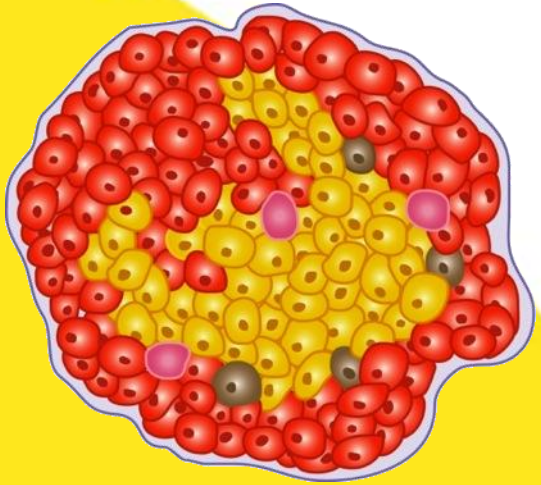
Cardiology Update 2011
Davos, February 14, 2011



2011: New Drugs for Diabetes Treatment

University Hospital Zurich

Roger Lehmann
Department of Endocrinology and Diabetes

Unresolved Problems in the Treatment of Type 2 Diabetes

⇧ Diabetes Duration ⇨ Consequences:

⇩Beta-cell Function

⇧HbA1c, postprandial and fasting glucose

⇧ Risk Hypoglycemia

⇧ Weight

⇧ Mortality

Solution?

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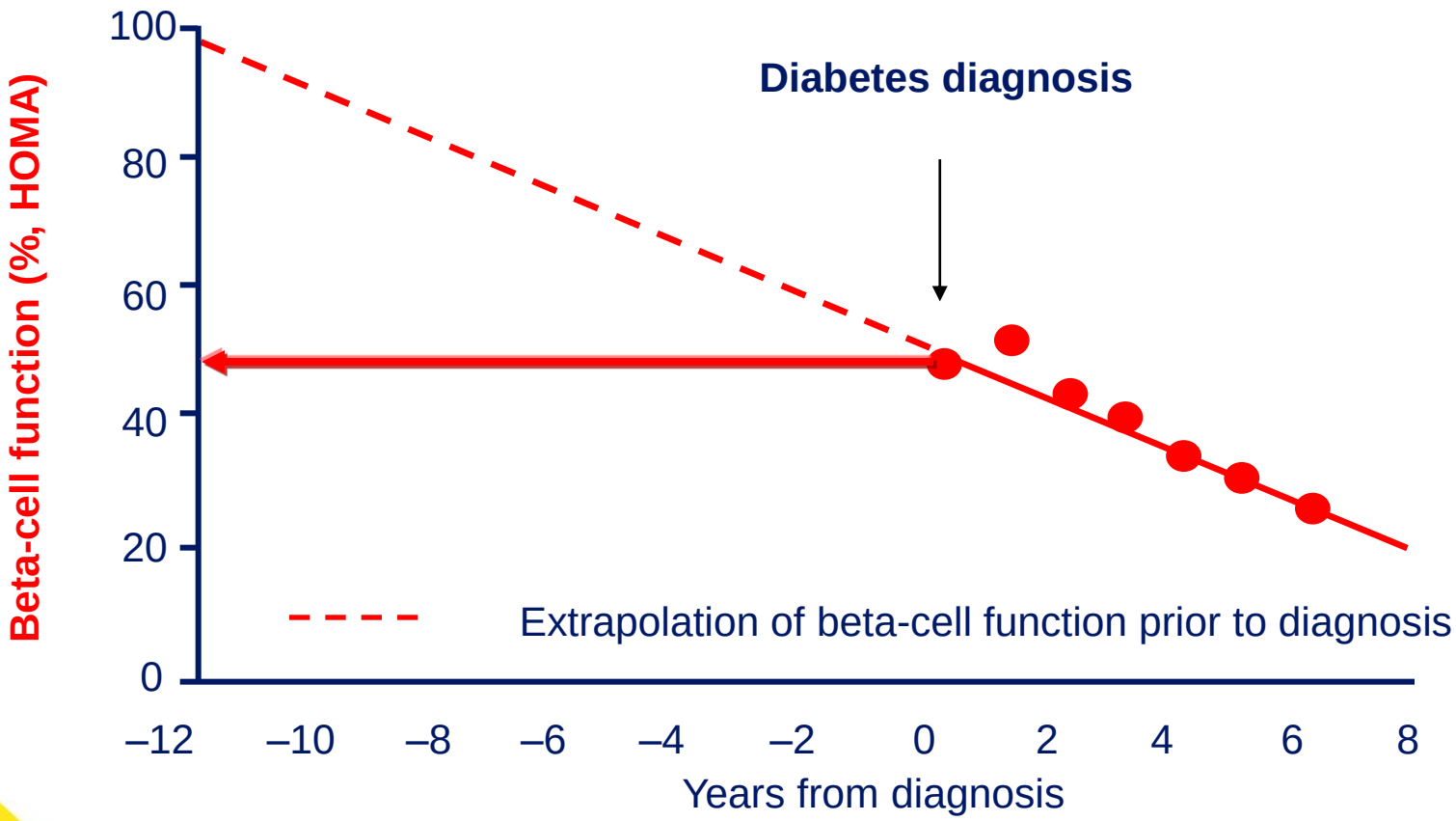
Beta-cell function progressively declines



UKPDS 16. *Diabetes* 1995;44:1249–58)

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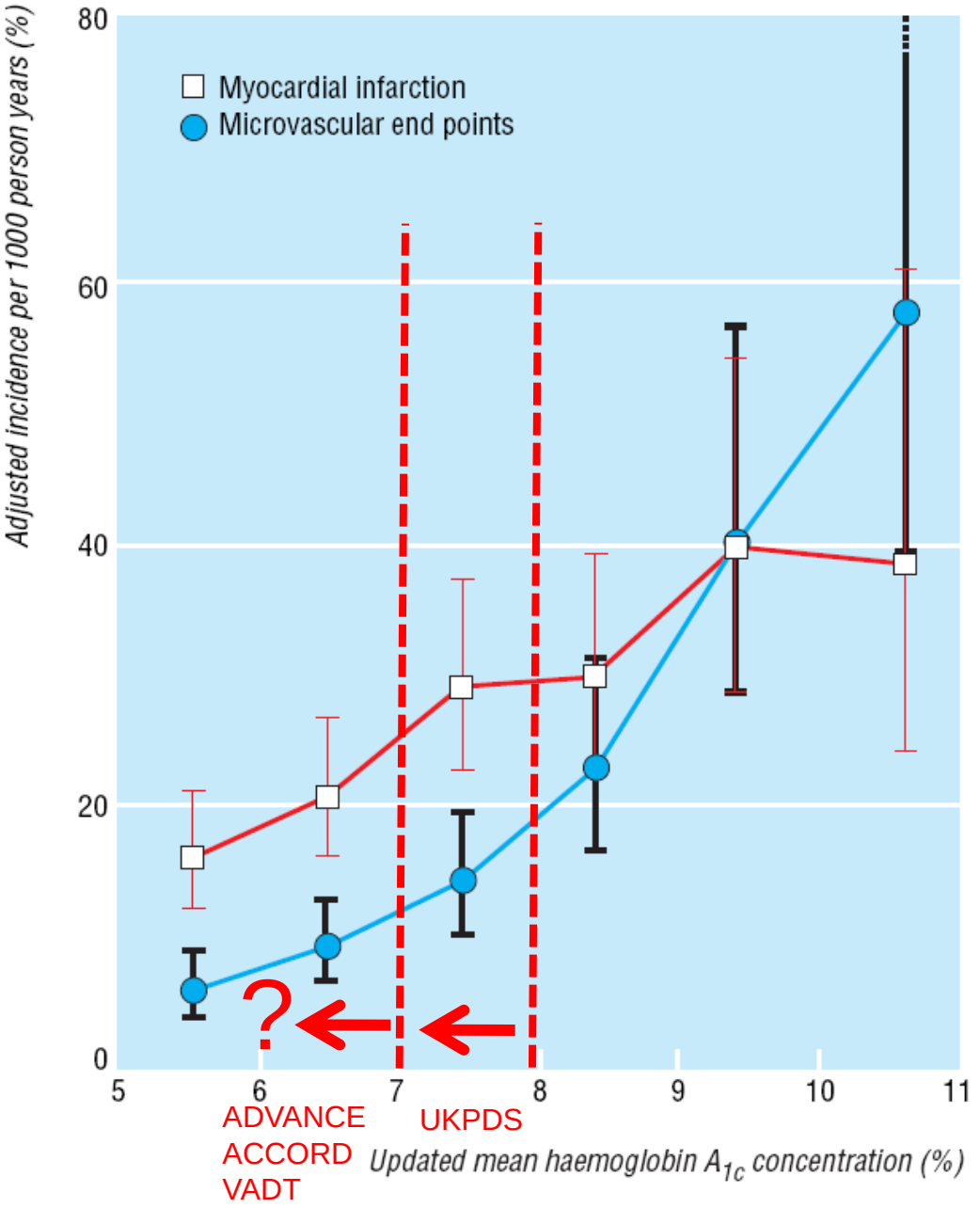
Glycemic Control and Vascular Risk: Evidence?



BMJ 2000; 321:405-12

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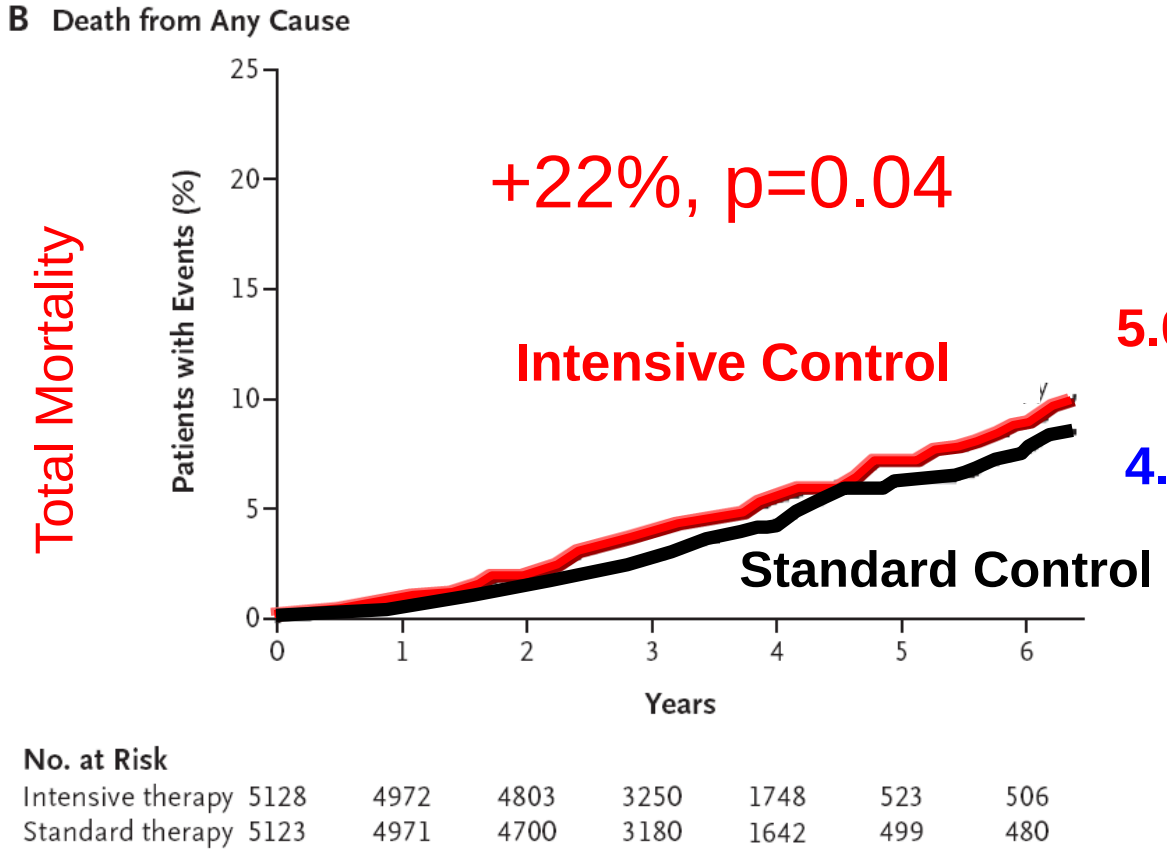
⇧Mortality ACCORD: Intensive vs. Standard Therapy



5.0%, HbA1c 6.4%

4.0%, HbA1c 7.5%

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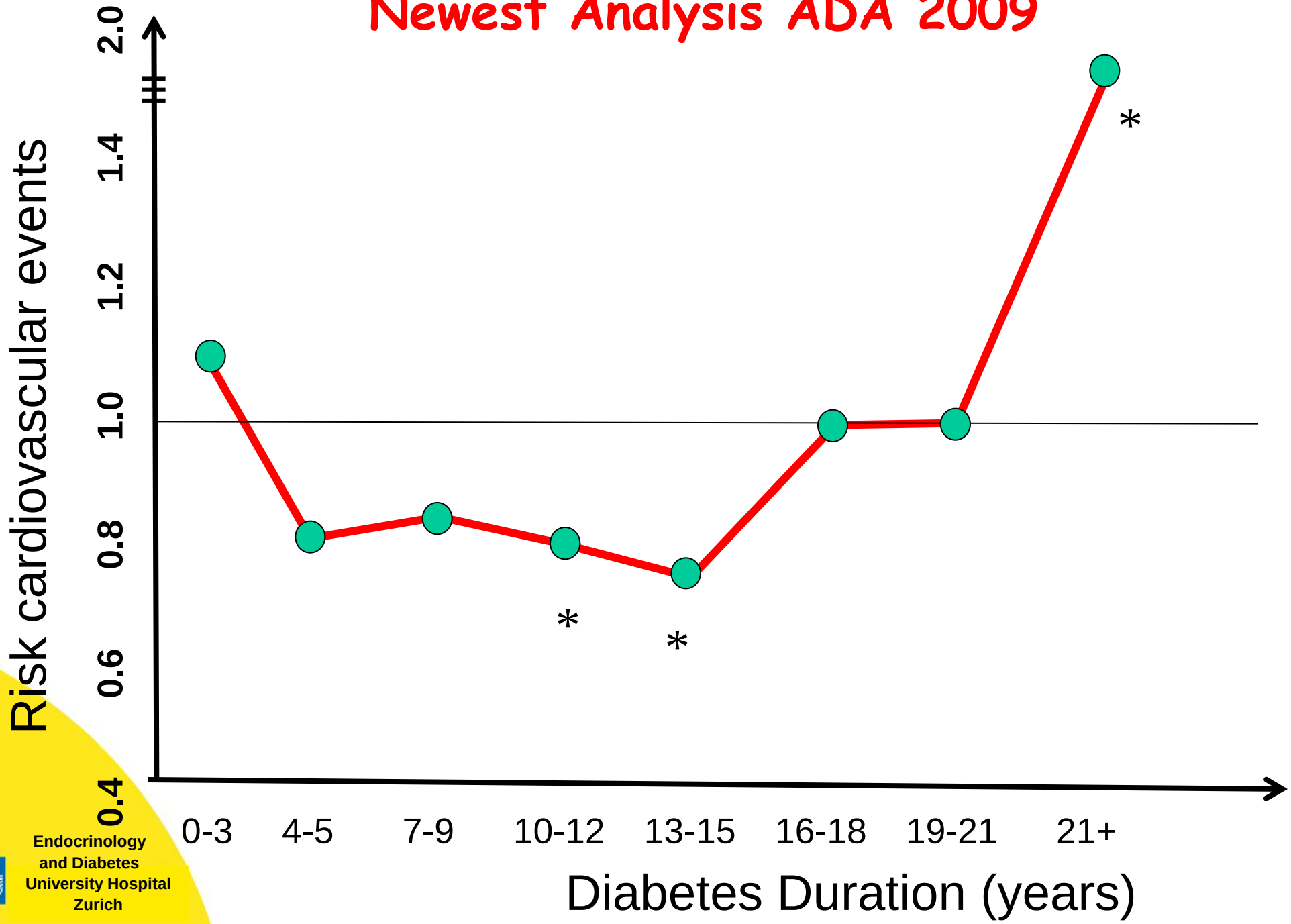
NEJM 2008; 358: 2545-592

VADT: Diabetes Duration and cardiovascular events

Newest Analysis ADA 2009



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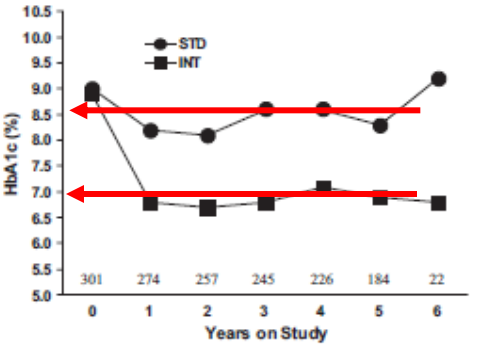
Coronary Artery Calcium and Cardiovascular Events
RACED (n= 301) substudy of VADT (n=1791)

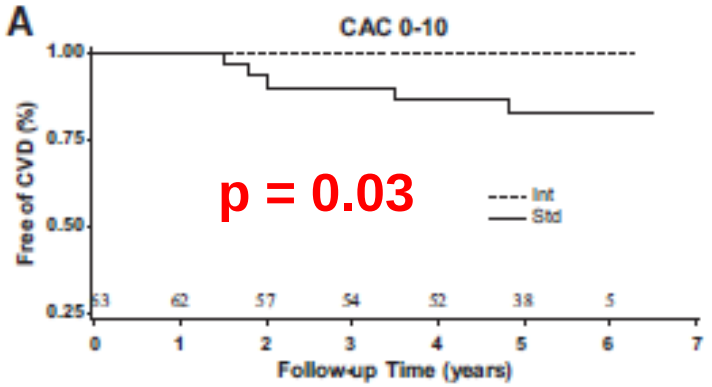


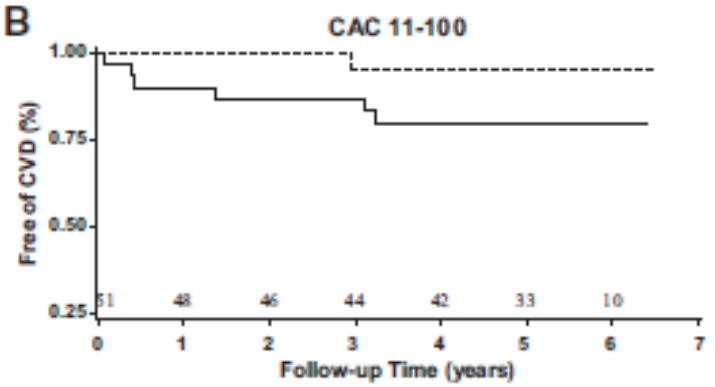
716 Type 2 Diabetes mean age 55 yrs: CHD within 8 years follow-up

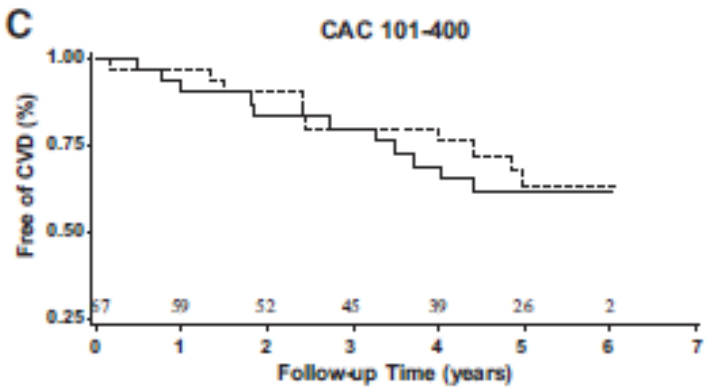
CAC 0-10: 3% CHD

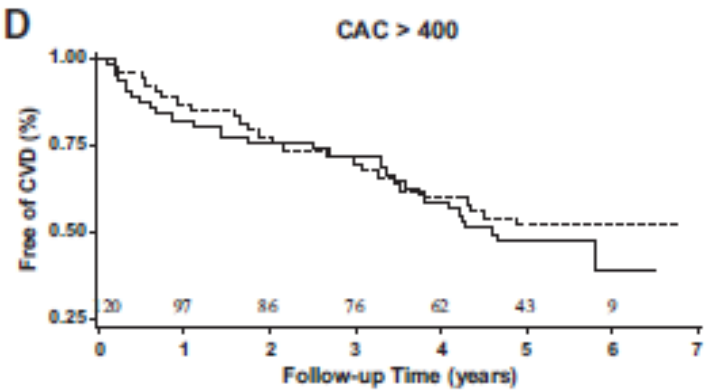
CAC >100: >30% CHD

BMC Cardiovasc Disord 2008; 8: 27









Age: 57 ±9 yrs
Duration DM: 9.8 ±7.5 yrs
HbA1c: 9.5 ±1.4%
HDL: 1.01 ±0.3 mM
TG: 2.2 ±1.4 mM

