# Novel and Emerging Combinations to Achieve Glycemic Control and Reduce Cardiometabolic Risk: A Focus on Incretin-Based Therapy and SGLT2 Inhibitors

Supported by an educational grant from AstraZeneca

# Welcome and Introductory Remarks

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**Chicago, IL**

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- The session is being videotaped. Please turn off all cell phones and pagers.
- There will be a 5-minute Q&A at the end of each session. Questions can be asked via microphone at that time.
- During the panel discussion, please use Question Cards located on each table.
- Complete and return a CME Evaluation Form at the conclusion of the symposium.

# Role of Incretin Therapies and Effects on Glucose Homeostasis


## Richard Pratley, M.D.

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**Director , Florida Hospital Diabetes Institute**
**Senior Investigator, Translational Research Institute**
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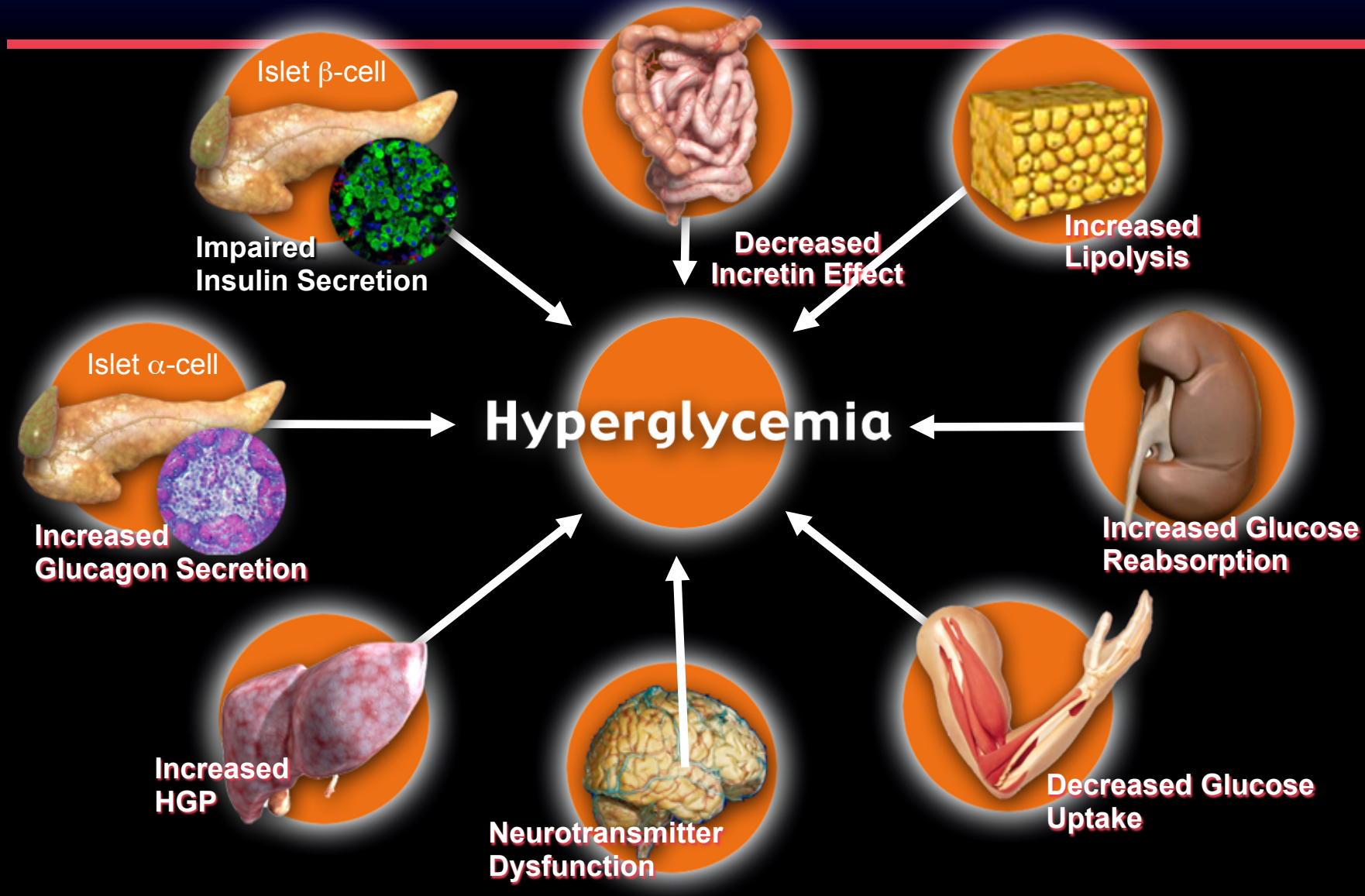
# Outline

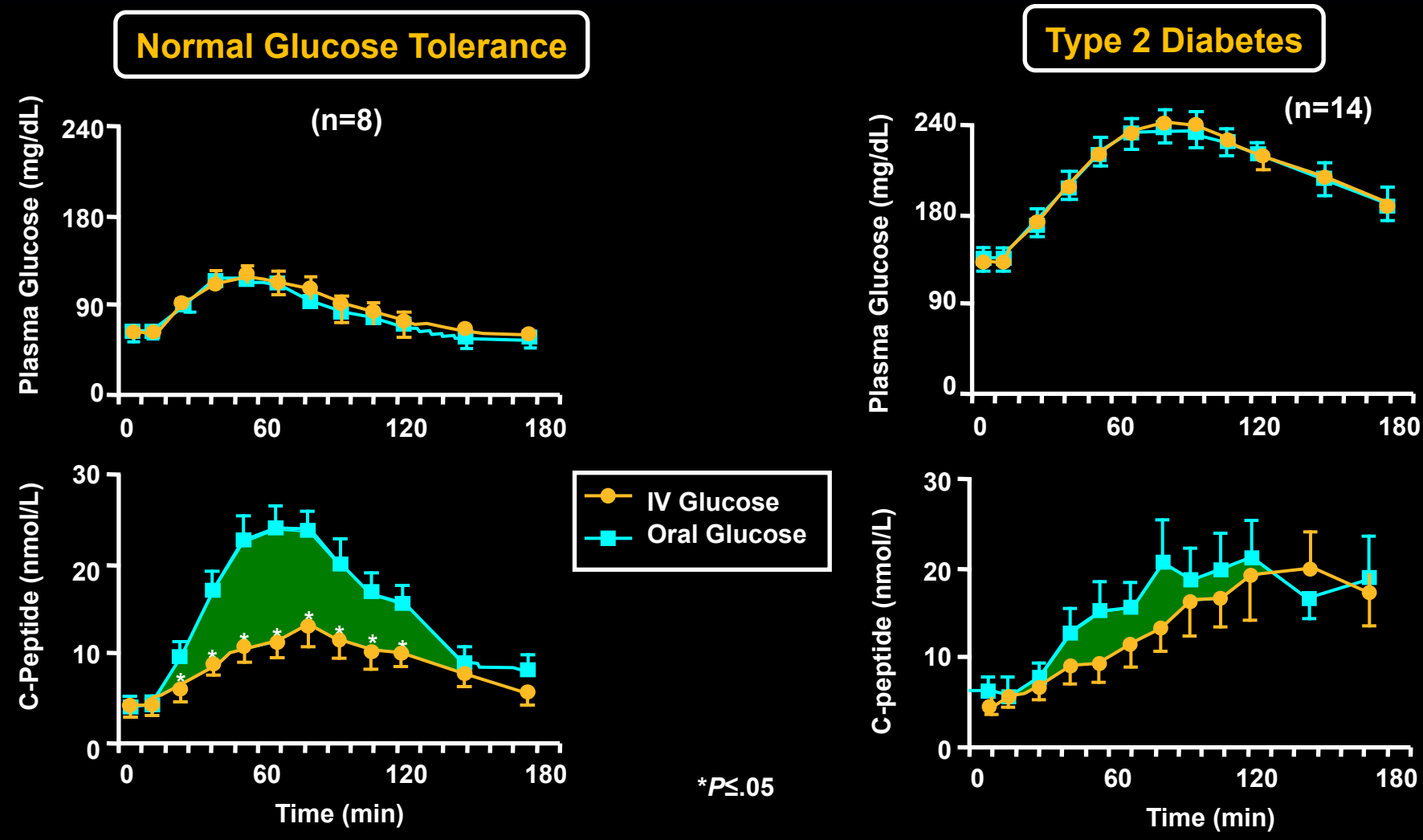
- Rationale for incretin therapy in T2DM
- Efficacy of DPP-4 inhibitors and GLP-1 receptor agonists in T2DM
- Effects on CV risk factors
- Risk vs. benefits of incretin therapies for T2DM

# Multiple Metabolic Defects Contribute to Hyperglycemia in T2DM



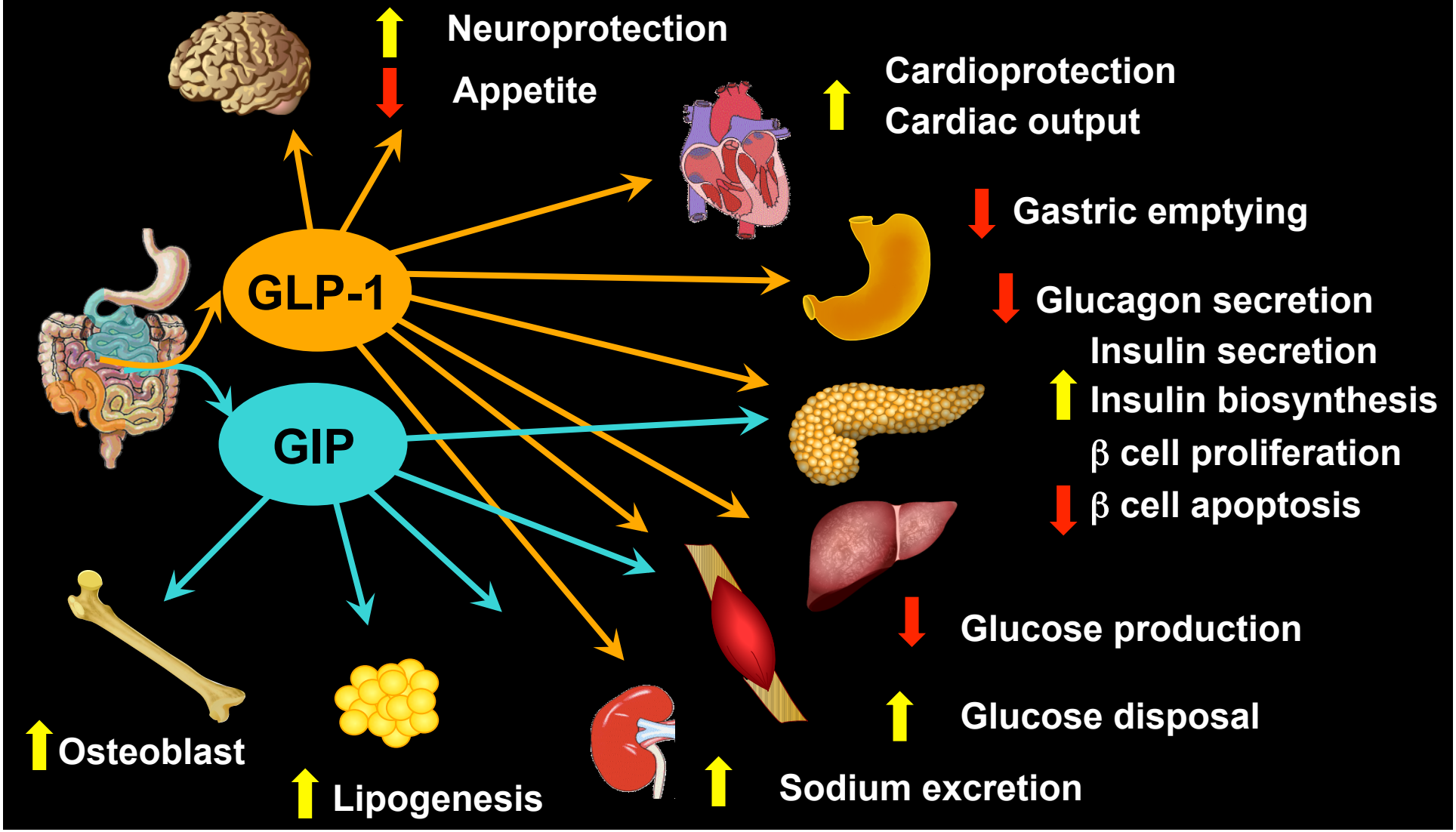

DeFronzo, Diabetes. 2009

# The Incretin Effect Is Diminished in Type 2 Diabetes

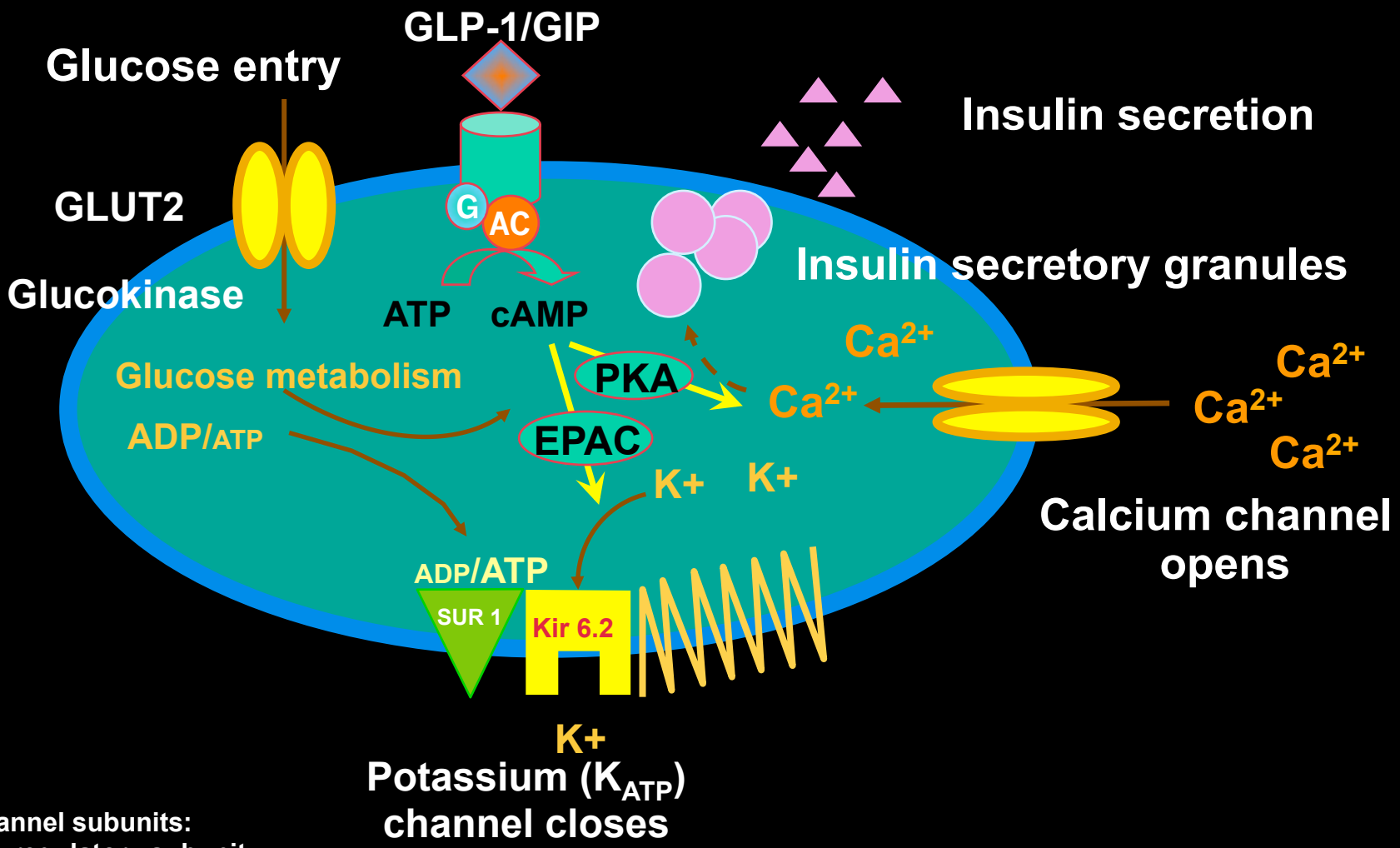



Nauck et al. Diabetologia. 1986;29:46-52.

# Physiological Actions of GLP-1 and GIP

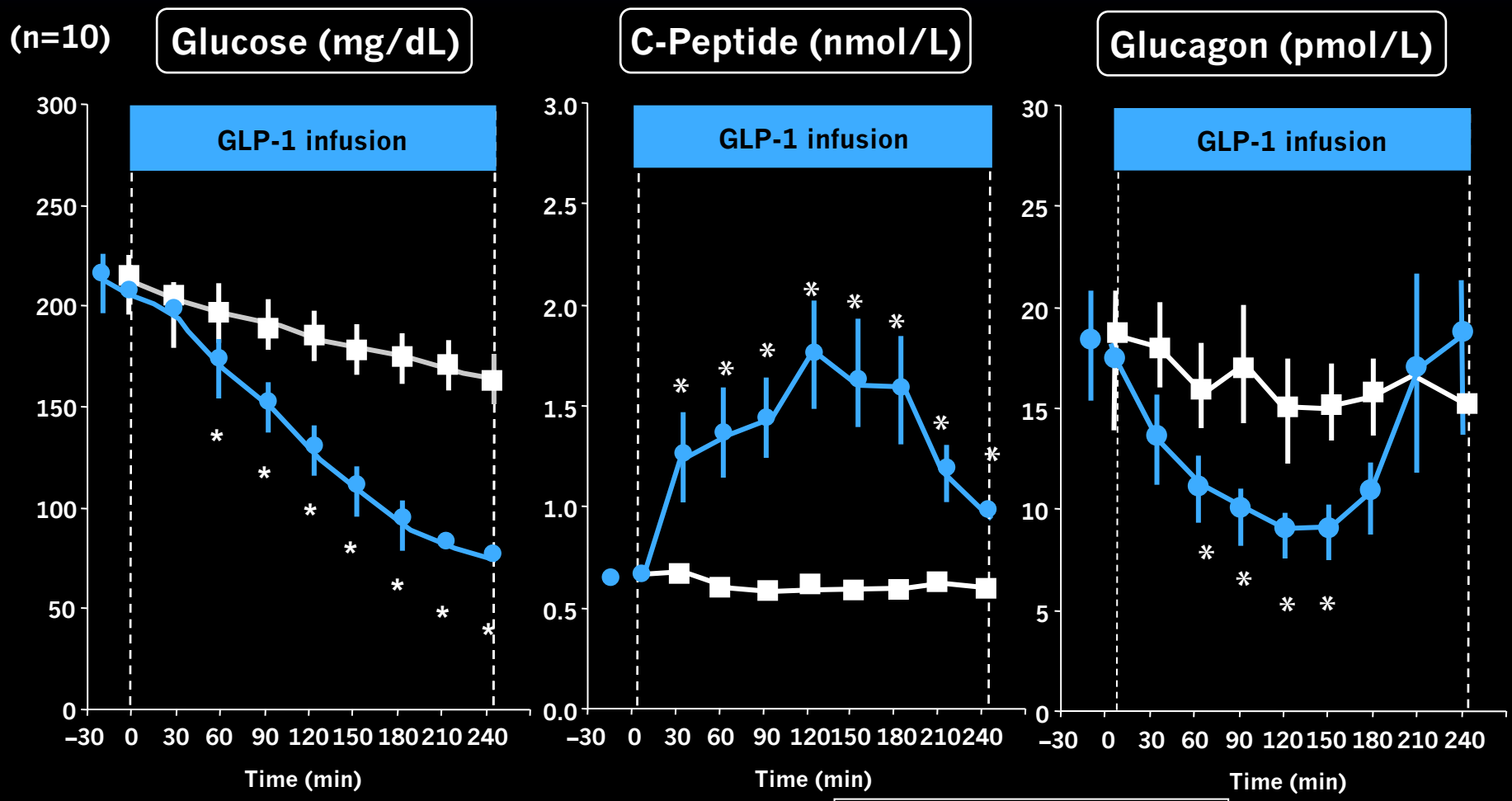


# GLP-1 and GIP Augment Insulin Secretion by the β-Cell in a Glucose-Dependent Manner



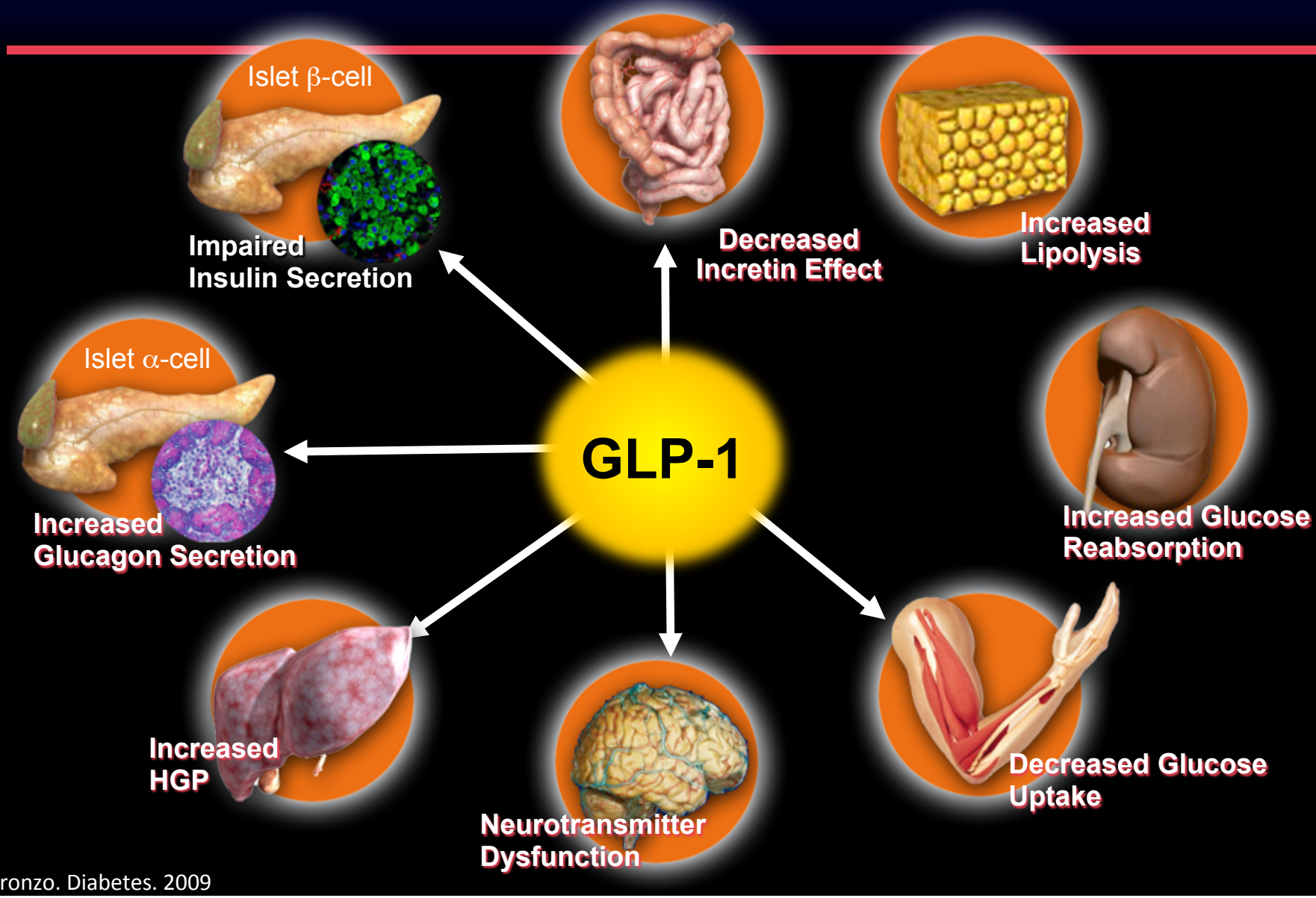

$K_{ATP}$ channel subunits:
SUR 1=regulatory subunit;
Kir 6.2=inward rectifying channel

# Glucose Dependent Effects of GLP-1 in T2DM




*$P$<0.05.
GLP-1 = glucagon-like peptide–1.
Adapted from Nauck et al. Diabetologia. 1993;36:741-44.

# GLP-1 Addresses Multiple Metabolic Defects in T2DM




DeFronzo. Diabetes. 2009

# The Incretin Defect in T2DM

- Substantial impairment – 40% of normal response
- Not due to impaired secretion of GLP-1 or GIP
- Absent insulinotropic response to GIP
  - Beta-cell GIP receptor down-regulation
- Decreased response to GLP-1
  - Can be overcome by achieving higher than physiologic GLP-1 levels
- GLP-1 infusions that achieve higher levels effective at enhancing insulin secretion and suppressing glucagon in a glucose-dependent manner

Nauck et al. Diabetologia. 1986;29:46–52. Laakso et al. Diabetologia. 2008;51:502-11. Nauck et al. Diabetologia. 2011;54:10-8. Højberg et al. Diabetologia. 2009;52:199-207. Vilsbøll et al. Diabetologia. 2002;45:1111–19. Nauck et al. Diabetologia. 1993;36:741–44.

# Rationale for Using Incretin Therapies in the Treatment of Type 2 Diabetes

- Incretins play a key and early role in maintaining glucose homeostasis
- Incretin effects are diminished in patients with type 2 diabetes
- Incretin-based therapies
  - Target multiple defects of type 2 diabetes, including those not addressed by traditional medications
  - Do not cause hypoglycemia
  - Have favorable effects on weight

# 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*

**Human GLP-1:**

- Liraglutide
- Albiglutide
- Dulaglutide

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

**Oral agents**

- Sitagliptin
- Saxagliptin
- Linagliptin
- Alogliptin
- Vildagliptin*

***Not FDA approved**

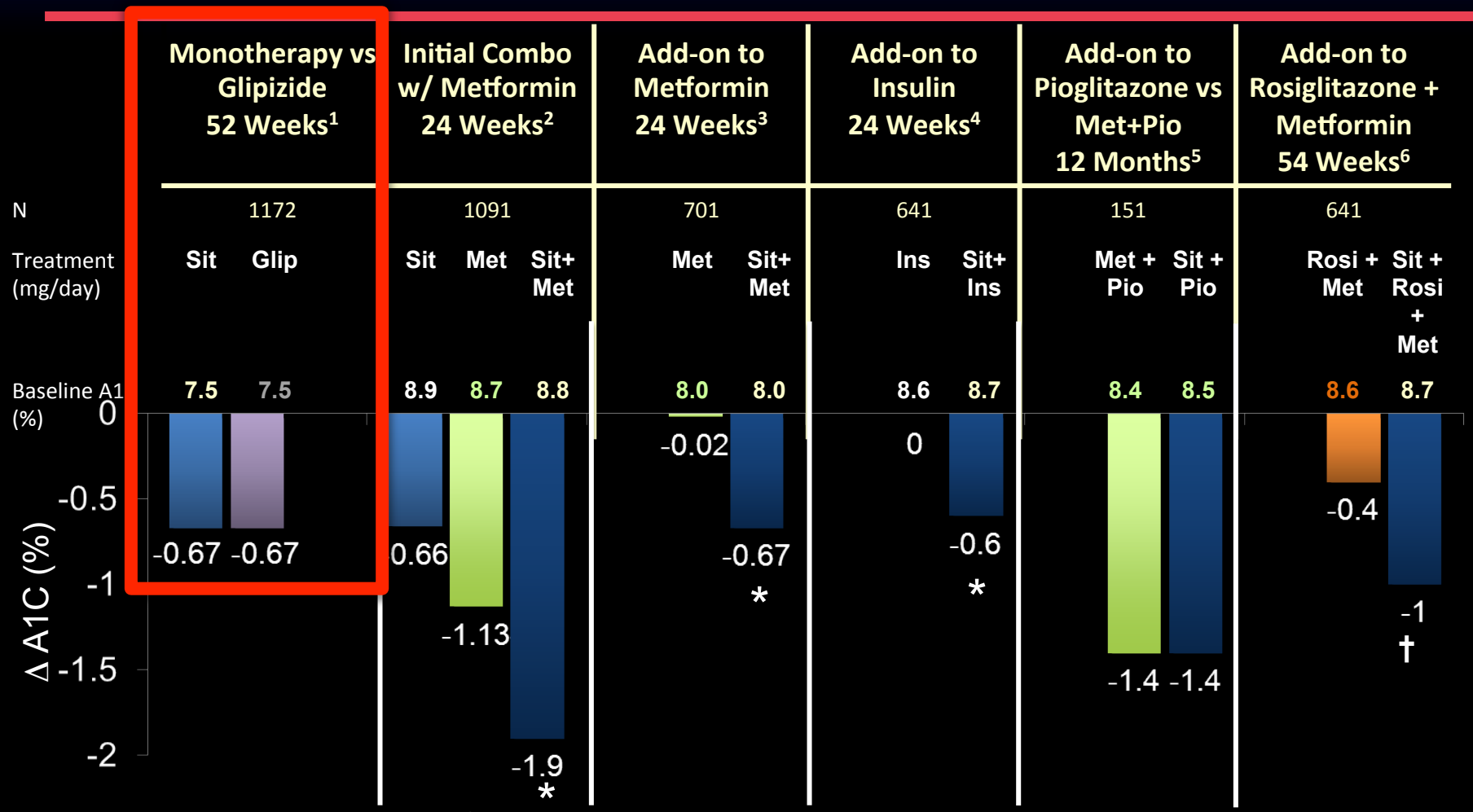
Drucker. Curr Pharm Des. 2001;7:1399-412. Drucker. Mol Endocrinol. 2003;17:161-71.

