ↓ | ↑↑ |
| **Gastric Emptying Rate** | ↓ | **No effect** (tachyphylaxis) |
| **Glucagon** | ↓ | ↓ |
| **BP** | ↓ | ↓ |
| **HR** | ↑ | ↑↑ |
| **Body Weight Reduction** | 1-5 Kg | 2-5 Kg |
| **Nausea** | 20-50%, attenuates slowly | 20-40%, attenuates quickly |
| **CV Benefit** | Neutral? | Benefit |

# Today's topics

- Overview of GLP-1RA physiology
- GLP-1RAs' similarities and differences
- **Dulaglutide molecule design & True Simplicity Pen device**
- Highlights of AWARD trials
- Real world cases

# Reasons of not initiating insulin from Dr.’s perspective

**The results came from a market research data which was conducted by a doctor.**



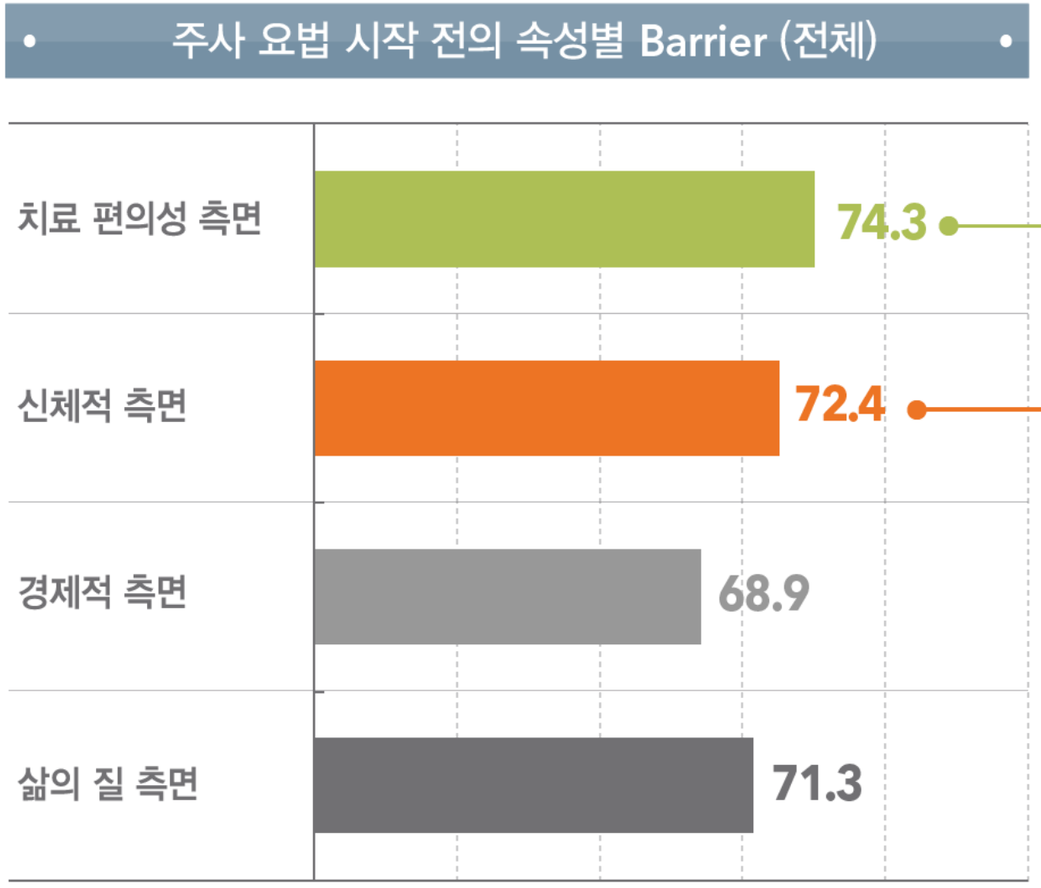

[Base: Physicians who have patients do not start insulin Tx after receiving insulin Tx recommendation, N=79, Unit: % of physician]

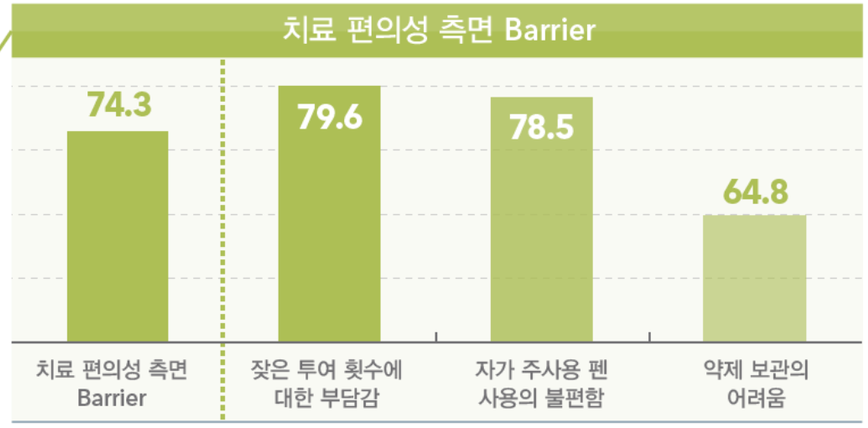
***Many doctors think*** *that the main reason why patient could not initiate insulin treatment is* ***psychological reason regarding negative perception on insulin and negative feeling of injection treatment.***

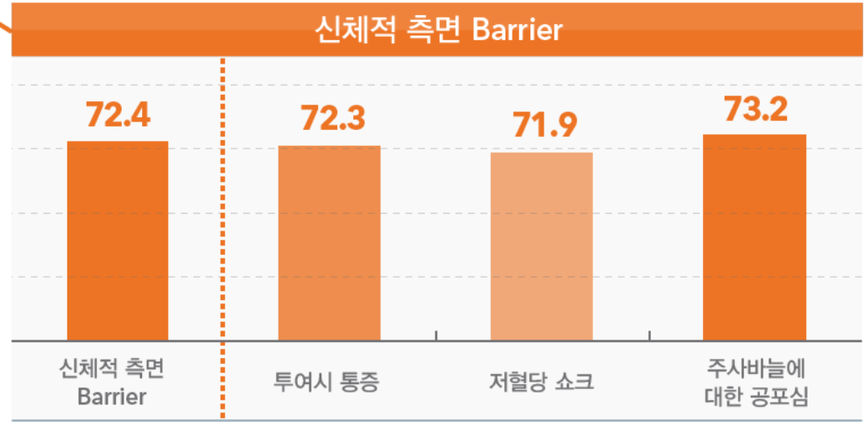
Physician Market research 2015

# Reasons of not initiating insulin from Patient's perspective

***According to the patient survey report, many patients respond the biggest reasons why they could not initiate insulin or injection treatment are inconvenience and physical barriers.***



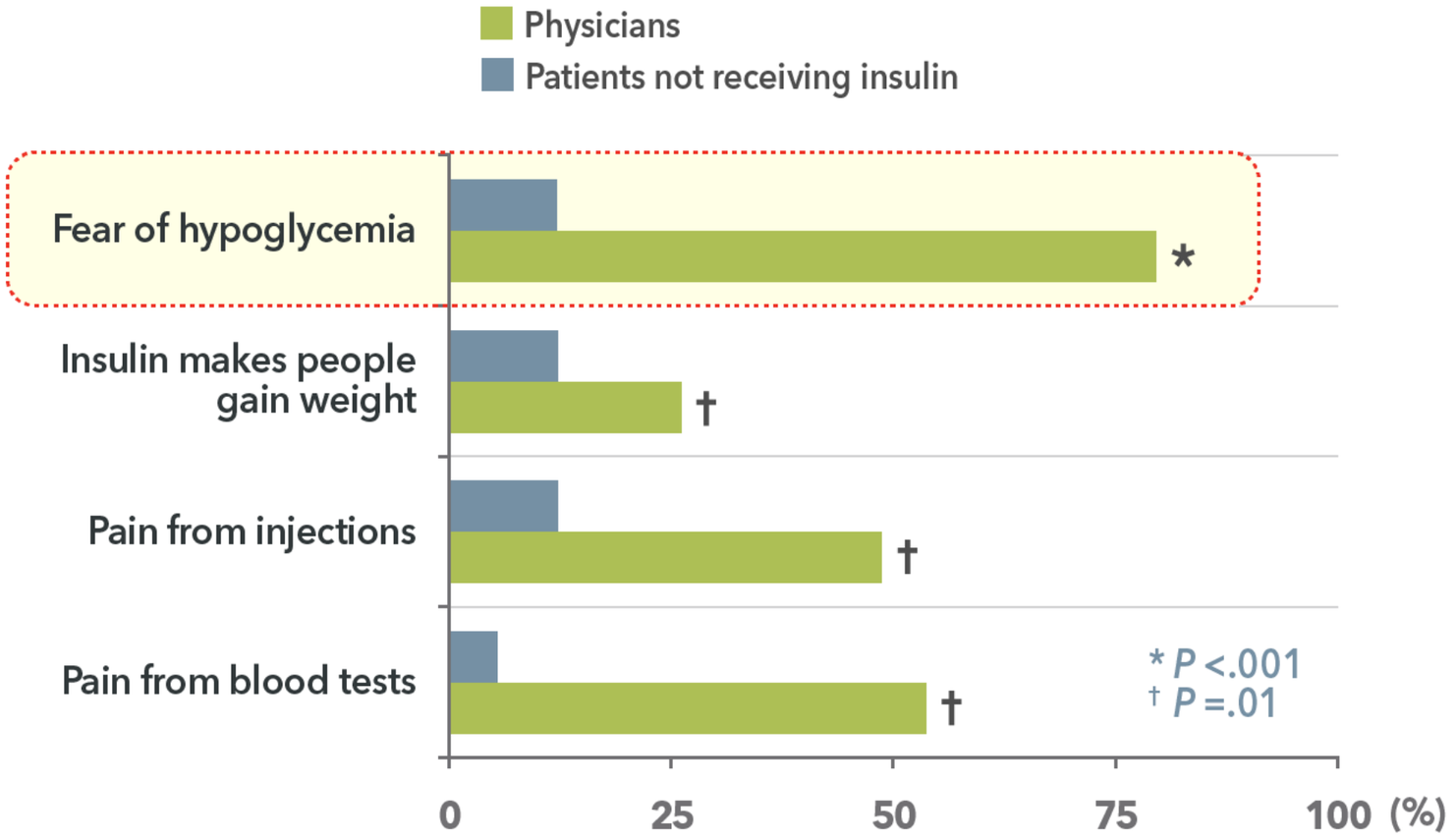




Patient survey report 2015

(n=300, 100점 만점 환산, 점)