Age: 64 ±9 yrs
Duration DM: 13.5 ±7.5 yrs
HbA1c: 9.1 ±1.4%
HDL: 0.97 ±0.23 mM
TG: 2.3 ±1.5 mM

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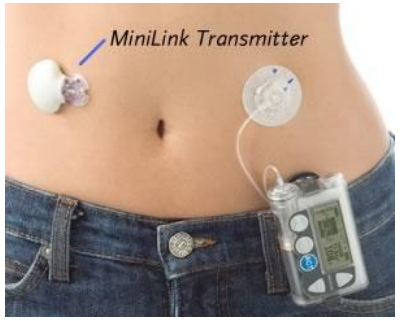
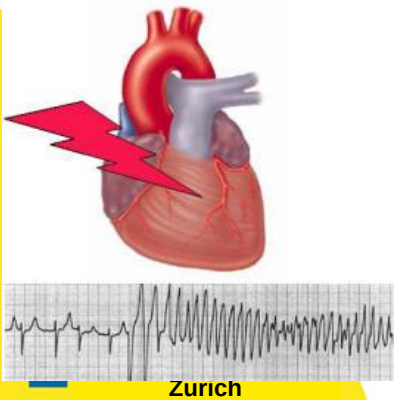
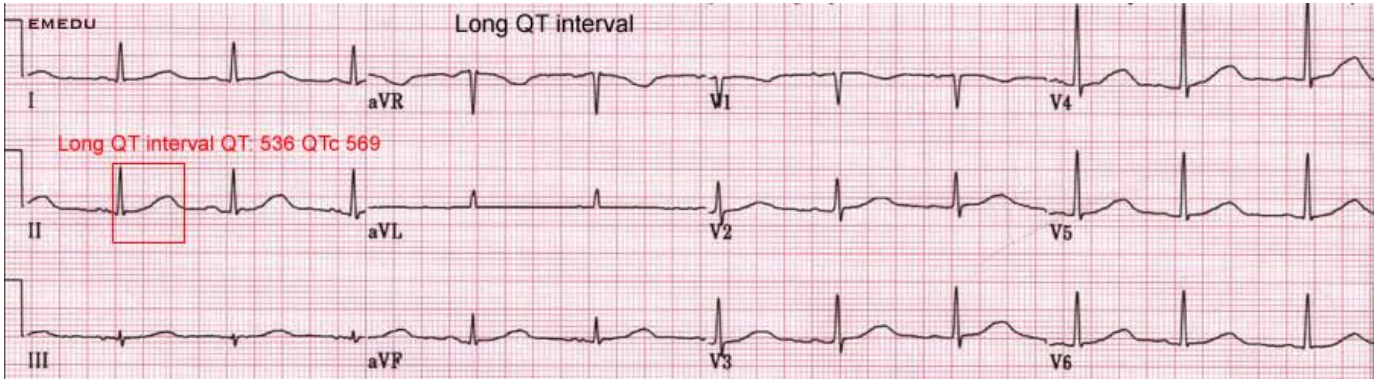
Reaven PD et al., Diabetes Care 2009; 58; 2642-8

Hypoglycemia and Mortality

- Hypoglycemia triggers angina
- Holter-EKG and CGMS: During hypoglycemia ➔ rhythm- and repolarisation disturbances (Long QT-Syndrom)
- Higher risk with autonomic neuropathy and long diabetes duration and recurrent hypoglycemia
- Pace maker cells lack energy during hypoglycemia to maintain membrane potential ➔death in adults and children without diabetes







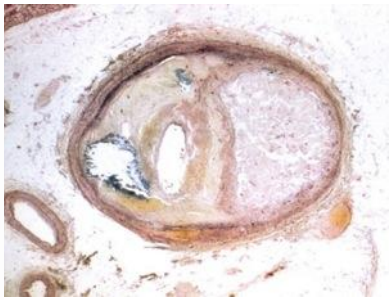
Lee SP et al, Diabetes 2004;53:1535-42

Flexible HbA1c Targets

- 3 Studies of ACCORD lead to one message:
- Not: the lower, the better, but flexible targets for glucose, lipids, and blood pressure

HbA1c-Target: 7.0% (avoid Hypoglycemia)

- Important Factors:
- Short Diabetes Duration ⇨ more intensive Therapy
- Short life expectancy ⇨ less intensive Therapy
- Risk Hypoglycemia
- Coronary Heart Disease



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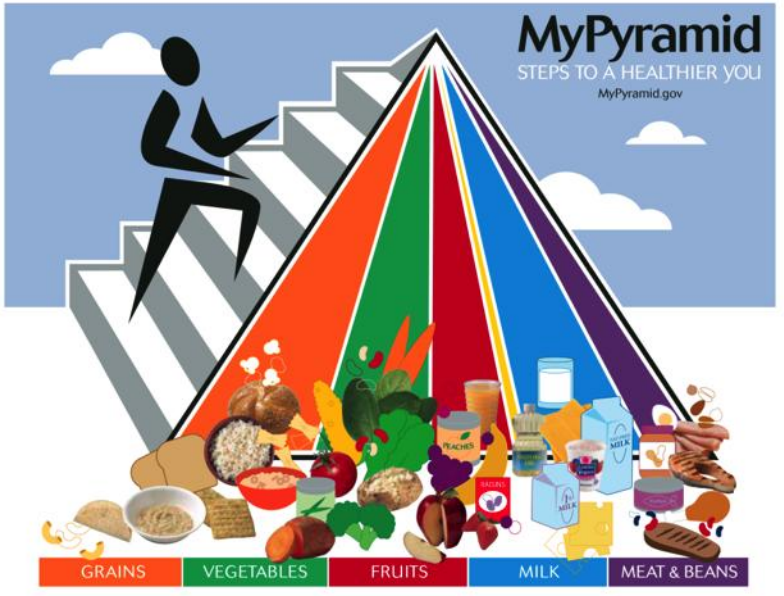
Which treatment options?



Inhalable insulin

Detemir

Glargine

New Drugs?
New Hope?

← Regular- + NPH Insulin

Glinide

Glitazone

←Metformin

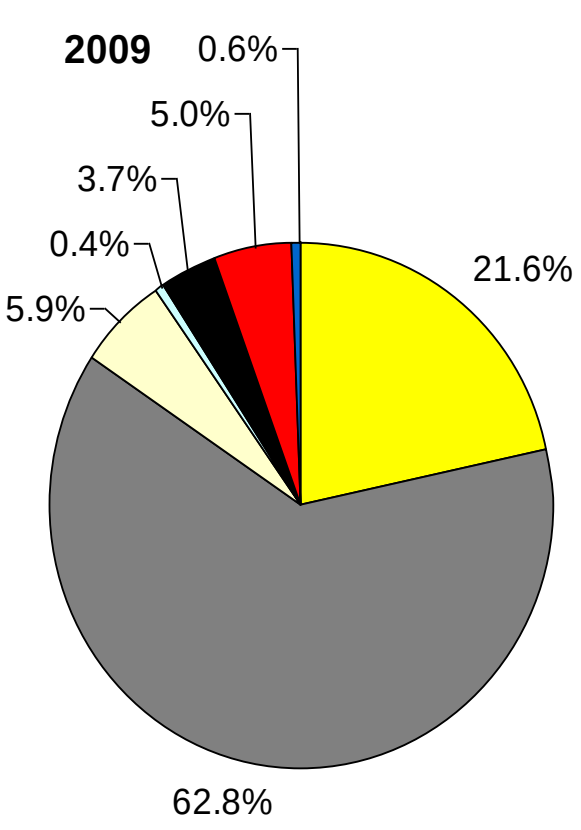
Self-Monitoring Blood Glucose

α-GI

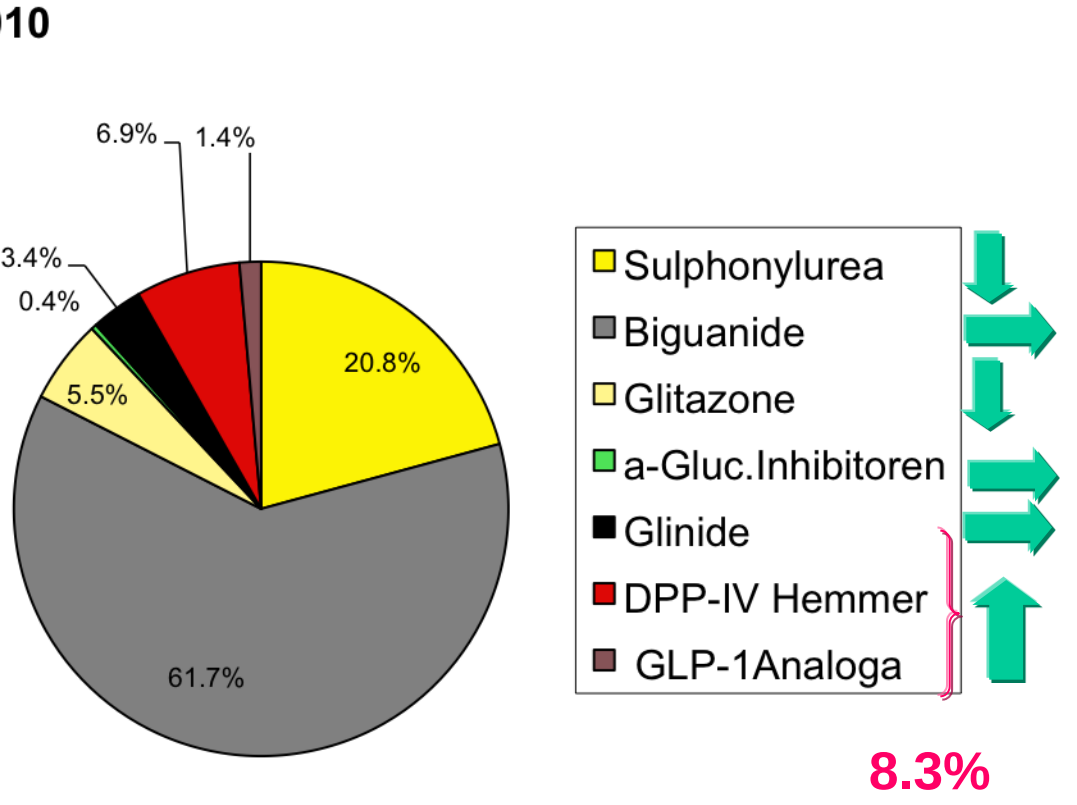
← Sulfonylureas

1960 1970 1980 1990 2000

% Market Share of oral antidiabetic Medication (packages)



5.6%

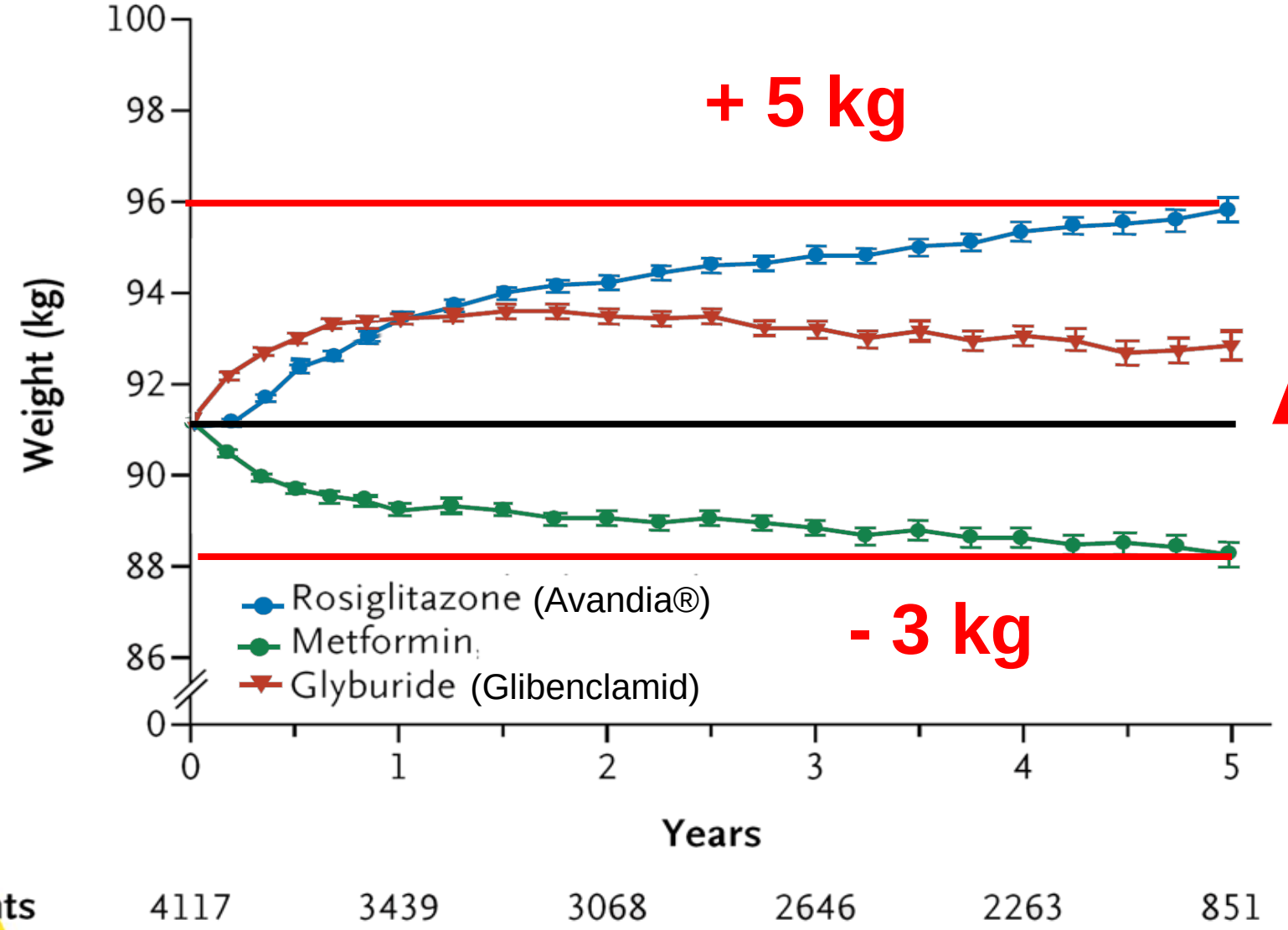


8.3%

IMS: In-market Packungsverkäufe, 2009 und Year to date Juli 2010

Weight change with Rosiglitazone-, Metformin- or Glibenclamid - Monotherapy

ADOPT-Study



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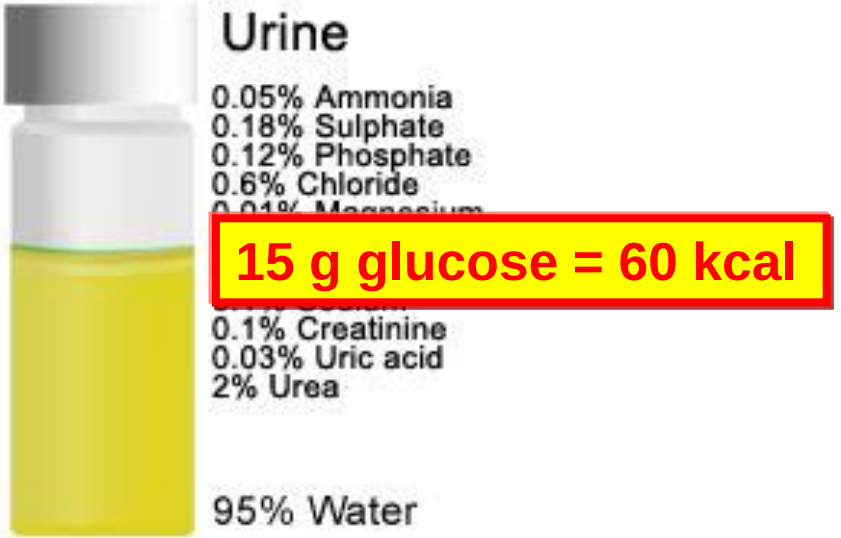
ADOPT Study, Kahn SE et al, N Engl J Med 2006;355:2427-43

Weight Increase with Antidiabetic Therapy

- Renal glucose threshold: 10 mM (~7.3% HbA1c)

- **Per 1% HbA1c ⇩: Weight ⇧ 3 kg per year (57 kcal/d = 8 g/day)**



Carson *et al*. *Diabetes* 1993;42:1700–707

Hypoglycemia?

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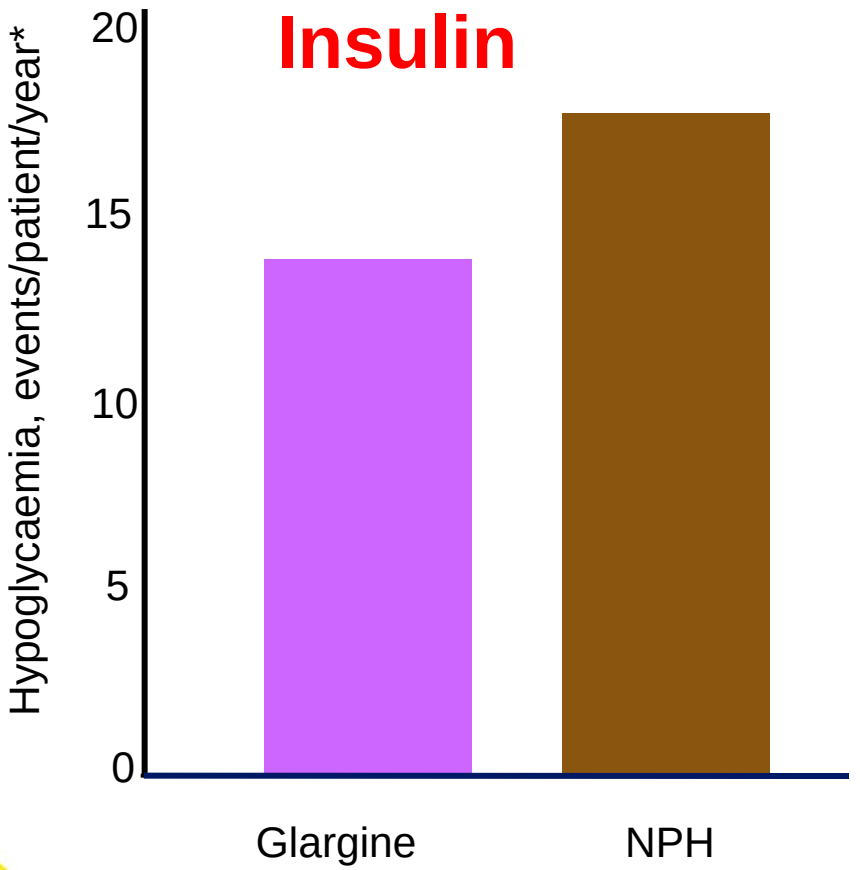
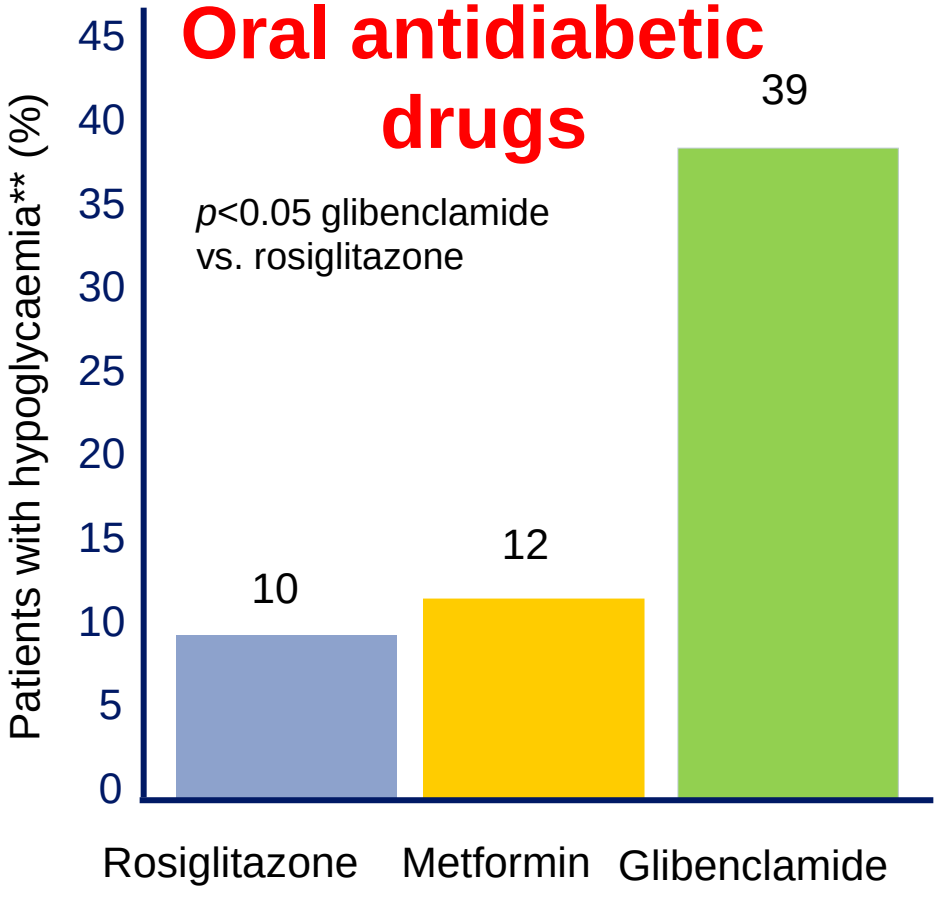
Current treatments increase risk of hypoglycaemia