# Comparison of DPP-4 Inhibitors

| | Sitagliptin | Alogliptin | Saxagliptin | Vildagliptin* | Linagliptin |
|---|---|---|---|---|---|
| Usual Phase 3 Dose | 25, 50, 100 mg QD | 6.25, 12.5, 25 mg QD | 2.5, 5 mg QD | 50 mg BD | 5 mg QD |
| Half Life (t1/2) | 12.4h | 12.5 to 21.1h (25mg) | 2.2 to 3.8h | 1.3-2.4h | > 100 h |
| DPP-4 inhibition at 24h | ~80% at 24h | ~78% at 24h (25 mg) | 5 mg: ~55% at 24h | ~50% at 24h (100 mg) | 75% at 24 h |
| Elimination | Kidney (mostly unchanged) | Kidney (mostly unchanged) | Liver and kidney Active metabolite | Kidney>>Liver Inactive metabolite | Bile (mostly unchanged) |
| Renal Dose Adjustments Required | Yes | Yes | Yes | Not recommended for moderate or severe impairment | No |
| Selectivity for DPP-4 | >2600 fold vs DPP-8 >10,000 fold vs DPP-9 | >10,000 fold vs DPP-8/9 | >400 fold vs DPP-8 >100 vs DPP-9 | >90 fold vs DPP-8 | >10,000 fold vs DPP-8/9 |
| Potential for DDI | Low | Low | Strong CYP3A4/5 inhibitors[d] | Low | Strong CYP3A4/5 inhibitors[d] |
| Food effect | No | No | No | No | No |

*Not FDA approved

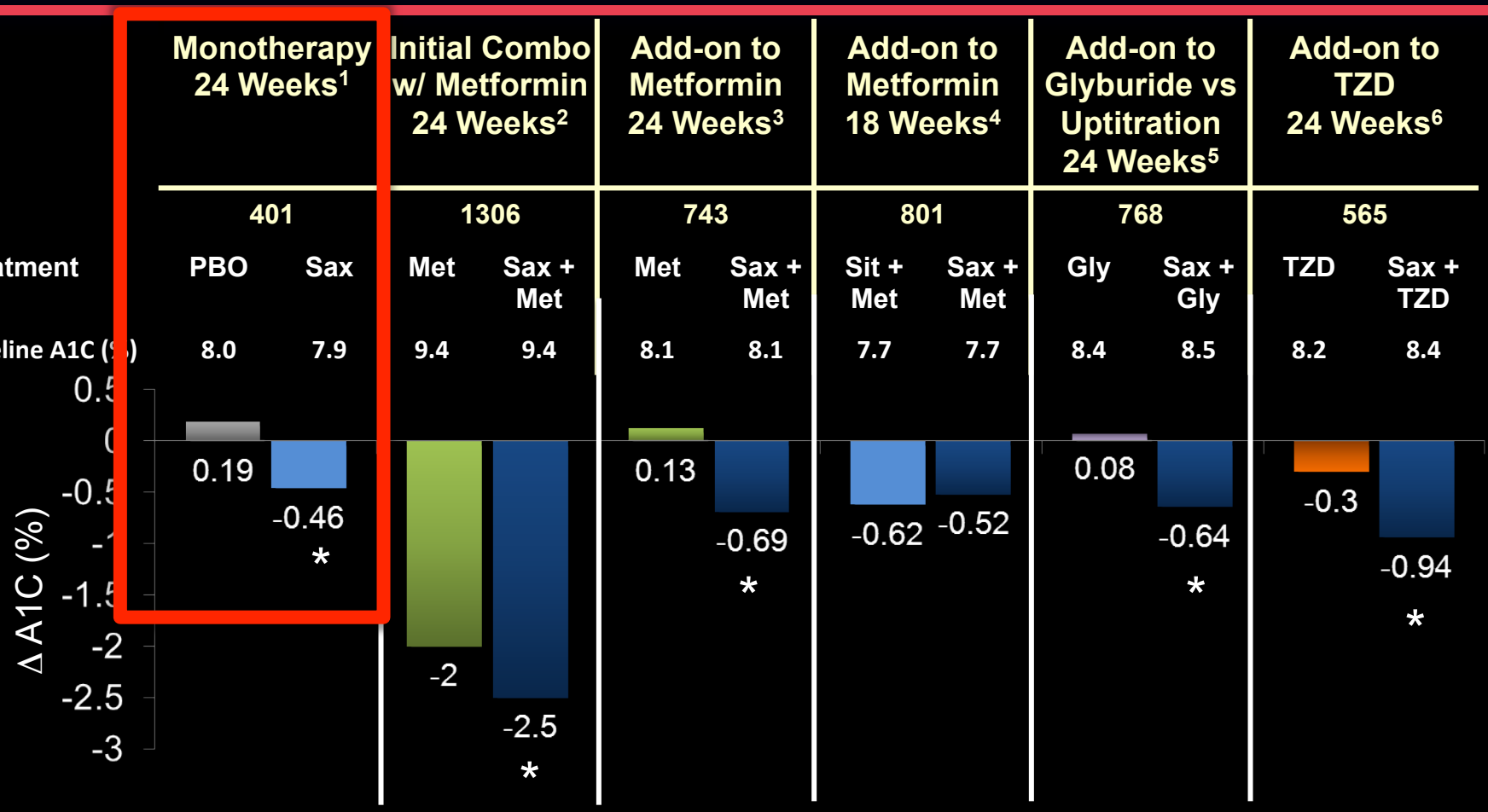
# Glucose Control With Sitagliptin: Mono and Combination Therapy




*$P$<0.001 vs active comparator monotherapy. †$P$<0.001 vs active comparator dual therapy.


1. Nauck et al. Diabetes Obes Metab. 2007;9:194-205. 2. Goldstein et al. Diabetes Care. 2007;30:1979-87.
3. Charbonnel et al. Diabetes Care. 2006;29:2638-43. 4. Vilsbøll et al. Diabetes Obes Metab. 2010;12:167-77.
5. Derosa et al. Metab Clin Exp. 2010;59:887-95. 6. Sitagliptin prescribing information. Whitehouse Station, NJ: Merck & Co. Inc. 2010.

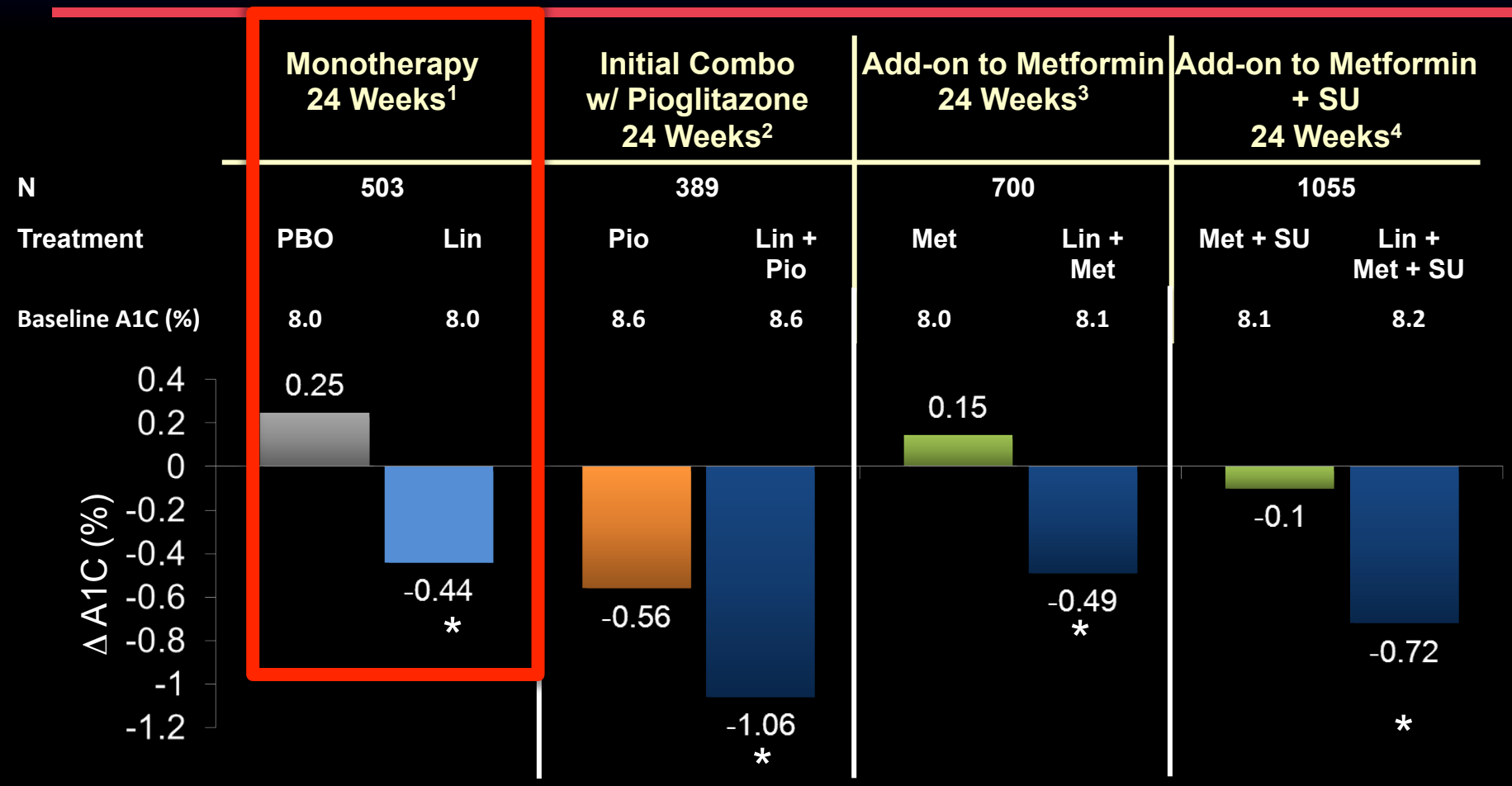
# Glucose Control With Saxagliptin: Mono and Combination Therapy




*$P$<0.0001 vs comparator.


1. Rosenstock et al. Curr Med Res Opin. 2009;25:2401-11. 2. Jadzinsky et al. Diabetes Obes Metab. 2009;11:611-22.
3. DeFronzo et al. Diabetes Care. 2009;32:1649-55. 4. Scheen et al. Diabetes Metab Res Rev. 2010;26:540-49.
5. Chacra et al. Int J Clin Pract. 2009;63:1395-1406. 6. Hollander et al. J Clin Endocrinol Metab. 2009;94:4810-19.

# Glucose Control With Linagliptin: Mono and Combination Therapy




*$P$<0.0001 vs comparator.

1. Del Prato et al. Diabetes Obes Metab. 2011;13:258-67. 2. Gomis et al. Diabetes Obes Metab. 2011;13:653-61. 3. Taskinen et al. Diabetes Obes Metab. 2011;13:65-74. 4. Owens et al. Diabetes. 2010;59(suppl 2): Abstr. 548-P.

# DPP-4 Inhibition: Role in T2DM Therapy

- Oral therapy, once daily
  - Endogenous GLP-1 and GIP levels are increased in response to meals and are transient
- Clinically significant A1c reductions
  - Comparable efficacy to rosiglitazone, glipizide
- Very well tolerated
  - No GI sx, no weight gain, low hypoglycemia, no edema
- Low risk for drug-drug interactions
- Adjust dose for CKD: except linagliptin
- Neutral effects on BP, lipids
- No apparent CVD risk: saxagliptin and alogliptin

# 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*

**Human GLP-1:**

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

**Oral agents**

- Sitagliptin
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- Alogliptin
- Vildagliptin*

*Not FDA approved

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

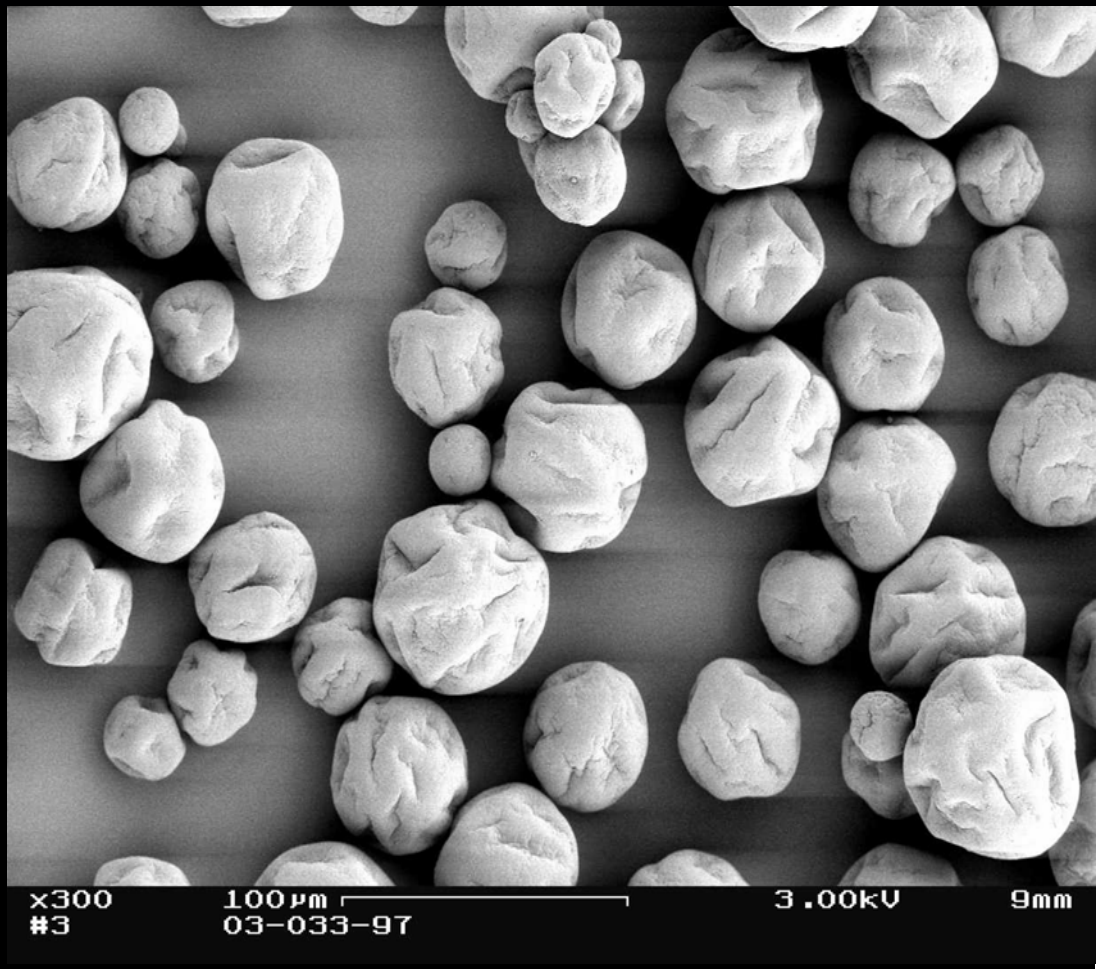

- 44 a.a. <50% homology to human GLP-1
- 1 proline has been deleted and 6 lysines have been added
- DPP-4 resistant
- Half-life ~ 3-4 hours

***Not FDA approved**

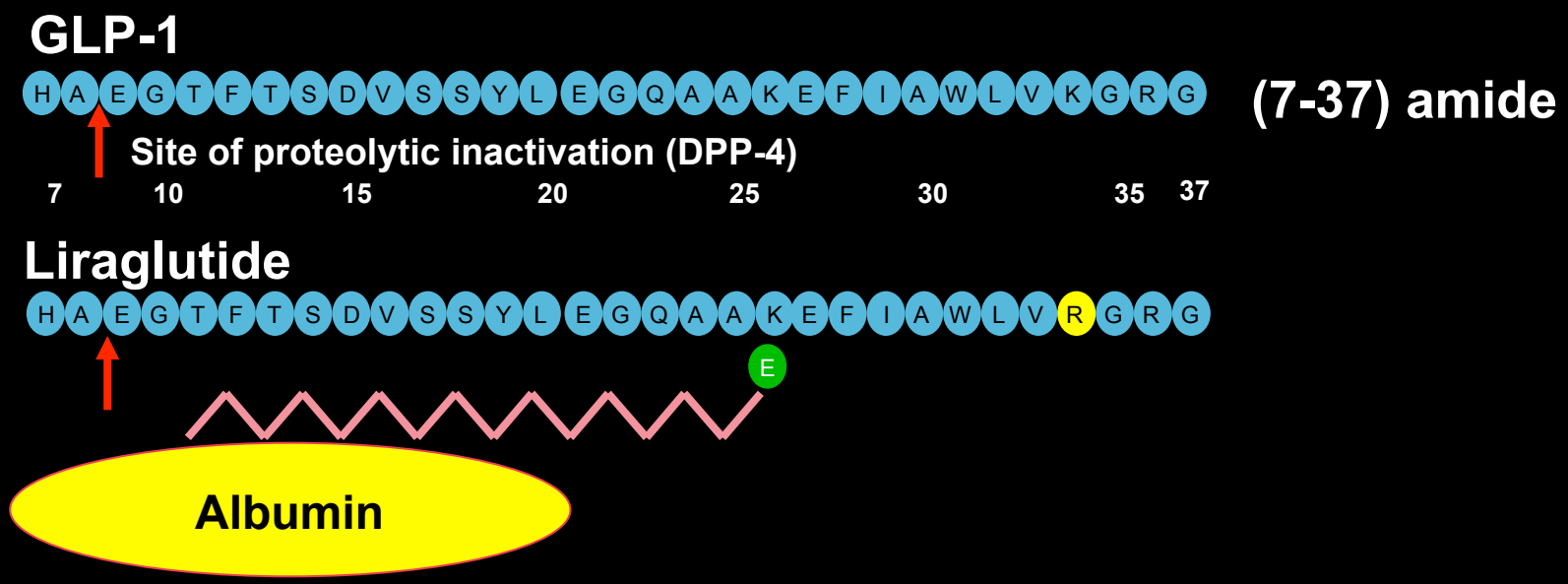
Meier. Nature Rev Endocrinol. 2012;8:728-42.

# Exenatide Once Weekly

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



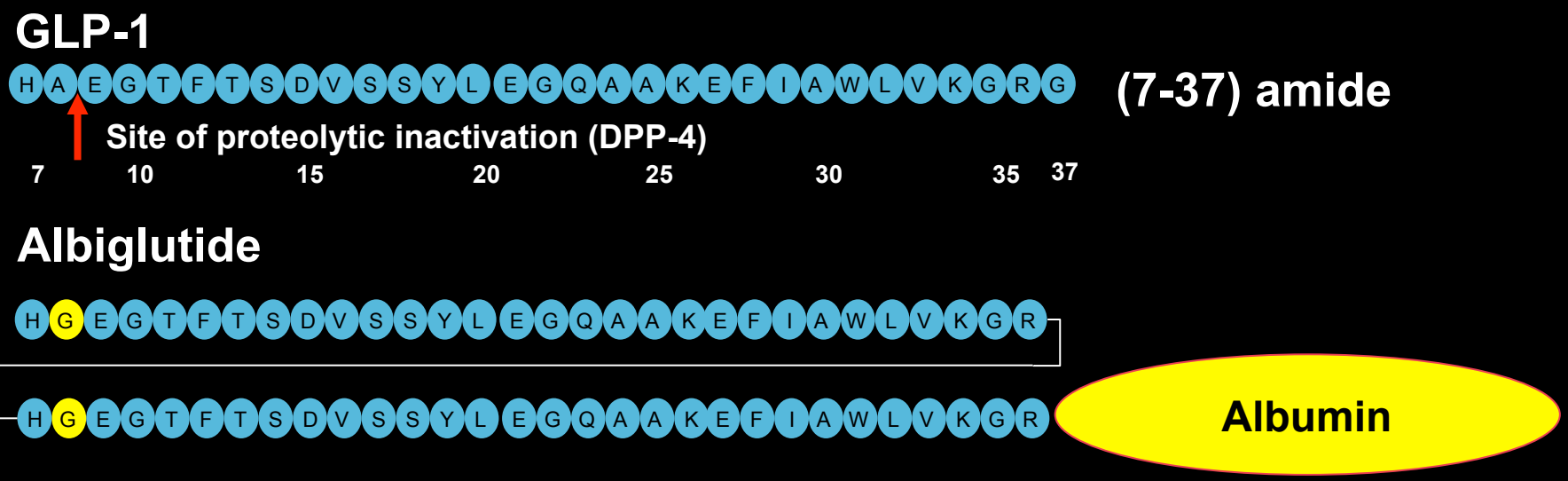
# Liraglutide




- ~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.

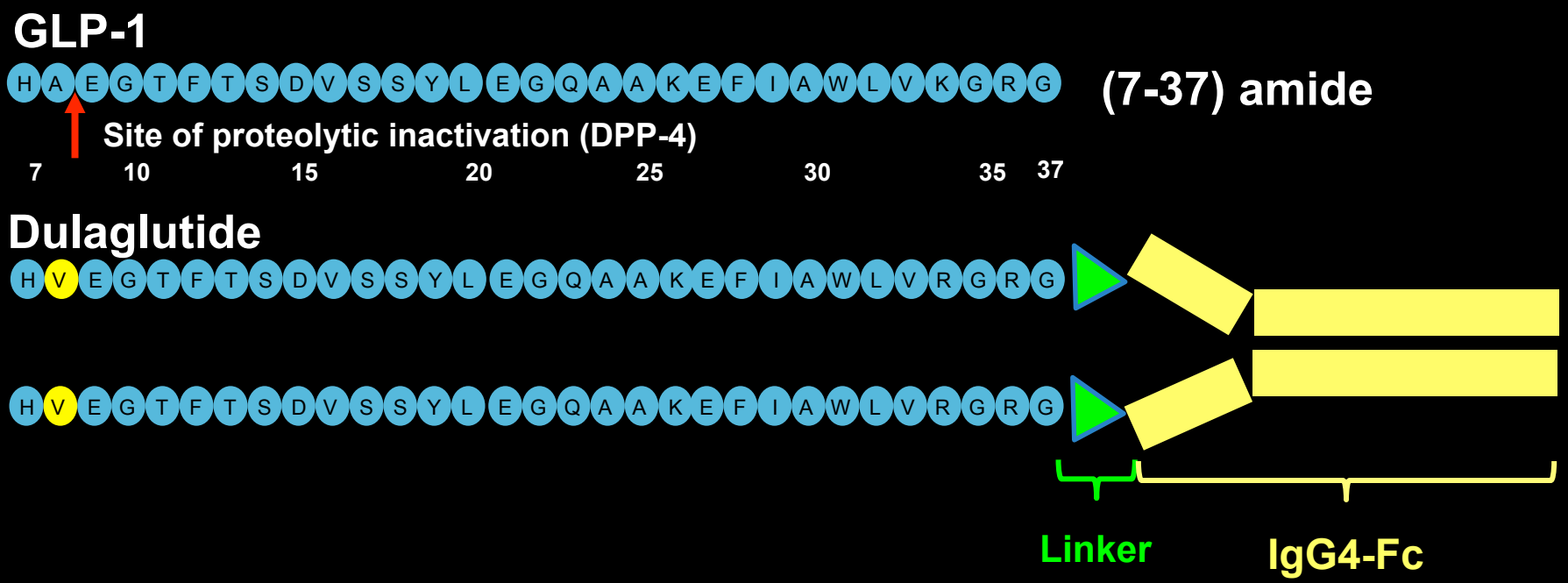
# Albiglutide




- 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

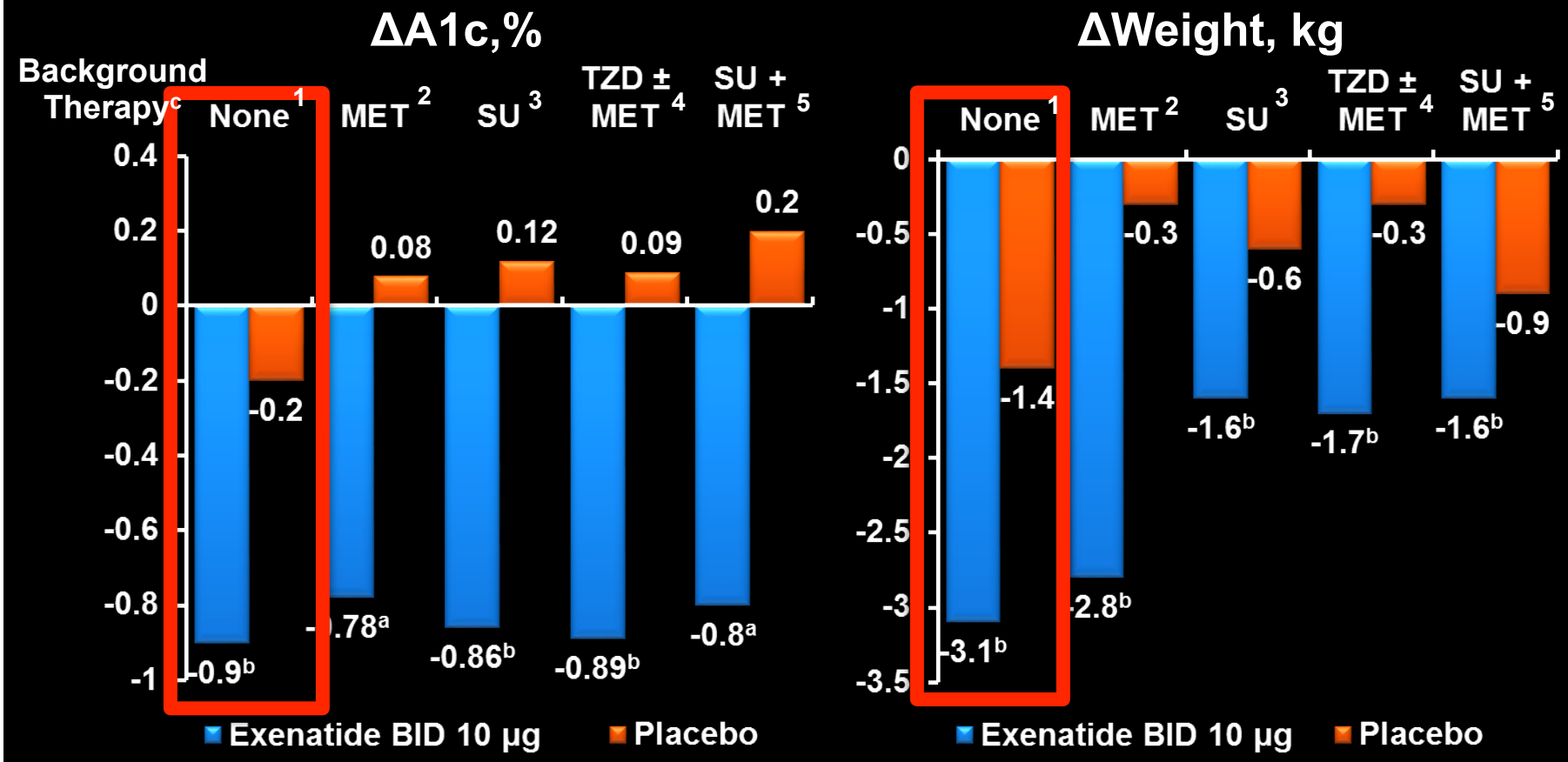



- Modified GLP-1 covalently bound to IgG4-Fc
- DPP-4 resistant
- Half-life ~ 4 days

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

# Exenatide BID

## *Glucose Control and Weight Loss*

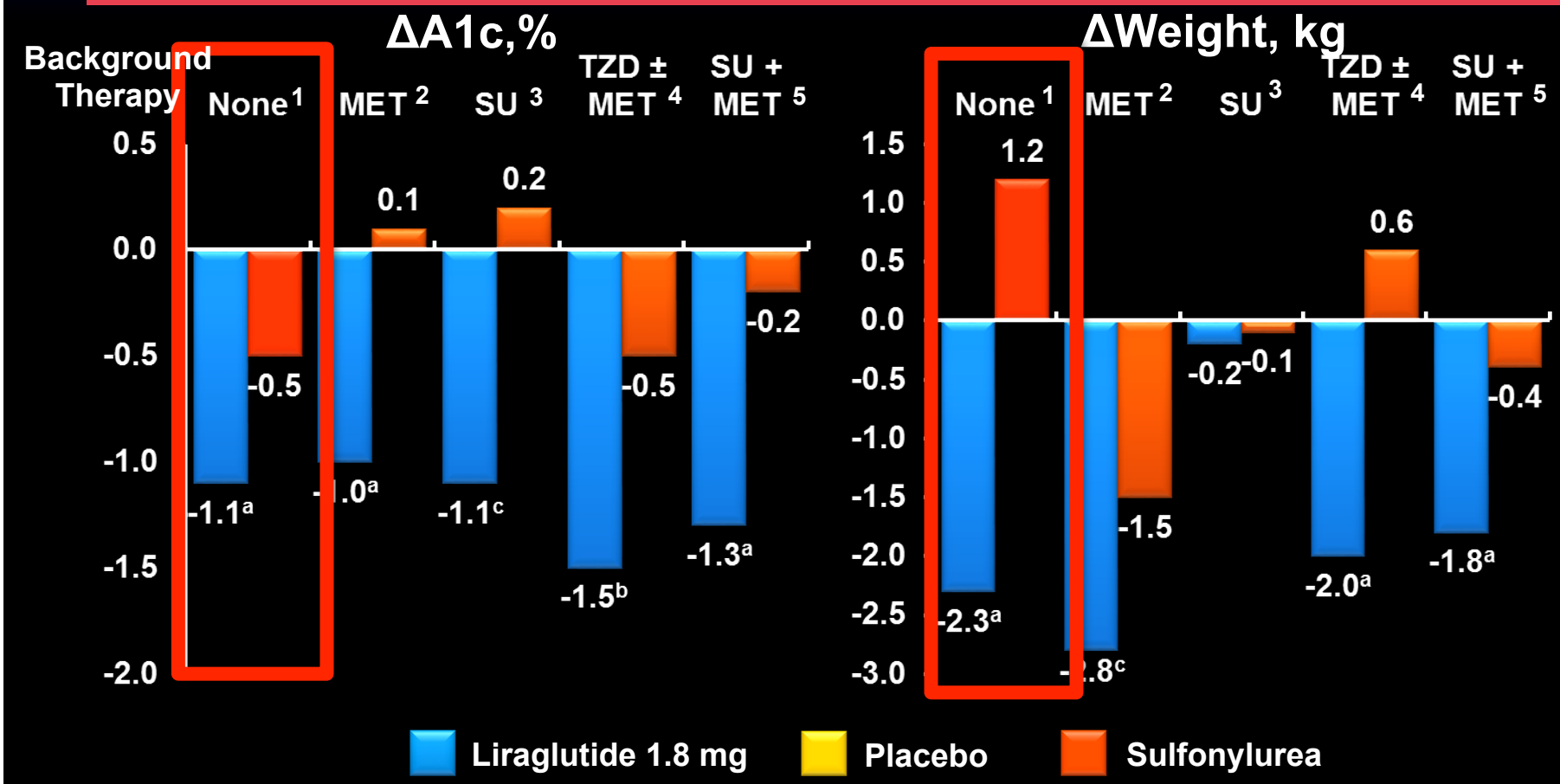



[a]*P*<0.0001 vs placebo; [b]*P*<0.001 vs placebo; [c]16 to 30 weeks, baseline A1c: 7.8%-8.7.
MET, metformin.