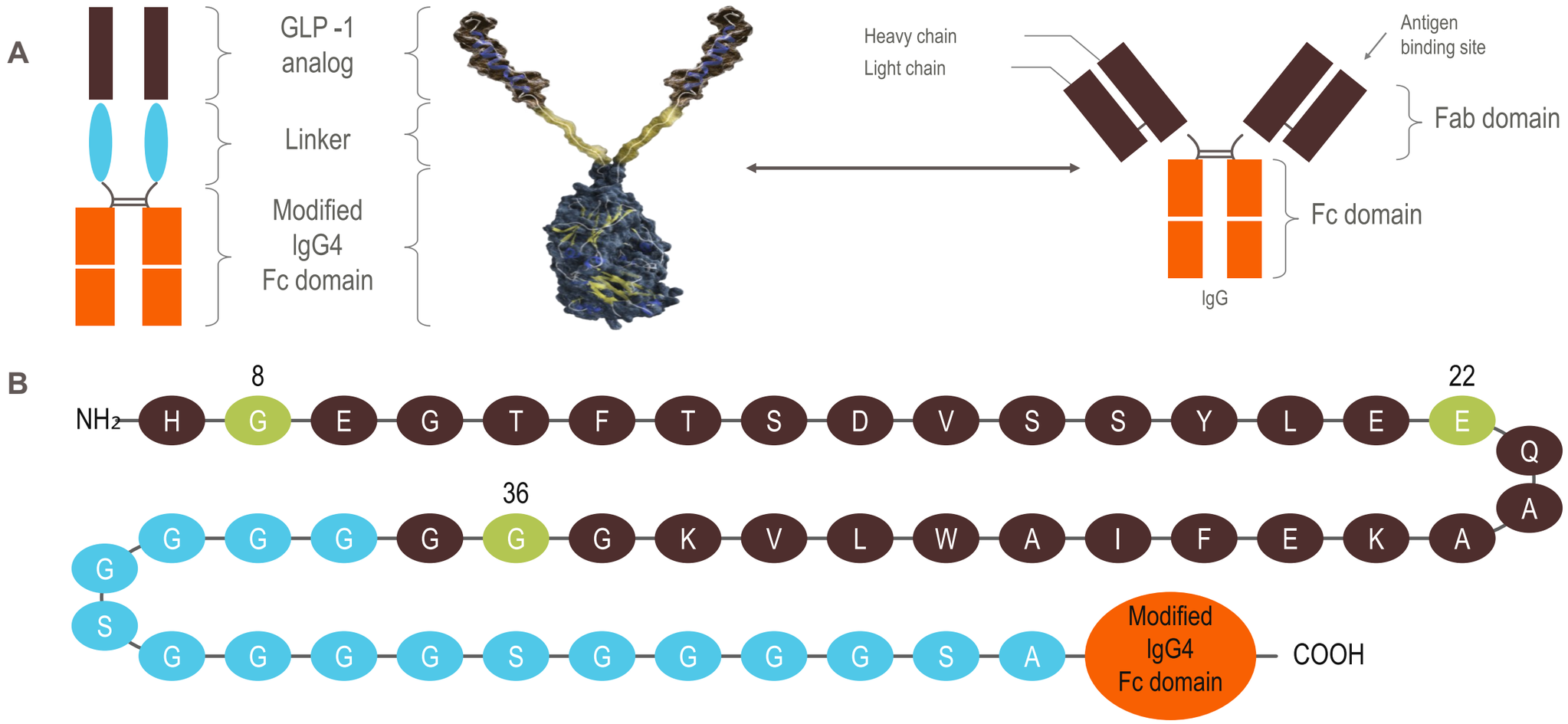
# Barriers to Insulin May Be More Prevalent Among Physicians Than Patients




- Case-control study found that physicians' misconceptions of patient's fears contributed to existing barriers
- Important for physicians to discuss insulin with patients early in the course of T2DM
- Reassure patients that starting insulin does not mean they have failed

Nakar S, et al. J Diabetes Complications. 2007;21:220-226.
PetznickAM.74m Osteopath Assoc. 2013;113 (Suppl 2):S6-S16.
Polonsky WH, et al. Diab Care. 2005;28:2543-2545.

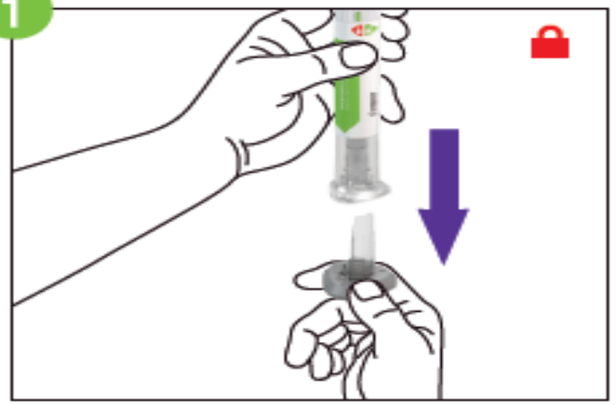
# Dulaglutide molecule design




Color code in B is representative of region color in A
GLP-1=glucagon-like peptide-1; IgG=immunoglobulin gamma; Fab=fragment antigen binding; Fc=fragment crystalizable

**Reference** 1. Glaesner et al. Diabetes Metab Res Rev 2010;26:287-296, 2. Kuritzky et al. Postgraduate Medicine 2014 Oct; 126(6)60-72

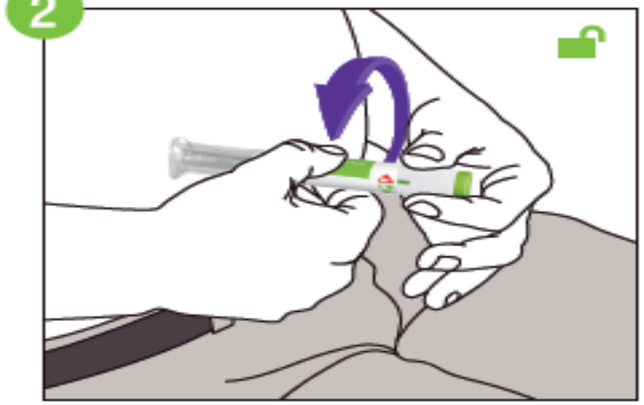
# Instructions for Use[1]




뚜껑 열기

**뚜껑 열기**

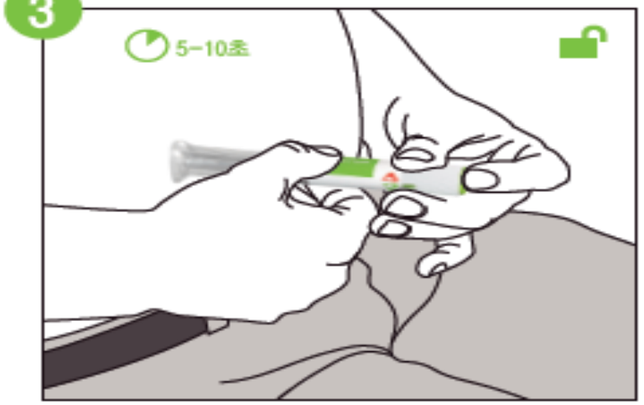
- 사용 전 펜이 잠겨 있는 지 확인한 후, 하단부의 회색 뚜껑을 당겨 제거합니다.
- 실제 펜을 사용할 때에는, 바늘에 손상우려가 있으니 하단 회색 뚜껑을 다시 닫지 않도록 환자에게 알려주십시오.
- 바늘을 만지지 마십시오.




주사 위치잡기와 잠금해제

**주사 위치잡기와 잠금해제**

- 주사를 투여할 위치에 펜의 하단부 끝을 대고 피부와 틈이 생기지 않도록 단단히 고정합니다.
- 펜의 잠금 링을 그림과 같이 돌리면서 잠금을 해제합니다.




주사 투여

**주사 투여**

- 펜 상단부의 녹색 버튼을 딸깍 소리가 날 때까지 누르고, 5초~10초 동안 버튼을 누른 채로 잡고 유지합니다.
- 두 번째 딸깍 소리가 날 때까지 계속 펜을 잡고 있다가, 회색 부분이 보이면 주사 투여가 완료된 것입니다.

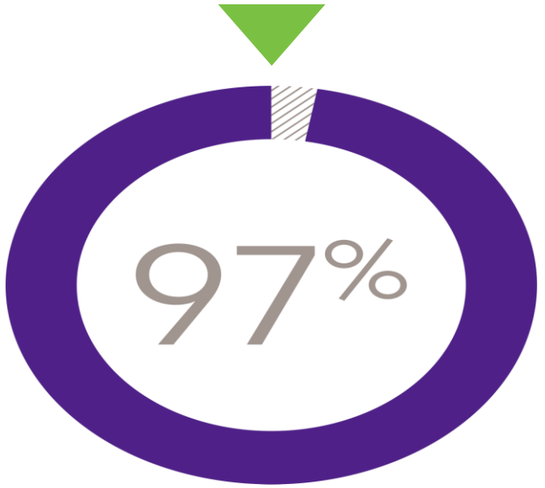
1. 트루리시티 사용 지침 (2015.9.23).

# Trulicity pen usability outcomes

In a usability study of injection-naïve patients, most patients were able to use the pen successfully and agreed or strongly agreed that Trulicity's ready-to-use pen was overall easy to use.


Final injection success rate


Rated easy to use




Willing to continue use

Matfin G, et al. J Diabetes Sci Technol. 2015;9(5):1071-9.

# Administration of GLP-1RAs

| | | | |
|---|---|---|---|
| **Daily GLP-1** |  <br>**Exenatide BID**<br>pre-filled pens<br>(5 and 10 µg)<br>Needle needs attaching prior to use |  <br>**Lixisenatide**<br>2 pre-filled pens<br>(10 and 20 µg)<br>Needle needs attaching prior to use |  <br>**Liraglutide**<br>1 pre-filled pens<br>(0.6, 1.2 and 1.8 mg)<br>Needle needs attaching prior to use |
| **Weekly GLP-1** |  <br>**Exenatide QW**<br>1 pre-filled pens (2 mg)<br>Needs reconstruction<br>Needle needs attaching prior to use |  <br>**Albiglutide**<br>2 pre-filled pens<br>(30 and 50 mg)<br>Needs reconstruction<br>Needle needs attaching prior to use |  <br>**Dulaglutide**<br>2 pre-filled pens<br>(0.75 and 1.5 mg)<br>No reconstruction<br>No needle attaching prior to use |

- Exenatide QW and Albiglutide QW both require reconstitution, a process that takes time for the provider and patient
- No mixing required with Dulaglutide QW; dose is administered via an “auto-injector” that hides needles from sight