*All symptomatic hypoglycaemic events



** Patients self-reporting (unconfirmed) hypoglycaemia

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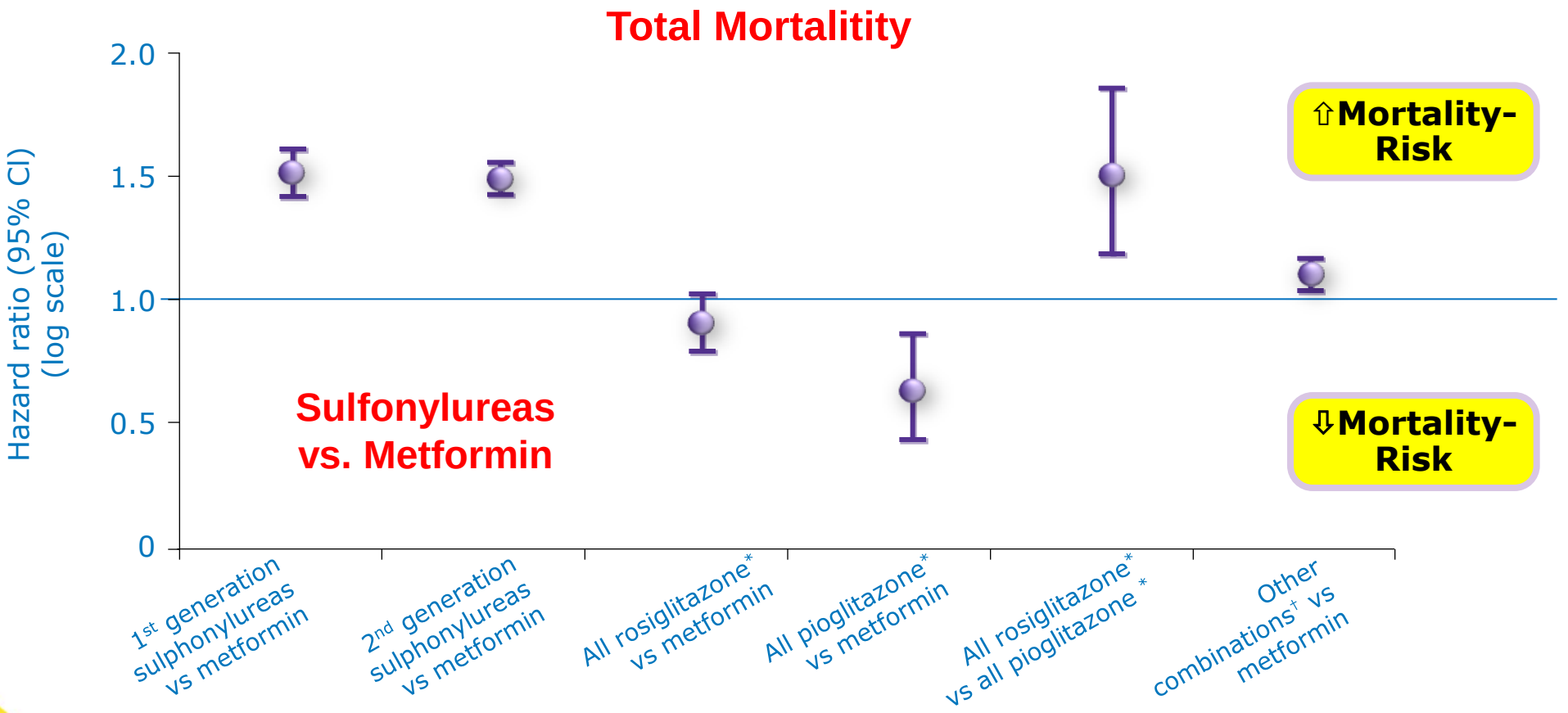
Riddle *et al. Diabetes Care* 2003;26:3080;
Kahn *et al* (ADOPT). *NEJM* 2006;355:2427–43

Mortality with oral antidiabetic treatment

Retrospective cohort study using UK general practice research database (1990-2005) **of 91,521 people with diabetes**



*Any therapy (monotherapy and combinations).
†Other drugs and combinations of any oral antidiabetes drugs excluding rosiglitazone and pioglitazone

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Tzoulaki I, Molokhia M, Curcin V et al. BMJ. 2009;339:b4731 doi:10.1136/bmj.b4731 (3 Dec 2009,e-pub ahead of print)

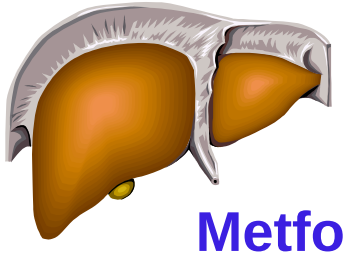
Mitochondria

↑ PGC-1

Glitazone

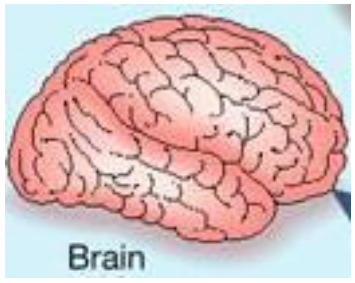
↓ Liver fat

Liver



Metformin

↓ Glucose production

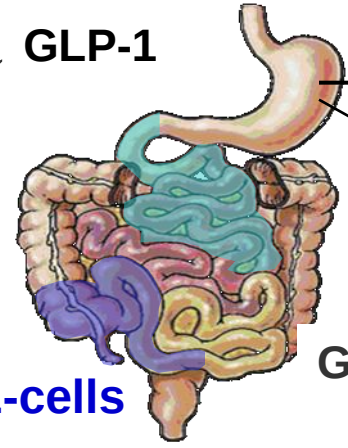


GLP-1

↓ Appetite

↑ Satiety

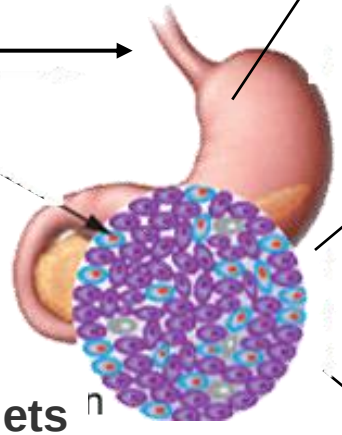
↓ GLP-1



L-cells

GI-Tract

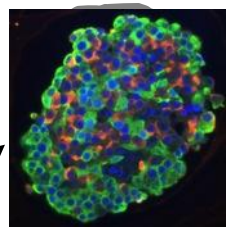
⇧ Glucose



Islets

↓Gastric Emptying

↓Glucagon secretion



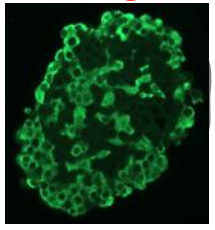
α-Cell

↑ Insulin secretion

↓ Glucagon secretion

GLP-1

DPP-4



β-cell

↓ Insulin synthesis

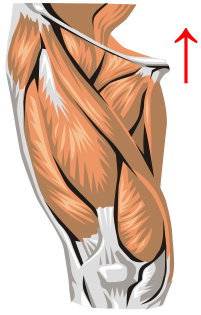
↓ β-cell proliferation

↑ β-cell apoptosis

Glinides

Sulfonylurea

↑ Insulin secretion

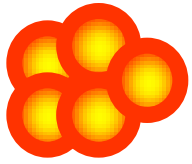


↑ Insulin sensitivity

Glitazone

Muscle

↑ Glucose uptake

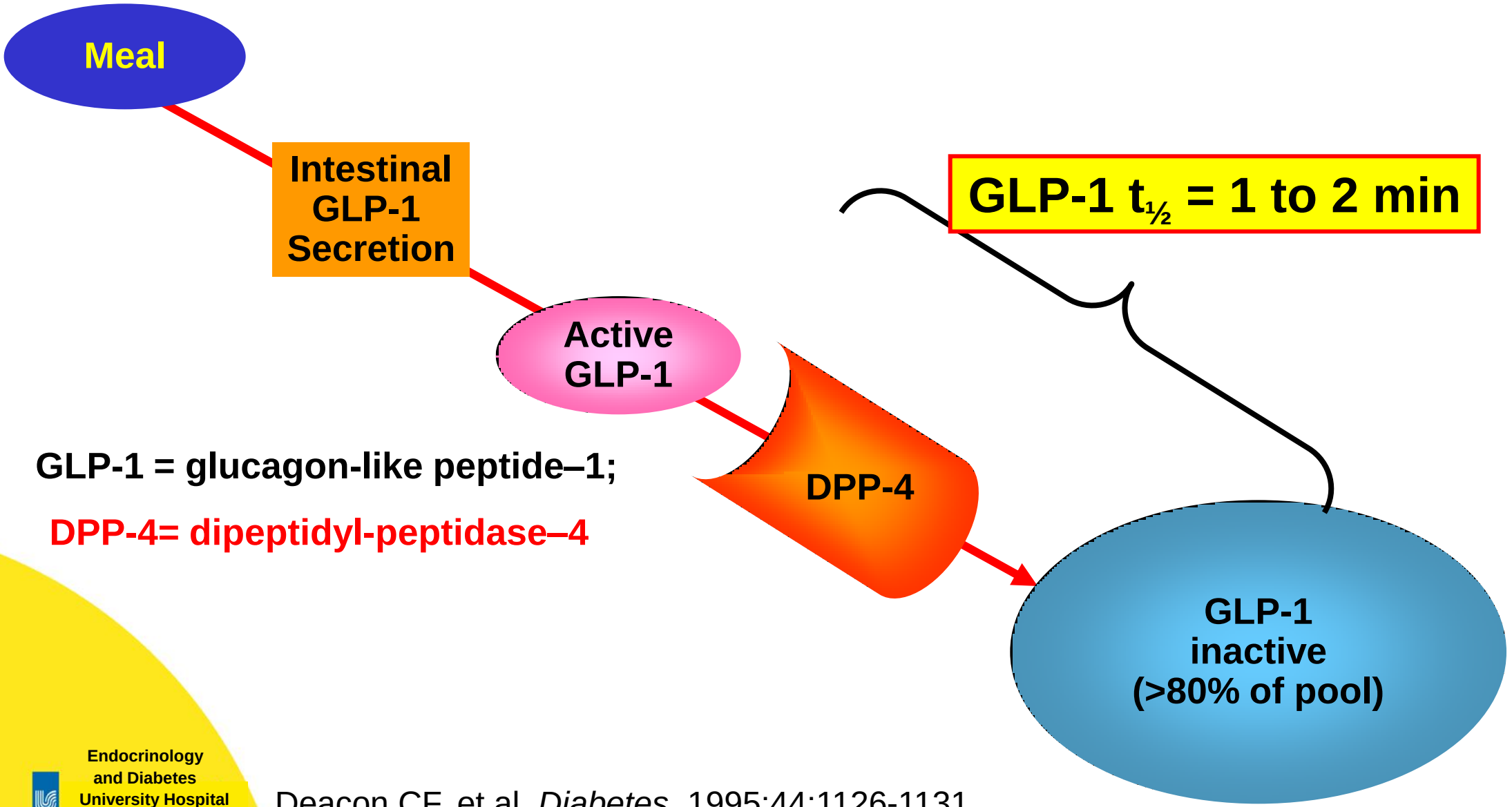


Adipocytes

↓ Free Fatty Acids

α-Glucosidase inhibitor

GLP-1 secretion and inactivation



GLP-1 = glucagon-like peptide–1;

DPP-4= dipeptidyl-peptidase–4

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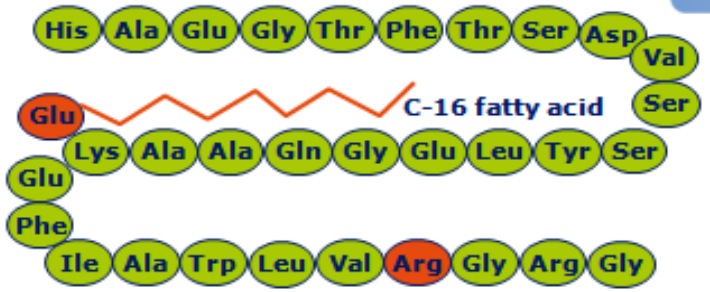
Deacon CF, et al. *Diabetes*. 1995;44:1126-1131.

Structure of native GLP-1 und two GLP-1 Receptor Agonists

Native human GLP-1

t/2:~ 1-2 minutes

Liraglutide



t/2:~ 13 hours

Exenatide

t/2:~ 33 minutes

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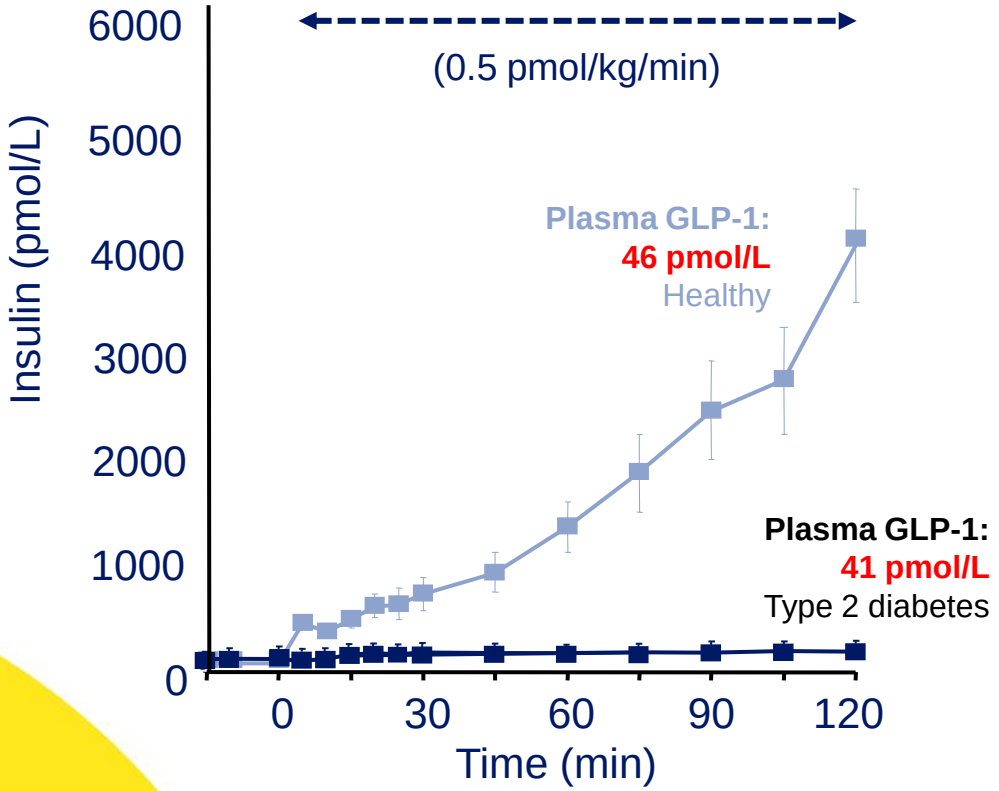
Impaired insulin responses to *physiological* levels of GLP-1 in T2D are restored by *pharmacological* doses

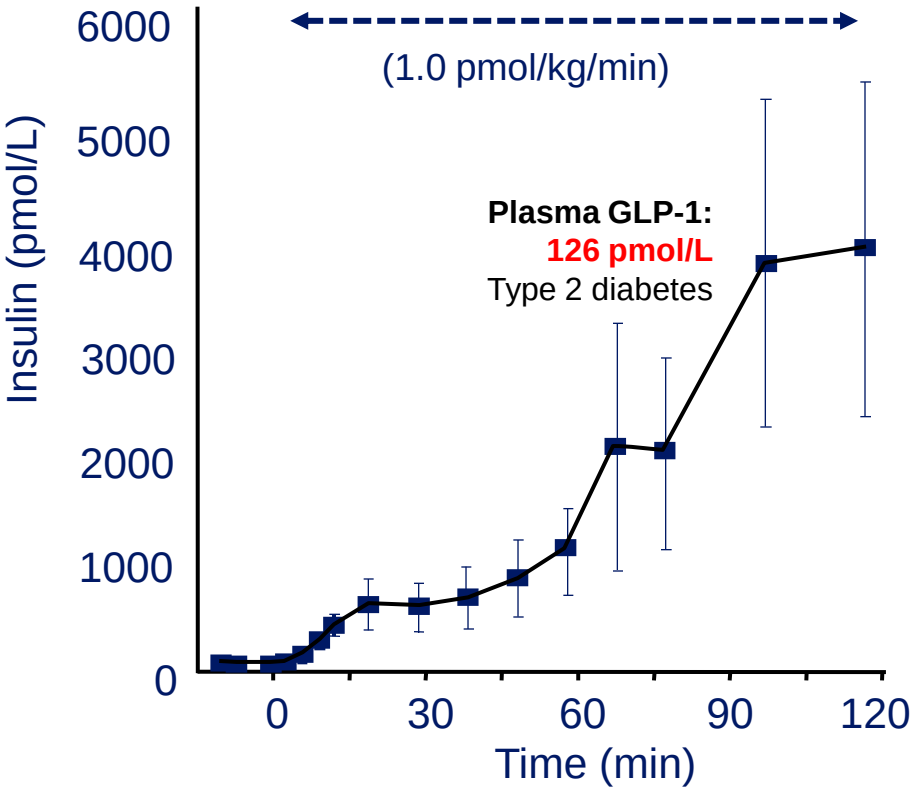
Physiological levels of GLP-1[1]

(15 mM hyperglycaemic clamp)



Pharmacological levels of GLP-1[2]

(15 mM hyperglycaemic clamp)