1. Moretto et al. Clin Ther. 2008;30:1448-60; 2. DeFronzo et al. Diabetes Care. 2005;28:1092-1100;
3. Buse et al. Diabetes Care. 2004;27:2628-35; 4. Zinman et al. Ann Intern Med. 2007;146:477-85;
5. Kendall et al. Diabetes Care. 2005;28:1083-91.

# Liraglutide

## *Glucose Control and Weight Loss*

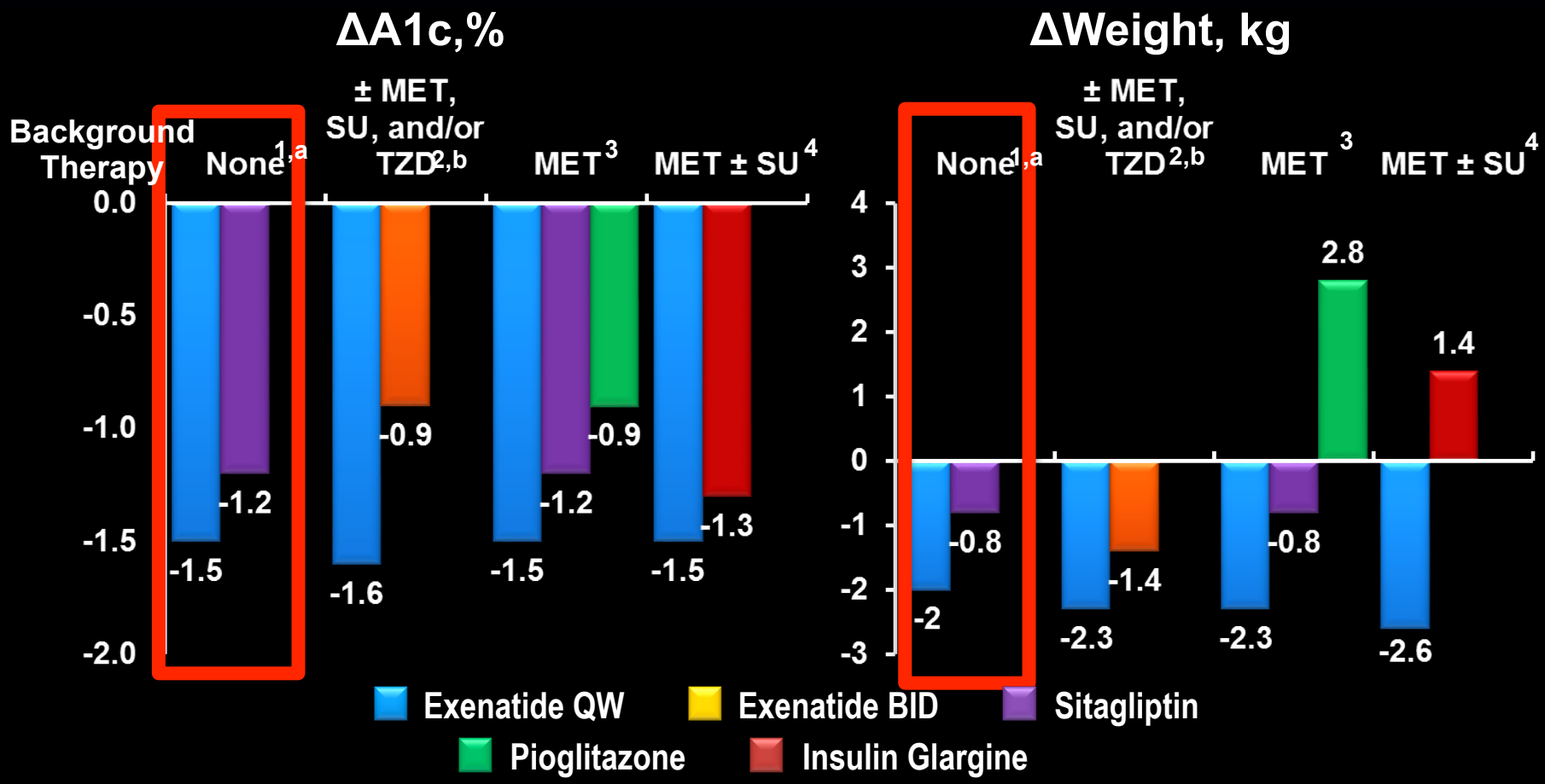



[a]*P*<0.0001 vs comparator; [b]*P*<0.001 vs comparator; [c]*P*<0.01 vs comparator;
[d]26 weeks (except 52 weeks for monotherapy), mean baseline A1c: 8.2%-8.6%.


1. Garber et al. Lancet. 2009;373:473-81; 2. Nauck et al. Diabetes Care. 2009;32:84-90;
3. Marre et al. Diabet Med. 2009;26:268-78; 4. Zinman et al. Diabetes Care. 2009;32:1224-30;
5. Russell-Jones et al. Diabetologia. 2009;52:2046-55.

# Exenatide QW

## *Glucose Control and Weight Loss*

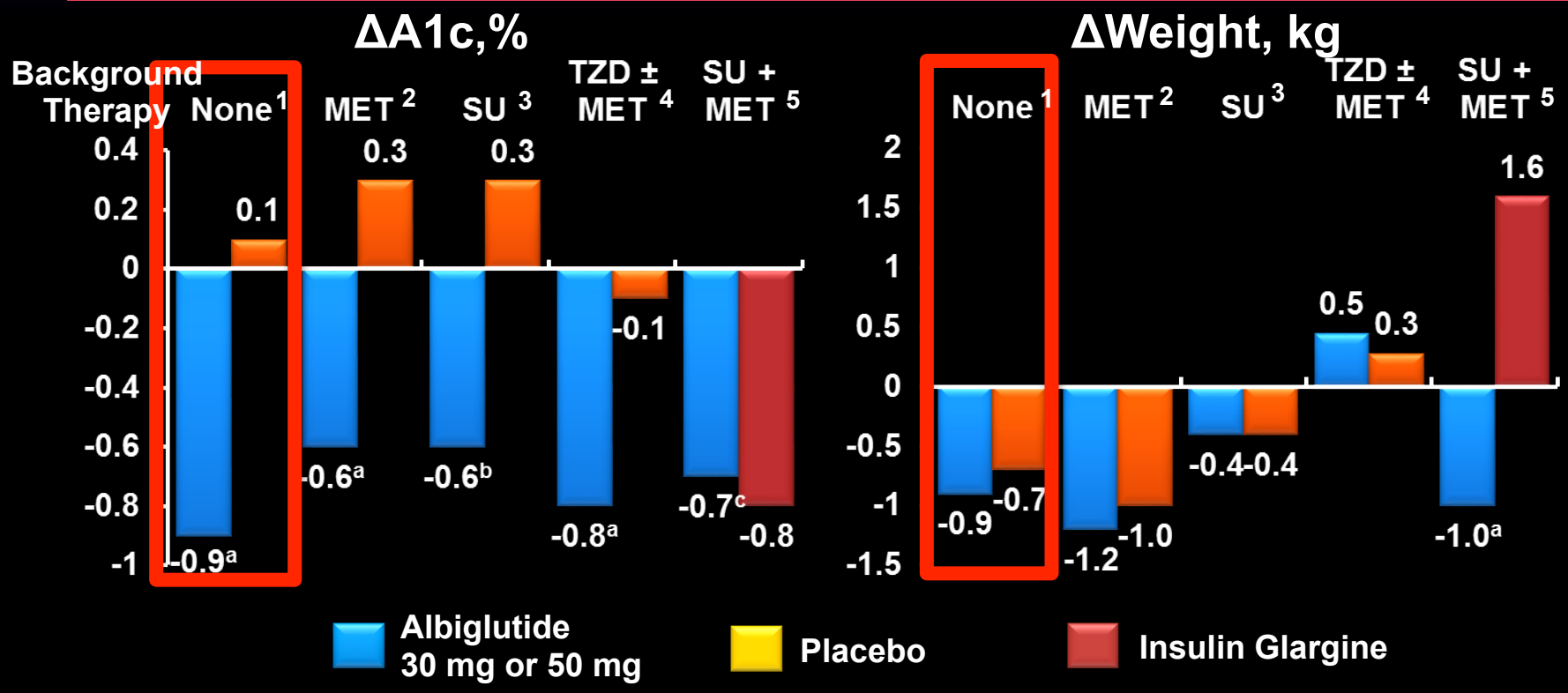



*P*<0.005 for all comparators vs exenatide QW 2 mg.
[a]Only SITA comparator shown (study also included MET and PIO as comparators); [b]Combination therapy allowed.

1. Russell-Jones et al. Diabetes Care. 2012;35:252-58; 2. Blevins et al. J Clin Endocrinol Metab. 2011;96:1301-10; 3. Bergenstal et al. Lancet. 2010;376:431-39; 4. Diamant et al. Lancet. 2010;375:2234-43.

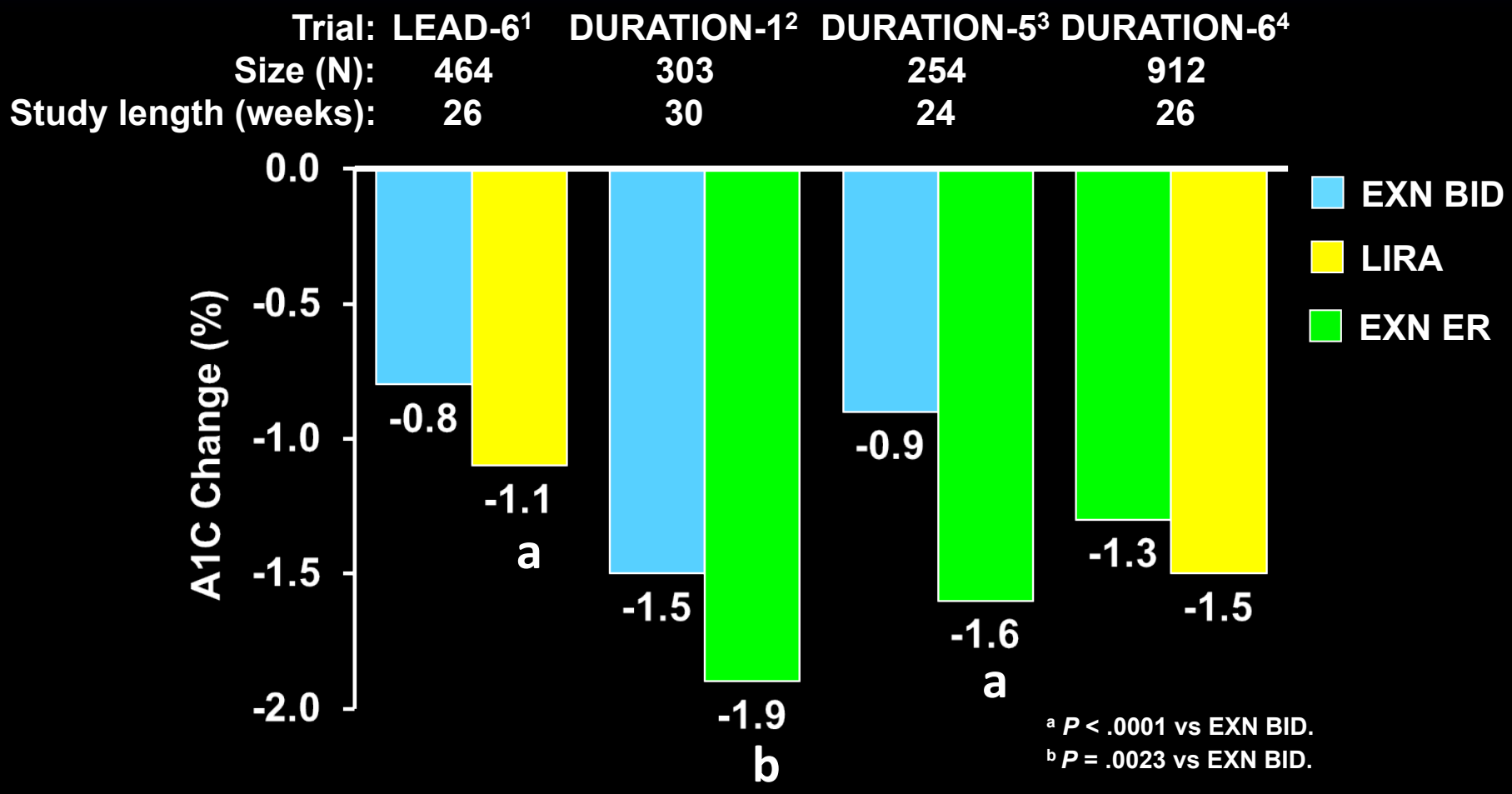
# Albiglutide

## *Glucose Control and Weight Loss*




Nauck et al. ADA 73rd Scientific Sessions; June 21-25, 2013; Chicago, IL. Stewart et al. 49th Annual Meeting for the EASD; September 23-27, 2013; Barcelona, Spain. Reusch et al. ADA 73rd Scientific Sessions; June 21-25, 2013; Chicago, IL. Pratley et al. ADA 73rd Scientific Sessions; June 21-25, 2013; Chicago, IL.

# Glycemic Control With GLP-1 RAs in Head-to-Head Clinical Trials

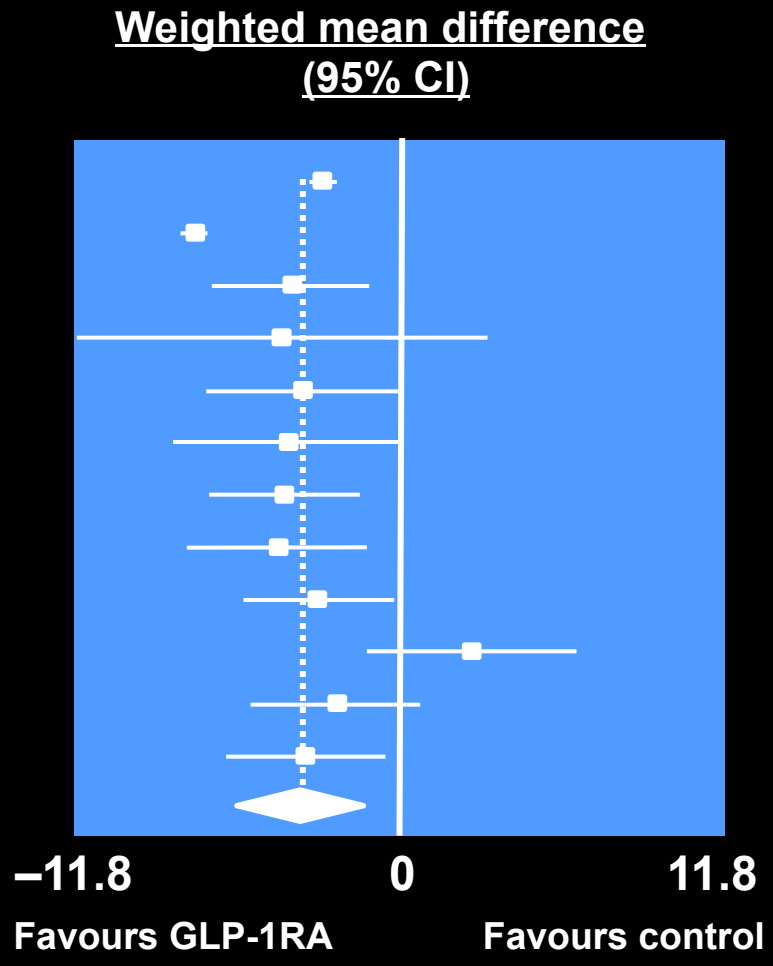




1. Buse et al. Lancet. 2009;374:39-47.
2. Drucker et al. Lancet. 2008;372:1240-50.
3. Blevins et al. J Clin Endocrinol Metab. 2011;96:1301-10.
4. Buse et al. EASD 47th Annual Meeting. 2011 [abstract 75].

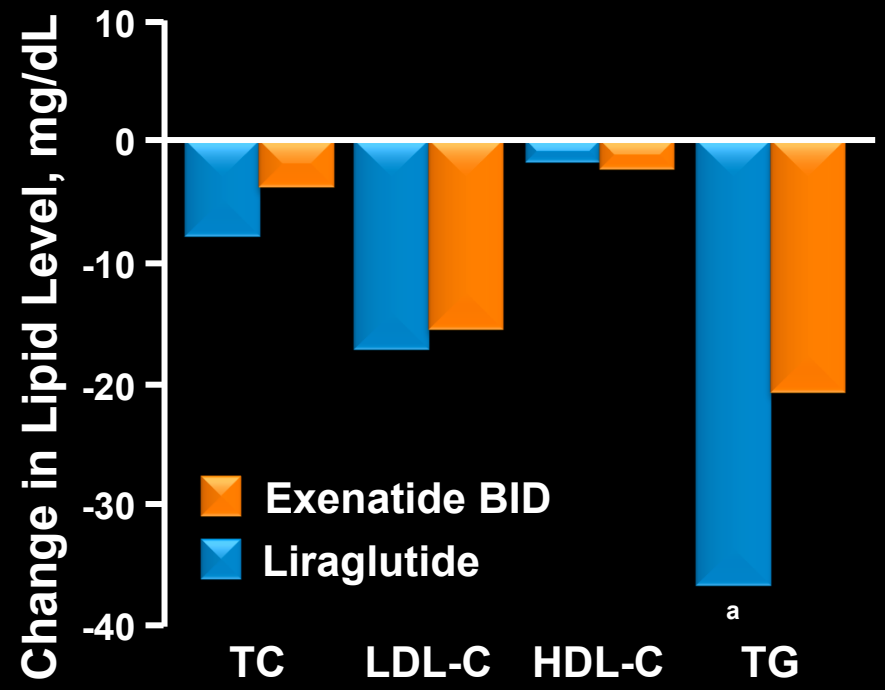
# GLP-1 RAs Lower Blood Pressure Compared to Controls

| 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; $p<0.01$ | | |

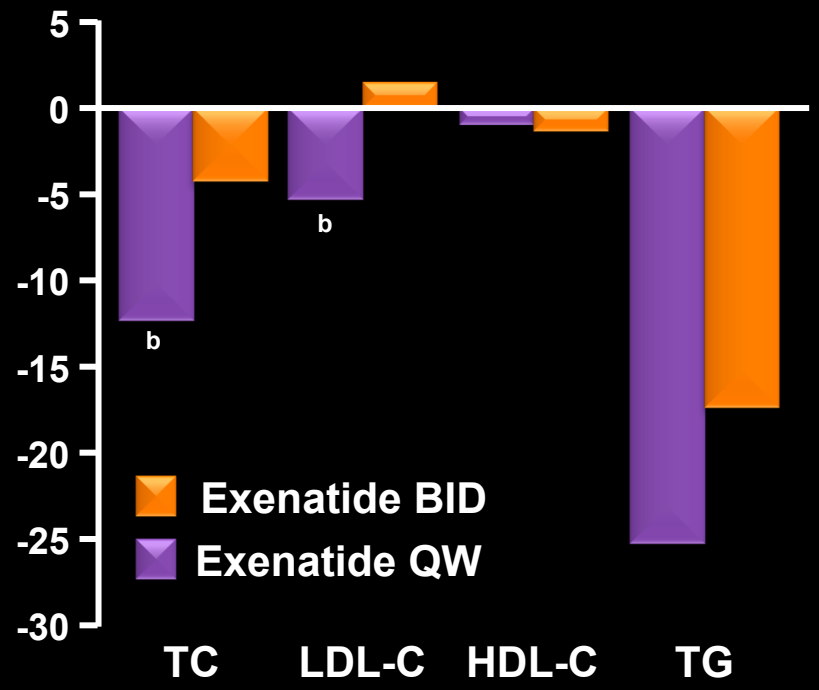



Adapted from Vilsbøll et al. Br Med J. 2012;344:d7771.

# 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.

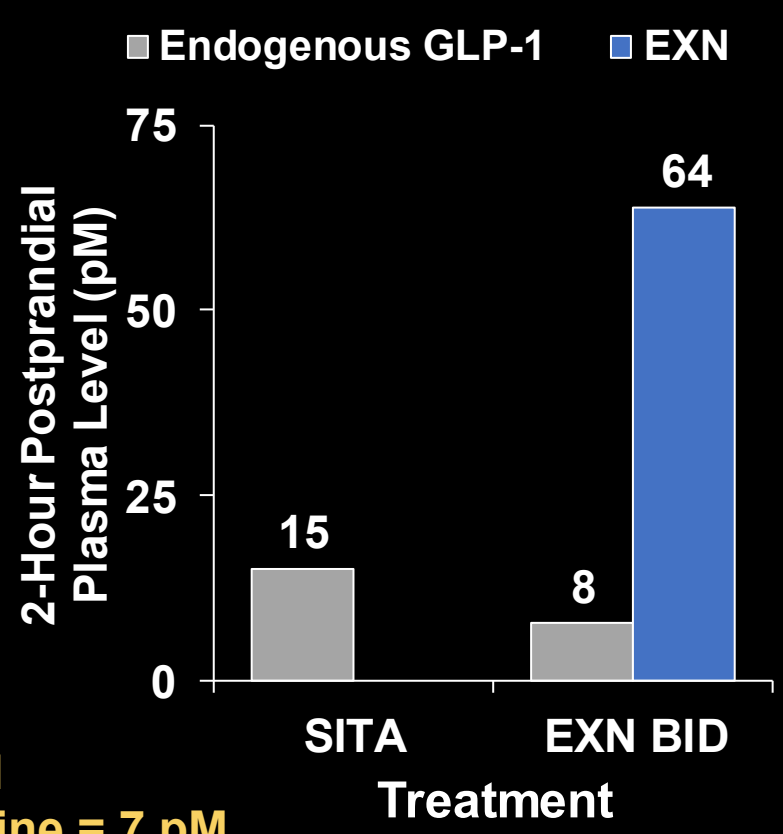
1. Buse et al. Lancet. 2009;374:39-47.
N=464 patients with inadequately controlled T2DM on maximally tolerated doses of metformin, sulfonylurea, or both.
2. Drucker et al. Lancet. 2008;372:1240-50.
N=295 patients with T2DM who were naive to drug therapy, or on 1 or more oral antidiabetic agents.

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

| Parameters | Short-Acting | Long-Acting |
|---|---|---|
| Half-life | 2-5 h | 12 h-several days |
| FBG levels | Modest reduction | Strong reduction |
| Fasting insulin secretion | Modest stimulation | Strong stimulation |
| PP hyperglycemia | Strong reduction | Modest reduction |
| PP insulin secretion | Reduction | Modest stimulation |
| Glucagon secretion | Reduction | Reduction |
| Blood pressure | Reduction | Reduction |
| Heart rate increase | None/small (↑ 0-2 bpm) | Moderate (↑ 2-5 bpm) |
| Body weight reduction | 1-5 kg | 2-5 kg |
| Gastric emptying rate | Deceleration | No substantial long-term effects |
| Nausea induction/attenuation | 20%-50%/weeks-months | 20%-40%/≈4-8 weeks |

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

# Differences in the Mechanisms of Action of DPP-4 Inhibitors and GLP-1 RAs




GLP-1 Baseline = 7 pM

- **GLP-1 RAs**[1,2,a]
  - Subcutaneous administration
  - Add exogenous GLP-1 activity
  - Increase GLP-1 activity ≈ 9-fold
  - Greater A1C and weight effects than DPP-4 inhibitors
- **DPP-4 inhibitors**[1,a]
  - Oral administration
  - Block DPP-4 degradation of GLP-1
  - Increase endogenous GLP-1 levels ≈ 2-fold
  - Increase endogenous GIP levels

EXN BID, exenatide twice daily; SITA, sitagliptin.

[a] Cross-over study, 2-week segments (N = 61).[1]

# Advantages and Disadvantages of DPP-4 Inhibitors

## Advantages

- Enhance insulin secretion
- Decrease glucagon
- Glucose dependent
- Physiologic route
- Oral, once daily
- Superior tolerability
- Weight neutral
- No apparent CV risk

## Disadvantages

- Cost
- Efficacy
- Unknown long term safety
- Durability?