Presenter’s own slide

# Number of injection times

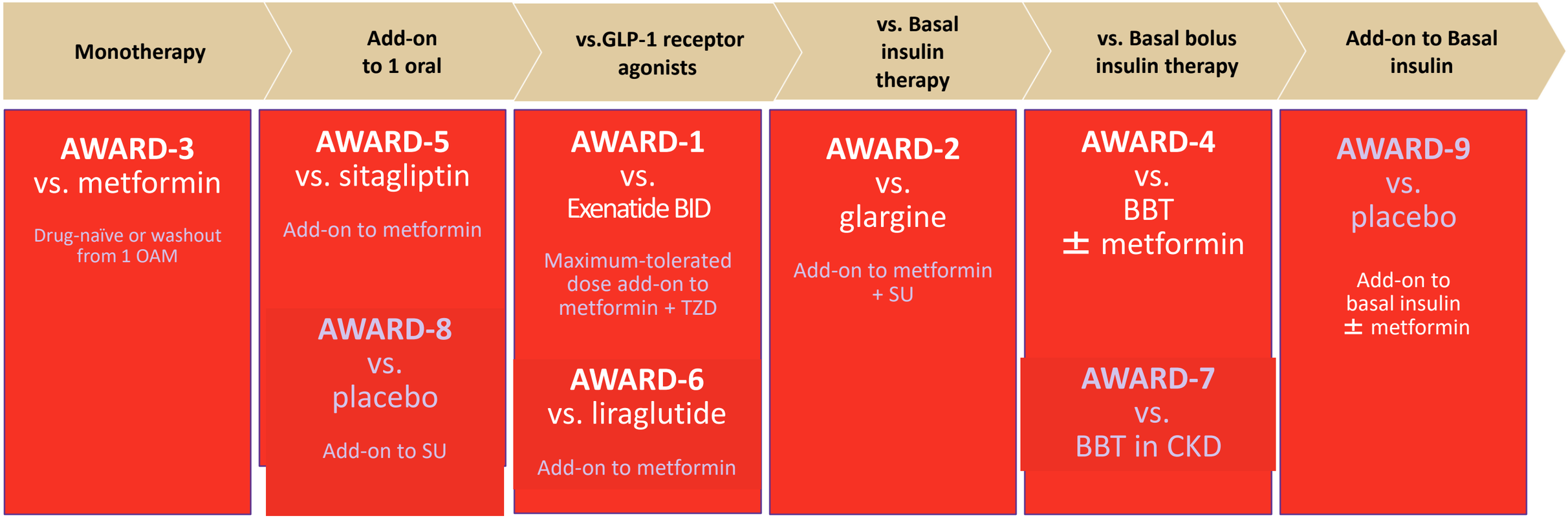
| Category | Week | Month | Year |
|---|---|---|---|
| **Basal insulin**<br>- Basal insulin<br>- Novel basal insulin<br>**Daily GLP-1RA**<br>- Lixisenatide<br>- Liraglutide | 7 | 30 | 365 |
| **Daily GLP-1RA**<br>- Exenitide BID | 14 | 60 | 730 |
| **Weekly GLP-1RA**<br>**- Dulaglutide** | **1** | **4-5** | **52** |

Liu SC, et al. Diabetes Obes Metab. 2012; 14:810-820.

# Today's topics

- Overview of GLP-1RA physiology
- GLP-1RAs' similarities and differences
- Dulaglutide molecule design & True Simplicity Pen device
- **Highlights of AWARD trials**
- Real world cases

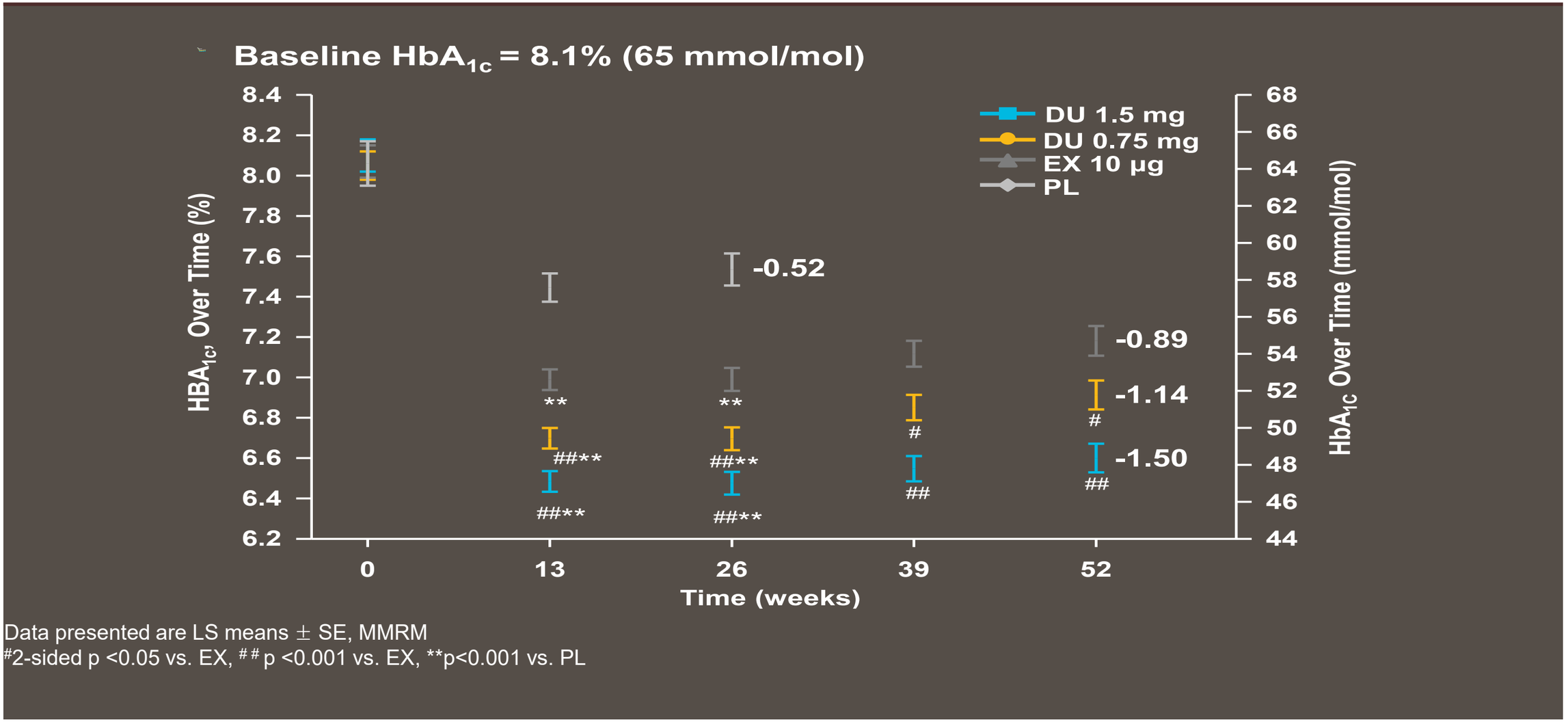
# Dulaglutide:
# Studies Across the T2D Treatment Continuum




- The 6 pivotal studies (AWARD-1 to -6) are completed
- 4 additional studies: AWARD-7, AWARD-8, AWARD-9 and REWIND are ongoing

  → REWIND is a long-term cardiovascular outcomes study, currently enrolling patients

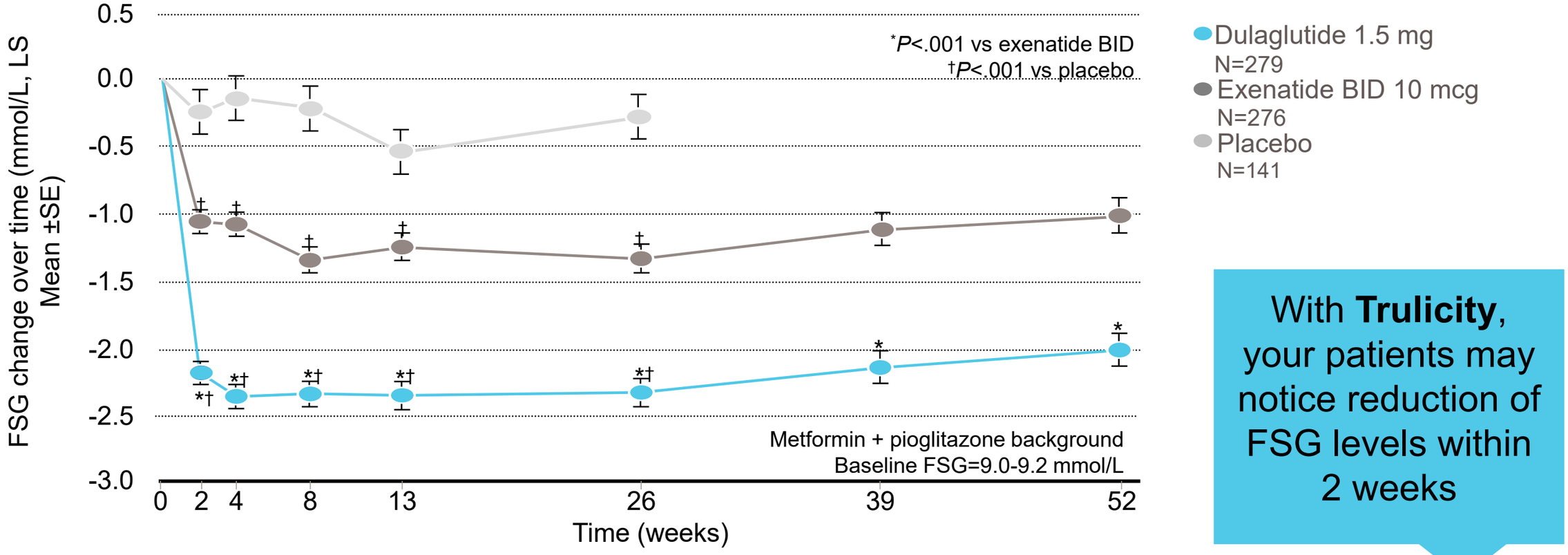
# Change in $HbA_{1c}$ over Time (AWARD-1)




Data presented are LS means ± SE, MMRM
#2-sided p <0.05 vs. EX, ## p <0.001 vs. EX, **p<0.001 vs. PL

Wysham C, et al. Diabetes Care. 2014;37(8):2159-2167.

# Change in Fasting Glucose over Time (AWARD-1)



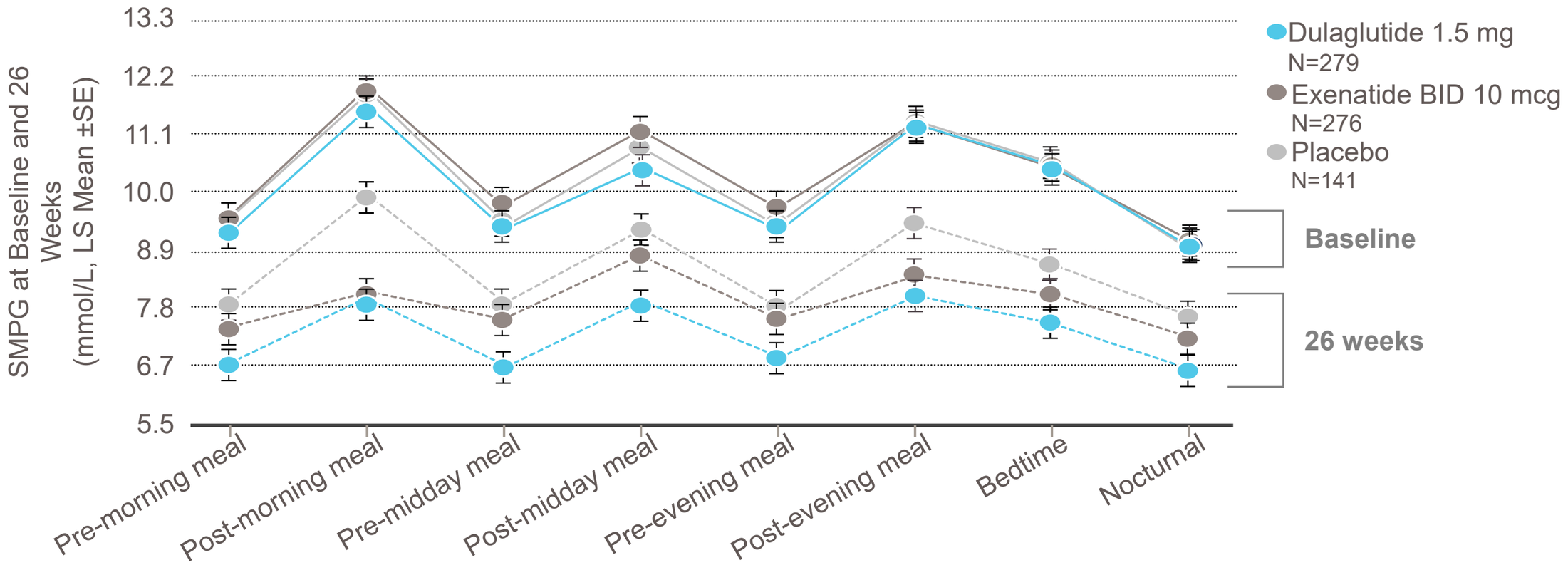

With **Trulicity**, your patients may notice reduction of FSG levels within 2 weeks

The recommended initiating dose of TRULICITY is 0.75mg once weekly. The dose may be increased to 1.5mg once weekly for additional glycemic control.