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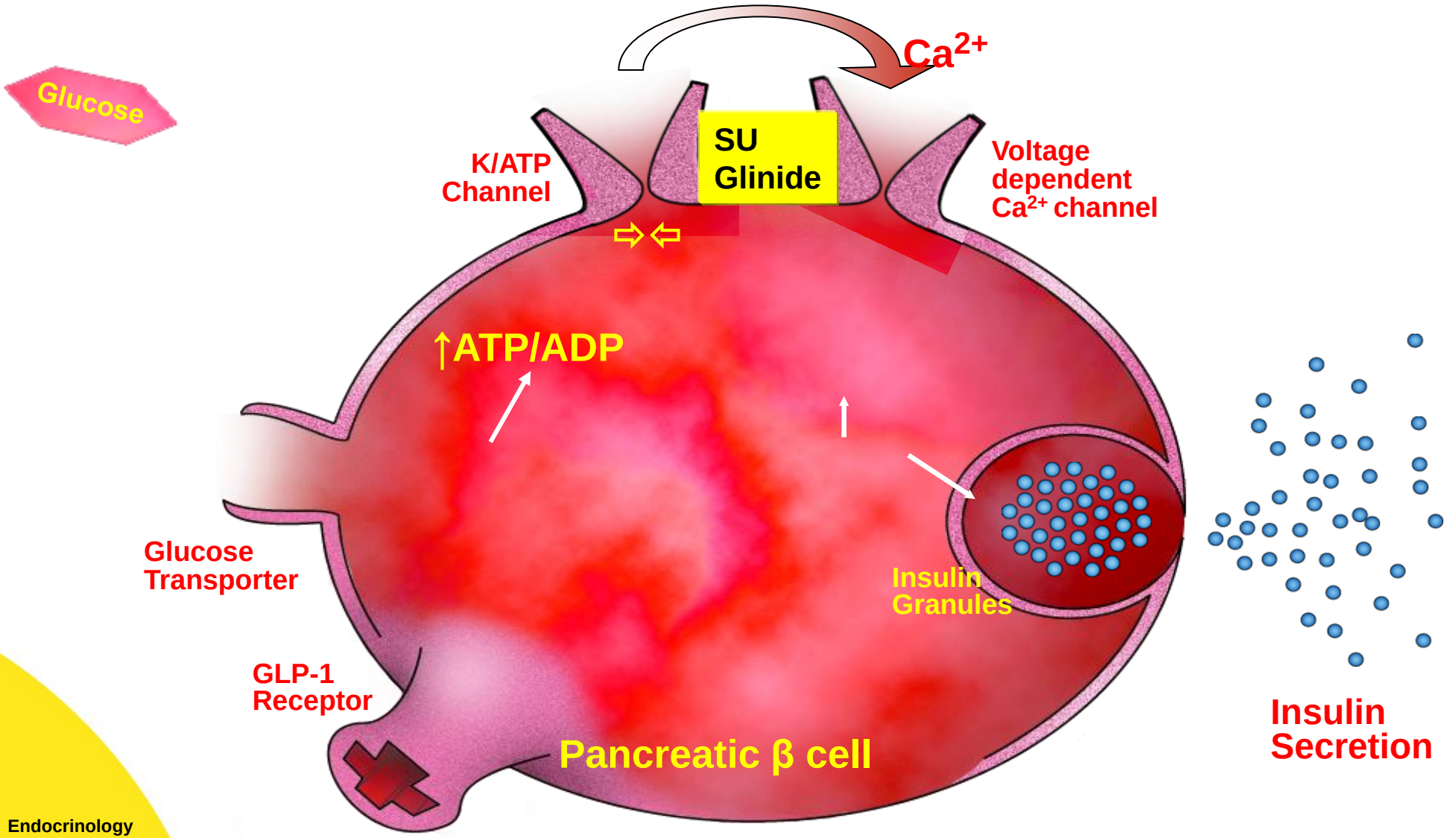
1. Højberg *et al*. *Diabetologia* 2008 [Epub ahead of print]. 2. Vilsbøll *et al*. *Diabetologia* 2002;45:1111–9

Insulin Secretion by Glucose



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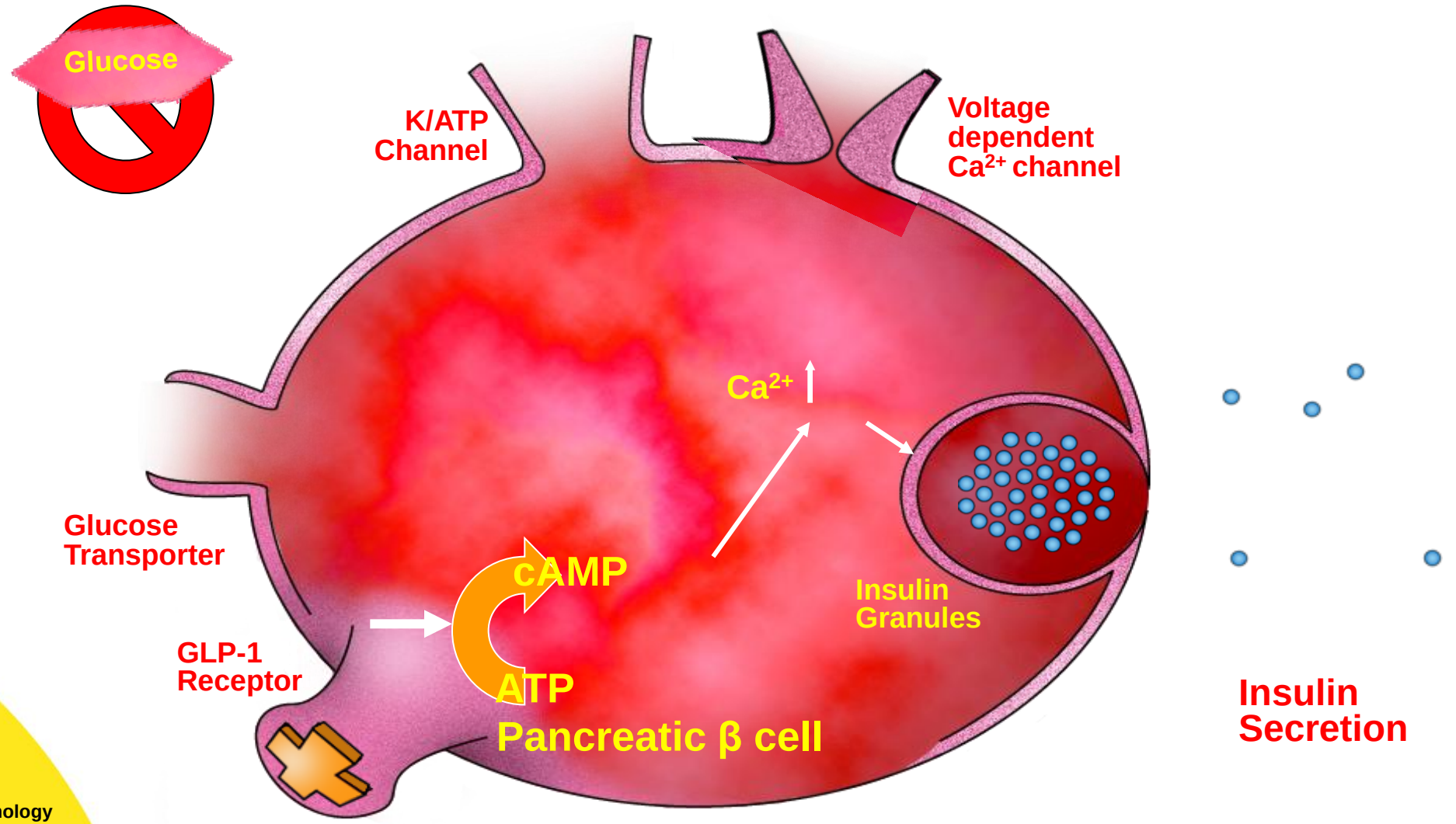
Gromada J, et al. *Pflugers Arch – Eur J Physiol.* 1998;435:583-594;
MacDonald PE, et al. *Diabetes.* 2002;51:S434-S442.

Limited Insulin Secretion by GLP1 Receptor Stimulation without Glucose



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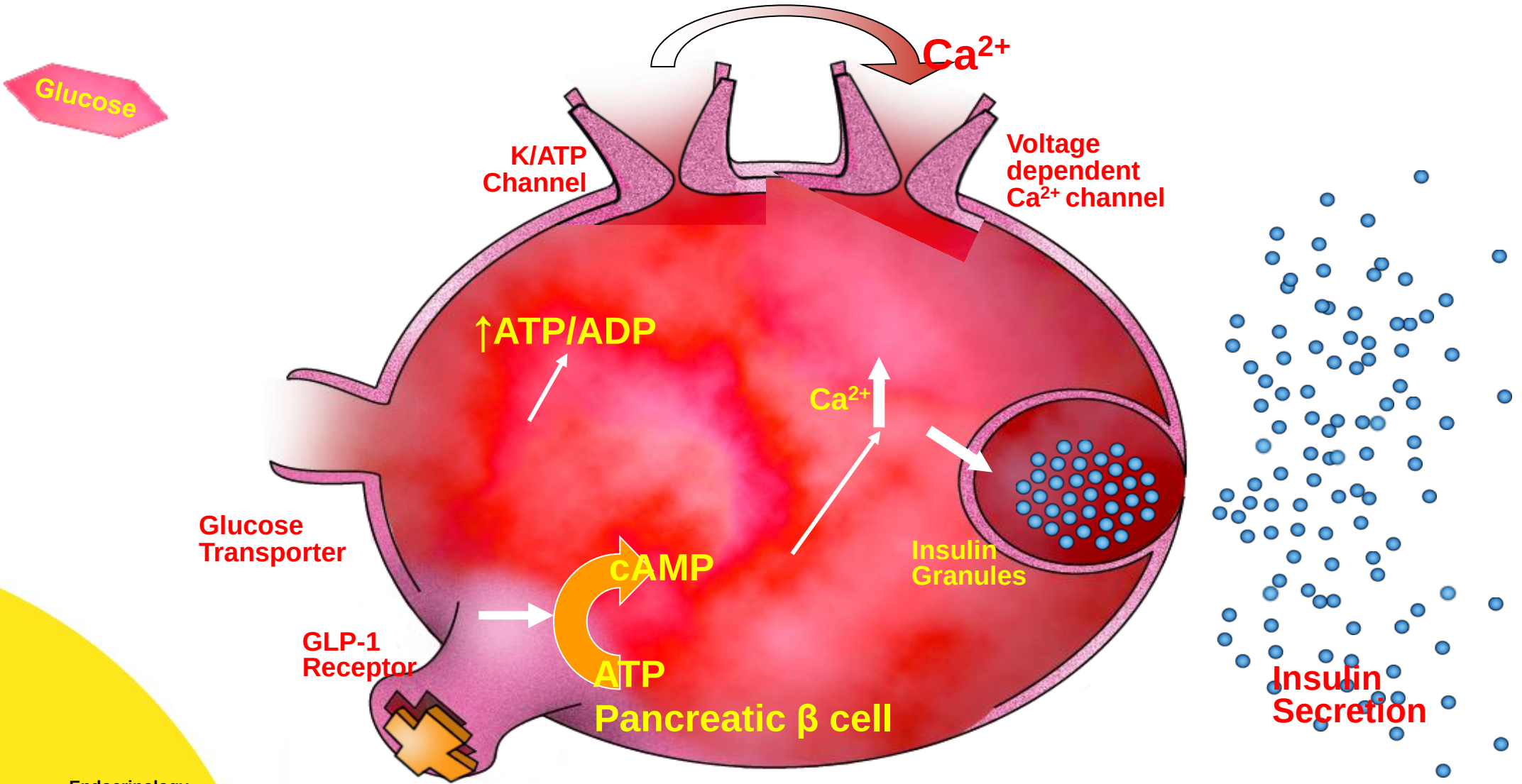
Gromada J, et al. *Pflugers Arch – Eur J Physiol.* 1998;435:583-594;
MacDonald PE, et al. *Diabetes.* 2002;51:S434-S442.

Insulinotropic Action of GLP-1 = glucose-dependent



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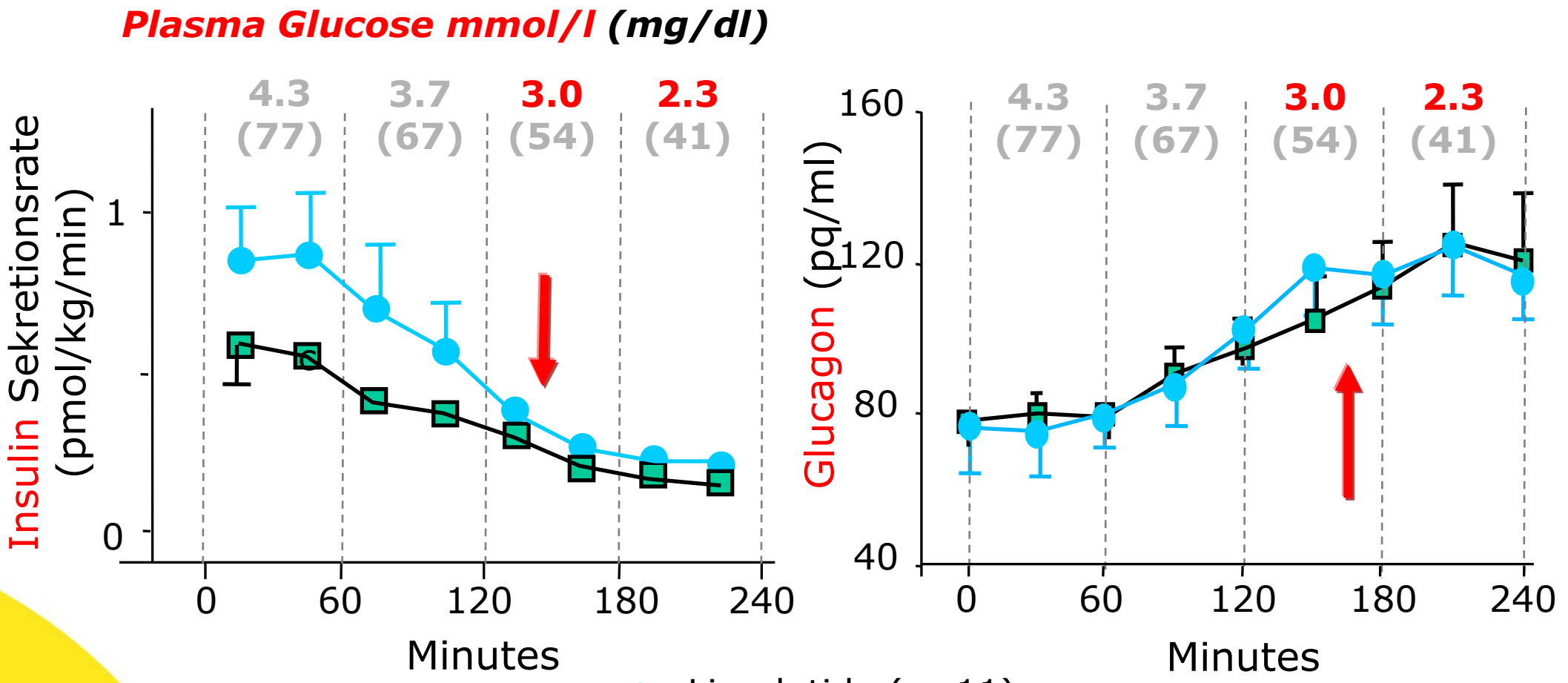
GLP-1 Analogues and Hyppoglycemia: ⇩ Insulin and ⇧ Glucagon Secretion



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Nauck et al. Diabetes 2003;52(Suppl 1):A128.

LEAD 1-6 Trial + LIRA-DDP-4 Trial

4456 patients

Liraglutide
monotherapy vs. SU
LEAD 3

Liraglutide+MET vs.
SU+MET
LEAD 2

Liraglutide+SU vs.
TZD+SU
LEAD 1

Add a third oral
or start insulin

Add another
oral agent

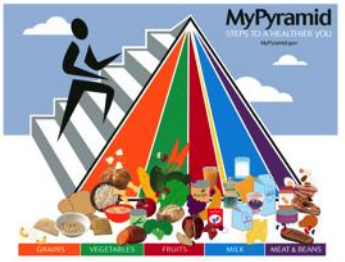
Liraglutide+MET+TZD
vs. MET+TZD
LEAD 4

Liraglutide+MET+SU
vs. **glargine**+MET+SU
LEAD 5

Start an oral agent

Liraglutide plus MET, SU or both
vs. exenatide plus MET, SU or both
LEAD 6

Diet/exercise



Liraglutide plus MET
vs. Sitagliptin plus MET
LIRA-DPP-4 Study

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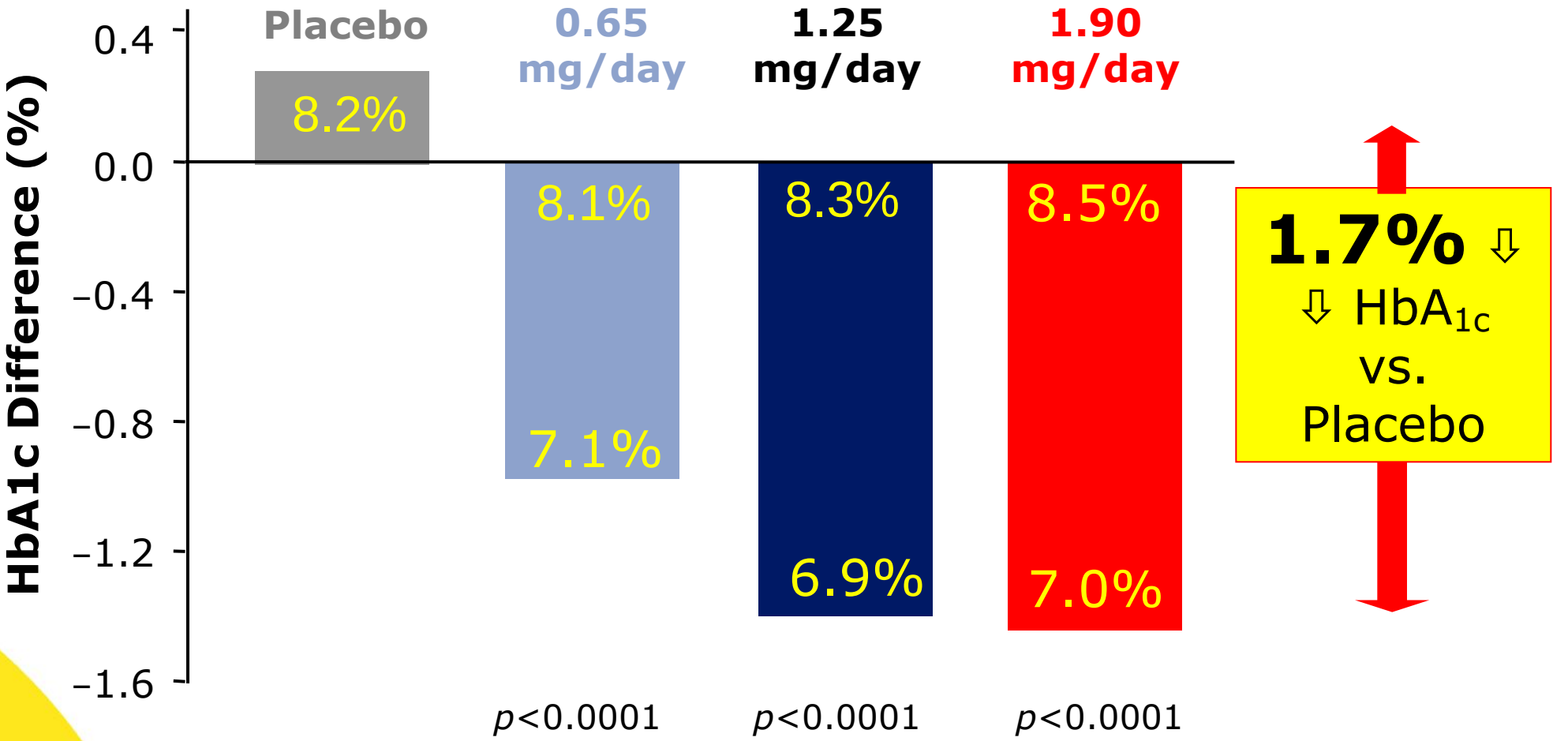
Liraglutide Monotherapy: ⇩HbA1c