# Advantages and Disadvantages of GLP-1 Receptor Agonists

## Advantages

- Enhances insulin secretion
- Decreases glucagon
- Glucose dependent
- Low risk of hypoglycemia
- Quick onset
- Superior efficacy
- Weight loss
- Low risk of drug-drug interaction

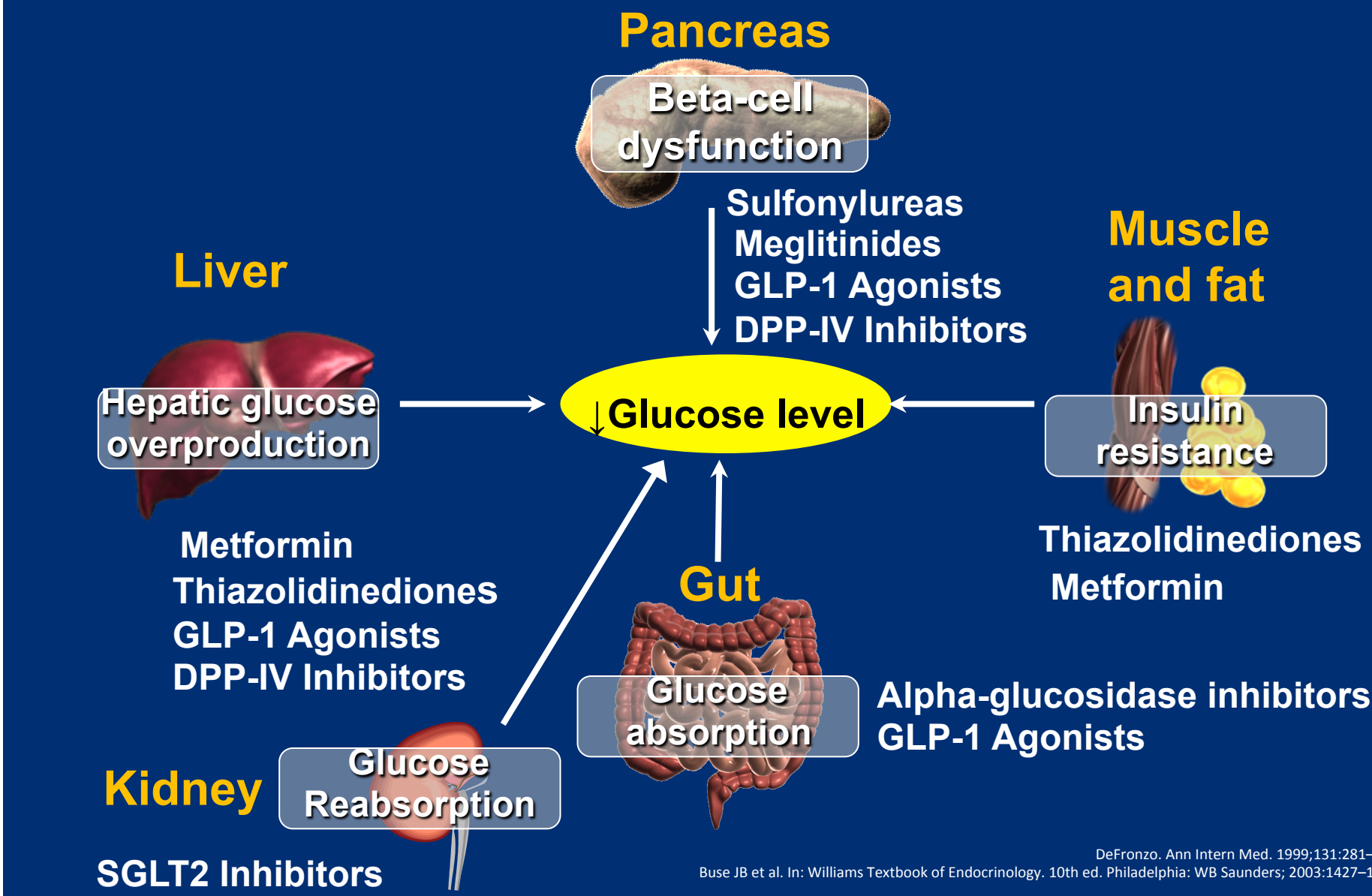
## Disadvantages

- Cost
- Injection
- Nausea
- Pancreatitis warning
- Unknown long term safety
- Durability?

# Renal Involvement in the Control of Plasma Glucose

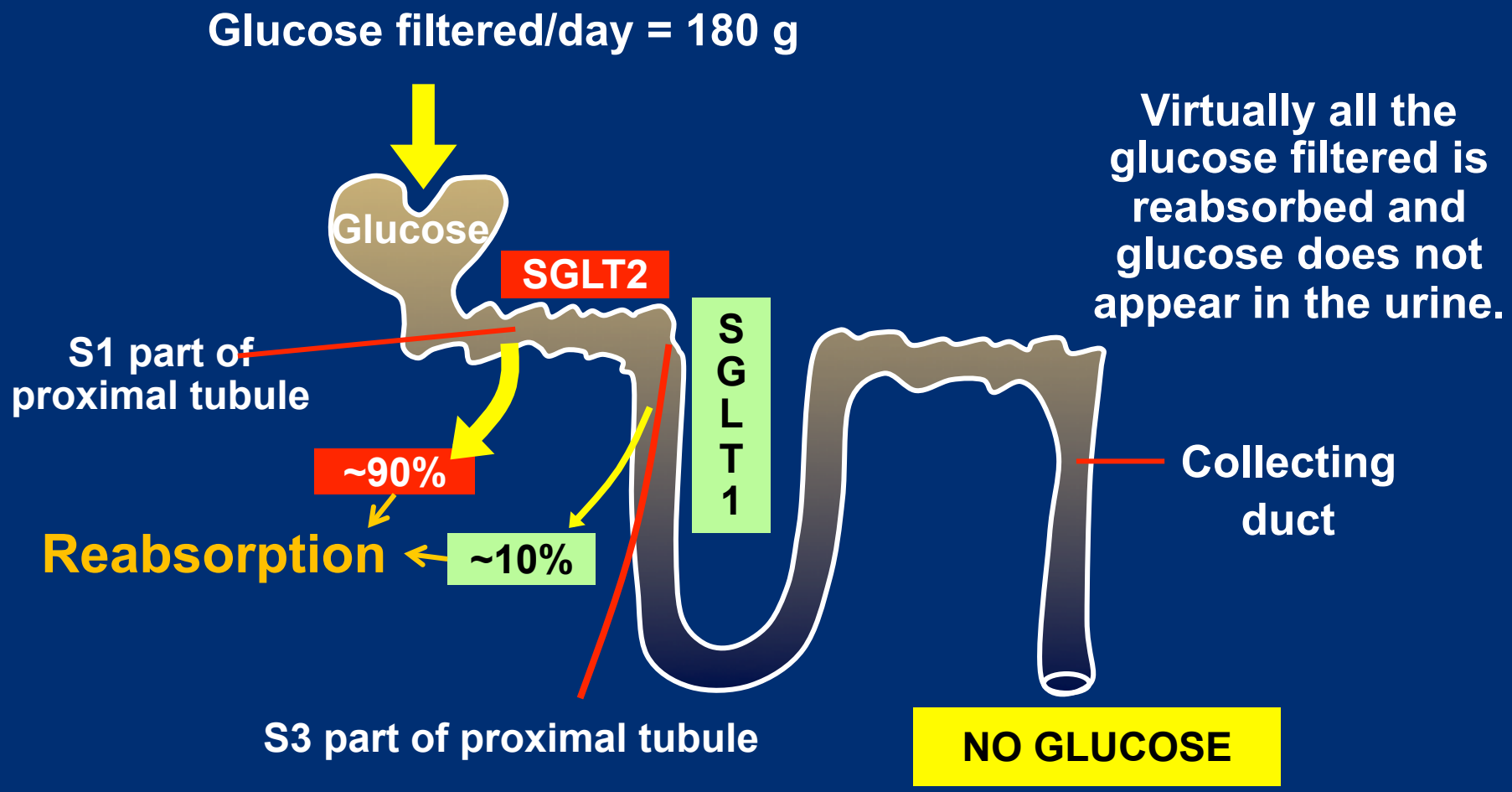
Mark E. Molitch, MD
Div. of Endocrinology,
Metabolism and Molecular Medicine
Northwestern Univ. Feinberg School of Medicine
Chicago, Illinois

# Major Targeted Sites of Drug Classes




DeFronzo. Ann Intern Med. 1999;131:281–303.
Buse JB et al. In: Williams Textbook of Endocrinology. 10th ed. Philadelphia: WB Saunders; 2003:1427–1483.

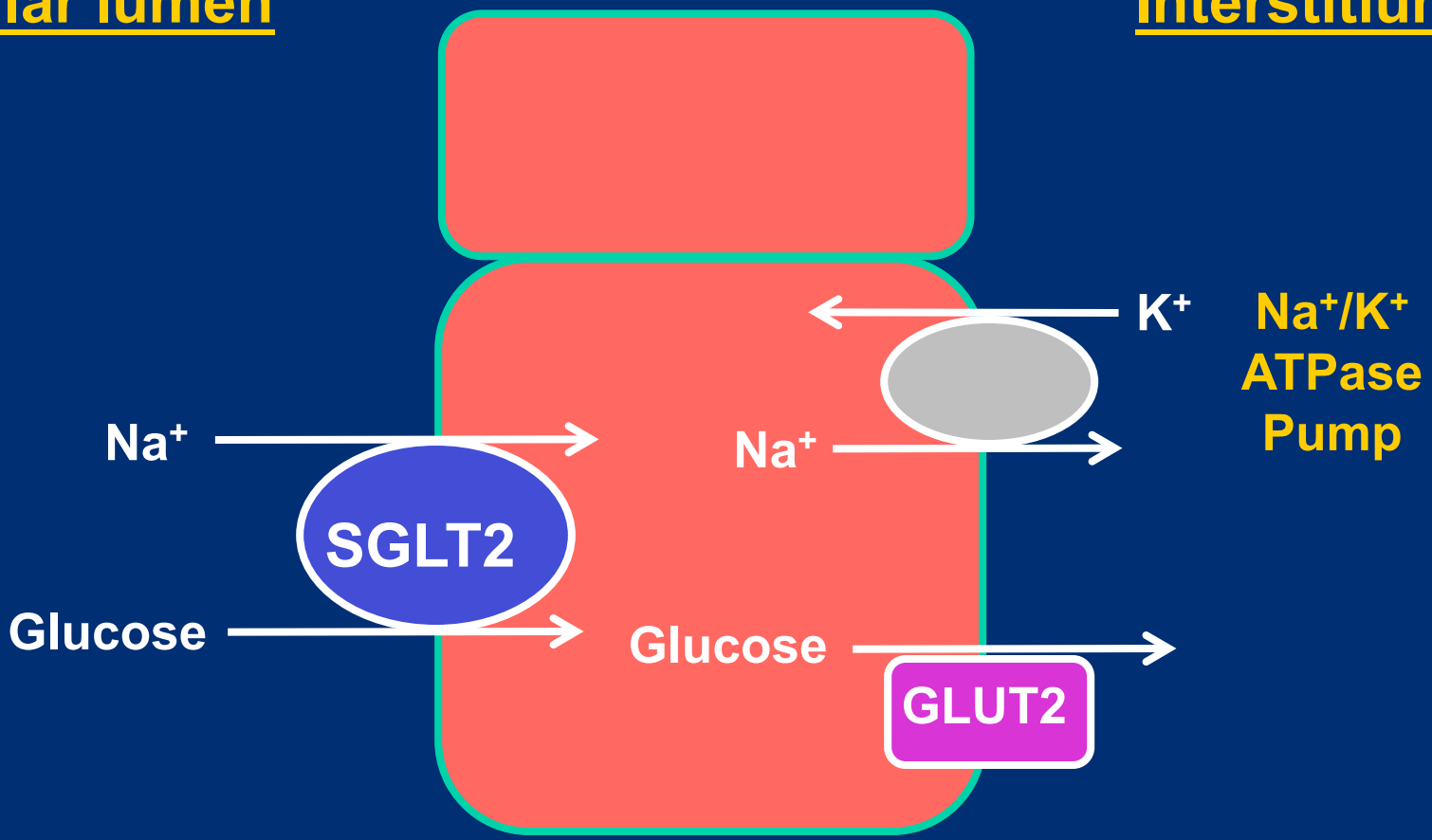
# Renal Handling of Glucose, Non-Diabetic Individual




SGLT, Sodium-glucose cotransporter

Wright. Am J Physiol Renal Physiol. 2001;280:F10-F18. Thorens B. Am J Physiol. 1996;270:G541-G553.

# Active (SGLT2) and Passive (GLUT2) Glucose Transport in a Renal Proximal Tubule Cell

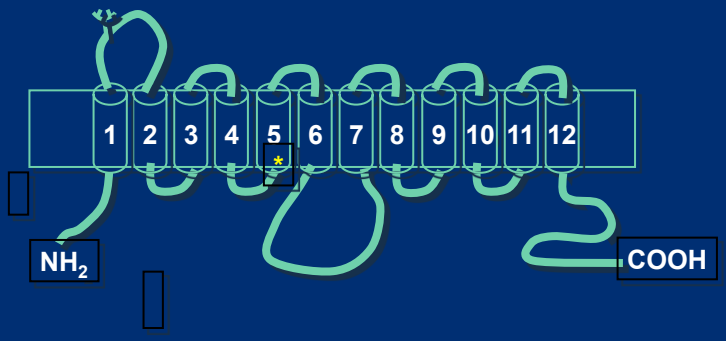



Nair et al. J Clin Endocrinol Metab. 2010;95:34-42.

# Two Families of Glucose Transporters

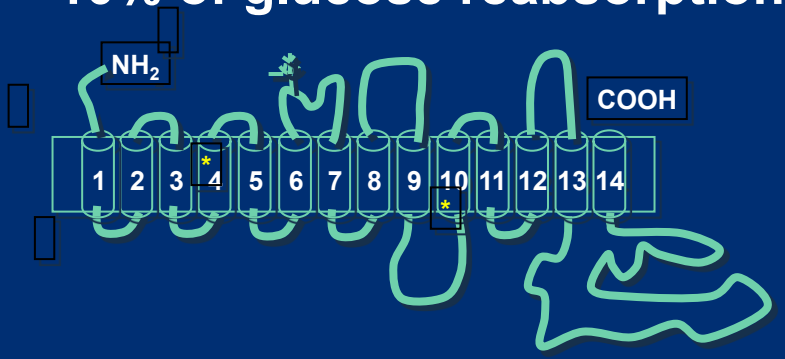
## GLUT Family

- Facilitated glucose transporters
- Passive, downhill transport
- GLUT1 (widespread including the kidneys)
- GLUT2 (kidneys and pancreas)
- GLUT4 (muscle and adipose tissue)




## SGLT Family

- Sodium coupled glucose cotransporter
- Active transport of glucose
- SGLT2 (proximal tubule) – 90% of glucose reabsorption
- SGLT1 (brush border of small intestine & proximal tubule) – 10% of glucose reabsorption



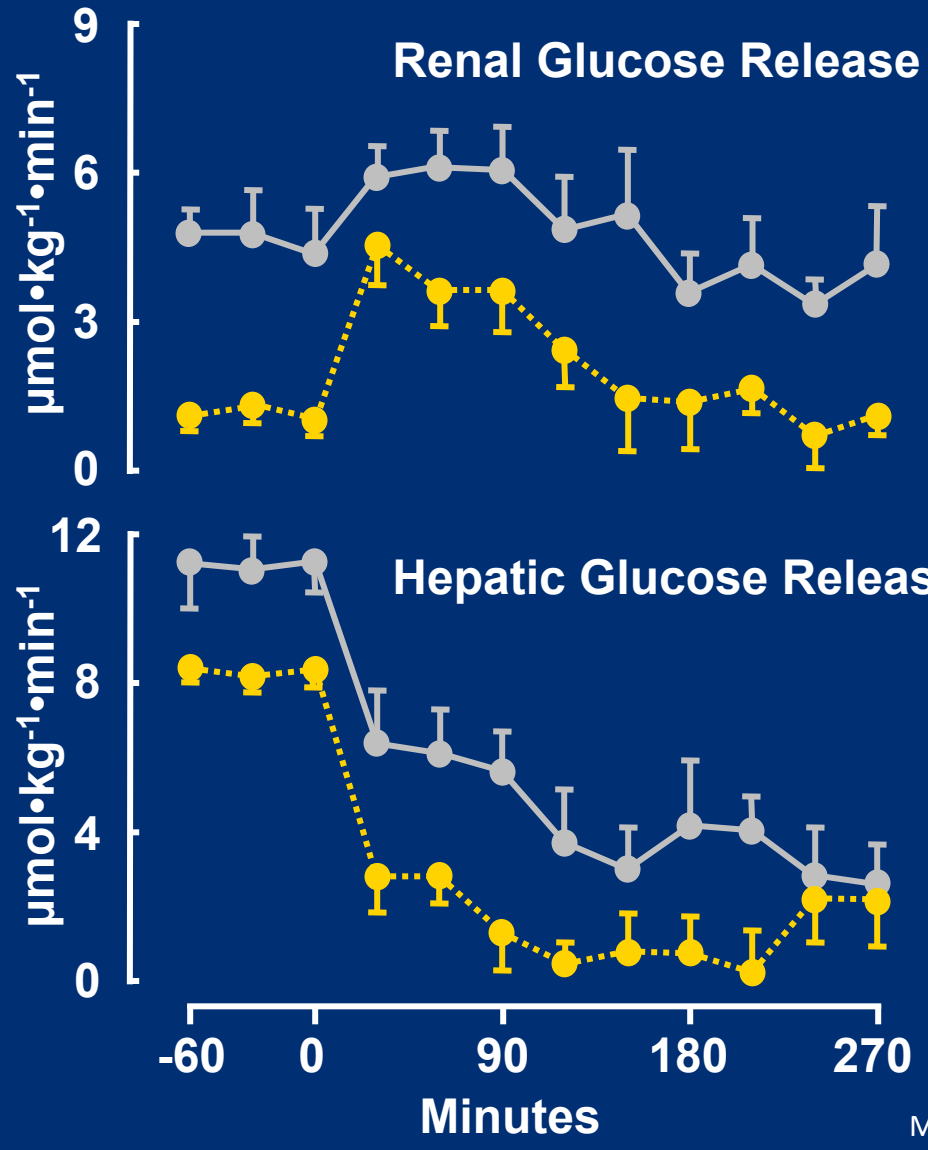

Longo et al. Adv Pediatr. 1998;45:293-313.

# Altered Renal Glucose Control in Diabetes

- Gluconeogenesis is increased in postprandial and postabsorptive states in patients with type 2 diabetes
  - Renal contribution to hyperglycemia
  - 3-fold increase relative to patients without diabetes
- Glucose reabsorption
  - Increased SGLT2 expression and activity in renal epithelial cells from patients with diabetes vs normoglycemic individuals

Marsenic. Am J Kidney Dis. 2009;53:875-83.
Bakris et al. Kidney Int. 2009;75:1272-77.
Rahmoune et al. Diabetes. 2005;54:3427-34.

# Renal and Hepatic Glucose Release After Glucose Ingestion in Patients With Diabetes




- Increased baseline gluconeogenesis
- Insulin resistance with decreased suppression of gluconeogenesis
- Increased free fatty acids in DM stimulates gluconeogenesis in kidney & liver

With diabetes (n = 10)

Without diabetes (n = 10)

Meyer et al. Am J Physiol Endocrinol Metab. 2004;287:E1049-E1056.

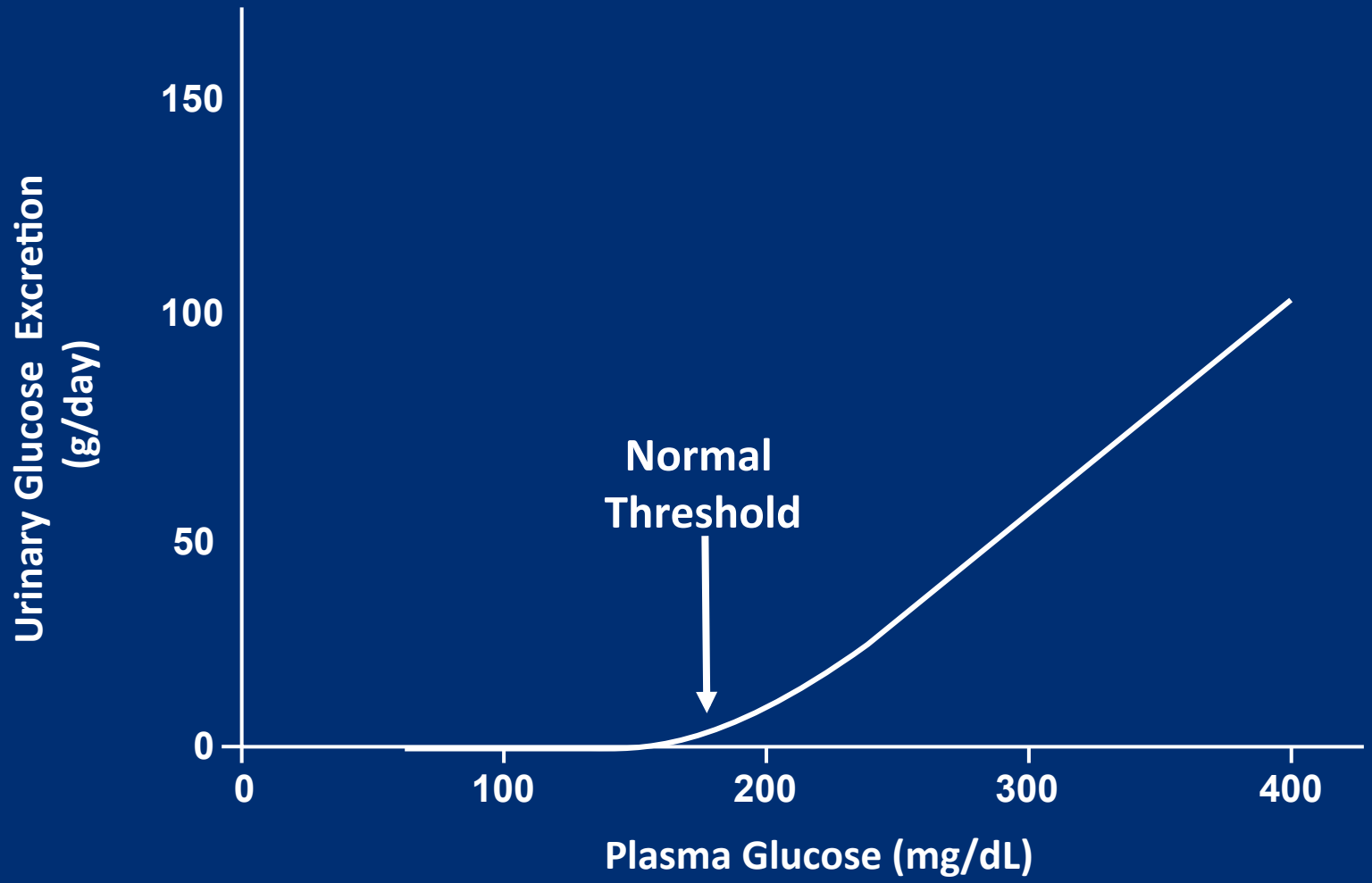
# Max Tubular Glucose Reabsorption ($TM_G$) is Increased in Diabetes

| Type 1 Diabetes (N=10) | | Controls (N=9) |
|---|---|---|
| 419 ± 16 | vs | 352 ± 24 mg/min |

| Type 2 Diabetes (N=12) | | Controls (N=9) |
|---|---|---|
| 424 ± 30 | vs | 357 ± 46 mg/min |

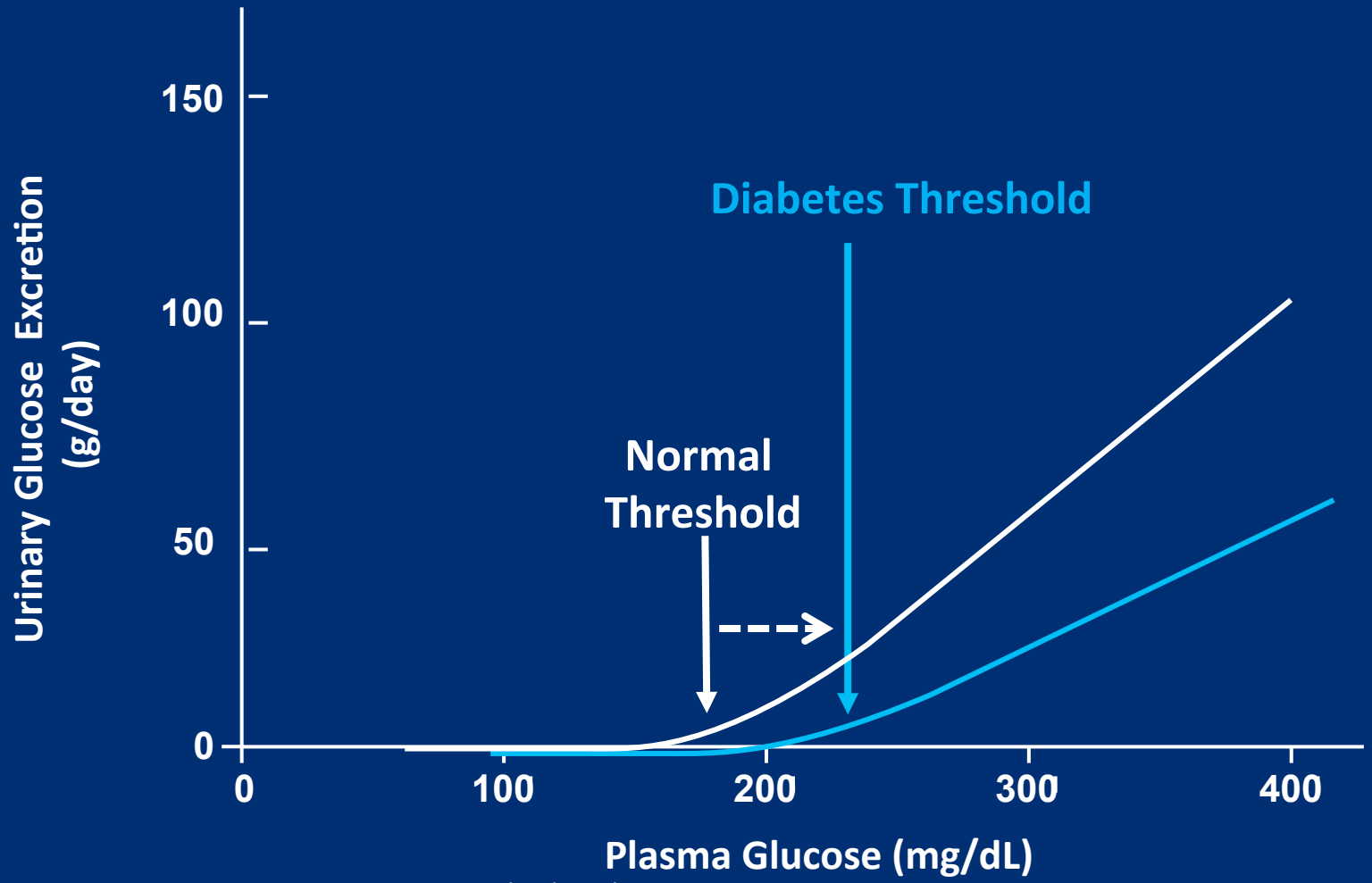
Mogensen.Scand J Clin Lab Invest. 1971; 28:101. Farber et al. J Clin Invest. 1951; 30:125.

# Renal Glucose Handling



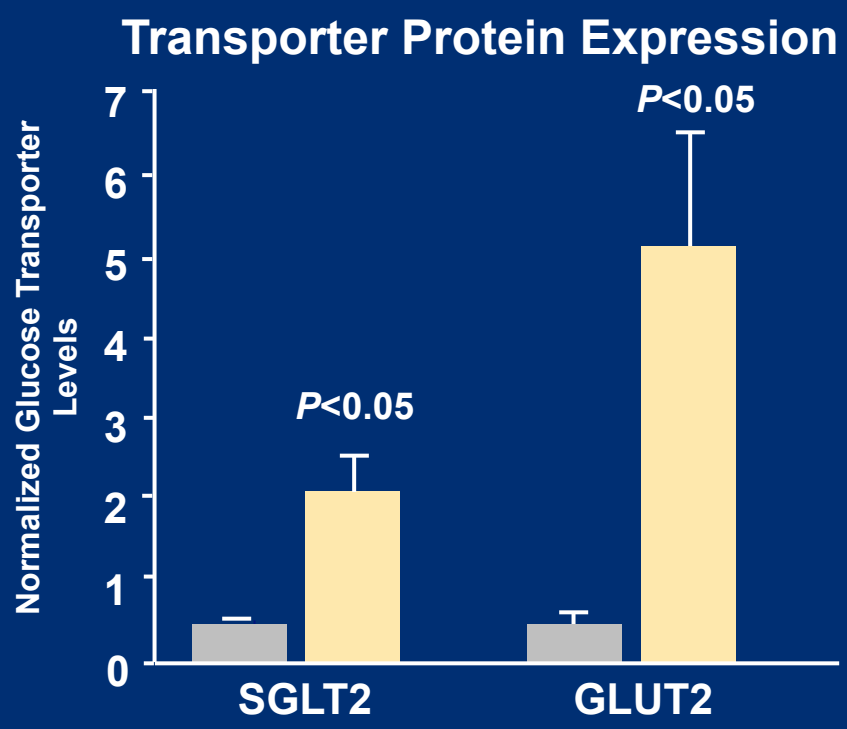

Farber et al. J Clin Invest 1951 30:125-29; Morgensen. Scand J Clin Lab Invest 1971; 28:101-09;
Silverman, Turner. Handbook of Physiology. In: Windhager EE, ed. Oxford University Press; 1992:2017-38;
Cersosimo et al. Diabetes 2000;49:1186-93; DeFronzo et al. Endocrine Practice 2008 14: 782-90.