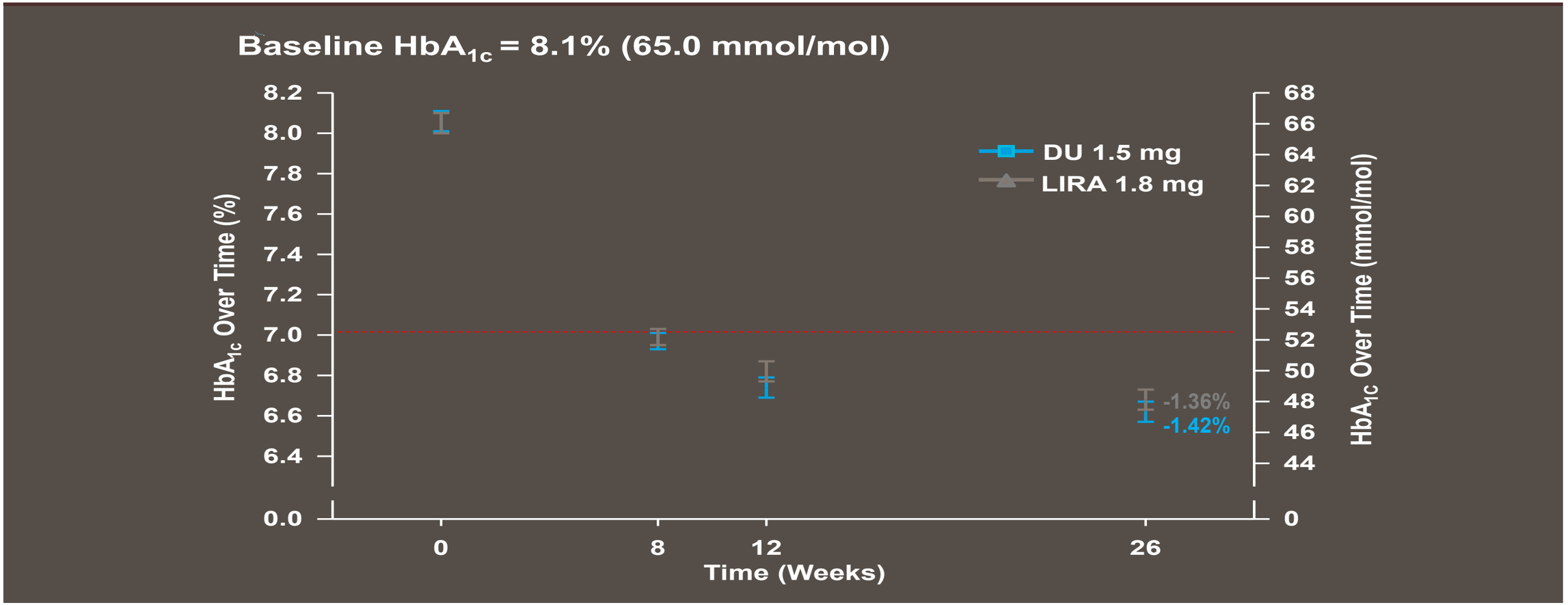
FSG = fasting serum glucose

Wysham C, et al. *Diabetes Care*. 2014;37(8):2159-2167.

# Blood Glucose Profiles Dulaglutide vs. Exenatide (AWARD 1)



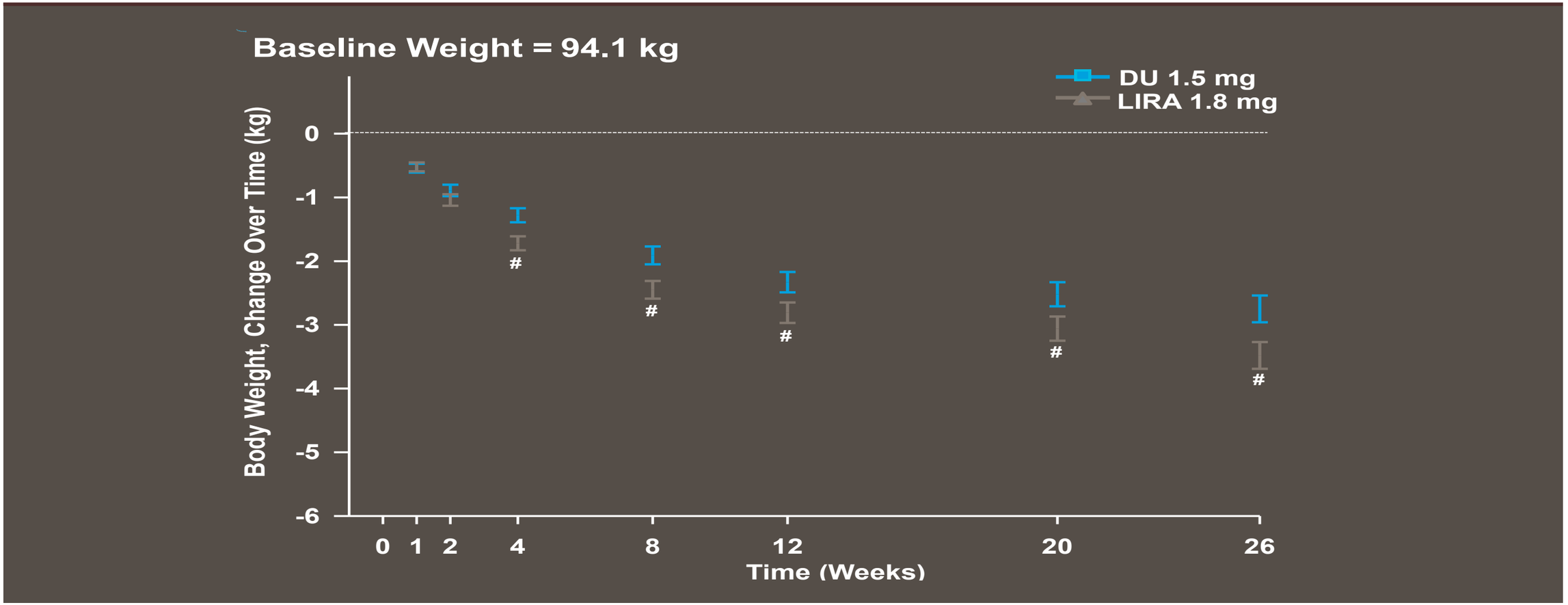
# $HbA_{1c}$ from Baseline to Week 26 (AWARD-6)




Data presented are LS means 1± SE, MMRM

Dungan, et al. *Lancet*. 2014. 384(9951):1349-1357.