14 Weeks



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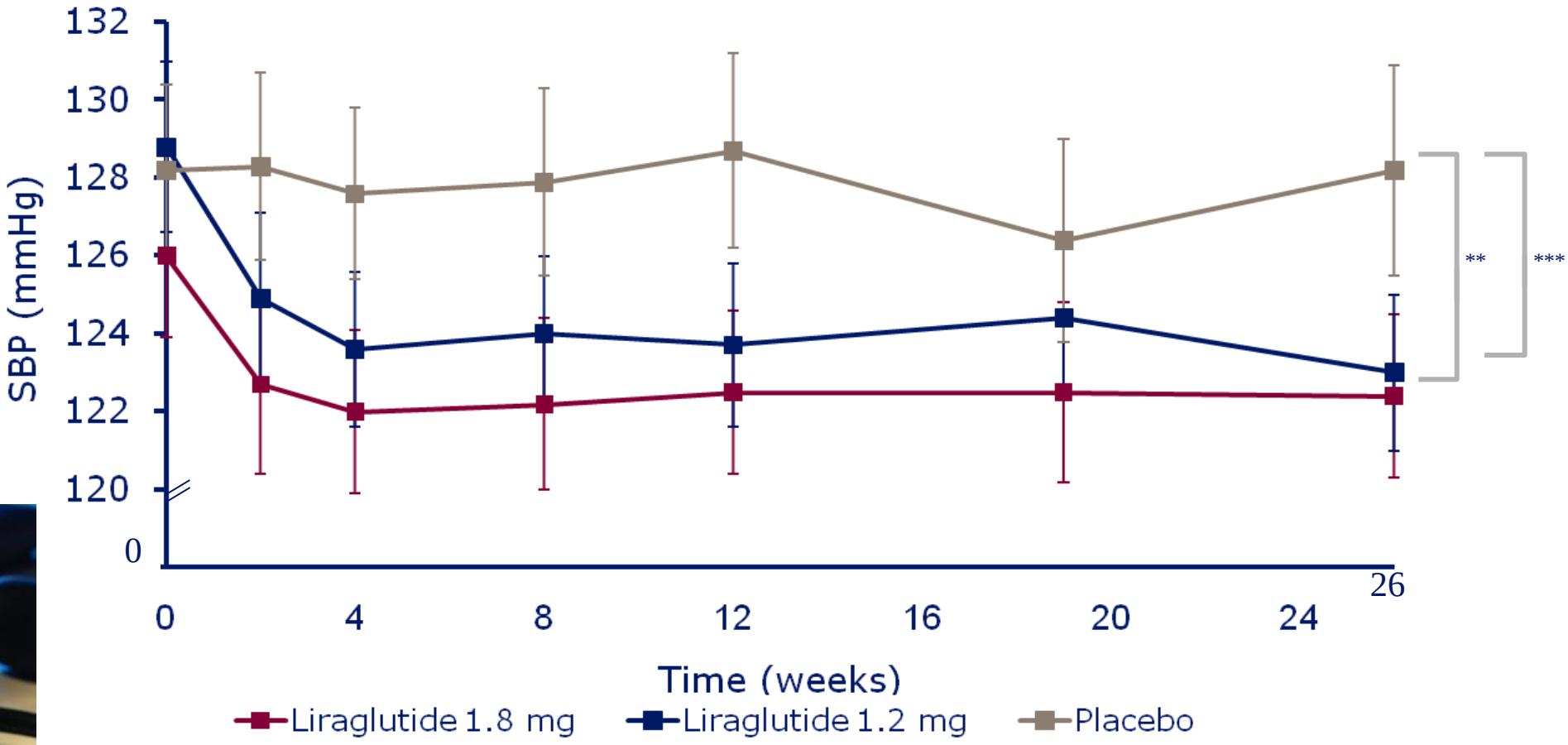
Vilsbøll et al, Diabetes Care, Diab Care 2007;30:1608-10

Reduction of systolic blood pressure before any major effect on weight

**p<0.001 and ***p<0.0001 for change from baseline



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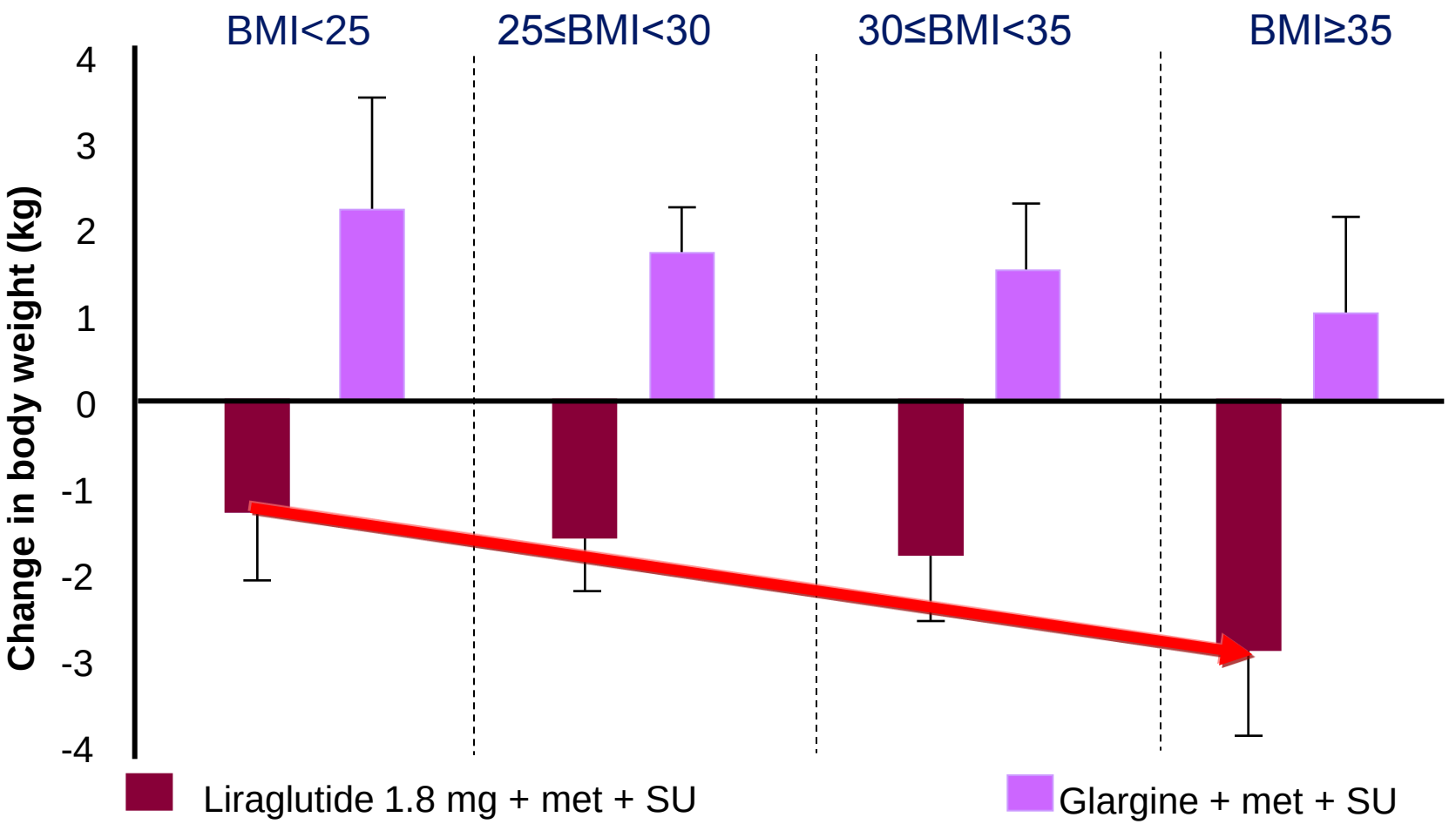
Zinman *et al. Diabetes Care* 2009; DOI:10.2337/dc08-2124 (LEAD-4)

Liraglutide: Higher weight loss with higher baseline BMI

25% of patients: 7.5 kg weight loss



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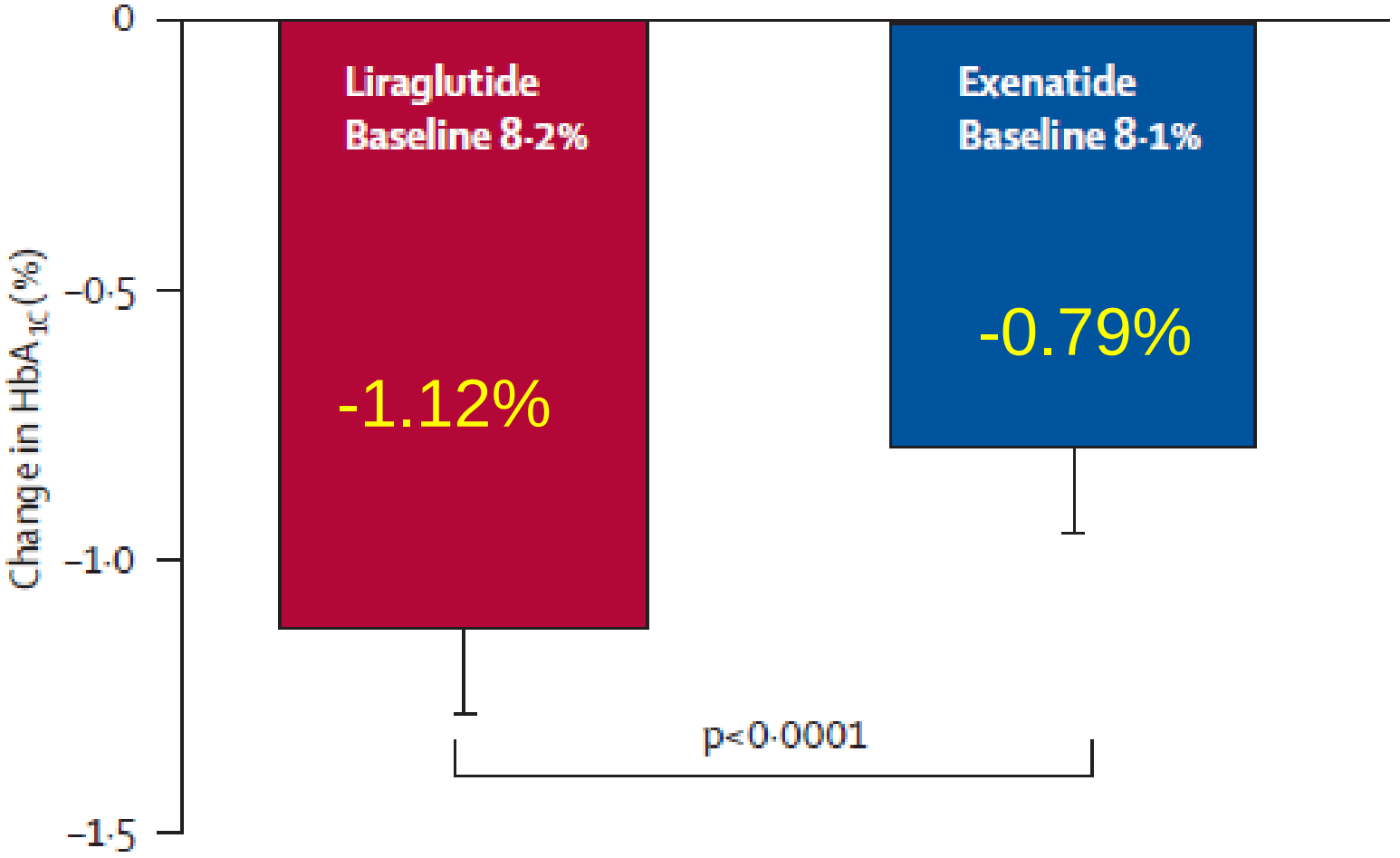
Russell-Jones *et al. Diabetologia 2009; 52; 2046-55* (LEAD-5)

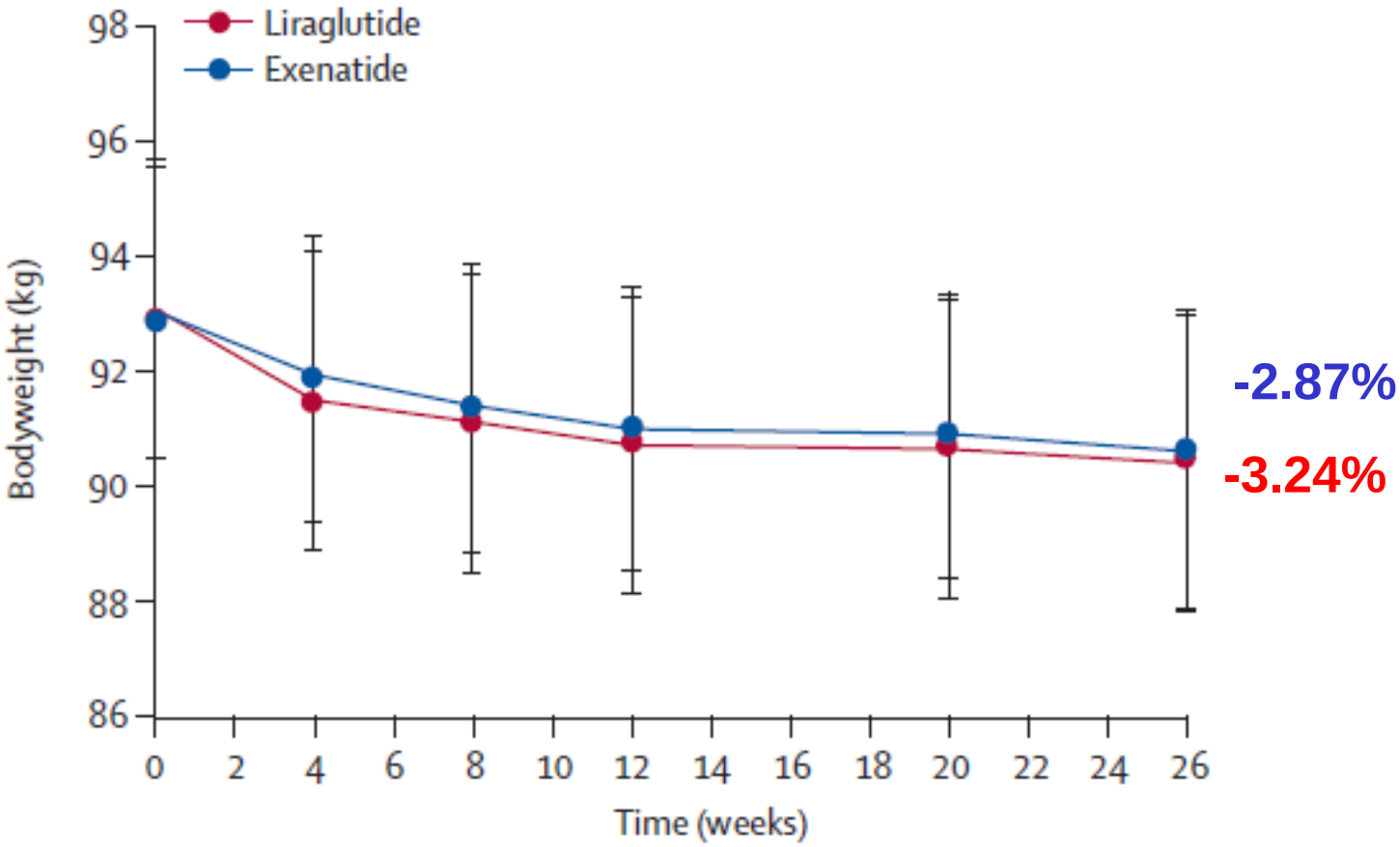
Which GLP-1 Analog? Change in HbA_{1c}

Liraglutide vs. Exenatide (LEAD 6)



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

No difference in body weight loss
~ 3 kg in 6 months



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

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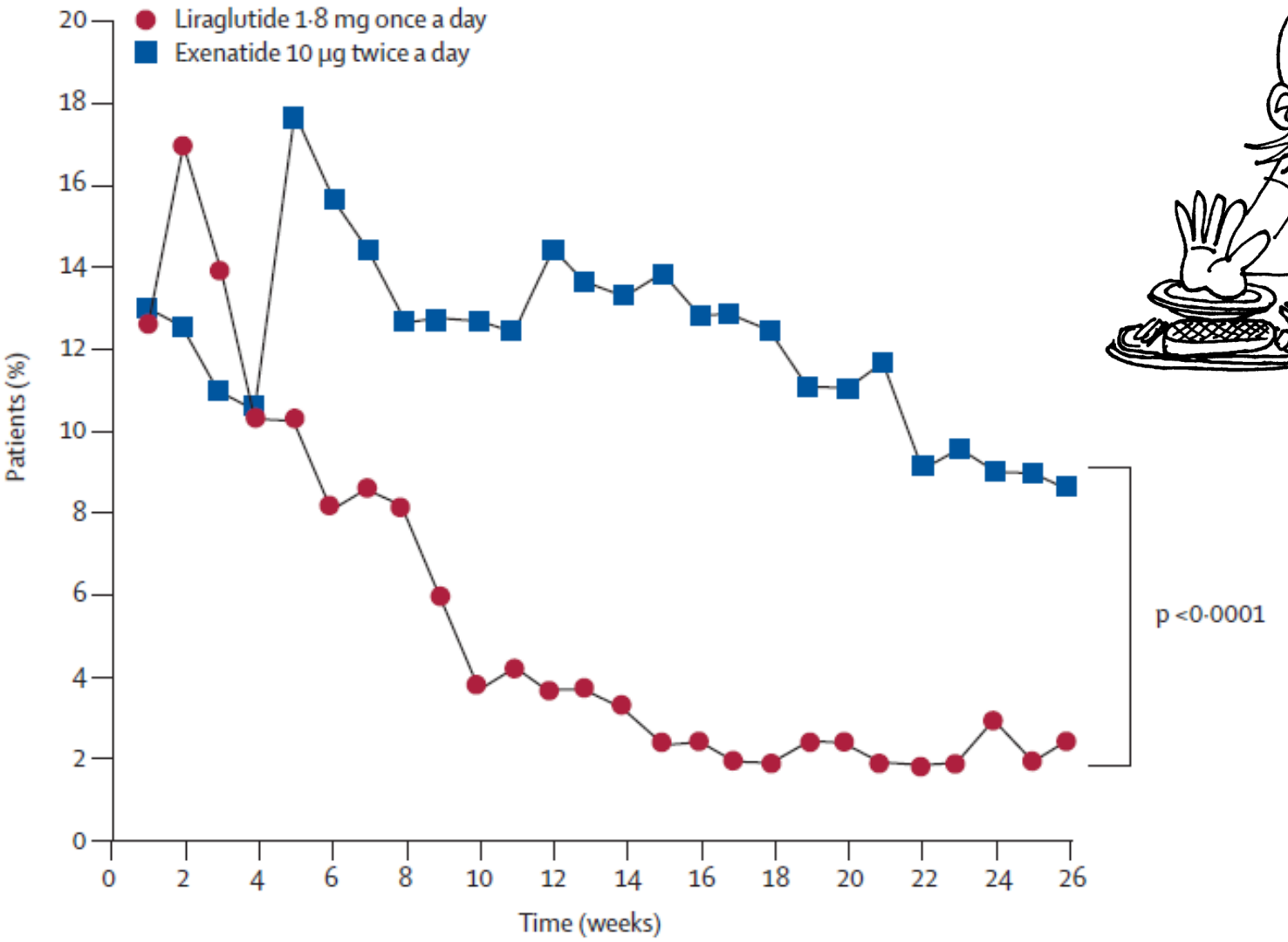
Nausea ⇩ over time with Liraglutide



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

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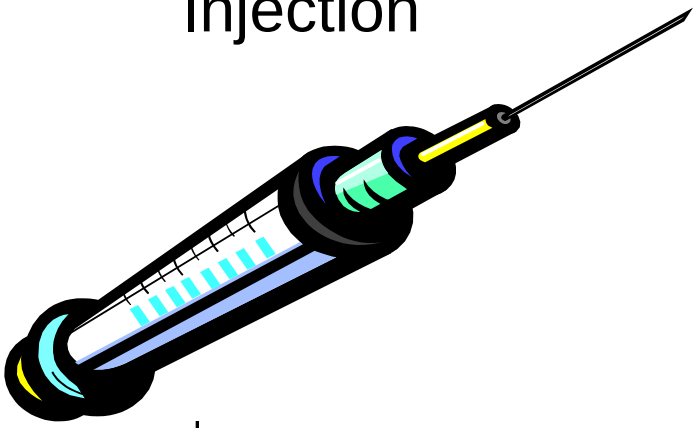
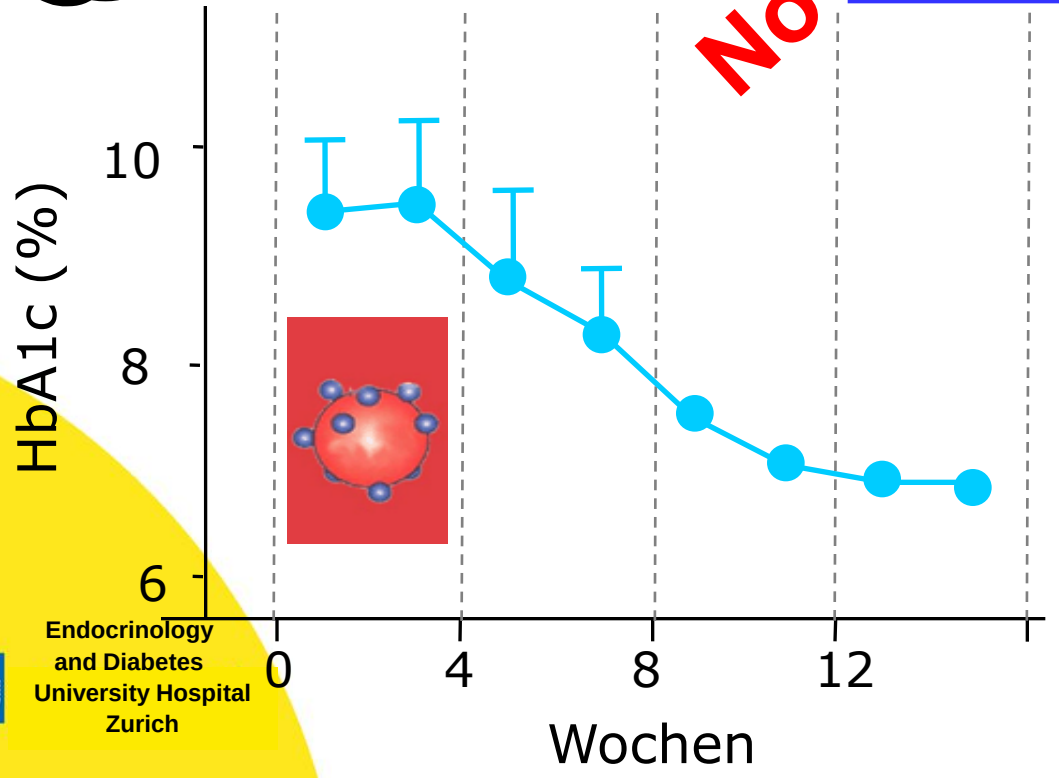
Major Advantages and Disadvantages of GLP-1 Receptor Agonists

Injection



No hypoglycemia



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Why not DPP-4 Inibitors?