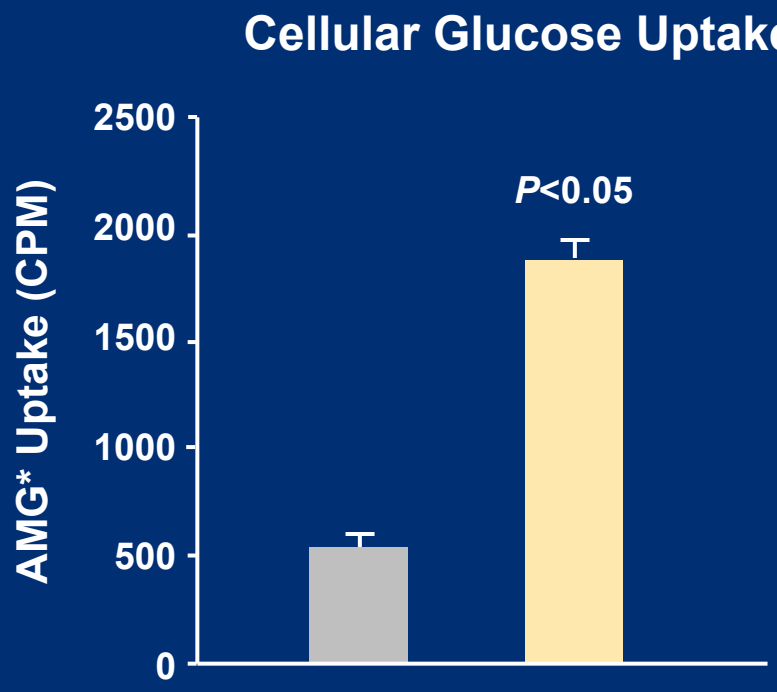
# Renal Glucose Handling in Diabetes




Farber et al. J Clin Invest 1951 30:125-29; Morgensen. Scand J Clin Lab Invest 1971; 28:101-09;
Silverman, Turner. Handbook of Physiology. In: Windhager EE, ed. Oxford University Press; 1992:2017-38;
Cersosimo et al. Diabetes 2000;49:1186-93; DeFronzo et al. Endocrine Practice 2008 14: 782-90.

# Upregulation of SGLT2 Transporter and Enhanced Glucose Uptake in T2DM*




*Primary Cultured Proximal Tubule Epithelial Cells

Healthy (n=4) Type 2 Diabetes (n=4)

AMG, methyl-α-D-[U-$^{14}$C]-glucopyranoside

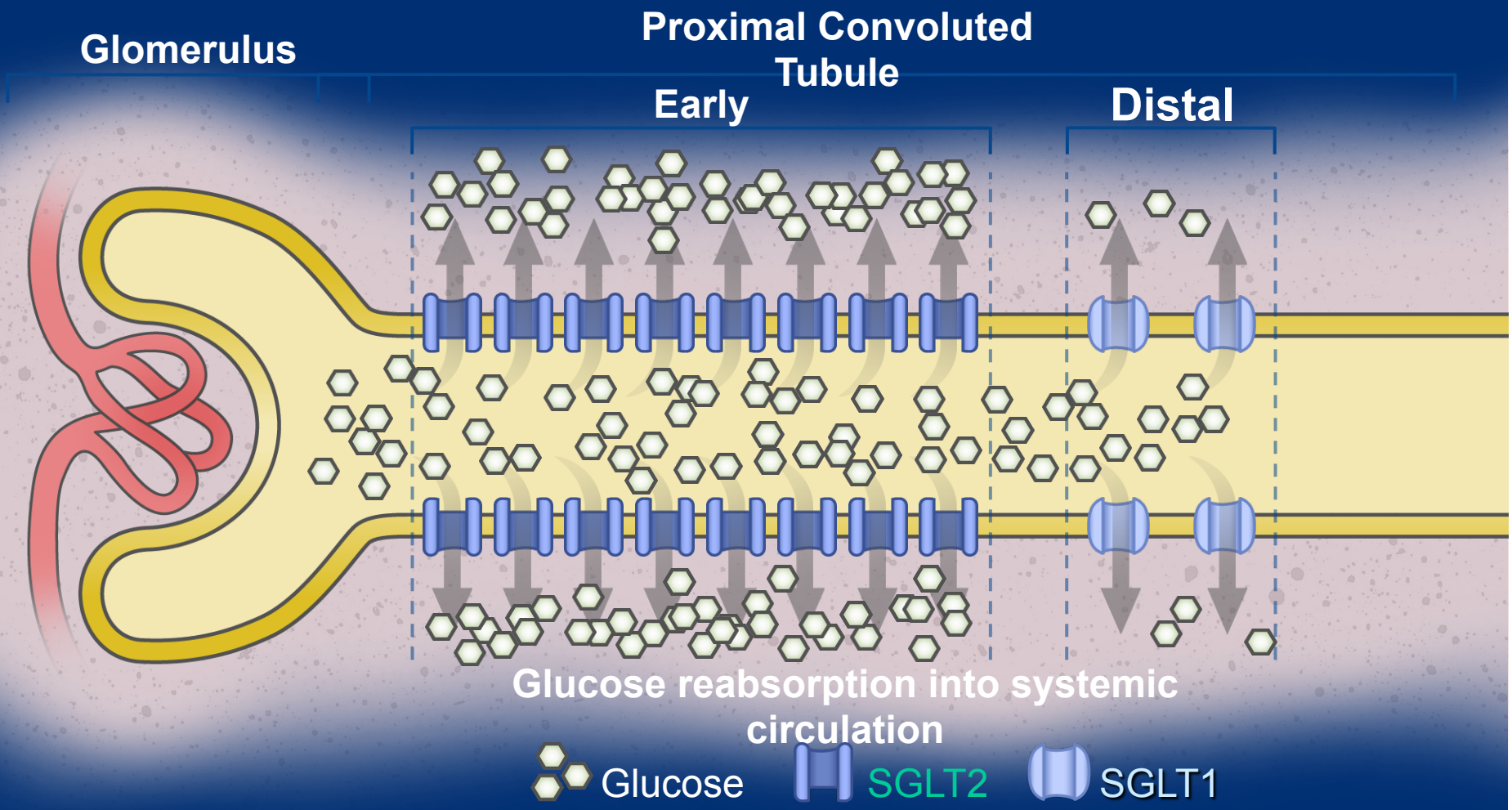
Rahmoune et al. Diabetes. 2005;54:3427-34.

# Implications

- An adaptive response to conserve glucose (i.e. for energy needs) becomes *maladaptive* in diabetes

- Moreover, the ability of the kidney to conserve glucose may be augmented by an absolute increase in the renal Tm for glucose

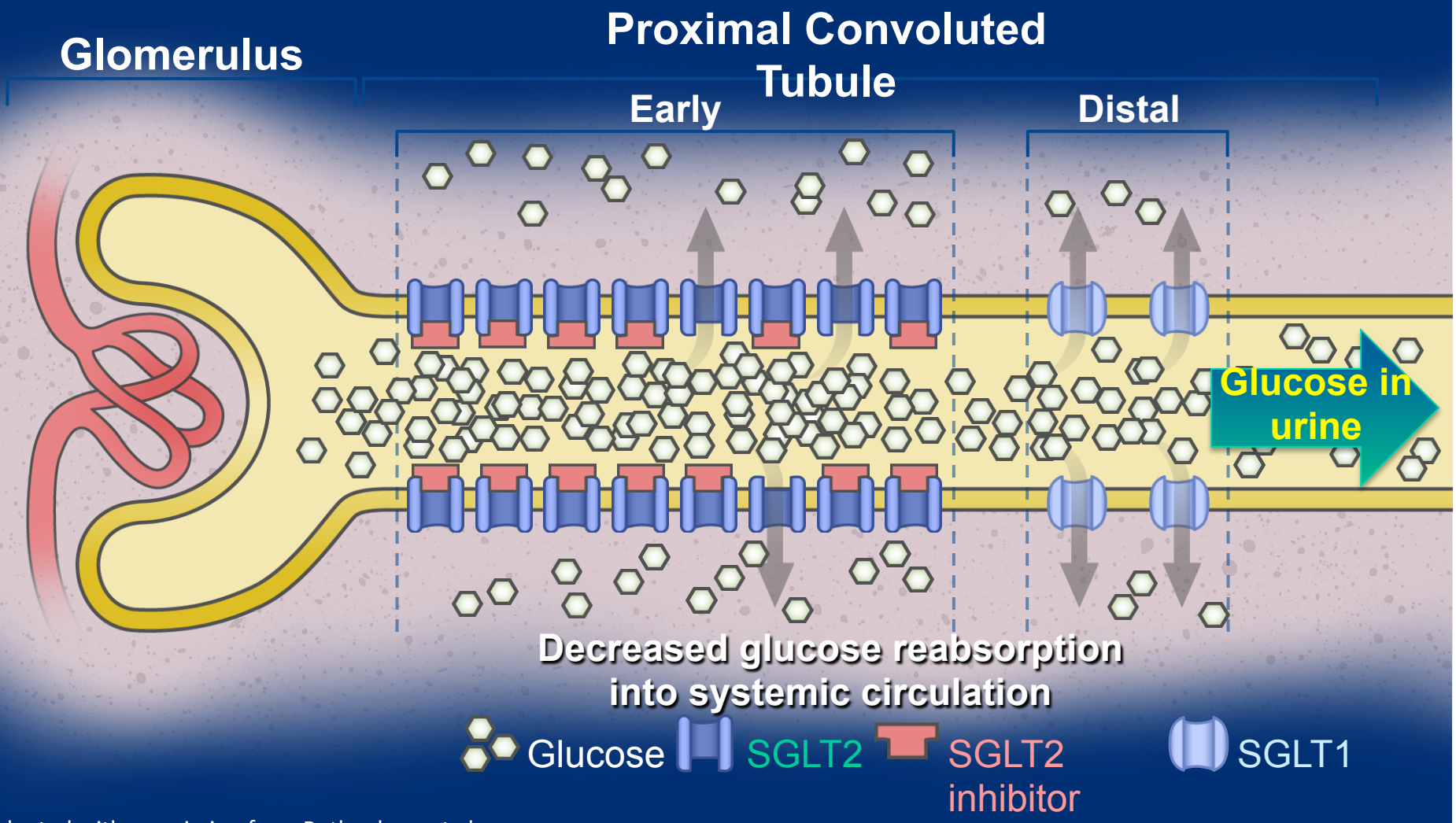
# Normal Kidney




Adapted with permission from Rothenberg et al.
SGLT = sodium-glucose co-transporter.

1. Kanai et al. J Clin Invest. 1994;93:397-404. 2. You G et al. J Biol Chem. 1995;270:29365-29371. 3. Rothenberg et al. Presented at: 46th European Association for the Study of Diabetes Annual Meeting; September 20-24, 2010; Stockholm, Sweden.

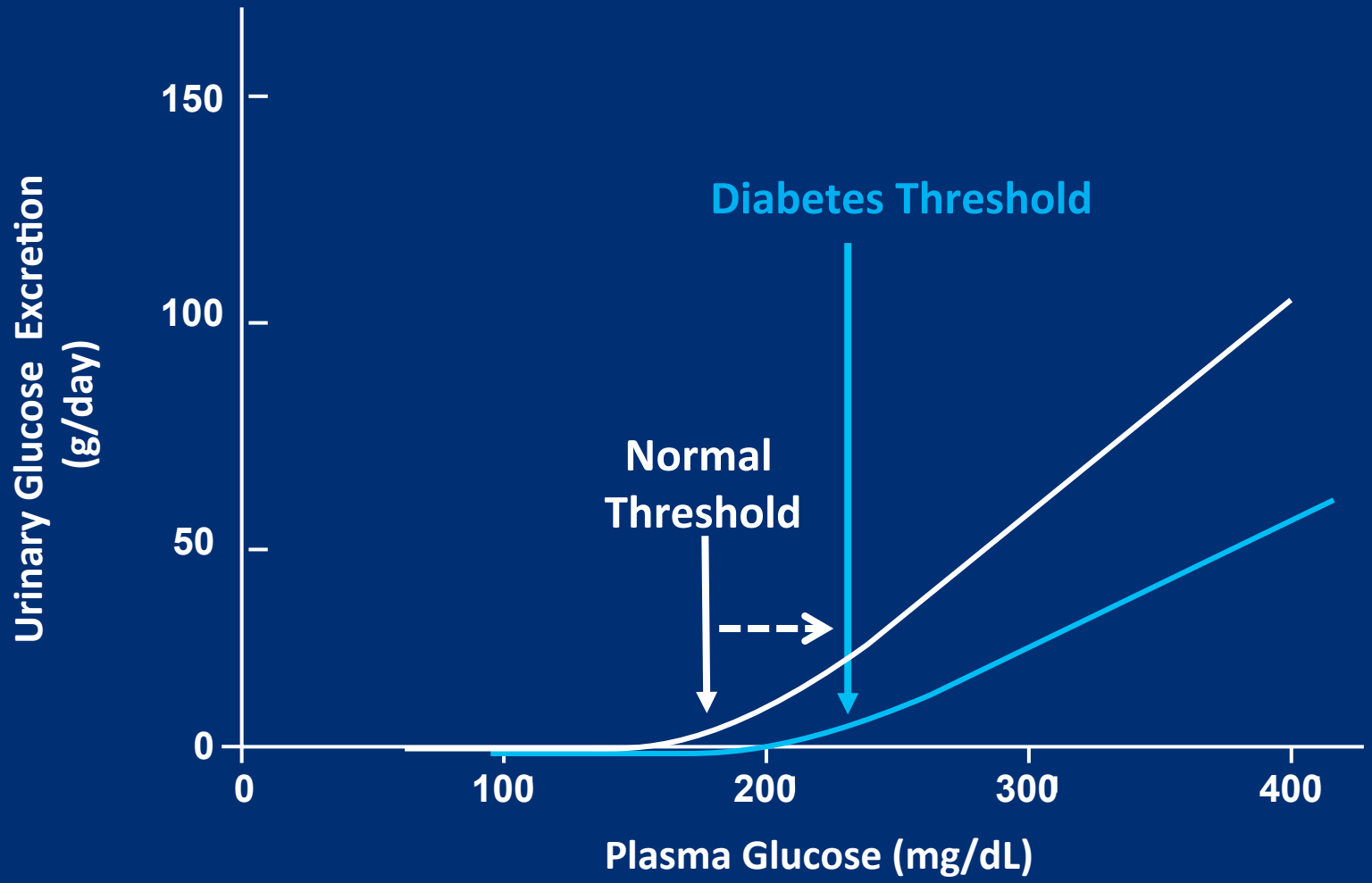
# Treatment with SGLT-2 Inhibitor




Adapted with permission from Rothenberg et al.
SGLT = sodium-glucose co-transporter.

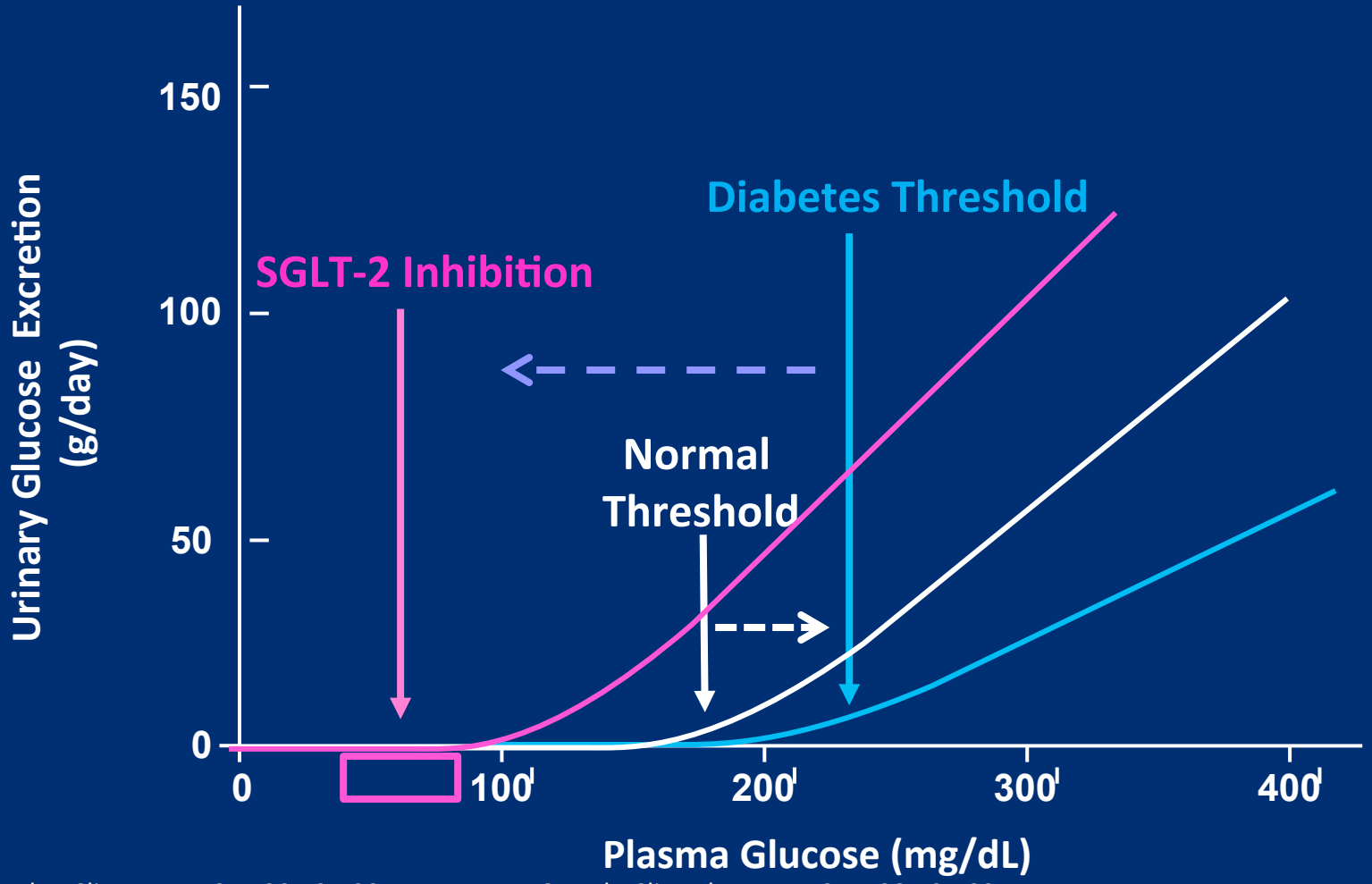
1. Rothenberg et al. Poster presented at: 46th European Association for the Study of Diabetes Annual Meeting; September 20-24, 2010; Stockholm, Sweden. 3. Cowart, Stachura. In: Walker HK et al, eds. Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd ed. Boston, MA: Butterworths; 1990:653-657. 4. Abdul-Ghani, DeFronzo. Endocr Pract. 2008;14(6):782-790. 5. Oku et al. Diabetes. 1999;48:1794-1800.

# Renal Glucose Handling After SGLT-2 Inhibition




Farber et al. J Clin Invest 1951 30:125-29; Morgensen. Scand J Clin Lab Invest 1971; 28:101-09; Silverman, Turner. Handbook of Physiology. In: Windhager EE, ed. Oxford University Press; 1992:2017-38; Cersosimo et al. Diabetes 2000;49:1186-93; DeFronzo et al. Endocrine Practice 2008 14: 782-90.

# Renal Glucose Handling After SGLT-2 Inhibition




Farber et al. J Clin Invest 1951 30:125-29; Morgensen. Scand J Clin Lab Invest 1971; 28:101-09; Silverman, Turner. Handbook of Physiology. In: Windhager EE, ed. Oxford University Press; 1992:2017-38; Cersosimo et al. Diabetes 2000;49:1186-93; DeFronzo et al. Endocrine Practice 2008 14: 782-90.

# Familial Renal Glucosuria

- Autosomal recessive mutation causing a deficiency of SGLT2
- Characterized by persistent urinary glucose excretion, with normal plasma glucose concentration
- Urinary glucose excretion varies from a few grams to >100 grams per day

# Familial Renal Glucosuria

- No evidence of renal glomerular or tubular dysfunction
- Usually asymptomatic
- Hypoglycemia and hypovolemia are rarely, if ever, observed
- Normal lifespan
- The large majority of patients have no clinical manifestations
  - Both renal histology and renal function are normal
  - The incidence of diabetes, chronic renal failure, and urinary tract infection are not increased

# Rationale for Renal Sodium-Glucose Cotransporter 2 (SGLT2) Inhibitors

- SGLT2 is a low-affinity, high-capacity glucose transporter located in the proximal tubule and is responsible for 90% of glucose reabsorption
- Mutations in SGLT2 transporter linked to hereditary renal glycosuria, a benign condition in humans
- Selective SGLT2 inhibitors could reduce blood glucose levels due to increased renal excretion of glucose
- Selective SGLT2 inhibition, therefore, would cause urine loss of the calories from glucose, potentially leading to weight loss

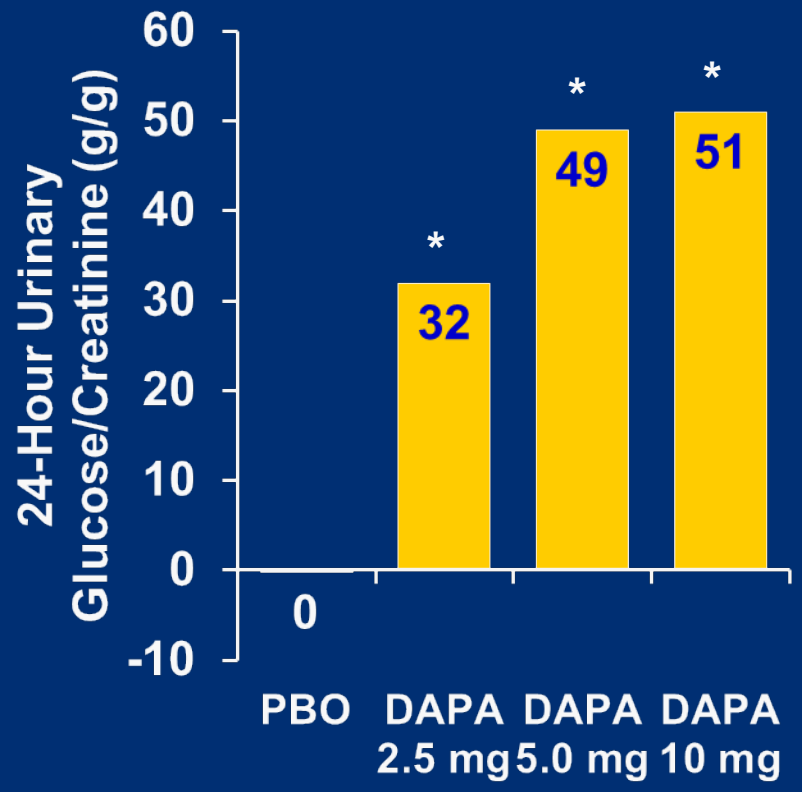
Brooks, Thacker. Ann Pharmacother 2009;43:1286

# Desirable Properties of an SGLT2 Inhibitor

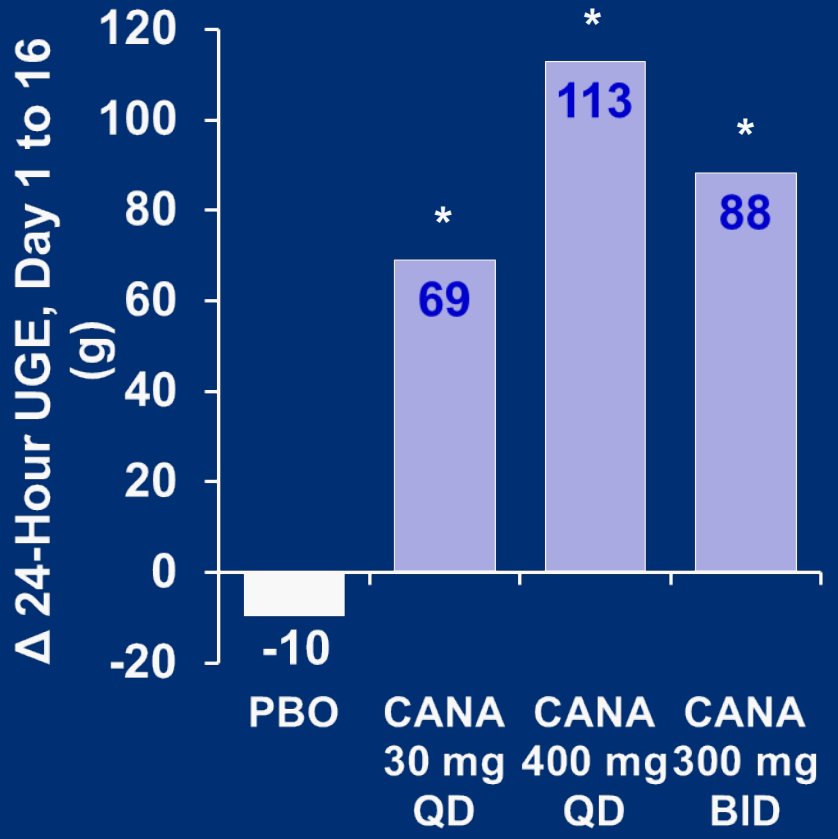
- High potency and selectivity for SGLT2, resulting in good efficacy in the treatment of diabetes
- Metabolic stability
- Oral bioavailability and convenient dosing
- Good tolerability
- Suitability for use in combination with other antidiabetic drugs

# SGLT2 Inhibitors Increase Urinary Glucose Excretion

## Dapagliflozin monotherapy[1] 12-week (phase 2)




## Canagliflozin monotherapy[2] 2-week (phase 1b)




*p < .01 vs PBO.

1. List et al. Diabetes Care. 2009;32:650-57;
2. Rothenberg et al. Diabetologia. 2011;54(suppl 1):876.

# Monotherapy Trials

| | Canagliflozin 100 mg[1] (n=75) | Canagliflozin 300 mg[1] (n=75) | Dapagliflozin 10 mg[2] (n=70) |
|---|---|---|---|
| Duration (wk) | 12 | 12 | 24 |
| Total patients in trial | 383 | 383 | 485 |
| Age (yrs) | 57.7 ± 10.5 | 57.1 ± 10.1 | 50.6 ± 9.97 |
| BMI (kg/m$^2$) | 25.61 ± 4.64 | 25.89 ± 3.68 | 33.6 ± 5.4 |
| Initial A1C (%) | 8.05 ± 0.86 | 8.17 ± 0.81 | 8.01 ± 0.96 |
| Placebo-corrected change in A1C (%) | –0.91 P<0.01* | –0.99 P<0.01* | –0.66 P<0.0001* |
| Placebo-corrected change in Wt (kg) | –1.73 P<0.01* | –2.41 P<0.01* | –1.0 (NS) |

**P* value versus placebo. n=number of patients in treatment arm; BMI=body mass index; Wt=weight; Pbo=placebo; kg=kilograms; NS=not significant.

1. Inagaki et al. Diabetes Obes Metab. 2013; 15:1136
2. Ferrannini et al. Diabetes Care. 2010;33:2217-24.

# Monotherapy Trials

| | Empagliflozin 25 mg[1] (n=82) | Ipragliflozin 50 mg[2] (n=67) |
|---|---|---|
| Duration (wk) | 12 | 12 |
| Total patients in trial | 408 | 363 |
| Age | 57 yrs | 52.6±10.7 yrs |
| BMI (kg/m$^2$) | 28.3 | 32.2±5.9 |
| Initial A1C (%) | 7.8 ± 0.8 | 8.05 ± 0.81 |
| Placebo-corrected change in A1C (%) | –0.67<br>P<0.0001* | –0.65<br>P<0.001* |
| Placebo-corrected change in Wt (kg) | –2.03<br>P<0.0001* | –0.66 |

**P* value versus placebo.

†Metformin >1000mg/d -0.055%

1. Ferrannini et al. Diabetes Obes Metab. 2013;15:721-28;
2. Fonseca et al. J Diabetes Complications. 2013;27:268-73.

# Monotherapy Trials

| | Canagliflozin 100 mg[1] (n=75) | Canagliflozin 300 mg[1] (n=75) | Dapagliflozin 10 mg[2] (n=70) |
|---|---|---|---|
| Δ SBP (mmHg) | –7.1 ± 1.2 P<0.01* | −8.7 ± 1.2 P<0.01* | –3.6 ± 1.9 |
| Δ DBP (mmHg) | –3.9 ± 0.9 P<0.05* | −4.2 ± 0.8 P<0.01* | –2.0 ± 1.1 |
| Genital infections [N (%)] | 1 (1.4) [Pbo: 0] | 1 (1.4) [Pbo:0] | 9 (12.9) [Pbo: 1 (1.3)] |
| UTI [N (%)] | 0 [Pbo: 0] | 0 [Pbo: 0] | 4 (5.7) [Pbo: 3 (4)] |
| Hypoglycemia [N (%)] | 1 (1.4) [Pbo: 0] | 1 (1.3) [Pbo: 0] | 2 (2.9) [Pbo: 2 (2.7)] |

**P* value versus placebo; SBP=systolic blood pressure; DBP=diastolic blood pressure; Hct=hematocrit; UTI=urinary tract infection.