# Change in Body Weight Over Time (AWARD-6)

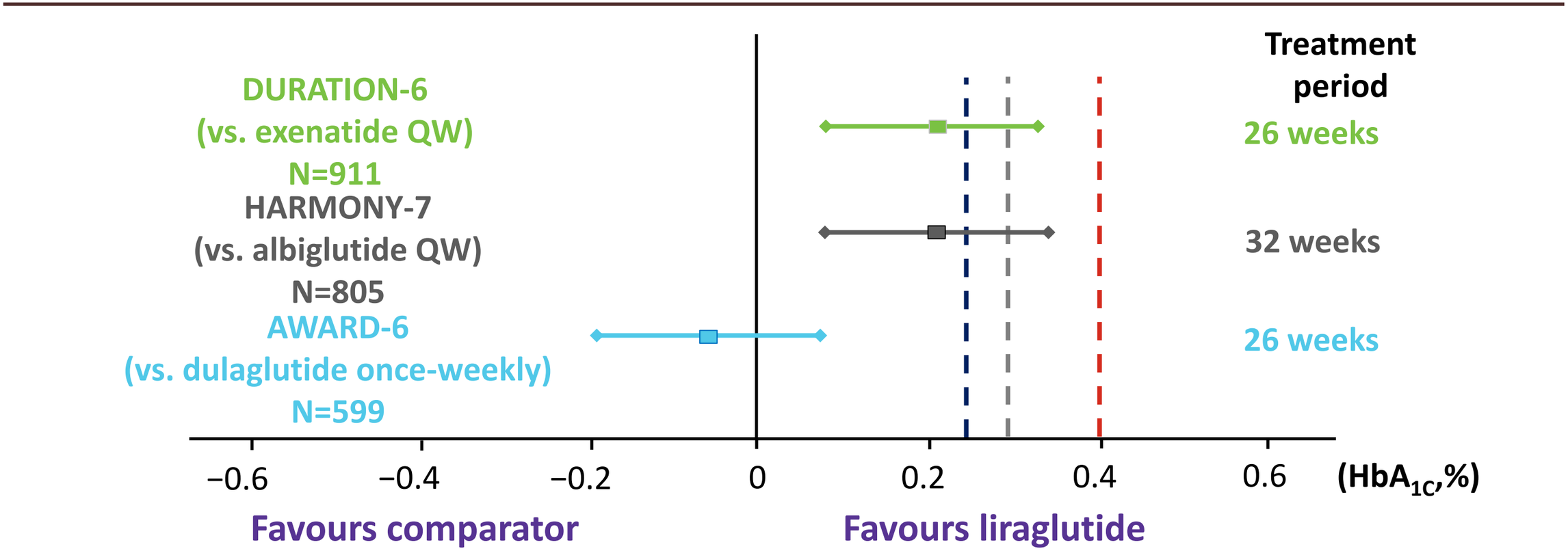



Data presented are LS means ± SE, MMRM #p<0.05 vs dulaglutide

**Trulicity is not indicated for weight loss, and weight change was a secondary endpoint in clinical trials.**

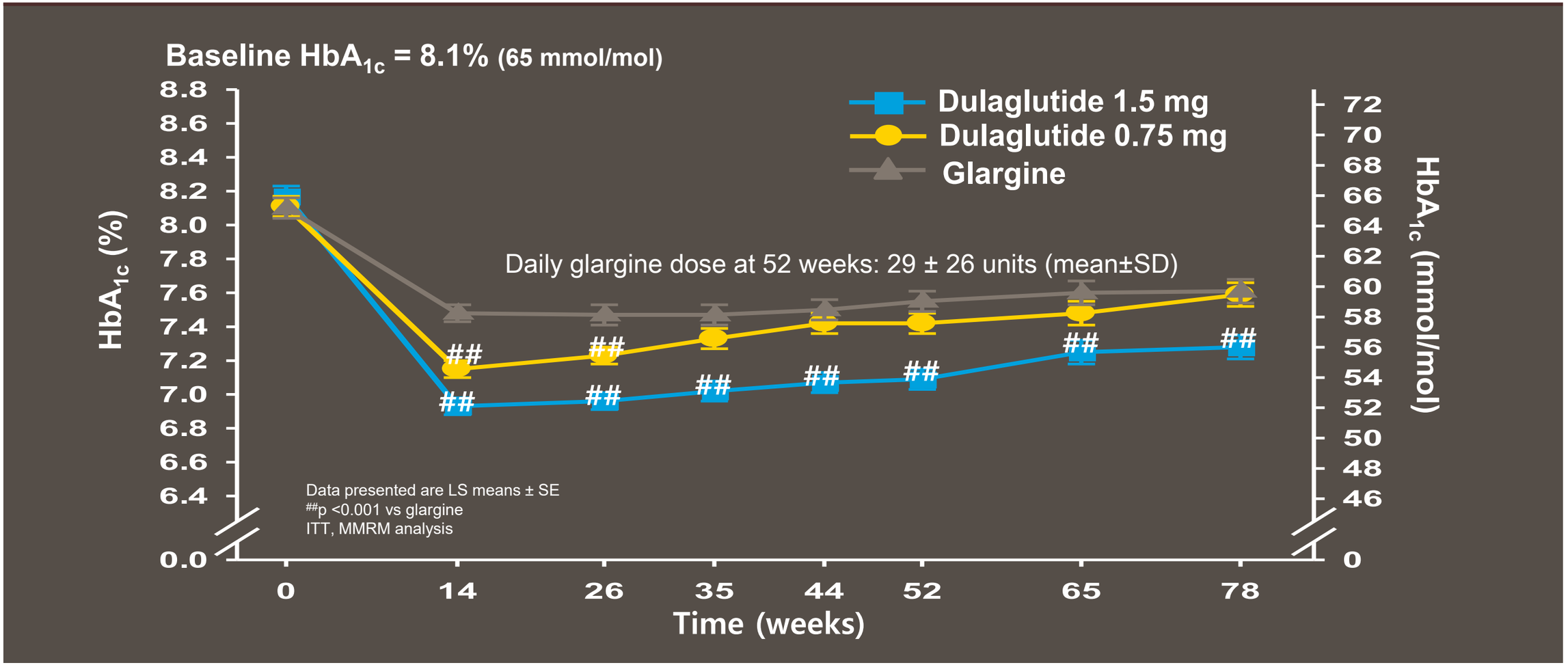
Dungan, et al. *Lancet*. 2014. 384(9951):1349-1357.

# Treatment Differences in $HbA_{1C}$ Reduction in Studies of Liraglutide vs. Weekly GLP-1 RA



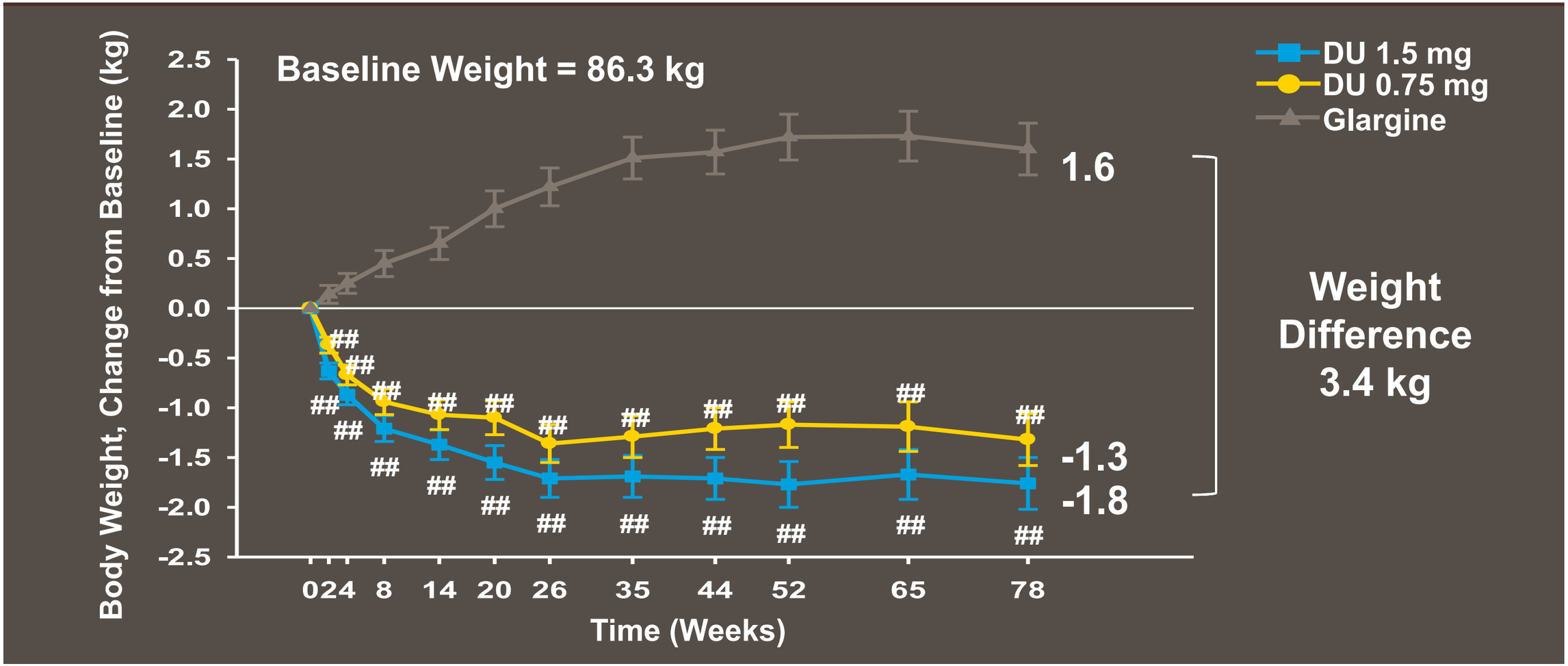

Buse JB et al. *Lancet* 2013;381:117−24; Pratley RE et al. *Lancet Diabetes Endocrinol* 2014;2:289−297;
Dungan KM, et al. Lancet. 2014. 384(9951):1349-1357.
Povedano ST et al. EASD 2014 Oral presentation, AWARD-6; Boye KS et al. EASD 2014 Poster presentation AWARD-6.

# $HbA_{1c}$ Over Time to 78 Weeks (AWARD 2)




Giogino F, et al. Diabetes Care. 2015;38(12):2241-2249.

# Body Weight Change Over Time (AWARD 2)




Data presented are LS means ± SE; ##p <0.001 vs glargine, ITT, MMRM analysis

**Trulicity is not indicated for weight loss, and weight change was a secondary endpoint in clinical trials.**

Giogino F, et al. Diabetes Care. 2015;38(12):2241-2249.

# Today's topics

- Overview of GLP-1RA physiology
- GLP-1RAs' similarities and differences
- Dulaglutide molecule design & True Simplicity Pen device
- Highlights of AWARD trials
- **Real world cases**

# Patient case 1

- F/43, DM since 2013
- 171 cm/63 Kg, BMI=21.55
- BP 113/80, HR 100/min, 살 찌는 것 싫어함.

- FPG=159 mg/dl, HbA1c 7.7%
  (METFORMIN 1g BID, GLIMEPIRIDE 2 mg BID, Dapagliflozin 10mg QD)

Dapagliflozin d/c
Trulicity 0.75 mg * 4 weeks
Trulicity 1.5 mg * 8 weeks

- 62.2 Kg, BMI=21.27
- FPG=108 mg/dl, HbA1c 6.5% (4번 못 맞음)
- GI trouble (-)
- Appetite change (-)

# Patient case 2

- M/25, DM since 2010
- 181.6 cm/100.7 Kg, BMI=30.53
- BP 141/82, HR 96/min

- FPG=188, HbA1c 8.1%, S/E at high dose Metformin
  (GLIMEPIRIDE 4 mg BID, SITAGLIPTIN 100 mg QD, Dapagliflozin 10mg QD)

Metformin 250mg QD add on
SITAGLIPTIN d/c
Dapagliflozin-> 비급여 전환
Trulicity 0.75 mg * 4 weeks
Trulicity 1.5 mg * 8 weeks

- 98.6 Kg, BMI=29.90
- FPG=97 mg/dl, HbA1c 6.2%
- GI trouble (+)->(-)
- 식욕 감소는 약간

# Patient case 3

- M/60, DM since 2010
- 163.6 cm/63 Kg, BMI=23.54
- BP 141/80, HR 97/min

- FPG=127 mg/dl, HbA1c 11.8%
  (METFORMIN 850 mg QD, Gliclazide MR 30 mg QD, Sitagliptin 100mg QD)

Sitagliptin d/c
DIAMI3 -> DIAMI6
Trulicity 0.75 mg * 4 weeks
Trulicity 1.5 mg * 8 weeks

- 63 Kg, BMI=23.54
- FPG=108 mg/dl, HbA1c 7.7%
- GI trouble (첫 2주만)
- 식욕 감소 지속 (50% 감소)

# Patient case 4

- F/55, DM since 1996
- 160 cm/72.6 Kg, BMI=28.36
- BP 120/90

- FPG=104 mg/dl, HbA1c 8.4%
  (Lantus 40 U QD, TENELIAM 1T BID)

Lantus d/c, TENELIAM d/c
DIAMICRON 60 mg QD
MET 500 mg BID
Trulicity 0.75 mg * 4 weeks,
Trulicity 1.5 mg * 8 weeks

- 63.2 Kg, BMI=26.51
- FPG=207 mg/dl, HbA1c 8.0%
- 최근 한달 경구약제 (-)
- 식욕 감소는 모르겠다. GI trouble (-)

# Patient case 5

- M/54, DM since 2006
- 159 cm/67.5 Kg, BMI=26.6
- BP 135/78, LC, Child A

- FPG=180 mg/dl, HbA1c 10.6%
  (Lantus 30 U QD Irregular, Sitagliptin 100 m QD )

Lantus d/c, Sitagliptin d/c
Glimepiride 3mg BID
MET 850 mg BID
Trulicity 0.75 mg * 4 weeks,
Trulicity 1.5 mg * 8 weeks

- 65.6 Kg, BMI=25.88
- FPG=111 mg/dl, HbA1c 6.1%
- Hypoglycemia (-)
- 식욕 감소 (+). GI trouble (+)->(-)

# Summary: Advance of the first injectable option

- Once weekly administration
- Auto-injection device
- High patient preference
- Superiority A1c reduction versus Insulin glargine
- Low hypoglycemia
- Low side effect
- Weight reduction
- Protection of beta-cell

# QUIZ 1

- 다음 GLP-1 RA 중 FPG 보다는 PPG Control에 좀 더 효과적이라고 알려진 약제는 무엇인가?