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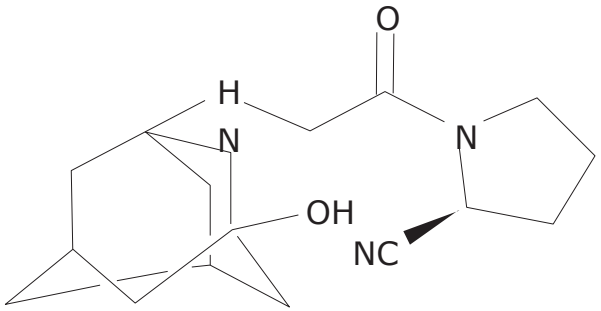
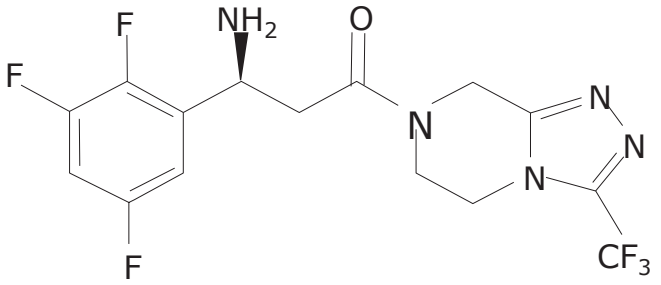
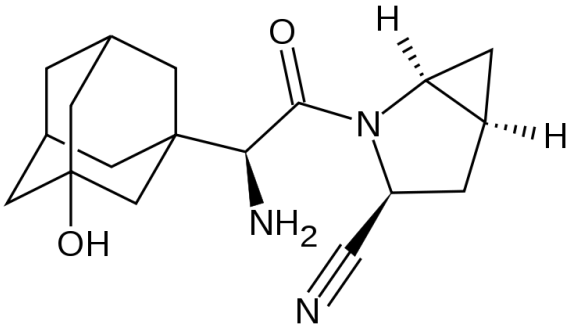
DPP-IV Inhibitors







Vildagliptin
(Galvus)

Sitagliptin
(Januvia)

Saxagliptin
(Onglyza)

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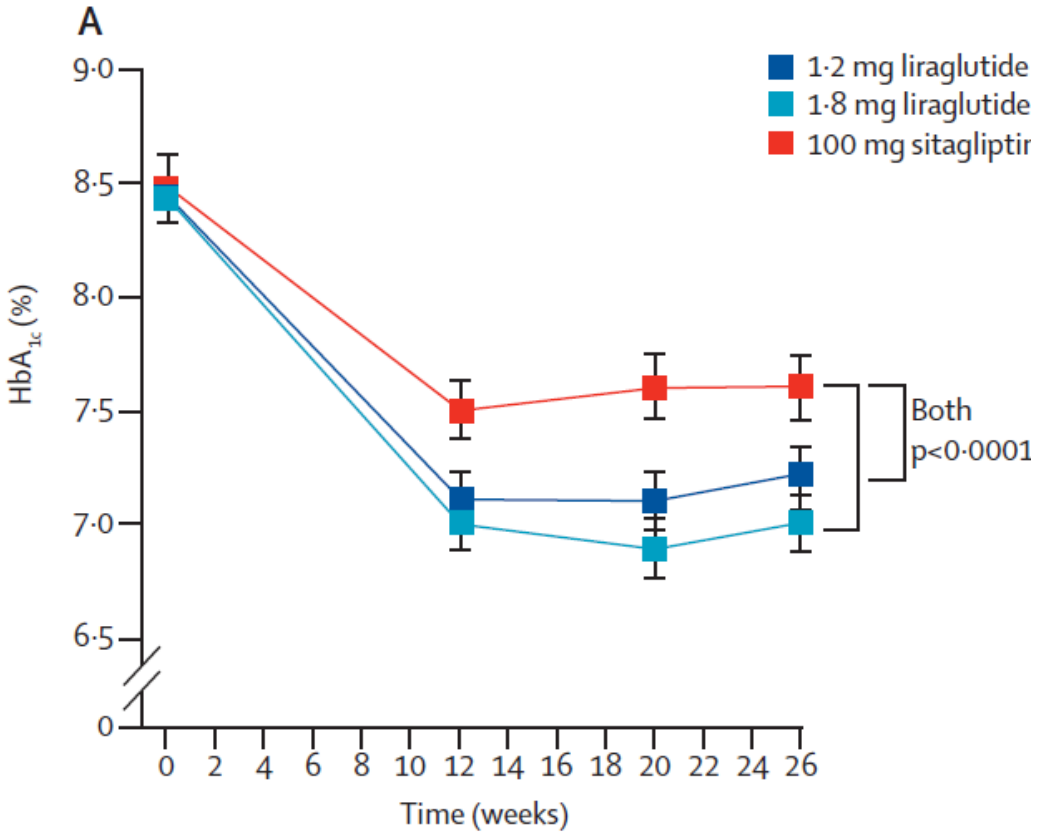
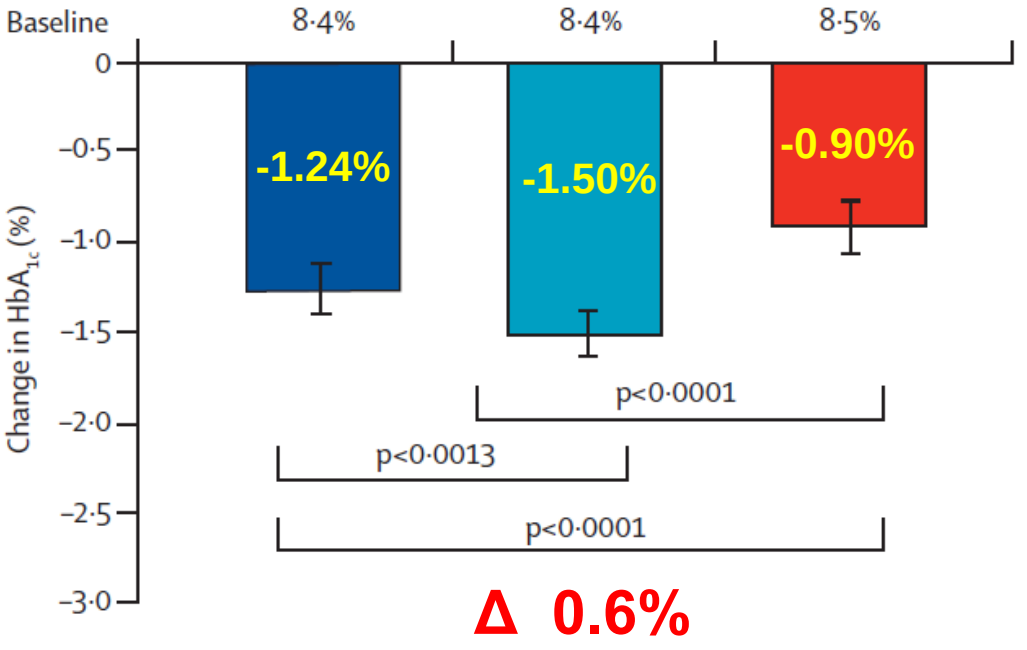
Greater HbA1c Reduction by Liraglutide vs. Sitagliptin (added to metformin)

Baseline HbA1c was 8.4%





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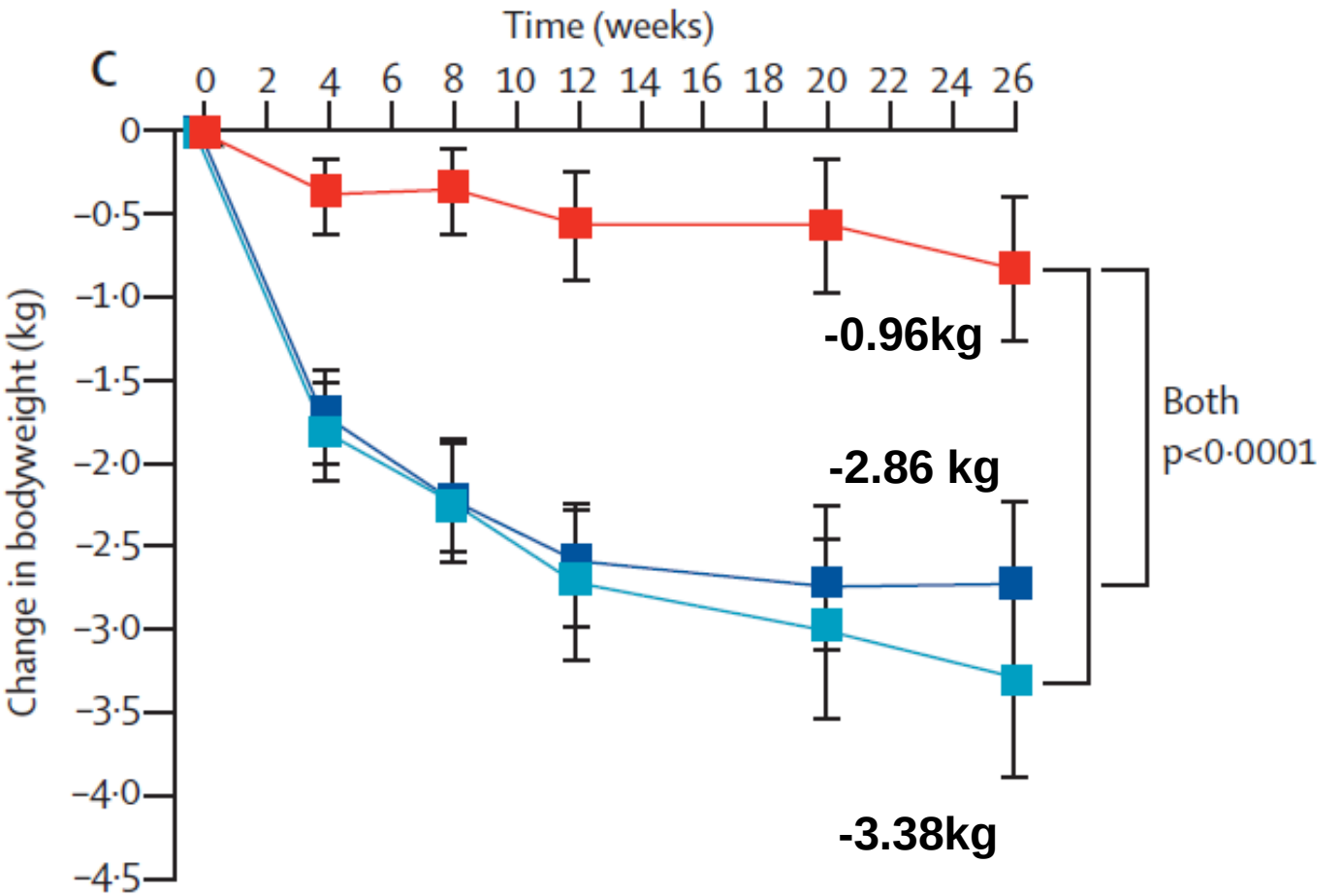
Pratley RE et al. Lancet 2010; 375:1447-56

Greater Reduction of Weight by Liraglutide vs. Sitagliptin (added to metformin)



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Pratley RE et al. Lancet 2010; 375:1447-56

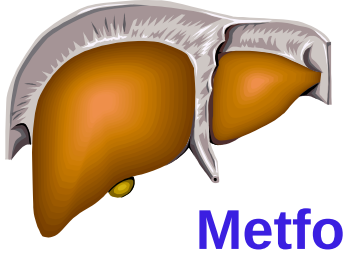
Mitochondria

↑ PGC-1

Glitazone

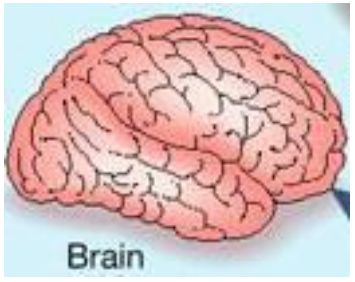
↓ Liver fat

Liver



Metformin

↓ Glucose production

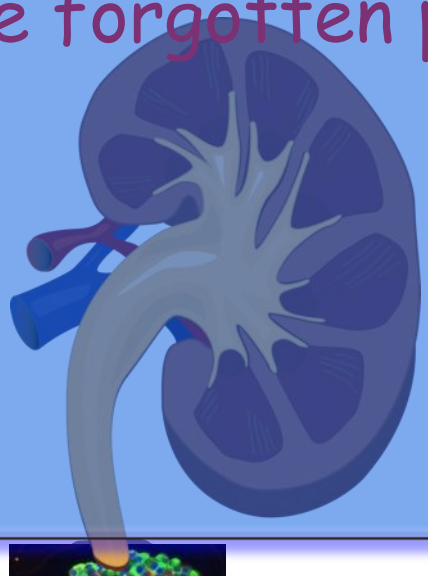


GLP-1

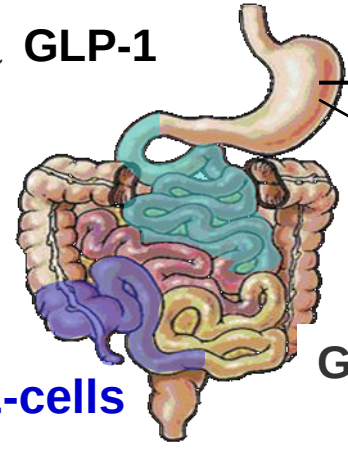
↓ Appetite

↑ Satiety

The forgotten player

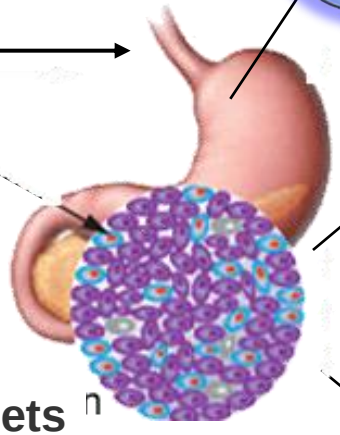


↓ GLP-1



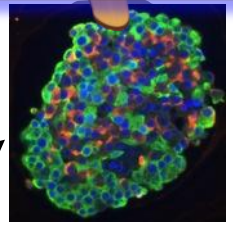
L-cells

GI-Tract



Islets

⇧ Glucose



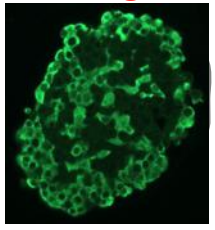
α-Cell

↑ Insulin secretion

↓ Glucagon secretion

GLP-1

DPP-4



β-cell

↓ Insulin synthesis

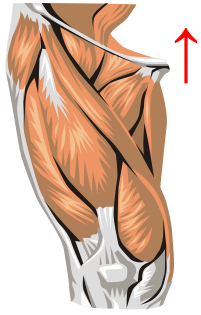
↓ β-cell proliferation

↑ β-cell apoptosis

Glinides

Sulfonylurea

↑ Insulin secretion

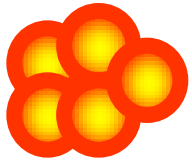


↑ Insulin sensitivity

Glitazone

Muscle

↑ Glucose uptake



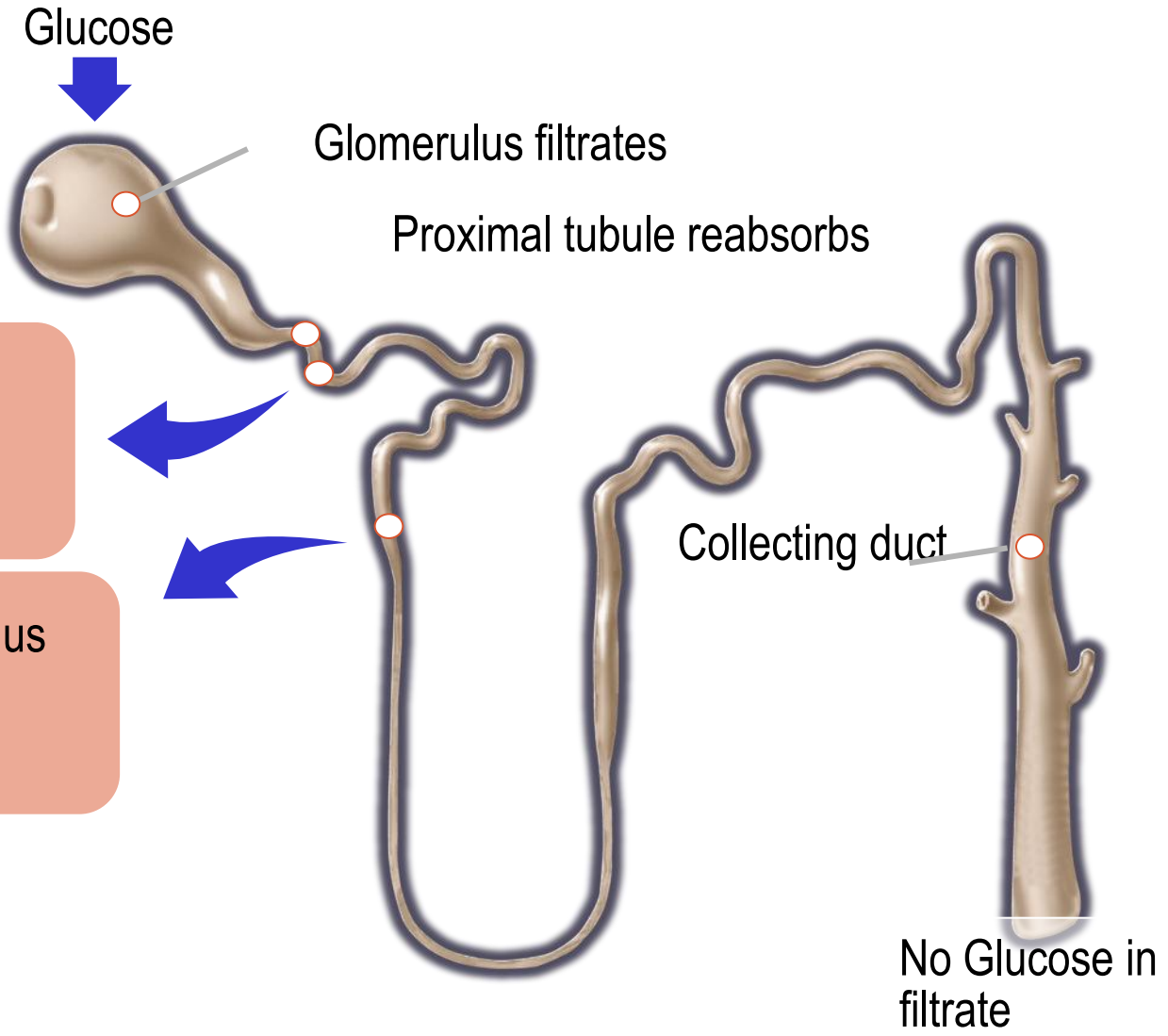
Adipocytes

↓ Free Fatty Acids

Glucose reabsorption in proximal tubule

Sodium dependent glucose transporters (SGLT)