1.Inagaki et al. Diabetes Obes Metab. 2013; 15:1136
2. Ferrannini et al. Diabetes Care. 2010;33:2217-24.

# Monotherapy Trials

| | Empagliflozin 25 mg[1] (n=82) | Ipragliflozin 50 mg[2] (n=67) |
|---|---|---|
| Δ SBP (mmHg) | – | –2.6 |
| Δ DBP (mmHg) | – | +1.2 |
| Genital infections [N (%)] | 2 (2.4) [Pbo: 0] | 8 (11.9) [Pbo: 1 (1.4)] |
| UTI [N (%)] | 1 (1.2) [Pbo: 1] | 9 (13.4) [Pbo: 6 (8.7)] |
| Hypoglycemia [N (%)] | 0 | 1 (1.5) [Pbo: 0] |

1. Ferrannini et al. Diabetes Obes Metab. 2013;15:721-28;
2. Fonseca et al. J Diabetes Complications. 2013;27:268-73.

# SGLT2 Inhibitors
## Adverse Effects

- Genital candida infections occur in up to 10% of patients in some series
  - Prior infections a risk factor for recurrence of infections during SGLT2 treatment
  - Infections easily treated with about 10% recurrences despite continued therapy
  - Balanitis occurred primarily in uncircumcised males
- Lower Urinary Tract Infections seen infrequently and inconsistently
- Postural hypotension symptoms rarely seen, especially in older individuals and at higher doses

# Current and Novel Approaches to Glycemia Management: A Focus on Combination Therapy

**Sunder Mudaliar, MD, FRCP, FACP, FACE**
**Clinical Professor of Medicine**
**Physician VA San Diego Healthcare System**
**University of California**
**San Diego, California**

# Objectives

- Review Current Treatment Guidelines

- Where do DPP-4 inhibitors, GLP-1 agonists and SGLT-2 inhibitors fit in?

- Evaluate the Potential of Different Treatment Strategies in Optimizing Glycemic Control

**In regard to the specific management of type 2 diabetes…**
**"If you want to keep a colleague, never talk about diabetes guidelines!"**

**If you really care to do the exercise by searching on PubMed, you will note that the search term "diabetes management" will result in 24,000 citations.**
**The use of "diabetes guidelines" or "diabetes algorithm"as search terms will yield 8,900 and 3,100 citations, respectively.**

Cefalu. Diabetes Care. 2012;35:1201-3.

# Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

## Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

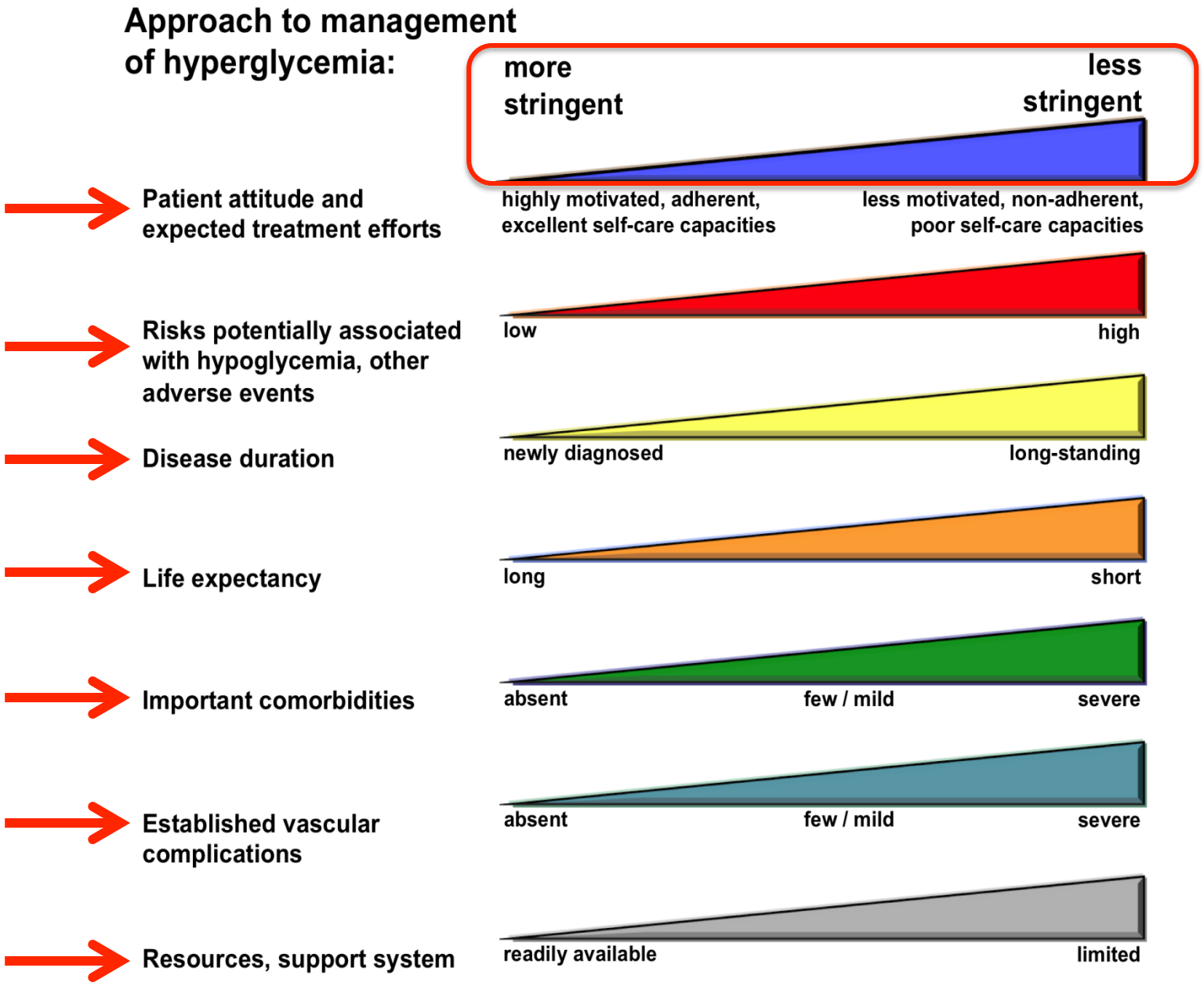
American Diabetes Association.

EASD

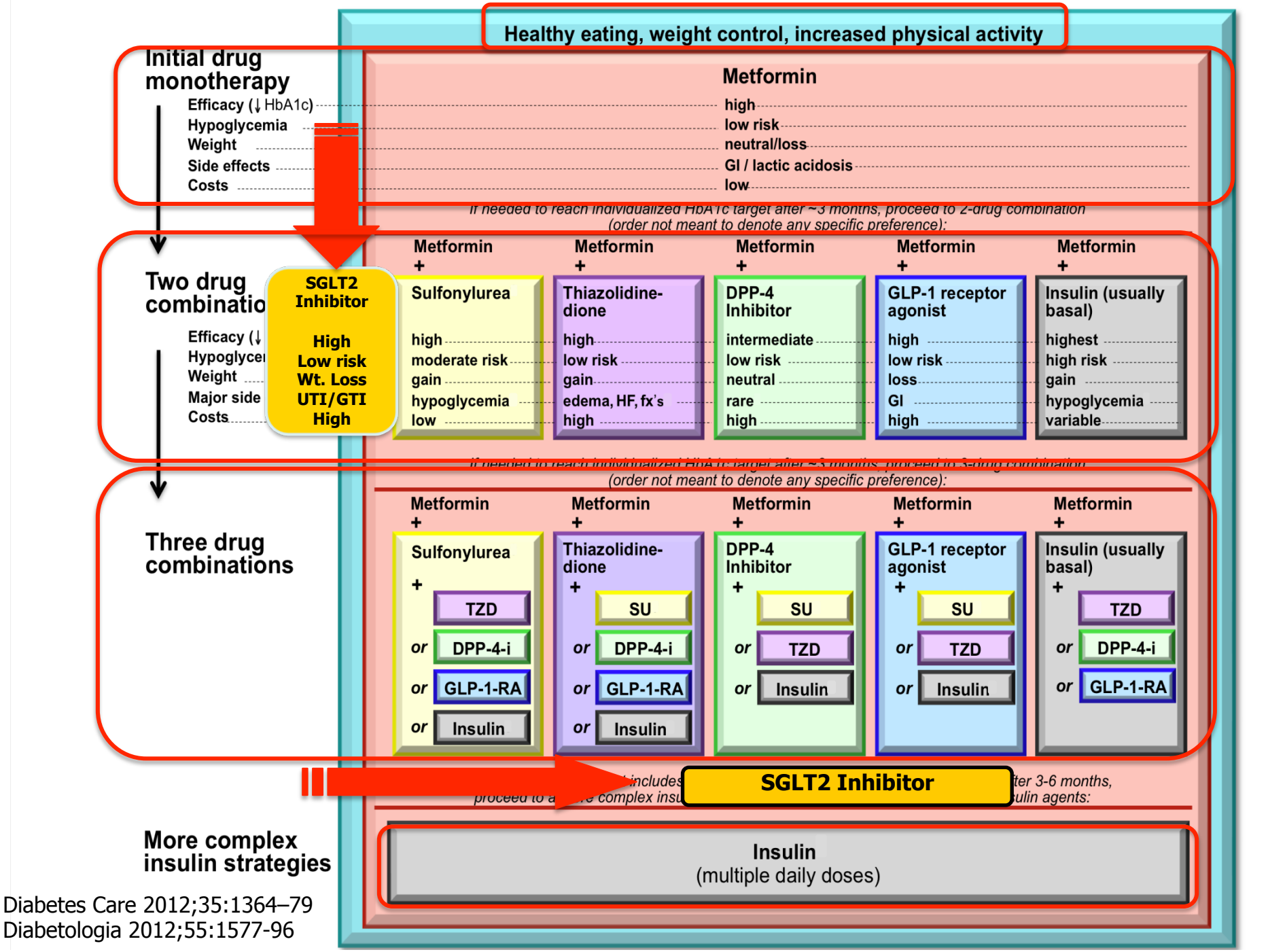
Diabetes Care 2012;35:1364–79
Diabetologia 2012;55:1577–96

# ADA Goal for HbA1C: <7%

Standards of Medical Care in Diabetes—2014 American Diabetes Association. Diabetes Care; 2014:37(Suppl 1) S14-S80.

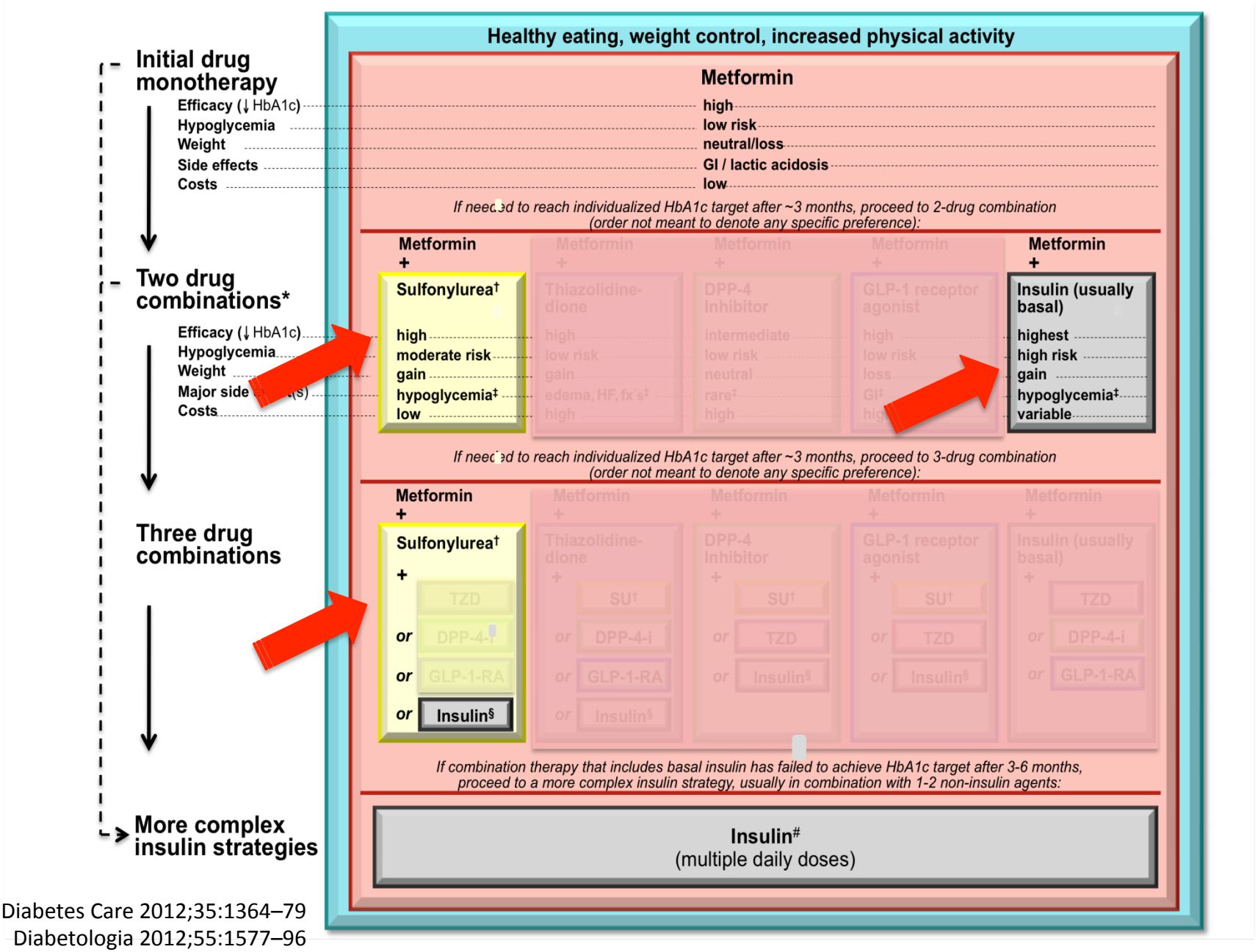



Standards of Medical Care in Diabetes—2014 American Diabetes Association. Diabetes Care; 2014:37(Suppl 1) S14-S80.



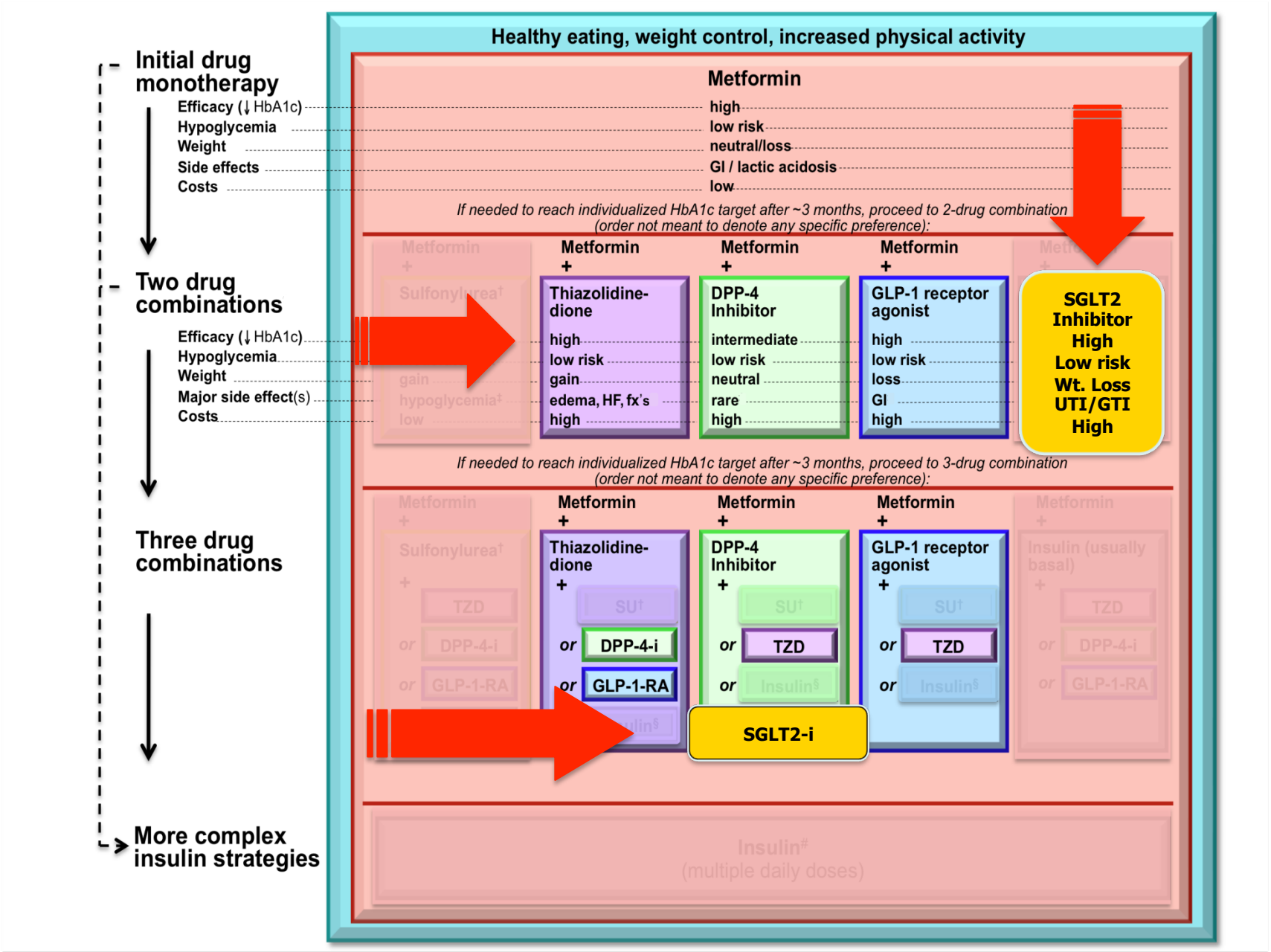

Diabetes Care 2012;35:1364–79
Diabetologia 2012;55:1577-96

# Adapted Recommendations: When Goal is to Minimize Costs

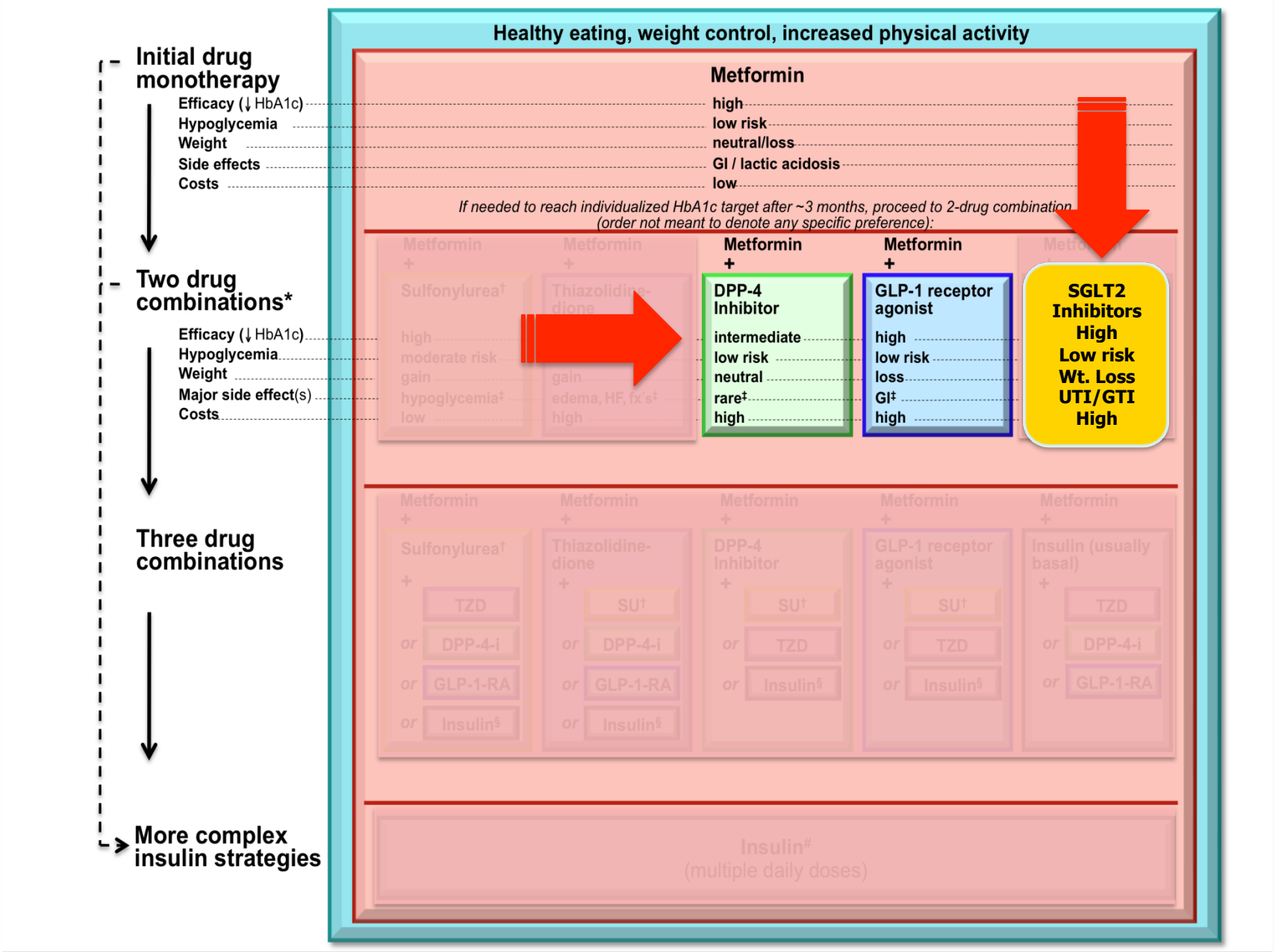



Diabetes Care 2012;35:1364–79
Diabetologia 2012;55:1577–96

# Adapted Recommendations: When Goal is to Avoid Hypoglycemia



# Adapted Recommendations: When Goal is to Avoid Weight Gain



# Goals for Glycemic Control

**A1c ≤ 6.5%**

For healthy patients without concurrent illness and at low hypoglycemic risk

**A1c > 6.5%**

Individualize goals for patients with concurrent illness and at risk for hypoglycemia

# 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**

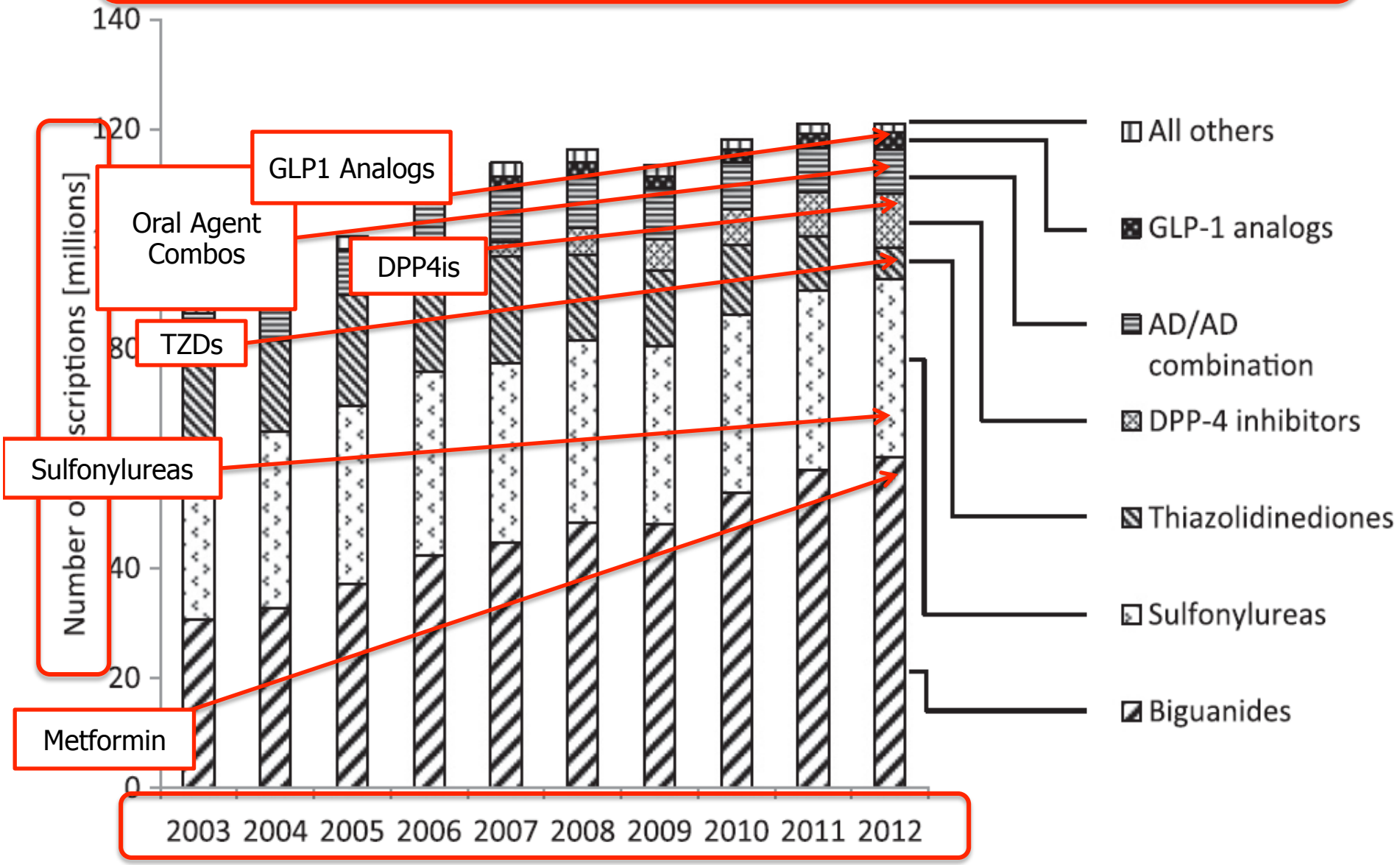
✓ = Few adverse events or possible benefits