1) Liraglutide QD
2) Lixisenatide QD
3) Exenatide QW
4) Albiglutide QW
5) Dulaglutide QW

# QUIZ 2

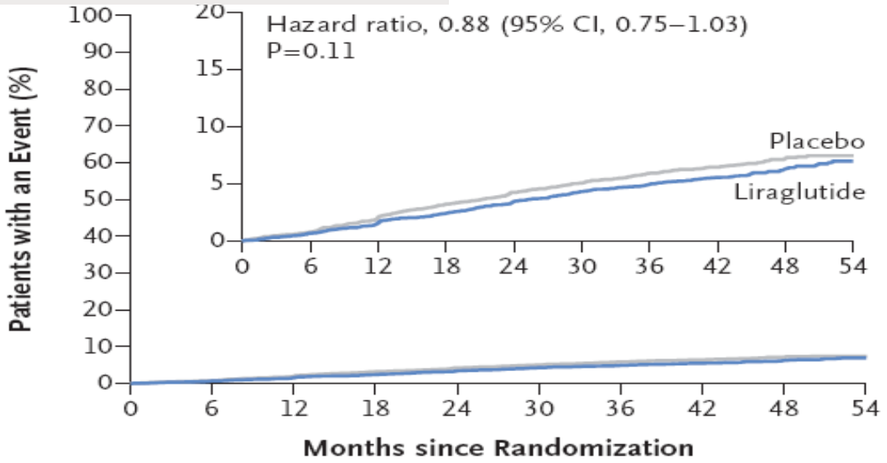
- 다음 GLP-1 RA 중 Liraglutide와 Head to Head Comparison Trial을 통해 HbA1c reduction 측면에서 Non-inferiority 를 입증한 약제는 무엇인가?

1) Exenatide BID
2) Lixisenatide QD
3) Exenatide QW
4) Albiglutide QW
5) Dulaglutide QW

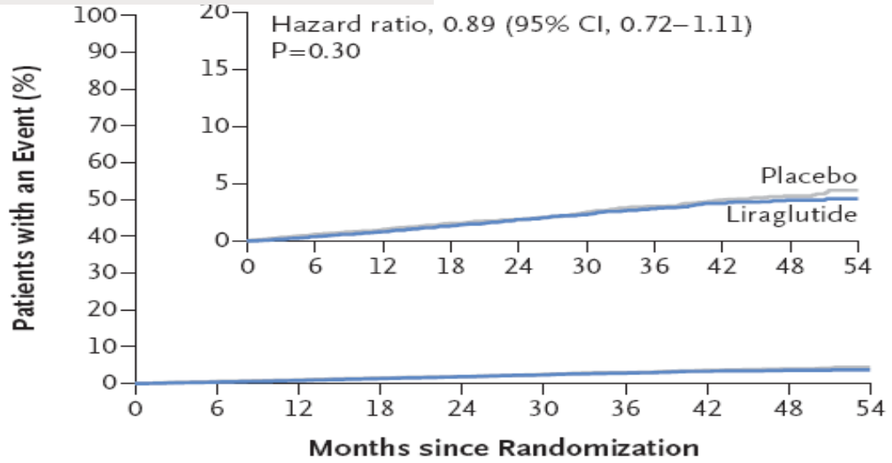
# 경청해 주셔서 감사합니다.

# GLP-1 RA CV Outcome Trials: LEADER

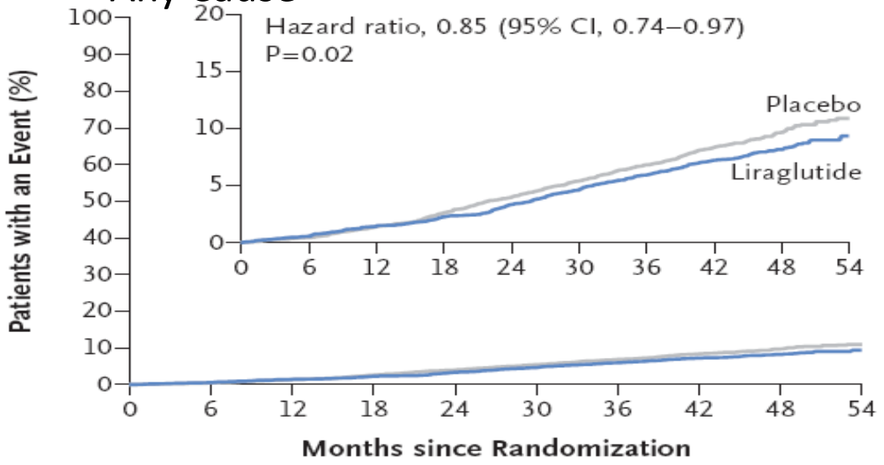
## Nonfatal MI



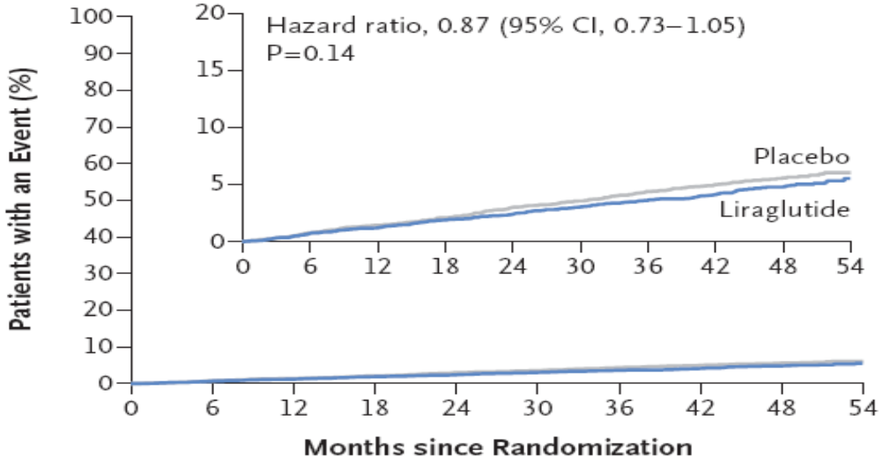

## Nonfatal Stroke




## Death from Any Cause



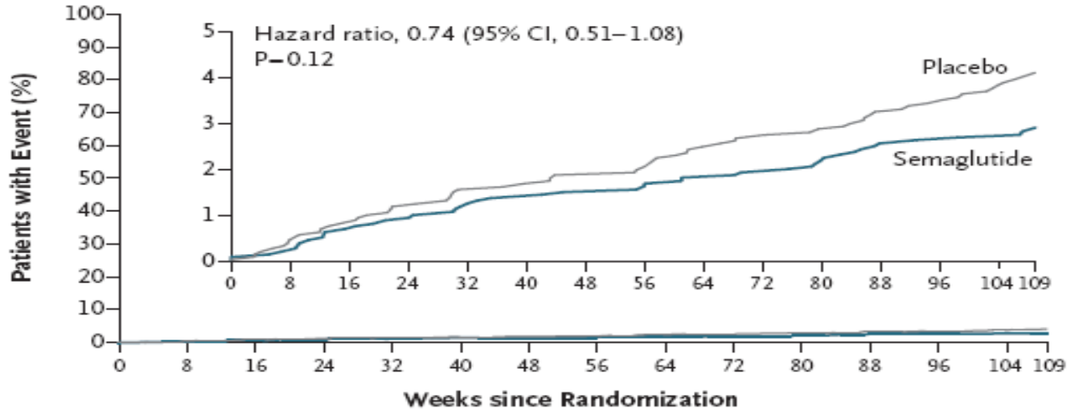

## HHF



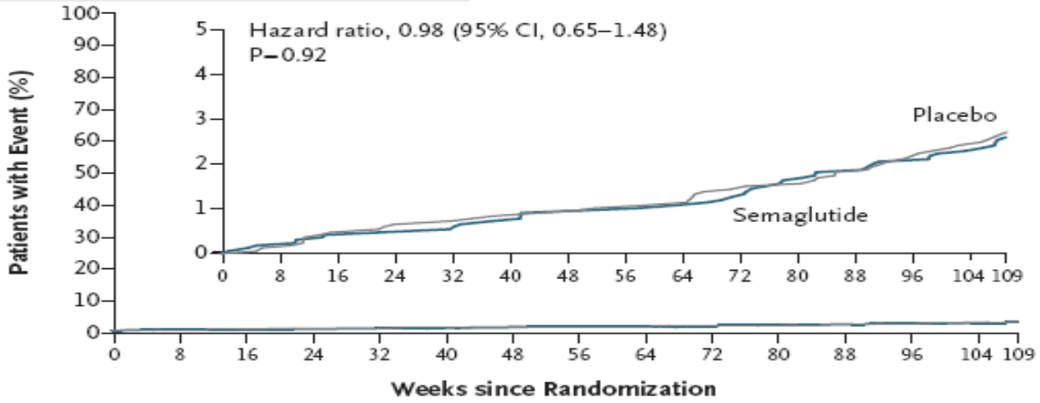

N Engl J Med. 2016;375:311-322.