Reabsorption ~ 180 g/d



S1-Segment of proximal Tubulus
- Reabsorption of ~90 % Glucose by SGLT2

Distal S3-Segment of proximal Tubulus
- Reabsorption of ~10 % Glucose
- by SGLT1

SGLT: sodium dependent glucose transporters

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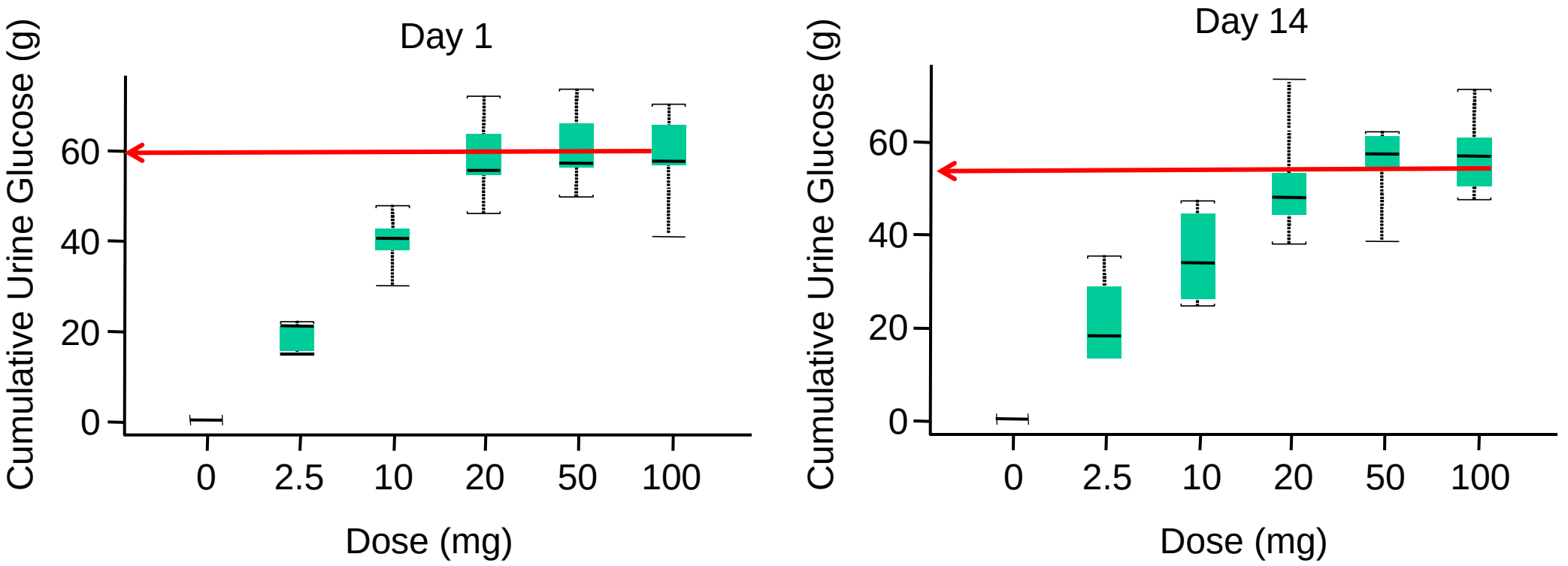
Silverman M, Turner RJ. In: Windhager EE, ed. Handbook of Physiology, Vol. II. New York, NY; 1992:2017-2038.
Bakris GL, et al. *Kidney Int.* 2009;75:1272-1277.

Phase: Cumulative Urinary Glucose Loss on Days 1 and 14

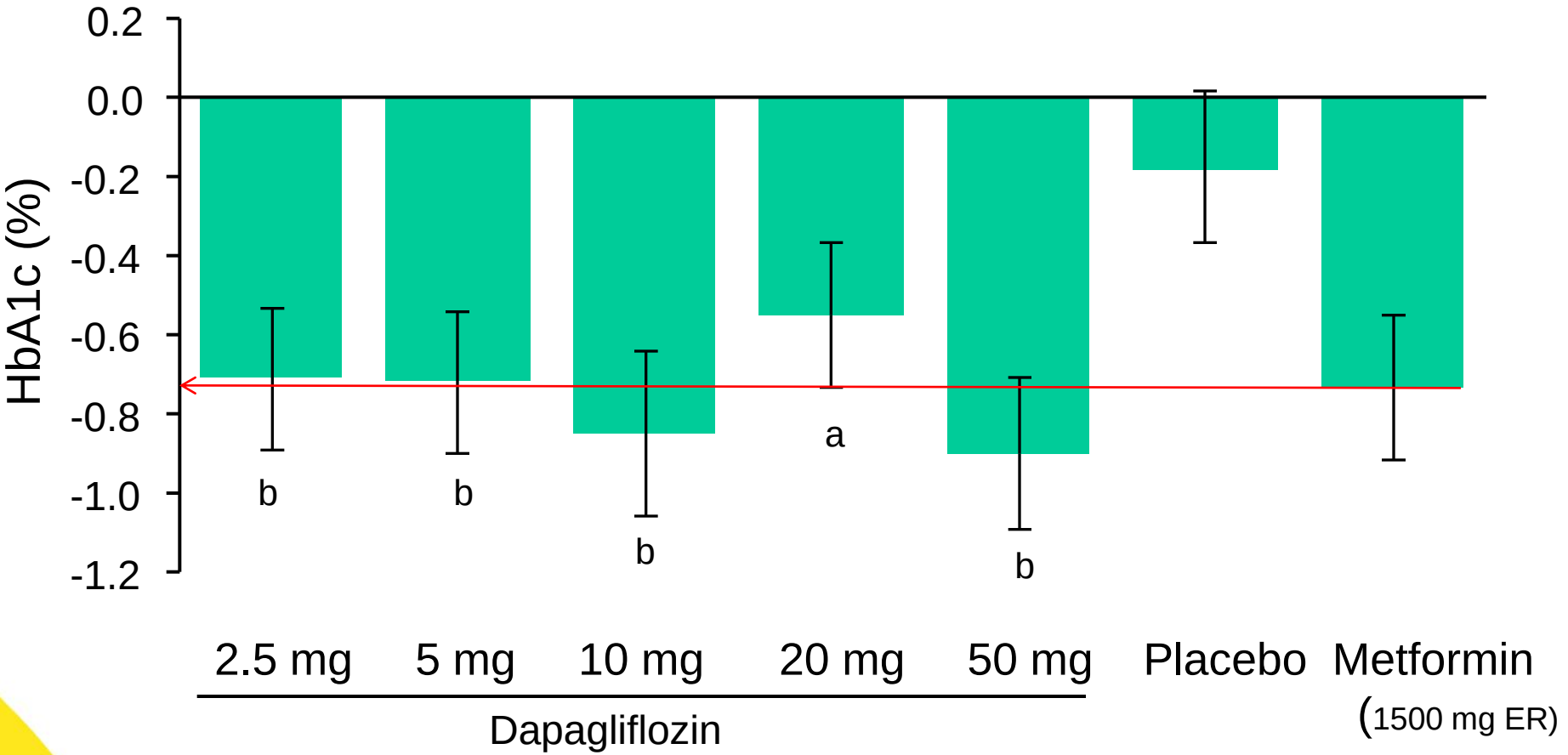


- Close-to-maximum glucose excretion per day with dapagliflozin 20–100 mg

Komoroski BJ, et al. *Clin Pharmacol Ther*. 2009;85:520-526.

Dapagliflozin vs. Metformin: HbA1c

389 drug naïve patients with T2D, HbA1c 7.6-8%, FU: 12 weeks



Data are means and 95% CI.
[a]P<0.01; [b]<0.001, compared to placebo

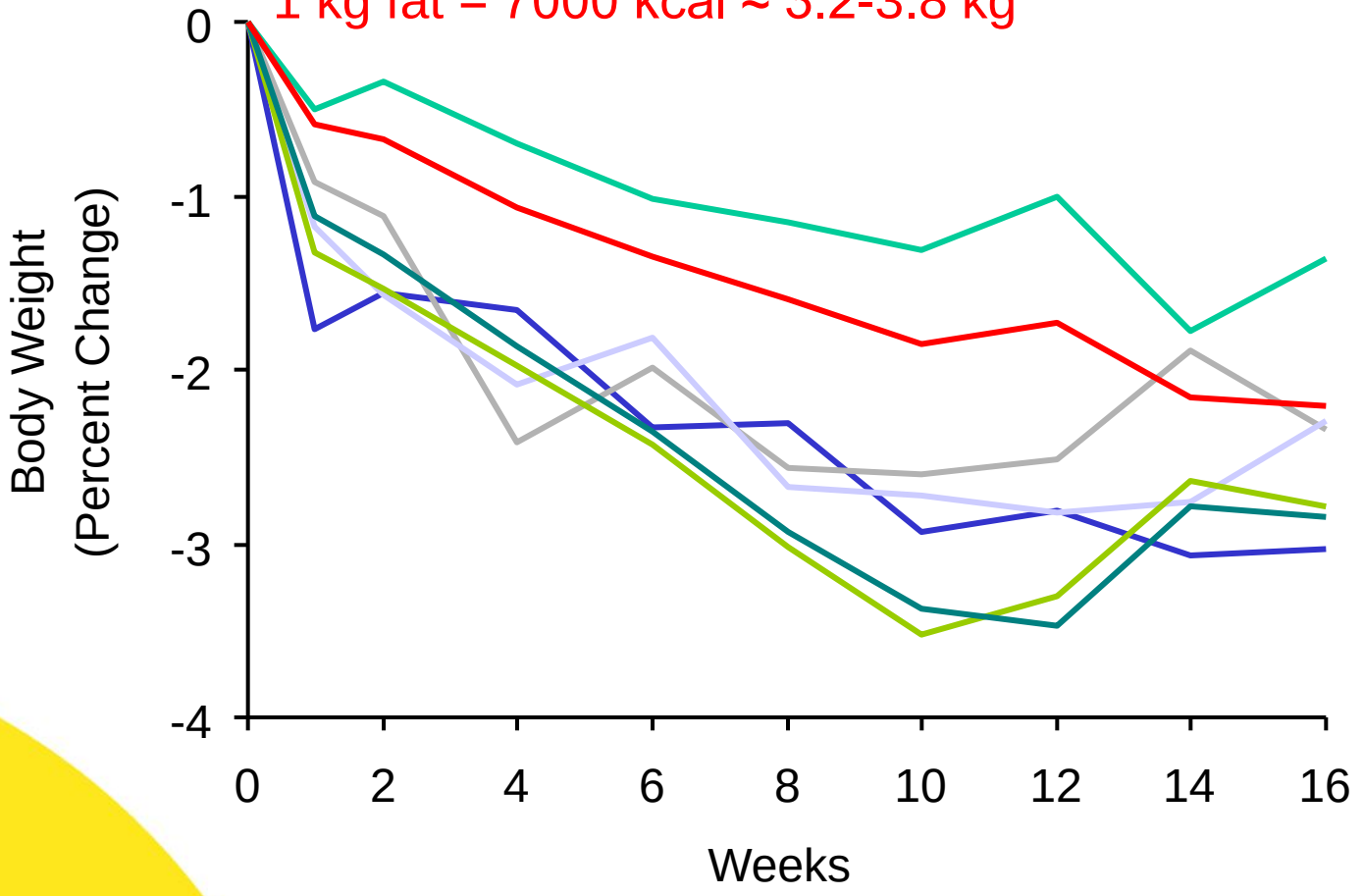
List JF, Diabetes Care. 2009;32:650-657

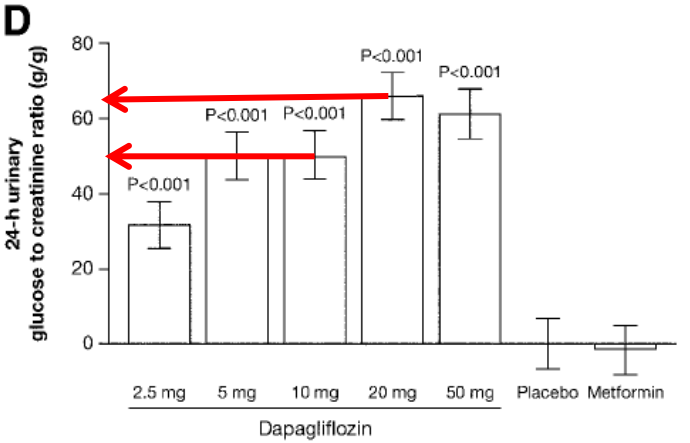
Body Weight and Glucosuria 12 wk Treatment and 4 wk FU

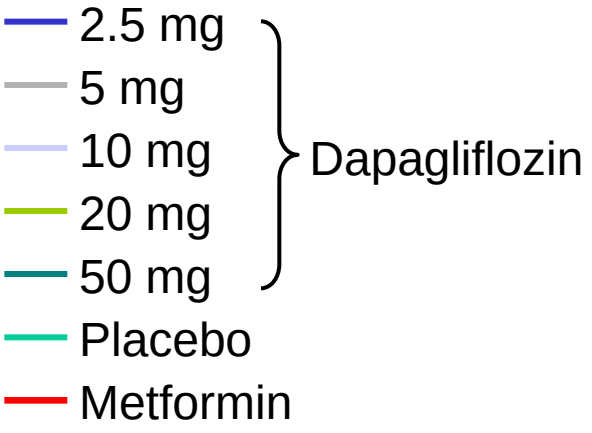
Calculated weight loss:

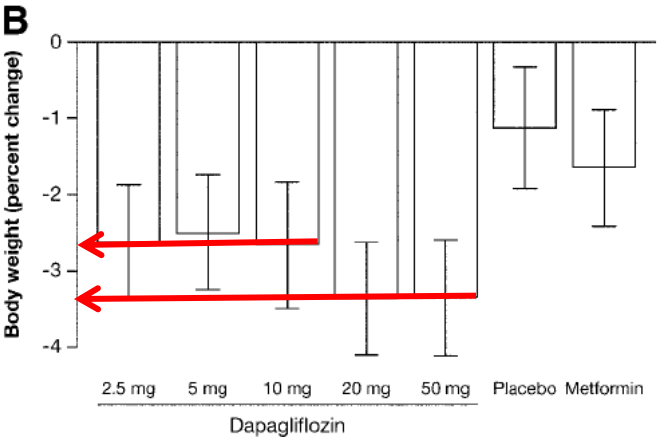
50-60g x 4 kcal x (16x7) d= 22‘400-26‘880 kcal

1 kg fat = 7000 kcal ≈ 3.2-3.8 kg









List JF, Diabetes Care. 2009;32:650-657

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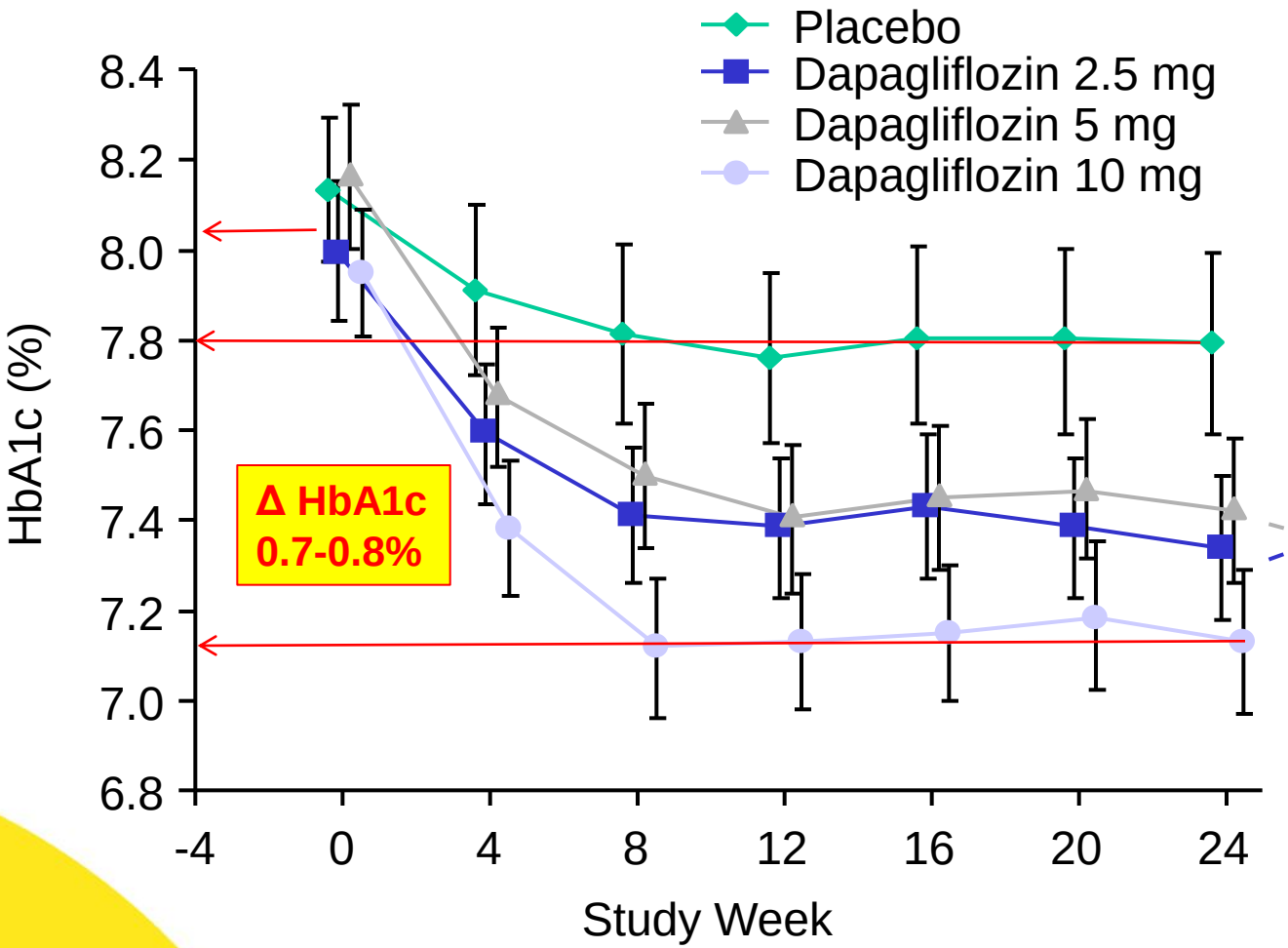
Dapaglifozin add-on to Metformin (≥1500mg)