⚠ = Use with caution

**PROGRESSION OF DISEASE**

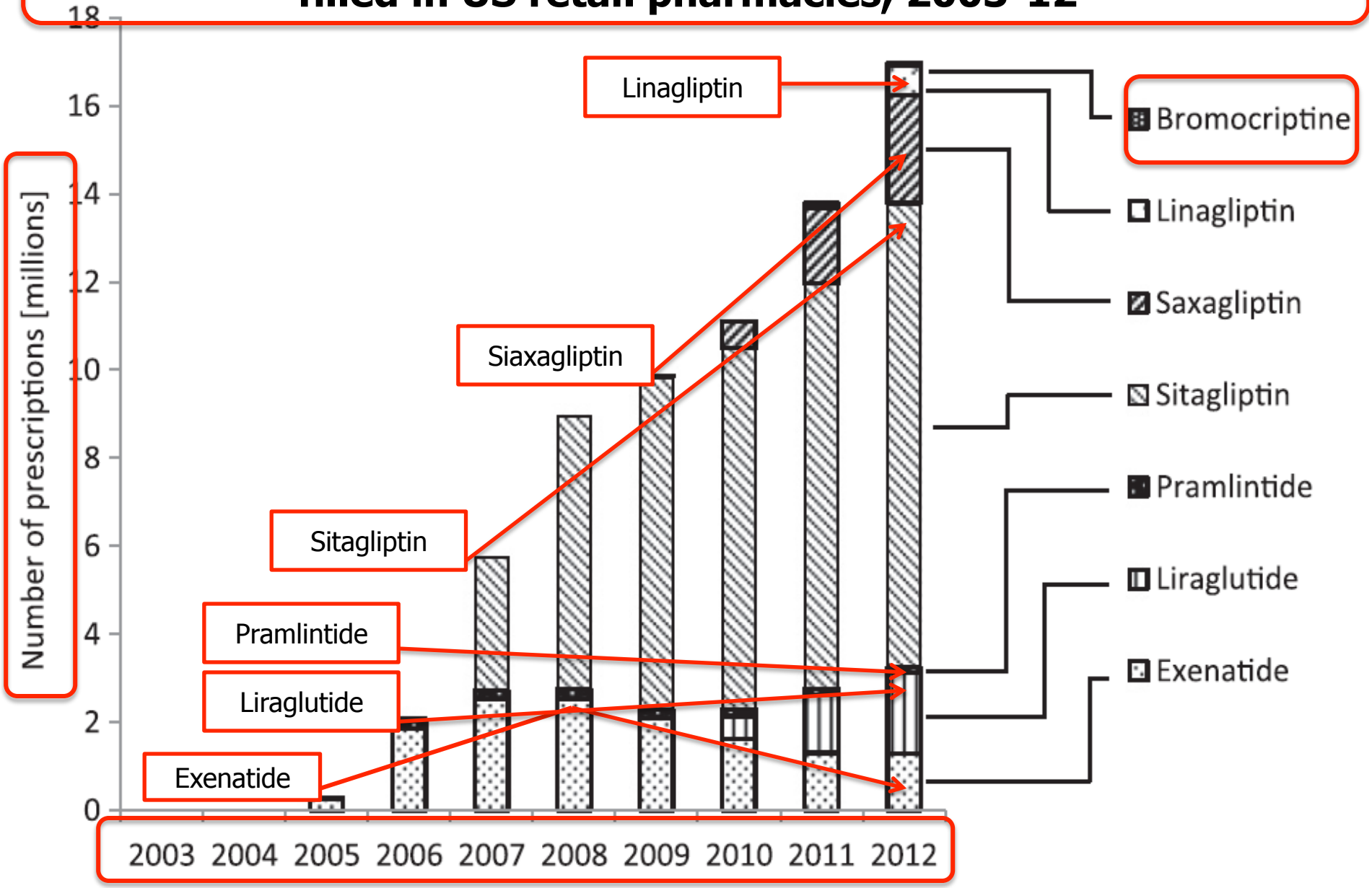
http://cache3.asset-cache.net/xc/164319497.jpg?v=1&c=IWSAsset&k=2&d=B53F616F4B95E55356EE9410A916D399C420627332D2675882768AC9380E6F53

# Trends in noninsulin antidiabetic drug prescriptions filled in US retail pharmacies 2003–2012



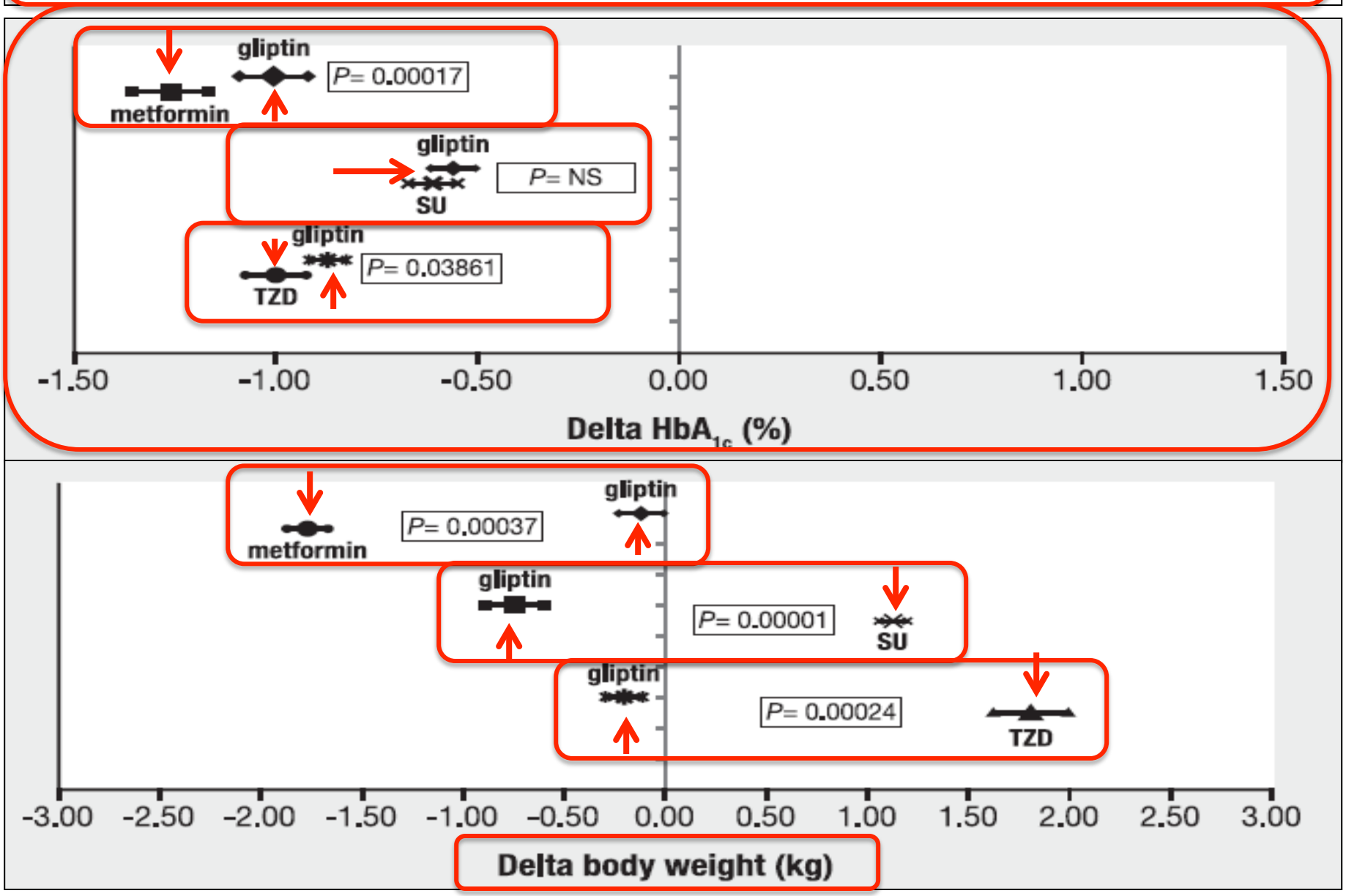

Hampp et al. Diabetes Care 2014;37:1367–74

# Prescriptions of recently approved noninsulin antidiabetic drugs filled in US retail pharmacies, 2003-12




Hampp et al. Diabetes Care 2014;37:1367–74

# DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials

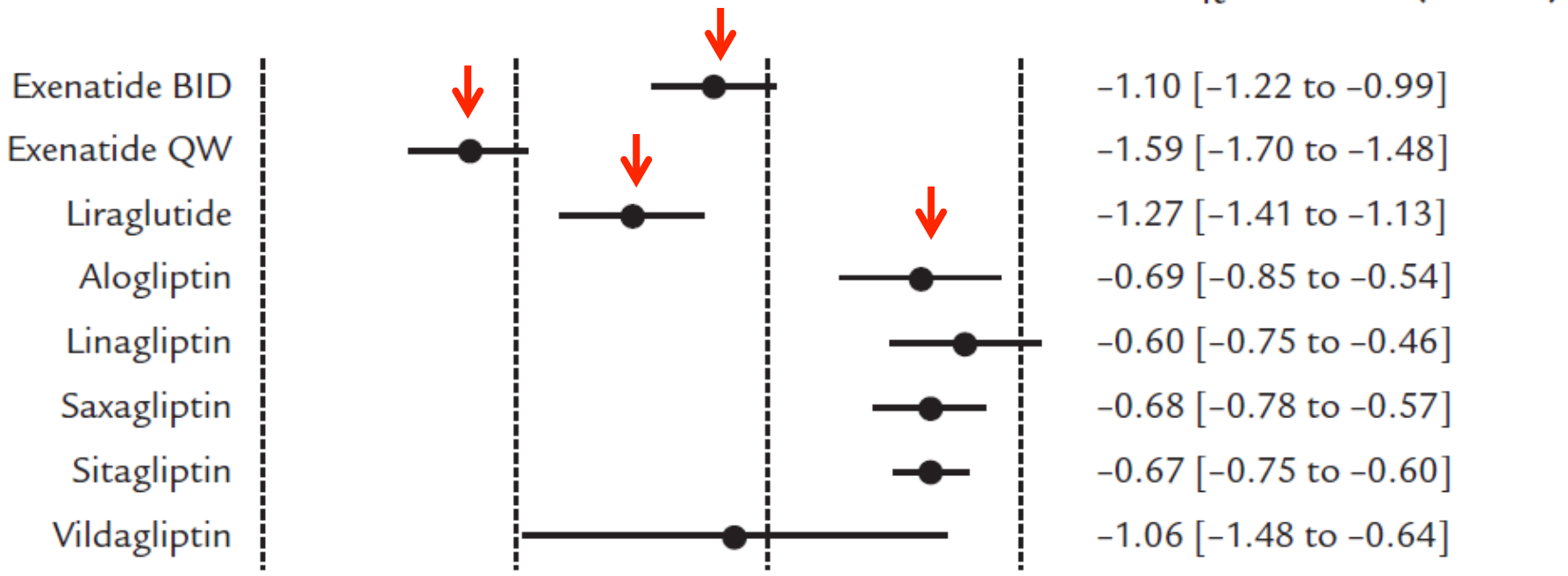



Scheen. Diabetes & Metabolism. 2012;38: 89–101.

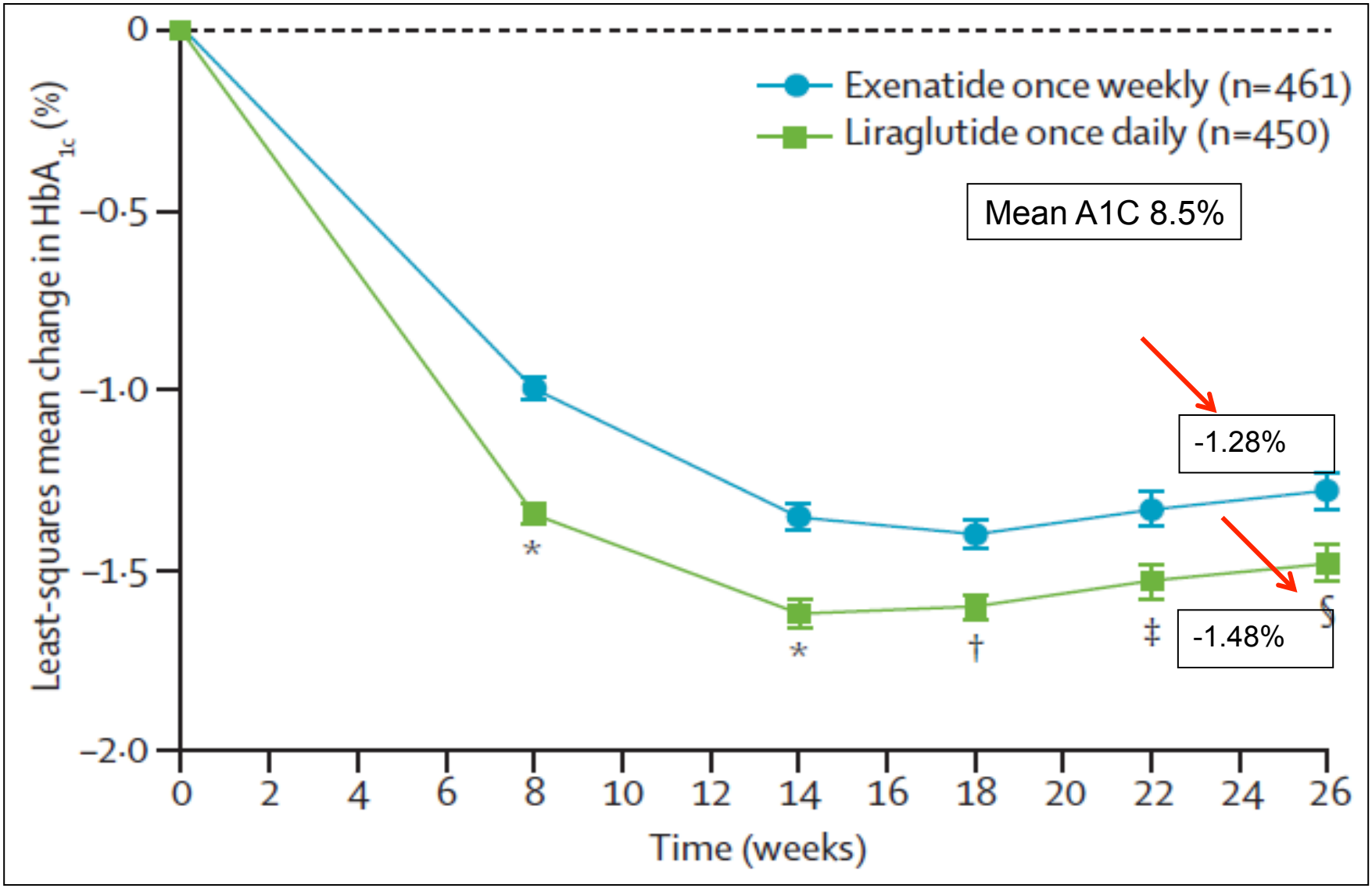
Clinical Therapeutics/Volume 34, Number 6, 2012

# Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review

Vanita R. Aroda, MD[1]; Robert R. Henry, MD[2]; Jenny Han, MS[3]; Wenying Huang, PhD[3]; Mary Beth DeYoung, PhD[3]; Tamara Darsow, PhD[3*]; and Byron J. Hoogwerf, MD[4]



# DURATION-6 Study Exenatide LAR QW vs Liraglutide QD

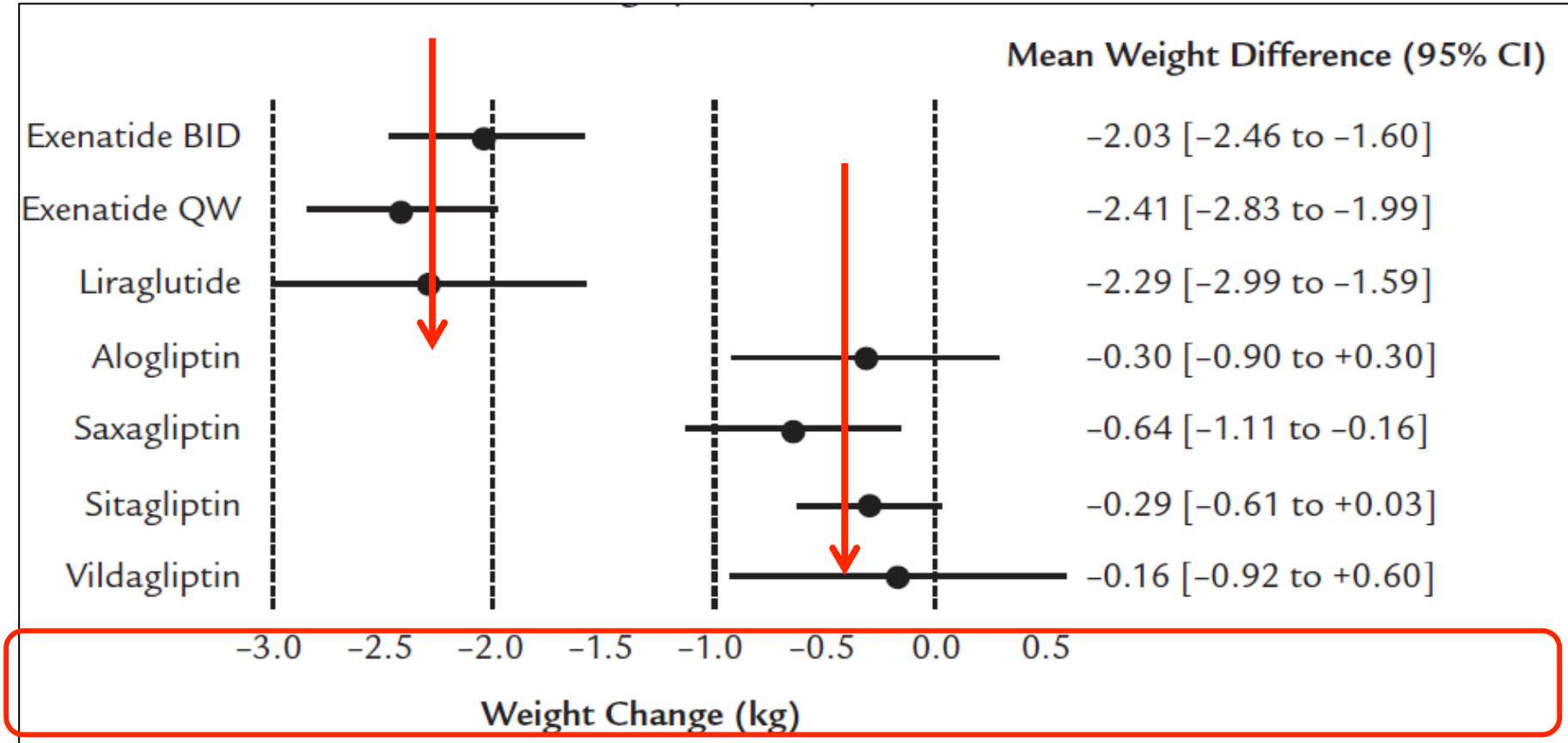



Buse et al. Lancet 2013; 381 117–24

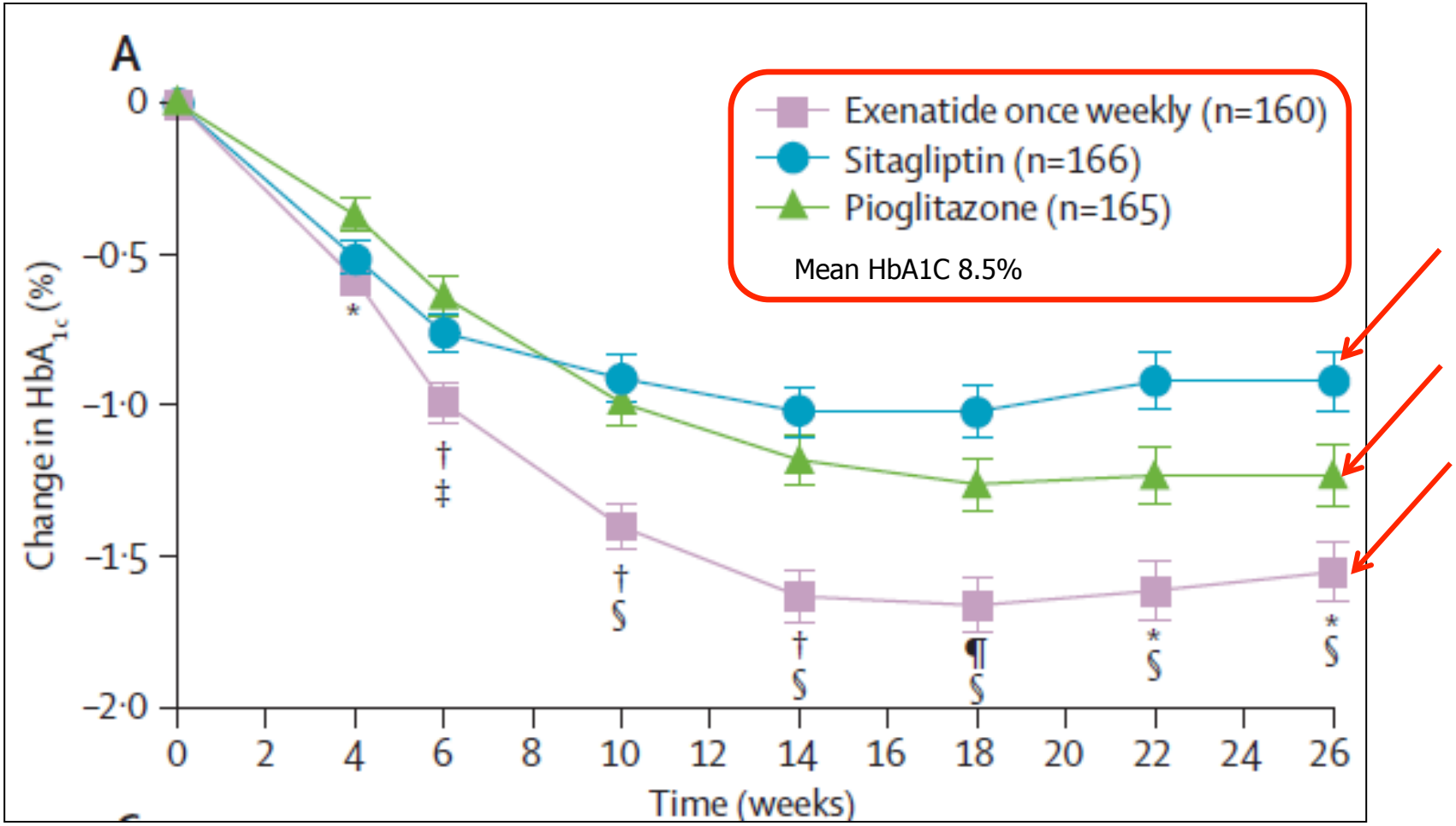
Clinical Therapeutics/Volume 34, Number 6, 2012

# Efficacy of GLP-1 Receptor Agonists and DPP-4 Inhibitors: Meta-Analysis and Systematic Review

Vanita R. Aroda, MD[1]; Robert R. Henry, MD[2]; Jenny Han, MS[3]; Wenying Huang, PhD[3]; Mary Beth DeYoung, PhD[3]; Tamara Darsow, PhD[3*]; and Byron J. Hoogwerf, MD[4]

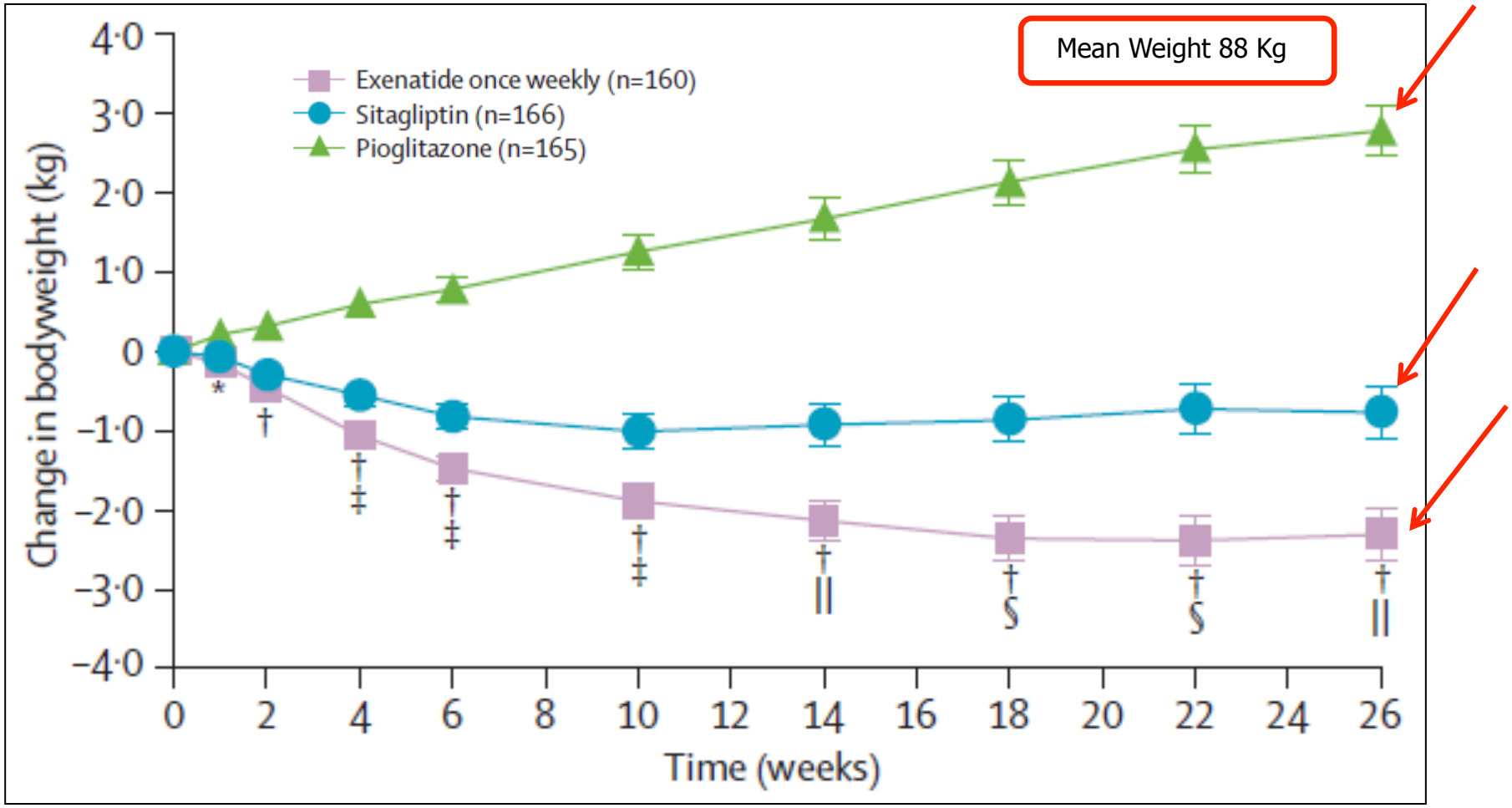


# Exenatide QW vs DPP-4i vs Pioglitazone – HbA1C




Bergenstal et al Lancet. 2010; 376:431-9.

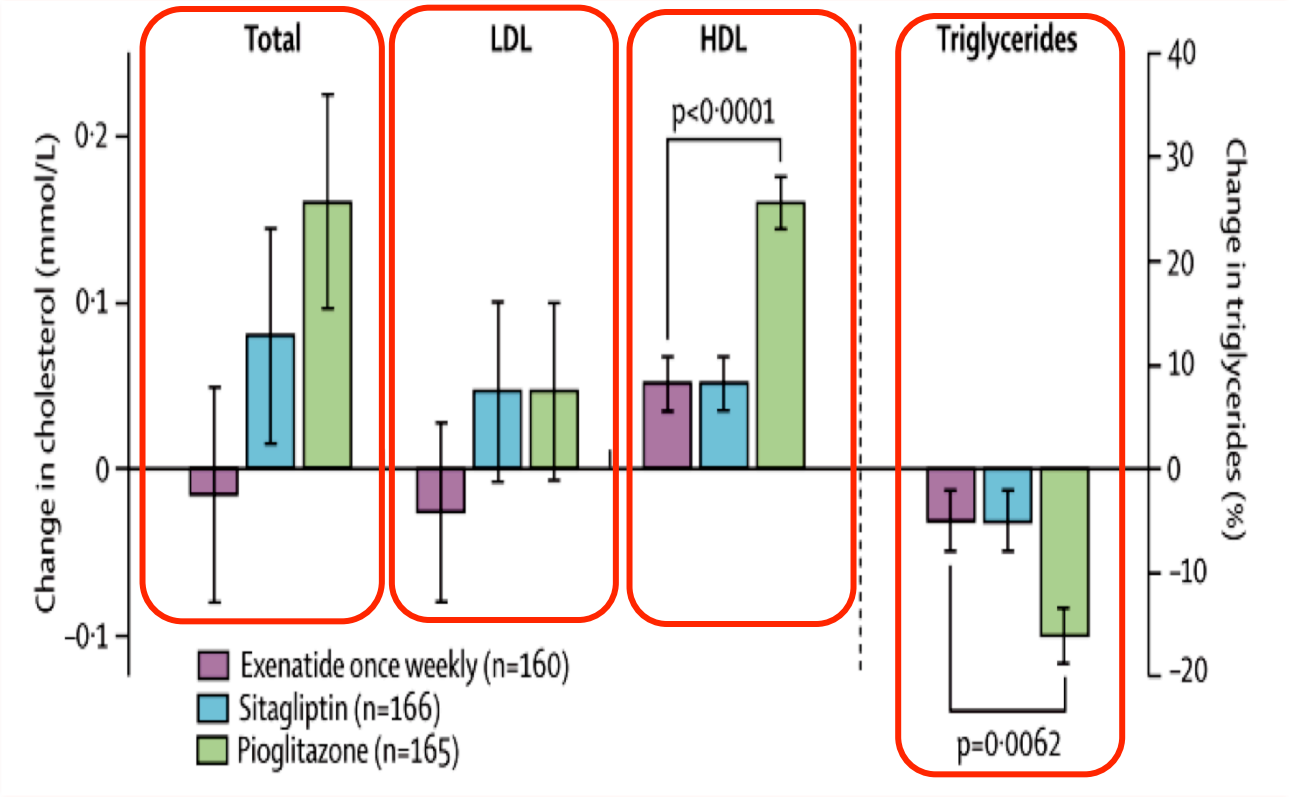
# Exenatide QW vs DPP-4i vs Pioglitazone – Body Weight




Bergenstal et al Lancet. 2010; 376:431-9.