# GLP-1 RA CV Outcome Trials: SUSTAIN-6

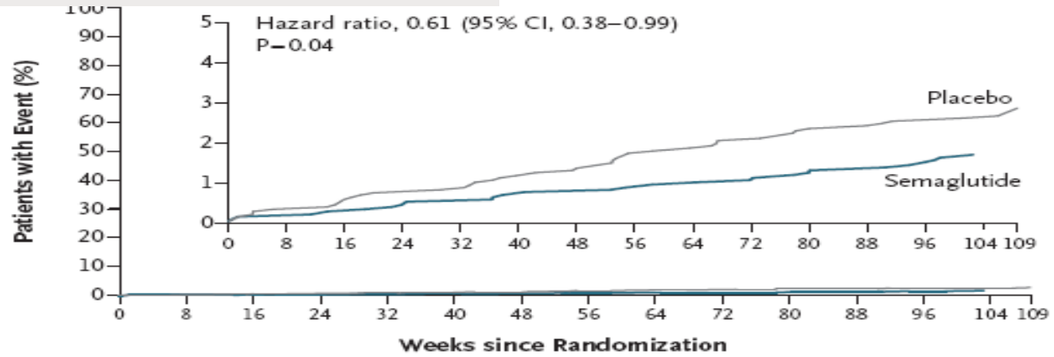
## Nonfatal MI




## Death from CV cause




## Nonfatal Stroke




N Engl J Med. 2016; Sep 15. Epub ahead of print

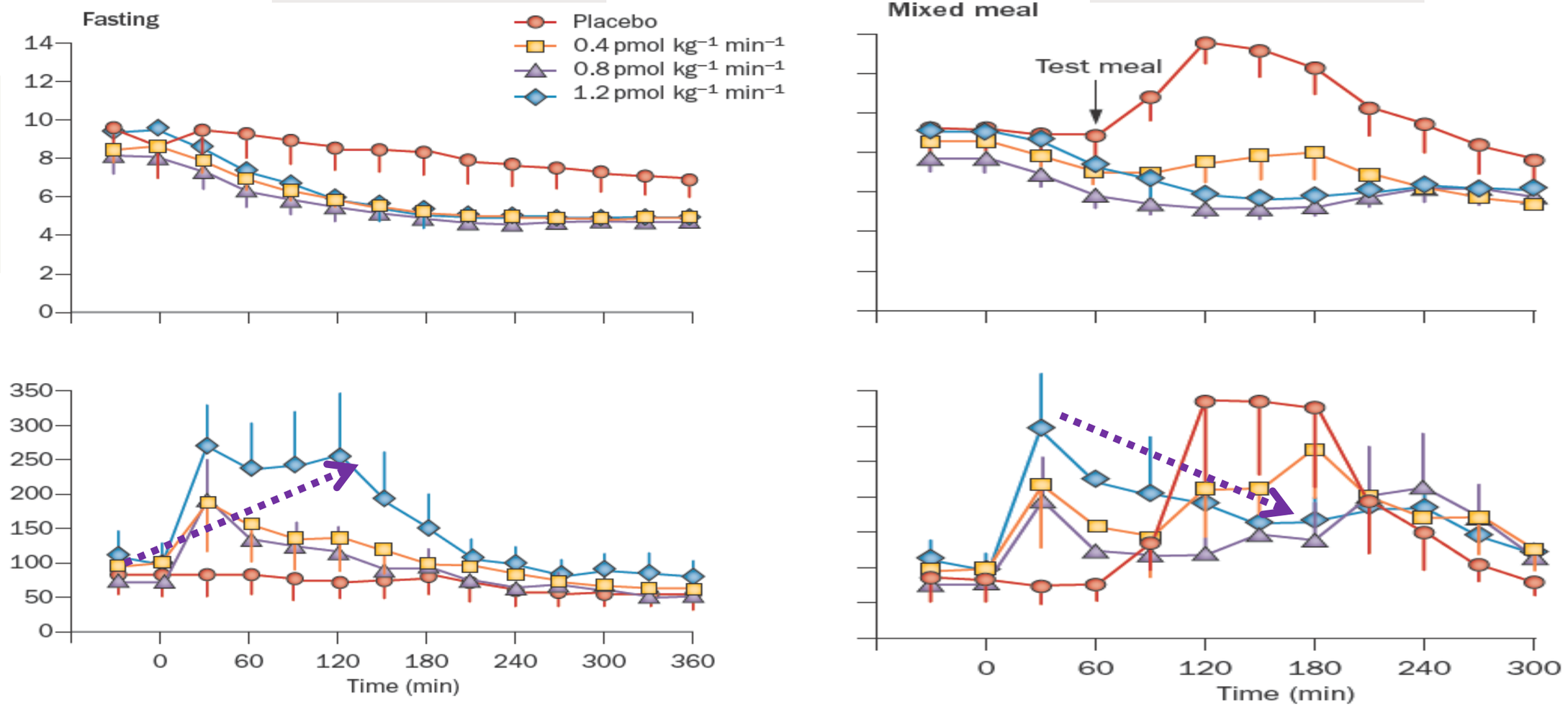
# Differential Effect of GLP-1 in the Fasting and Postprandial State

## Fasting

## Mixed Meal

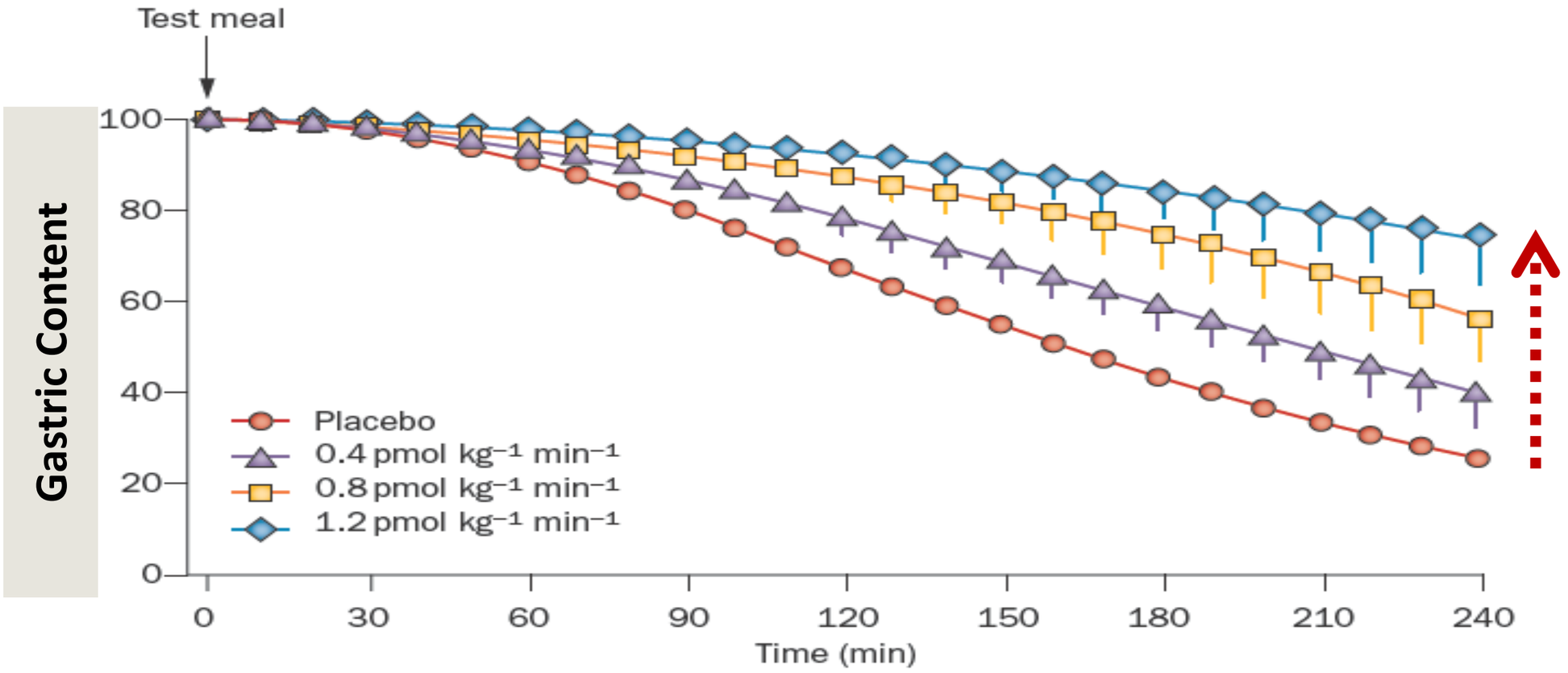
Glucose

Insulin




Nat. Rev. Endocrinol. 2012;8:728-742.

# The Effect of GLP-1 on Gastric Emptying

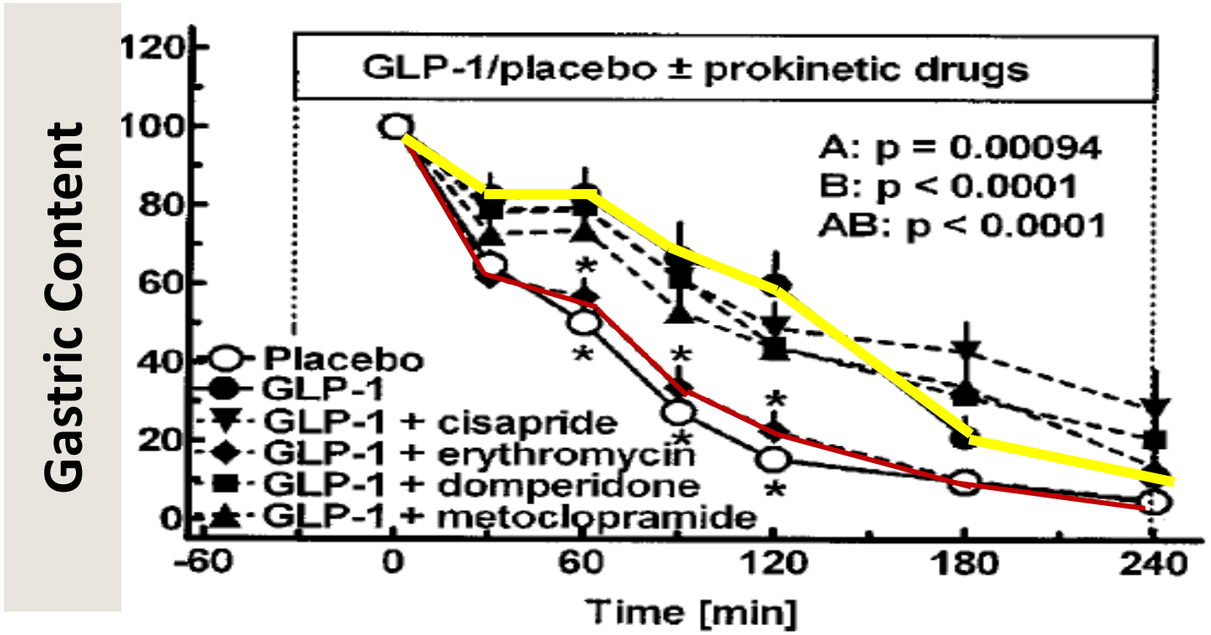


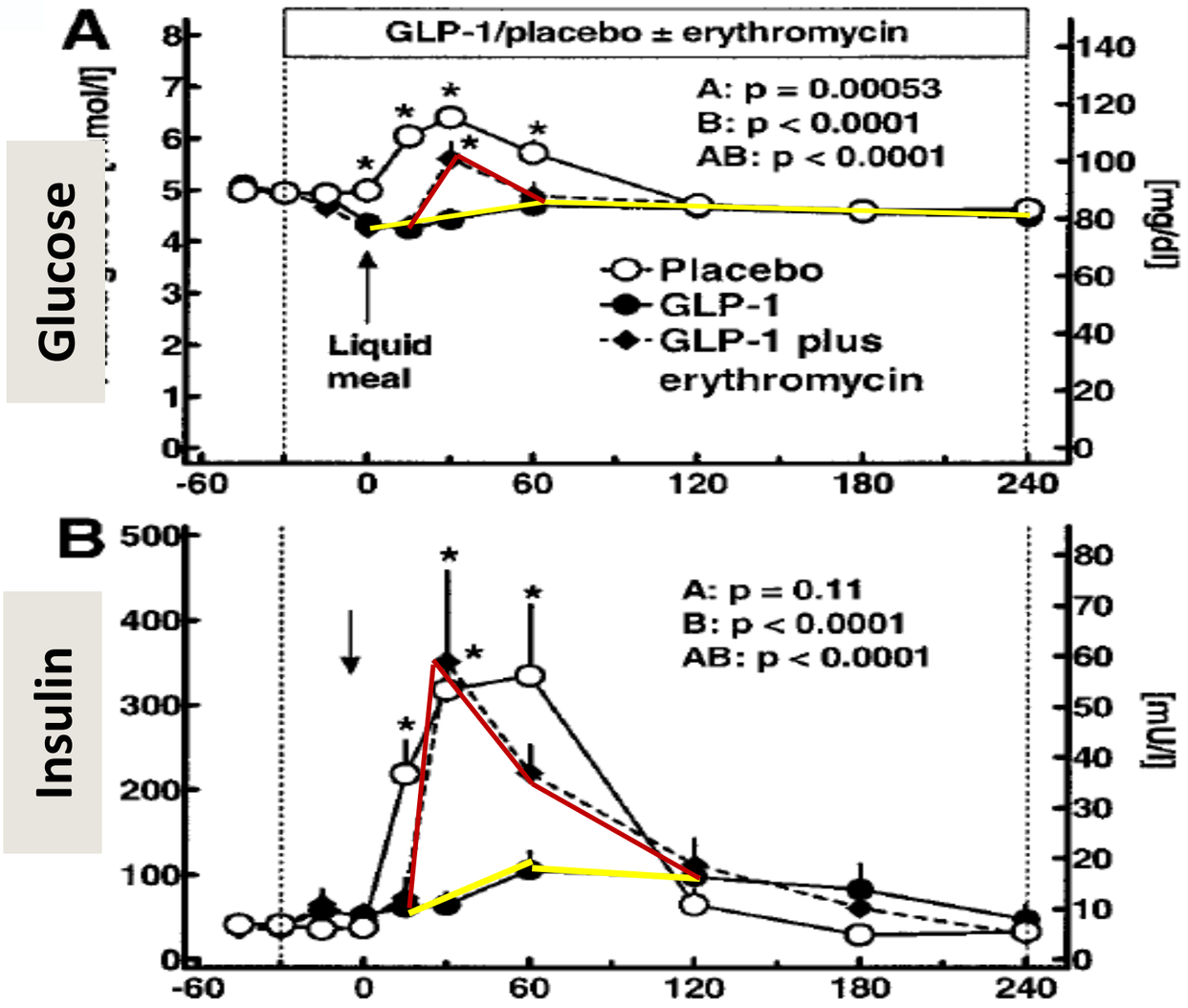

Nat. Rev. Endocrinol. 2012;8:728-742.