343 Patients with Type 2 Diabetes

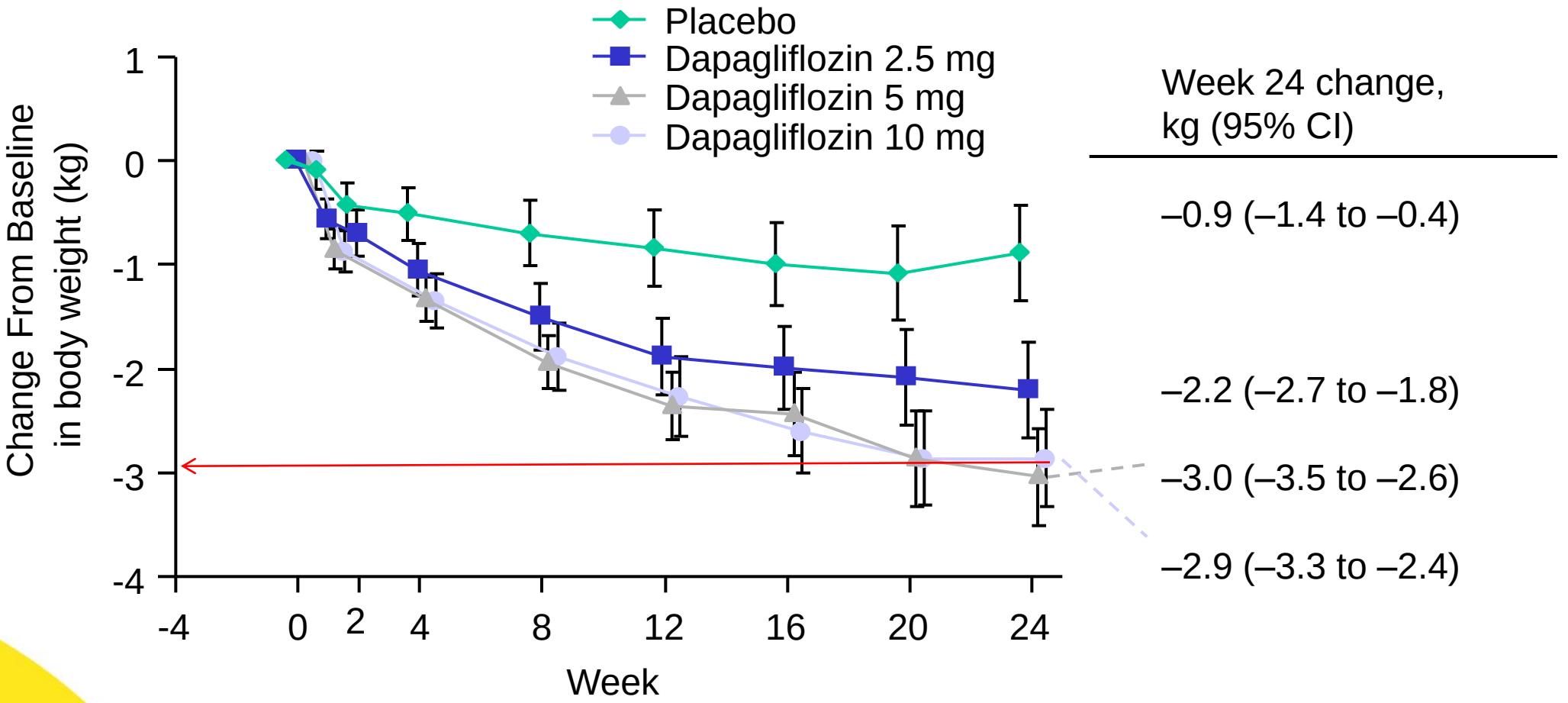


Week 24 value (95% CI)
7.79% (7.59 to 7.99)
7.34% (7.18 to 7.50)
7.42% (7.26 to 7.58)
7.13% (6.97 to 7.29)

Bailey CJ, et al. *Lancet*. 2010;375:2223-2233.

Dapaglifozin add-on to Metformin (≥1500mg)

343 Patients with Type 2 Diabetes



Bailey CJ, et al. *Lancet*. 2010;375:2223–2233.

Add-on to Insulin Study (48 Weeks): HbA1c, Body Weight, and Hypoglycemia

808 patients with T2D with insulin (77 U/d), HbA1c: 8.5%

Adjusted Mean Change From Baseline (SE) at Week 48	PLA + INS	Dapagliflozin Dose + Insulin		
			Δ -0.5%	
		2.5 mg	5 mg	10 mg
HbA1c (%)	–0.43 (0.07)	–0.74 (0.06)	–0.94 (0.06)	–0.93 (0.06)
Body weight (kg)	0.9 (0.3)		Δ -2.4 kg	–1.5 (0.3)

	Placebo + Insulin	Dapagliflozin Dose + Insulin		
		2.5 mg	5 mg	10 mg
Minor hypoglycemic events (%)	50.3	58.4	53.3	50.5

Wilding J, et al. *Diabetes*. 2010;59(suppl 1A):LB7. Abstract 0021-LB.

Side Effects of Dapaglifozin

- Urinary tract infections:
  - 5-12% Dapaglifozin vs. 6% Placebo and 9% Metformin
- Genital infections:
  - 8-13% Dapaglifozin vs. 5% Placebo
  - 2-7% Dapaglifozin vs. 0% Placebo, and 2% Metformin

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Bailey CJ, et al. *Lancet*. 2010;375:2223–2233.
List JF, Diabetes Care. 2009;32:650-657

New Developments?

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Future: Combinations?

Optimization: Advantages (⇩ Weight, Ø Hypos)
Reduction of disadvantages: ⇧ Weight, ⇧Hypos, ⇧Edema)

- **Bedtime Insulin + GLP-1 Analog**
  (without sulfonylureas but with metformin)
  - **Addititive ⇩HbA1c, ⇩ Risk of Hypo, ⇩ Weight**

- **GLP-1 Analog and Glitazone**
  (without Sulfonylureas, but with Metformin)
  - **Addititive ⇩ HbA1c, ⌀ Risk of Hypo, ⇩Weight**

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GLP-1 Analog (Lixisenatide) + Lantus

- Phase III Program: 2011-
- Combination GLP-1 Analog/Lantus in same injection

Bedtime Insulin + GLP-1 Analog:
Additive ⇩HbA1c, ⇩ Fasting- and pp Glucose,
⇩ Risk Hypo, ⇩ Weight

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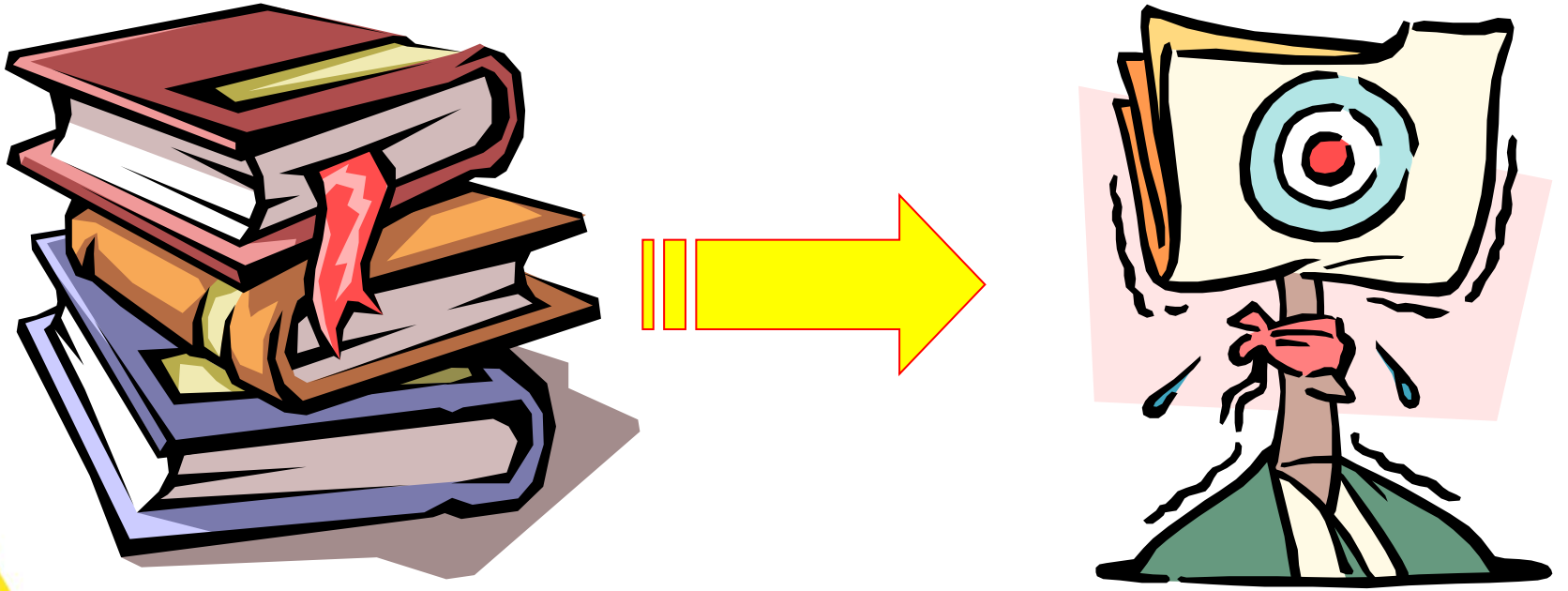
Take home messages



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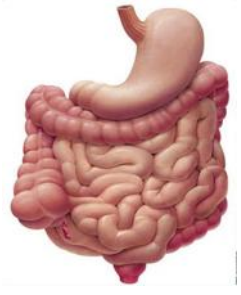
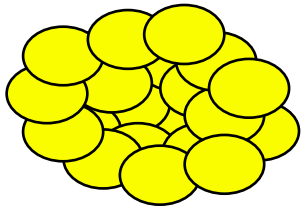
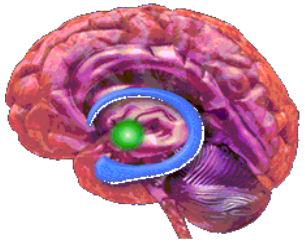
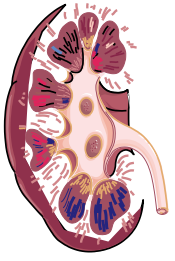
Advances in the Therapy of Type 2 Diabetes during the last 50 years

3 ⇨ 10 groups of drugs









Inhaleable Insulin

Detemir

Glargine

Aspart

Lispro-Insulin

SGLT-2 I.

DPP-4 I.

(Rimonabant)

GLP-1

(Amylin)

Glinide

Glitazone

α-GH

Blood glucose monitoring

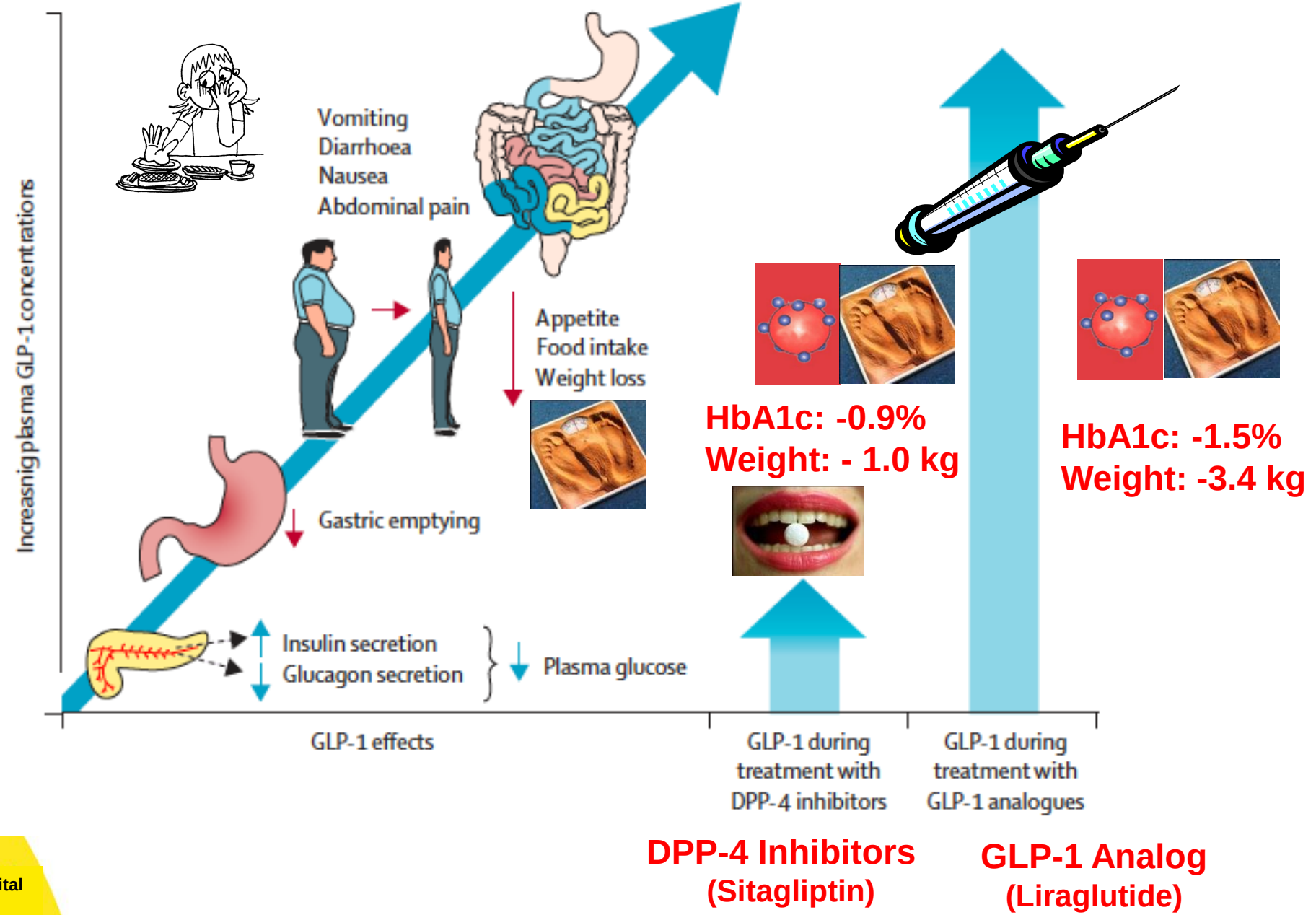
← Normal- + NPH Insulin

←Metformin

← Sulfonylurea

1960 1970 1980 1990 2000 2010...

Differences between DPP-4 Inhibitors and GLP-1 Analogs



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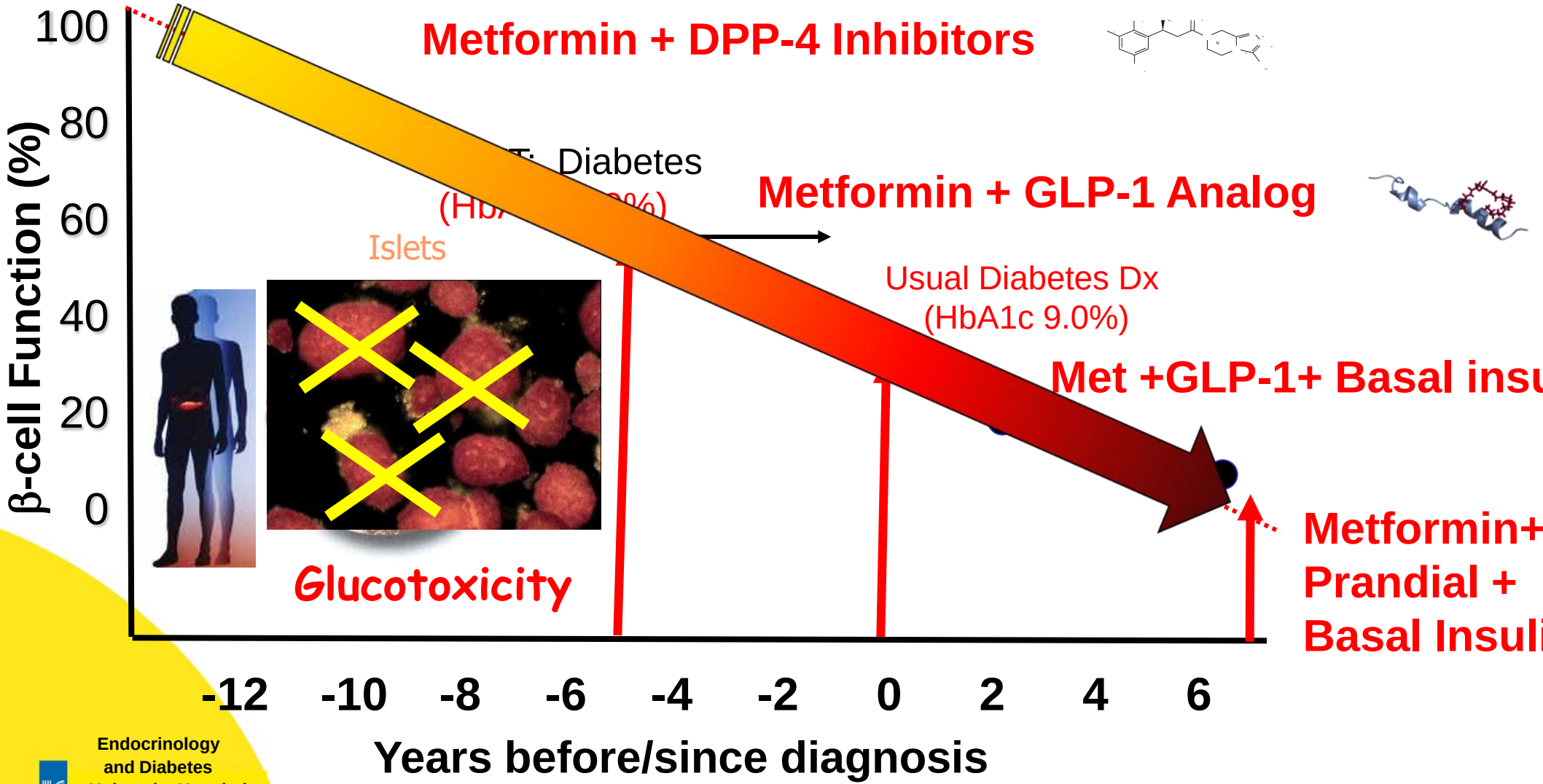
Modern therapeutical algorithm
⇨ ø hypglycemia and ø weight gain:

National Institute for Health and Clinical Excellence (NICE): Guideline on newer drugs 6/2009

	Intervention	⇩ HbA1c (%)	Weight (kg/yr) per ⇩1% HbA1c	Hypoglycemia Monotherapy
Schritt 1	Lifestyle (Nutrition, Physical Activity)	1-2	-4.0	No
	Metformin	1.5	-1.0-1.5	No
Schritt 2a or 2b	GLP-1 Analogue (Byetta, Victoza)	1.0-1.5	-3.0	No
Schritt 2 a or 2b	DPP-4 Inhibitor (Januvia, Galvus) Combination: Janumet, Galvumet	0.8 2.0	0.0 - -1.0	No
Schritt 2a or 2b	Sulfonylurea, Glinide	1.0-1.5	3.0	Yes
Schritt 2b	Glitazone	1.0	4.0	No
Schritt 3	Insulin (bedtime or prandial)	1.0-1.5	3.0	Yes
Schritt 4	Intensified insulin therapy	1.5-5.0	3.0	Yes

Steps depend on hypoglycemia, weight (BMI>35), life style, compliance

β-cell deterioration in type 2 diabetes
Early aggressive therapy with incretins and SGLT-2 inhibitors?



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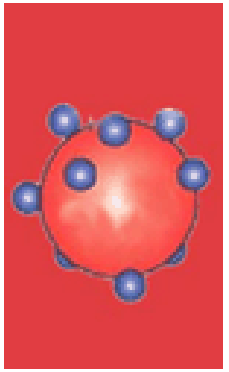
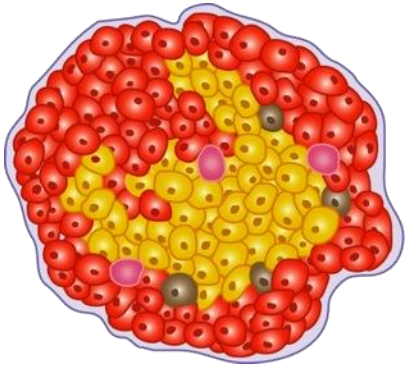
Thank you for your attention





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