# Exenatide QW vs DPP IV vs Pioglitazone - Lipids

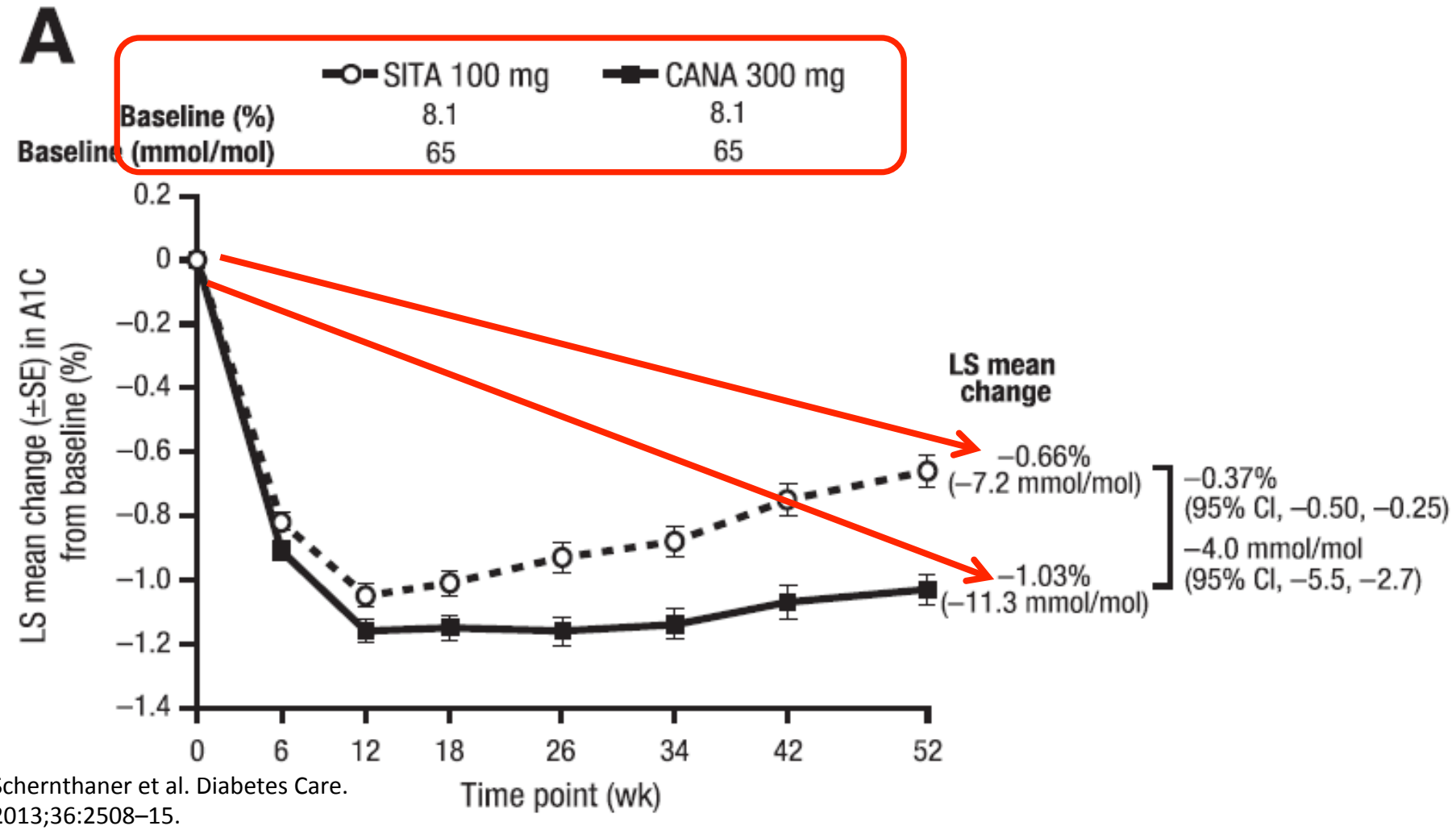
- DURATION-2 trial
- 26-week randomized, double-blind, double-dummy, superiority trial
- Type 2 Diabetes pts
- Baseline LDL
  - LDL 104 mg/dl
  - HDL 42.5 mg/dl
  - Triglycerides 168 mg/dl




EQW-Exenatide once weekly

Bergenstal et al Lancet. 2010; 376:431-9.

# Canagliflozin Compared With Sitagliptin for Patients With Type 2 Diabetes Who Do Not Have Adequate Glycemic Control With Metformin Plus Sulfonylurea

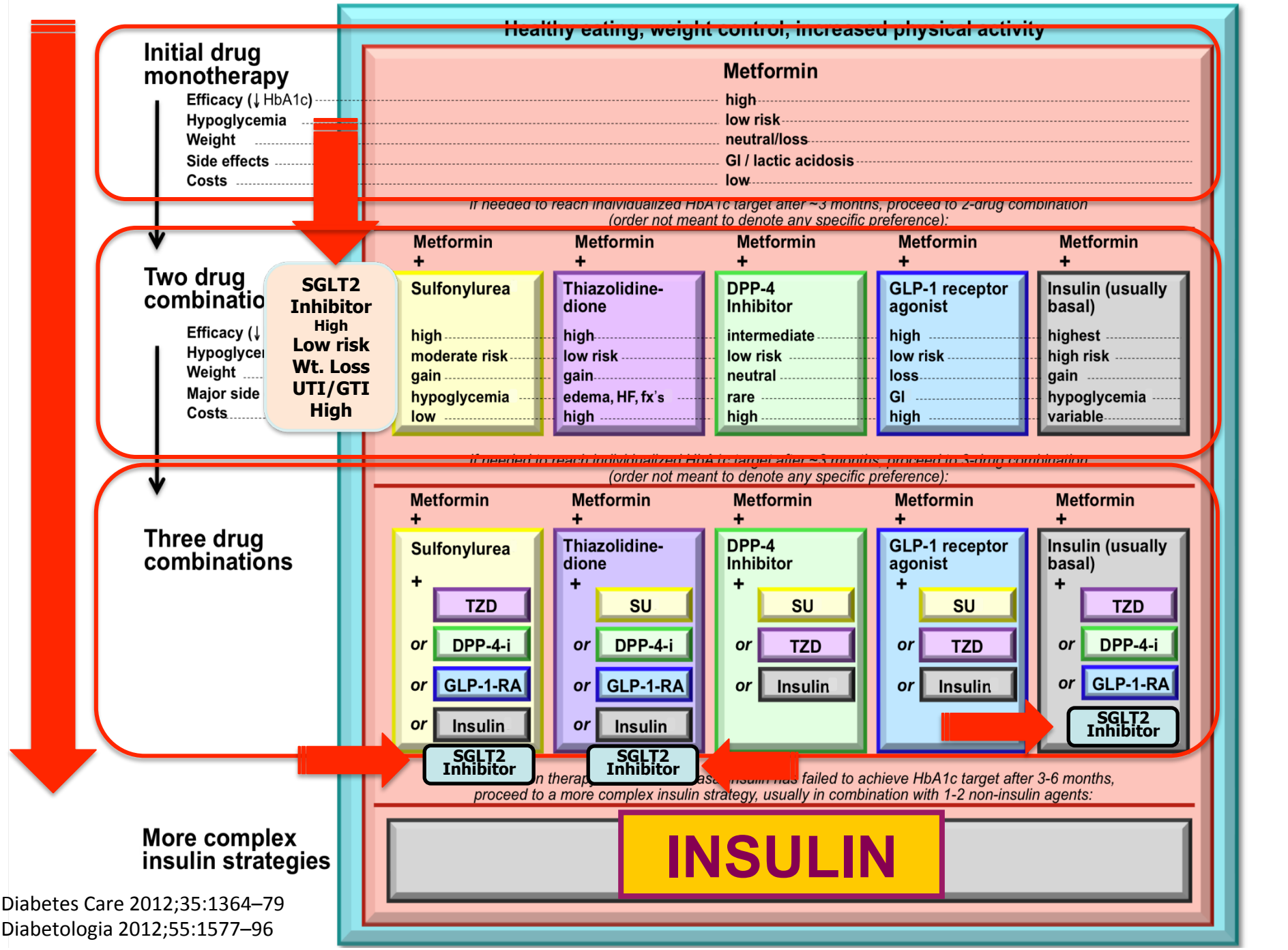



Schernthaner et al. Diabetes Care. 2013;36:2508–15.

# DPP-4 Inhibitors vs GLP-1 Agonists vs SGLT-2 Inhibitors

| Characteristic | DPP-4 Inhibitors | GLP-1 Agonists | SGLT2 Inhibitors |
|---|---|---|---|
| A1C Lowering | ~ 0.5% -1.0% | ~ 0.8% -1.9% | ~ 0.6% – 1.0% |
| Hypoglycemia Risk | Low | Low | Low |
| Weight effect | Neutral | Weight loss | Weight Loss |
| Common AEs | Headache, infections | Nausea, vomiting | GTIs, UTIs, Hypovolemia |
| SAEs of Interest | Pancreatitis | Pancreatitis/Pancreatic Ca Medullary Thyroid Ca | GTIs<br>Dapa – Bladder Ca |
| Administration | Oral | Injected | Oral |

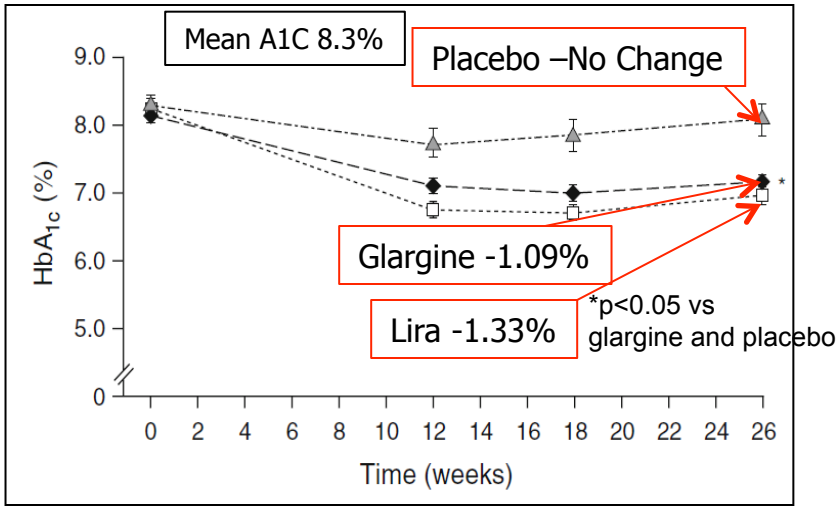
Since the above data were not obtained from simultaneous trials, the comparative data is only a rough approximation of the relative effectiveness as stage, severity of hyperglycemia, and type of patients studied varied in the above studies.

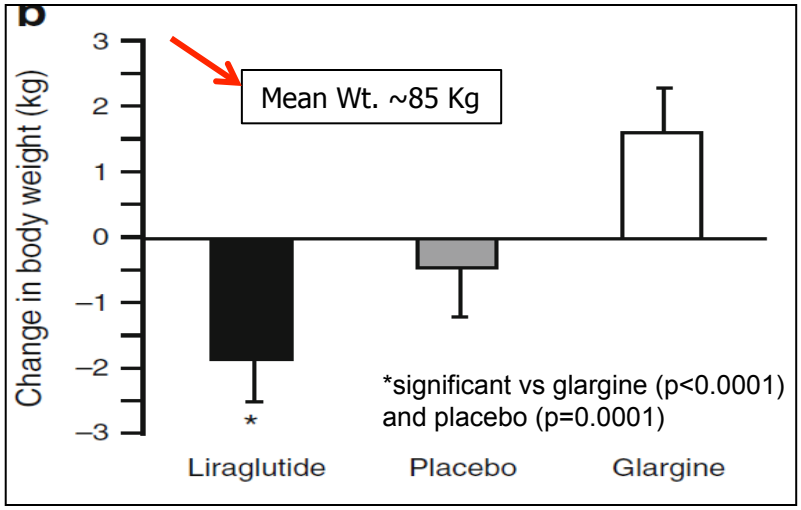



Diabetes Care 2012;35:1364–79
Diabetologia 2012;55:1577–96

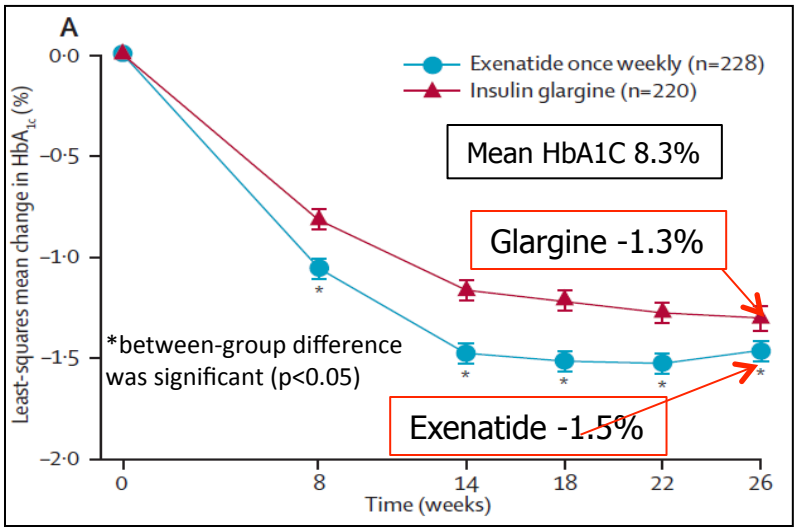
# GLP-1 Agonists Vs Basal Insulin: Making the Right Choice

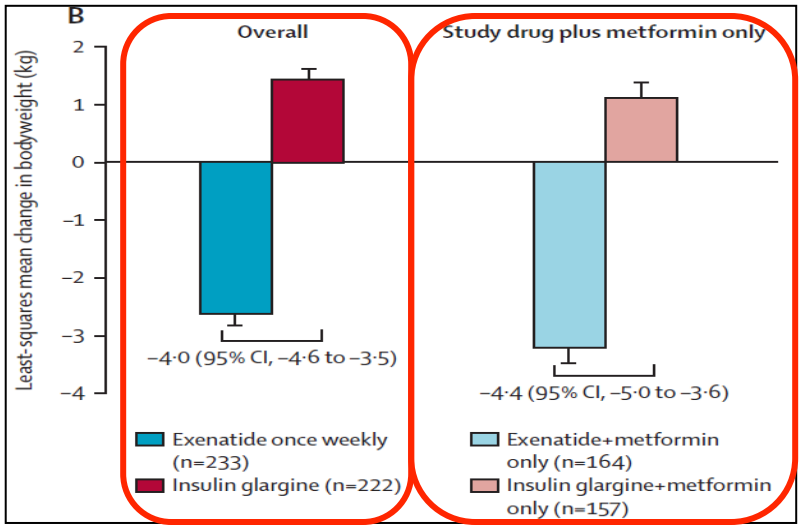
## LEAD 5 Study: Liraglutide vs Glargine and Placebo in combination with metformin and SU in type 2 DM




## DURATION 3 Study: Exenatide QW Vs Glargine in Combination with Metformin/SU in type 2 DM



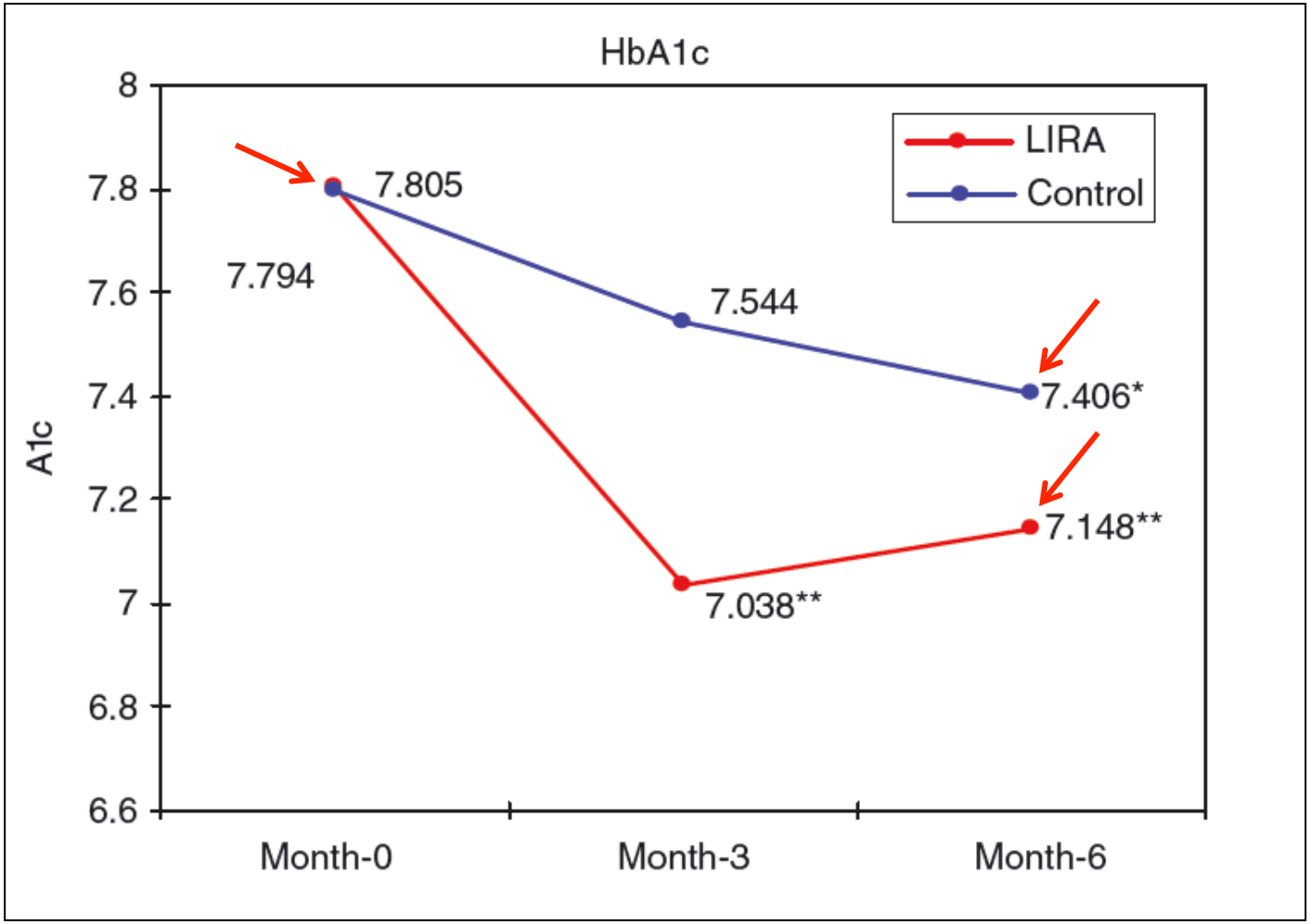




LEAD-5 Study Diabetologia. 2009;52:2046-55; DURATION-3 Study Lancet 2010; 375: 2234–43

# Combination GLP-1 Agonist and Insulin Therapy

## The effect of addition of liraglutide to high-dose intensive insulin therapy: a randomized prospective trial

W. Lane, S. Weinrib, J. Rappaport & C. Hale




Insulin Dose
↓199.6 to 131.6 units

Body Weight
↓by 5.27 Kg

No Difference in Incidence of Hypoglycemia ~5%

Diabetes Obes Metab. 2014 Sep;16(9):827-32.

# DPP-4 I vs GLP-1 Agonists vs SGLT-2i with Insulin

| Characteristic | DPP-4 Inhibitors | GLP-1 Agonists | SGLT2 Inhibitors |
|---|---|---|---|
| A1C Lowering | ~ 0.5% | ~ 1.0% | ~ 0.6% |
| Hypoglycemia Risk | Low | Low | Low |
| Insulin Dose | No Change | ↓ Decreased | ↓ Decreased |
| Weight Effect | Neutral | ↓ Weight loss | ↓ Weight Loss |
| Common AEs | Headache, infections | Nausea, vomiting | GTIs, ?UTIs, Hypovolemia |
| SAEs of Interest | Pancreatitis | Pancreatitis/Pancreatic Ca<br>Medullary Thyroid Ca | GTIs<br>Dapa: Bladder Ca |
| Administration | Oral | Injected | Oral |

Since the above data were not obtained from simultaneous trials, the comparative data is only a rough approximation of the relative effectiveness as stage, severity of hyperglycemia, and type of patients studied varied in the above studies.

# Optimal Drug for Type 2 Diabetes

- Effectively lower glucose levels
- Minimize risk of hypoglycemia
- Reduce body weight
- Improve insulin sensitivity
- Improve β-cell function
- Durable effect
- **Improve CVD Risk**

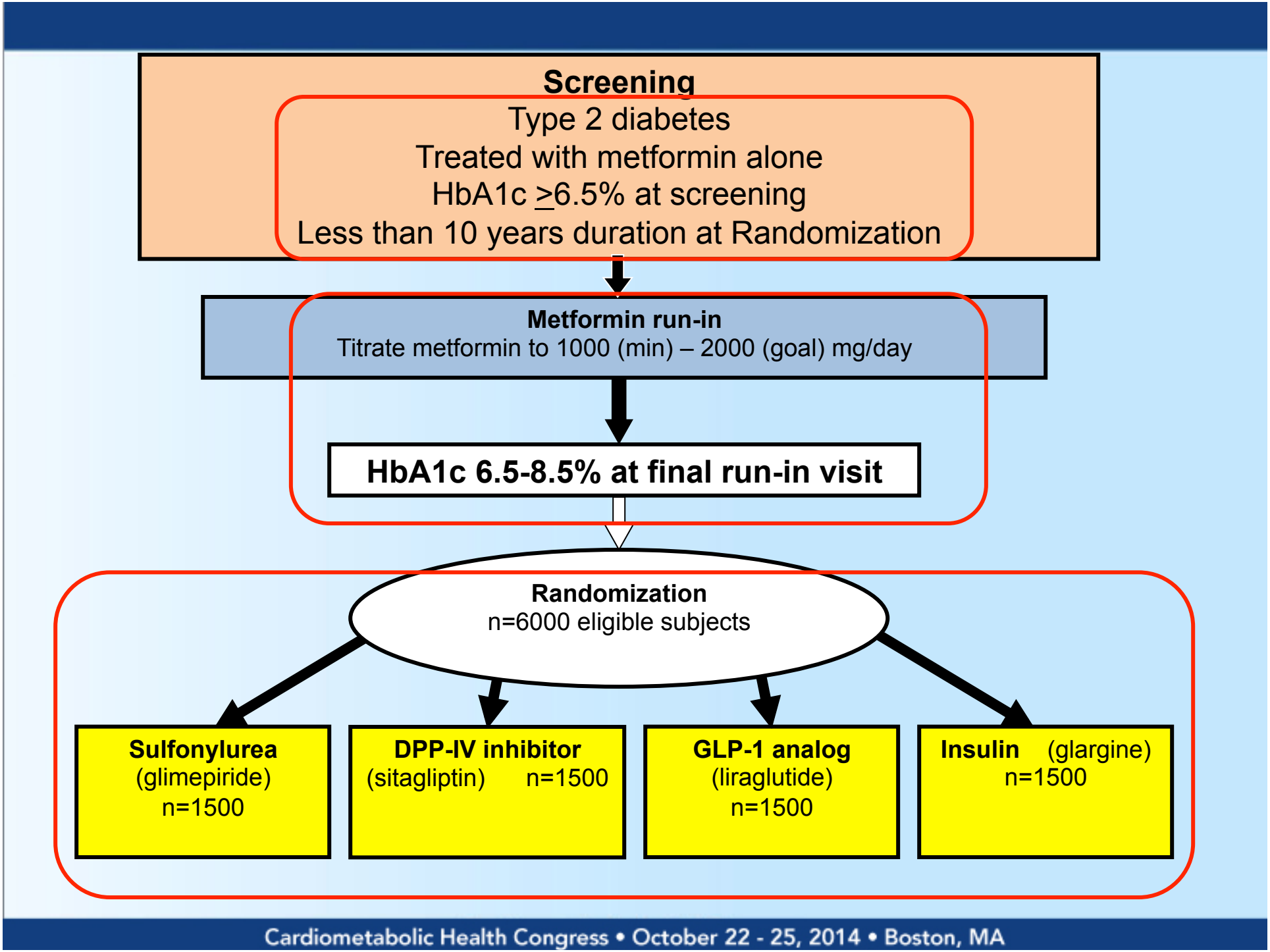
# Cardiovascular Outcomes Studies

| Drug | Trial Name | No. of Patients | Start Date | Completion Date |
|---|---|---|---|---|
| Saxagliptin | SAVOR-TIMI 53 | 16,500 | 2010 | 2014 |
| Alogliptin | EXAMINE | 5400 | 2009 | 2014 |
| Sitagliptin | TECOS | 14,000 | 2008 | 12/2014 |
| Linagliptin | CAROLINA | 6000 | 2010 | 2018 |
| Liraglutide | LEADER | 9340 | 2010 | 2015 |
| Exenatide | EXCEL | 14,000 | 2010 | 2018 |
| Lixisenatide | ELIXA | 6000 | 2010 | 2015 |

Samson. Metabolic Syndrome and Related Disorders.2014;12:303-10.

http://cache3.asset-cache.net/xc/164319497.jpg?v=1&c=IWSAsset&k=2&d=B53F616F4B95E55356EE9410A916D399C420627332D2675882768AC9380E6F53

# Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness Study (GRADE Study)


Screening
Type 2 diabetes
Treated with metformin alone
HbA1c ≥6.5% at screening
Less than 10 years duration at Randomization
Metformin run-in
Titrate metformin to 1000 (min) – 2000 (goal) mg/day
HbA1c 6.5-8.5% at final run-in visit
Randomization
n=6000 eligible subjects
Sulfonylurea
(glimepiride)
n=1500
DPP-IV inhibitor
(sitagliptin) n=1500
GLP-1 analog
(liraglutide)
n=1500
Insulin (glargine)
n=1500

# Different Treatment Strategies in Optimizing Glycemic Control

"There is a light at the end of every tunnel. Some tunnels just happen to be longer than others."

— Ada Adams

http://www.goodreads.com/quotes/521459-there-is-a-light-at-the-end-of-every-tunnel

# Exploring Synergistic Approaches to Improve Glucose Control and CV Risk Factors: Case-Studies, Panel Discussion, Audience Questions and Answers

George L. Bakris, MD

Mark E. Molitch, MD

Sunder Mudaliar, MD

Richard E. Pratley, MD

# Case Study

**Patrick is a 57-year-old male with T2DM for 6 years and has hypertension with minor background retinopathy and peripheral neuropathy. P.E. unremarkable except for trace edema.**

- BMI = 32.5 kg/m2
- BP = 142/86 mm Hg

**LABS:**

- Creatinine = 1.1mg/dl (estimated GFR > 60 mL/min/1.75 m2), Microalbuminuria (MAU)-42 mg/day
- HDL = 35 mg/dL
- LDL = 70 mg/dL
- Other laboratory tests are normal

**MEDICATIONS:**

- atorvastatin 20 mg/d, HCTZ 25 mg/d, amlodipine 10 mg/d, and lisinopril 40 mg/d

# Case Study (cont.)

**Past Medical History focus on diabetes:**

- Began treatment with metformin which has been titrated up to maximum dose for 2 years
- DPP4 added when HbA1c rose to 8.2%
- After initial improvement, his HbA1C was still at 7.8% over 4 years.
- On this regimen his fasting glucose ranges from 110-140 mg/dl but checks it occasionally 2 hours after meals and is over 200 mg/dl sometimes

**What options are best to optimize glycemic control and help with postprandial rise (e.g. HbA1c <7.0%)?**

- SU
- GLP-1 agonist
- SGLT2
- TZD
- Prandial insulin

# Case Study (cont.)

- SGLT-2 is selected because of effects on BP and weight and glycemic control

- Patrick returns in 1 month and has FBS-95-105 mg/dl and his BP is now 134/78 and has lost 2lbs. Complains of urinary frequency but he has it under control.

- He then returns in 3 months and HbA1c is 7.1% and has lost an additional 4lbs with BP 128/80 mmHg. Feels great but labs show that while HDL increased from 35 to 39 his LDL also increased from 70 to 75 mg/dl-Concerning??

# Case Study (cont.)



## Additional questions

- What if Patrick had a history of heart failure (diastolic dysfunction)? How would you approach him regarding DPP4 versus other agents for glucose management?

- Some say that the ideal combination for early management of diabetes is metformin, GLP-1 agonist, and SGLT2 to optimally preserve beta cell function- Thoughts?

# Panel Discussion

# Questions and Answers