# The Effect of GLP-1 on Gastric Emptying

GLP-1

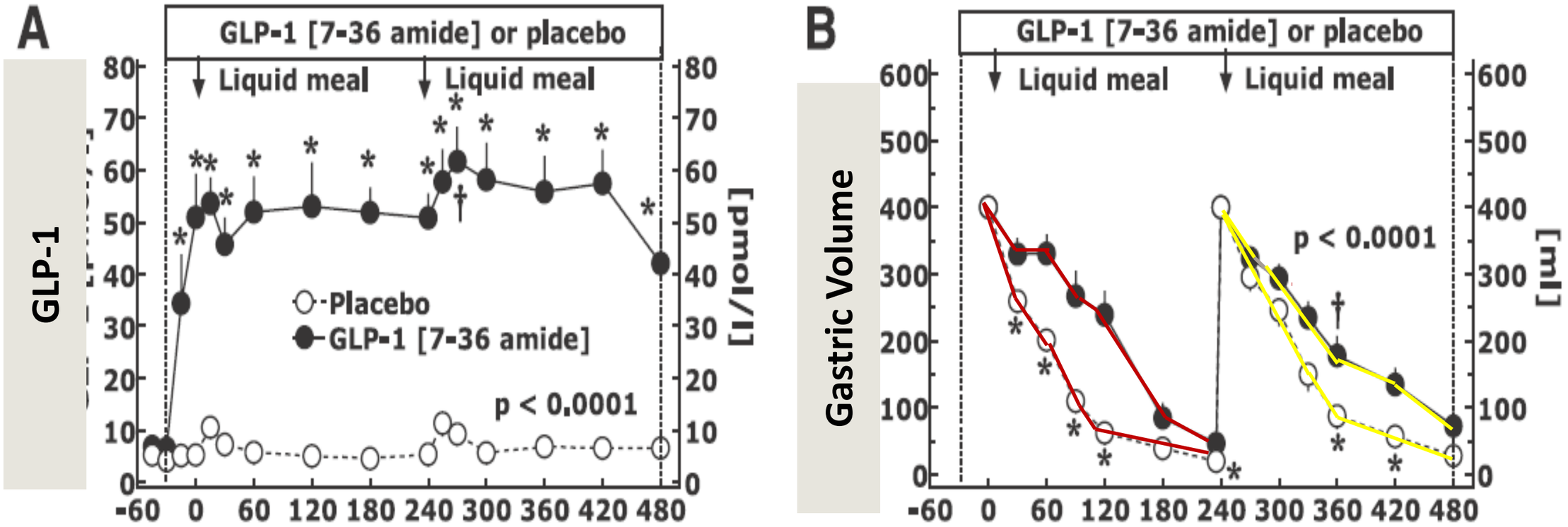
GLP-1 + Erythromycin



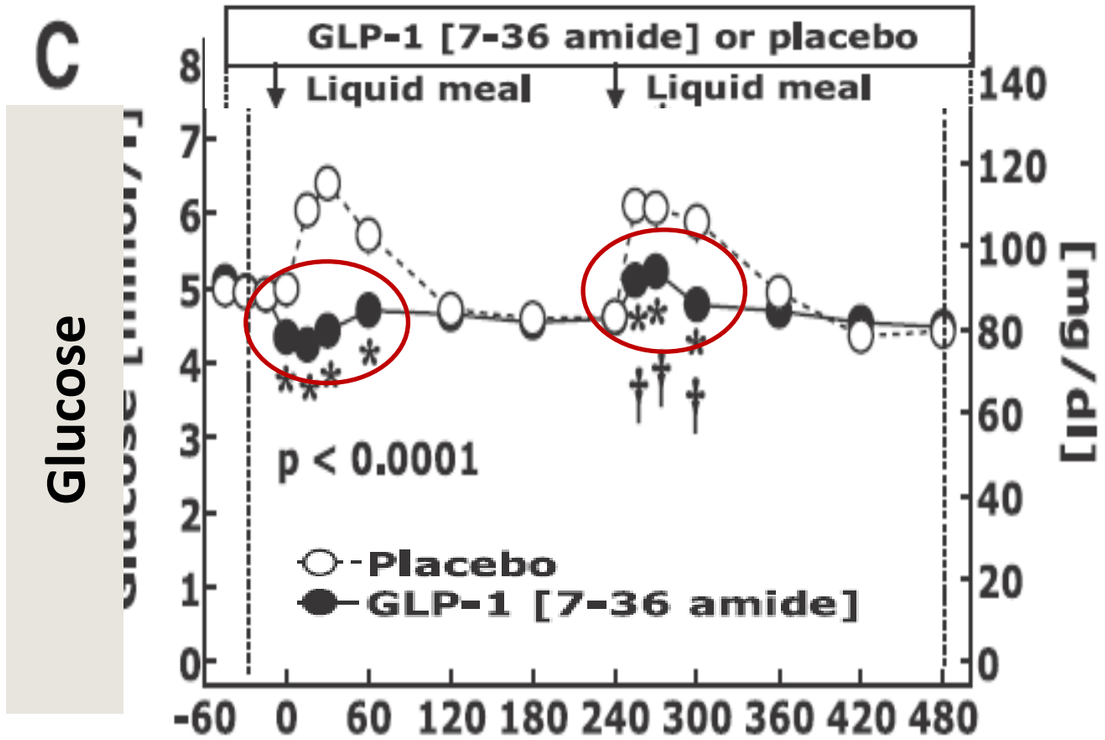

Diabetes. 2005;54:2212-2218.

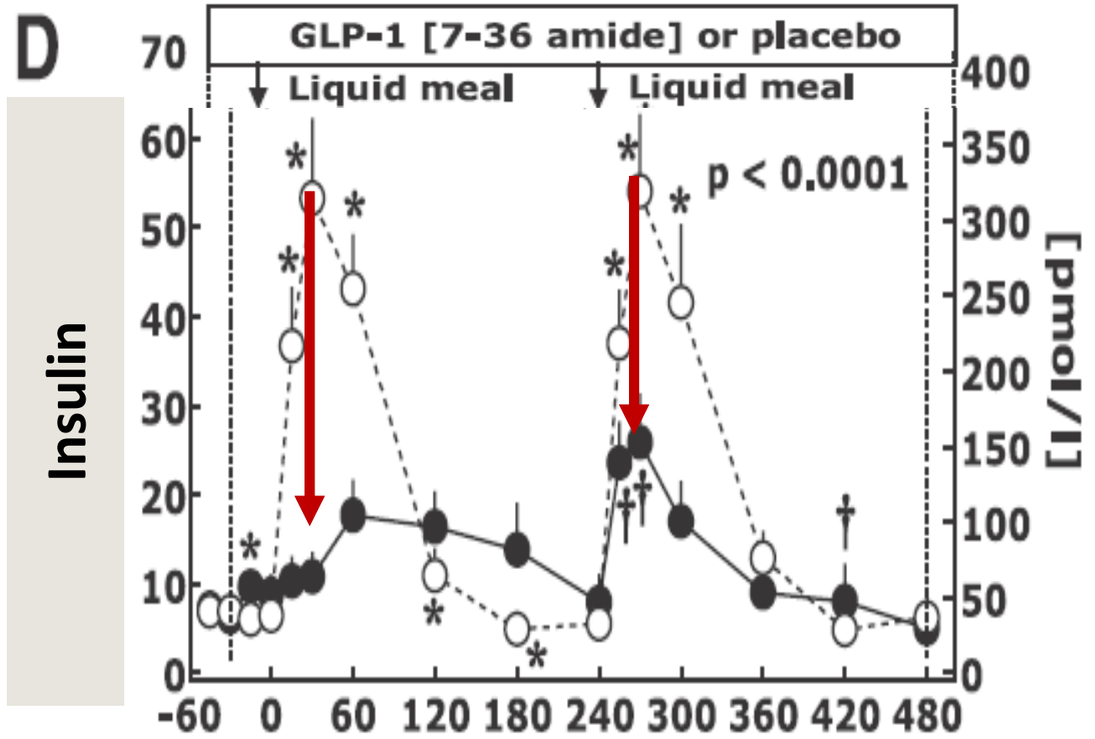
# Rapid Tachyphylaxis Phenomenon




Diabetes. 2011;60:1561-5.

# Rapid Tachyphylaxis Phenomenon




Diabetes. 2011;60:1561-5.

# Short-Acting GLP-1 RA

| Drug | Dosing | Use in renal impairment |
|---|---|---|
| Exenatide | 10 μg b.i.d. | - CrCl 30–50 mL/min (caution when escalating dose)<br>- CrCl <30 mL/min (avoid) |
| Lixisenatide | 10 μg OD<br>20 μg OD | - eGFR 30–50 mL/min · 1.73 $m^2$ (caution)<br>- eGFR <30 mL/min · 1.73 $m^2$ (avoid) |

Diabetes Care 2016;39(Supp. 2):S154-S164.

# Long-Acting GLP-1 RA

| Drug | Dosing | Use in renal impairment |
|---|---|---|
| Exenatide QR | 2 mg weekly | - CrCl 30–50 mL/min (caution)<br>- CrCl 30 mL/min (avoid) |
| Liraglutide | 1.2 mg OD<br>1.8 mg OD | - Mild–severe impairment<br>- No dose adjustments (use with caution) |
| Dulaglutide | 0.75 mg weekly<br>1.5 mg weekly | - No dose adjustments<br>- Caution during initiation and dose escalation |
| Albiglutide | 30 mg weekly<br>50 mg weekly | - No dose adjustments<br>- Caution during initiation and dose escalation |

Diabetes Care 2016;39(Supp. 2):S154-S164.