L’innovazione farmacologica: quanto può migliorare gli outcome di salute e di cura?

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Institut
D’Investigacions
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Conflitto di interesse:

Astra Zeneca

Bayer Pharma

BMS

Eli Lilly

MSD

Novo Nordisk

Roche Pharma

Summary

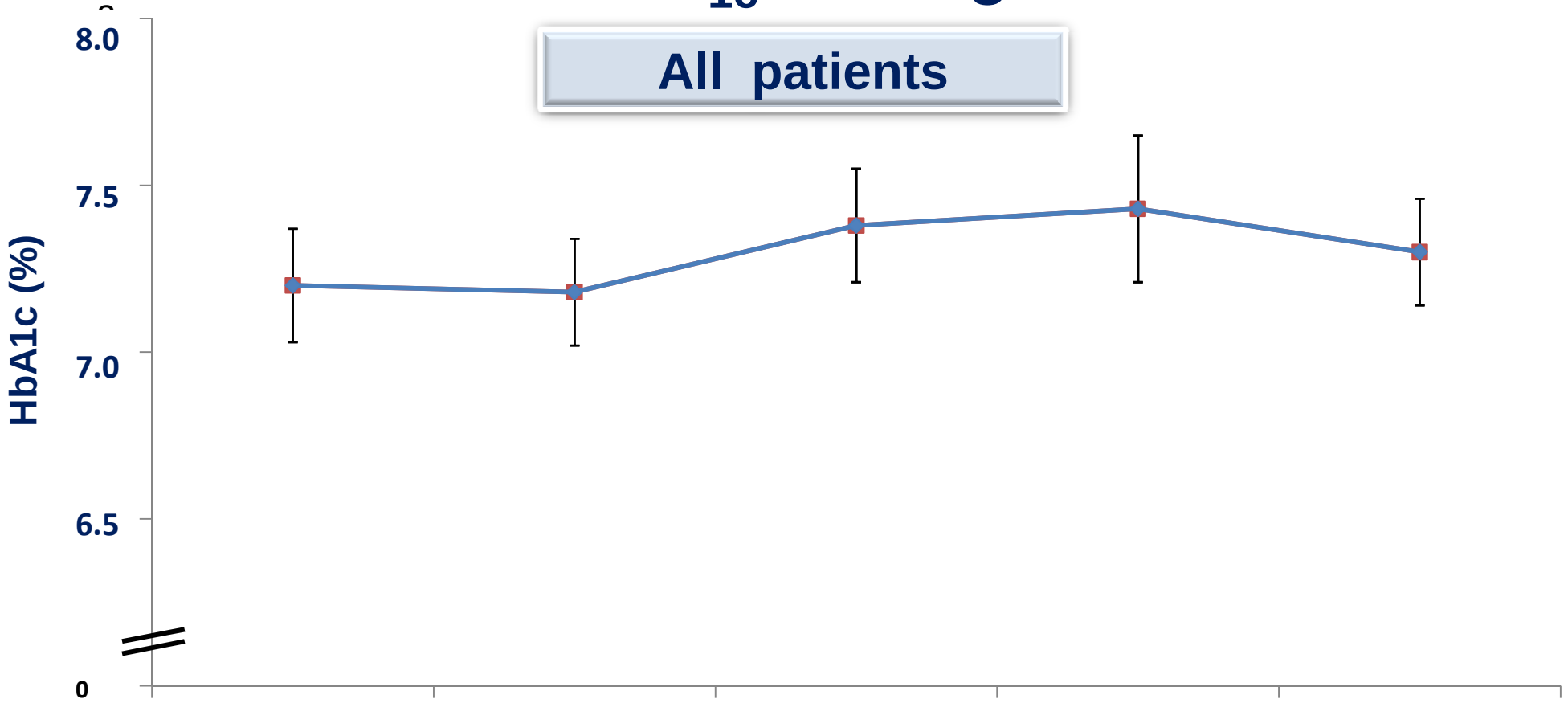
- Do we need new treatments for diabetes?
- Is there an inexorable decline in β-cell function?
- Which are the new antidiabetic agents in development?

ARE DIABETES MANAGEMENT GUIDELINES APPLICABLE IN THE REAL WORLD?

- **O**ne-year, open-label, interventional study
- Primary care unit
- 90 consecutive patients with type 2 diabetes
- ADA-EASD guidelines
- Usual resources available (Met, SU, NPH Ins)

Verçosa et al. 2010

HbA_{1c} Change

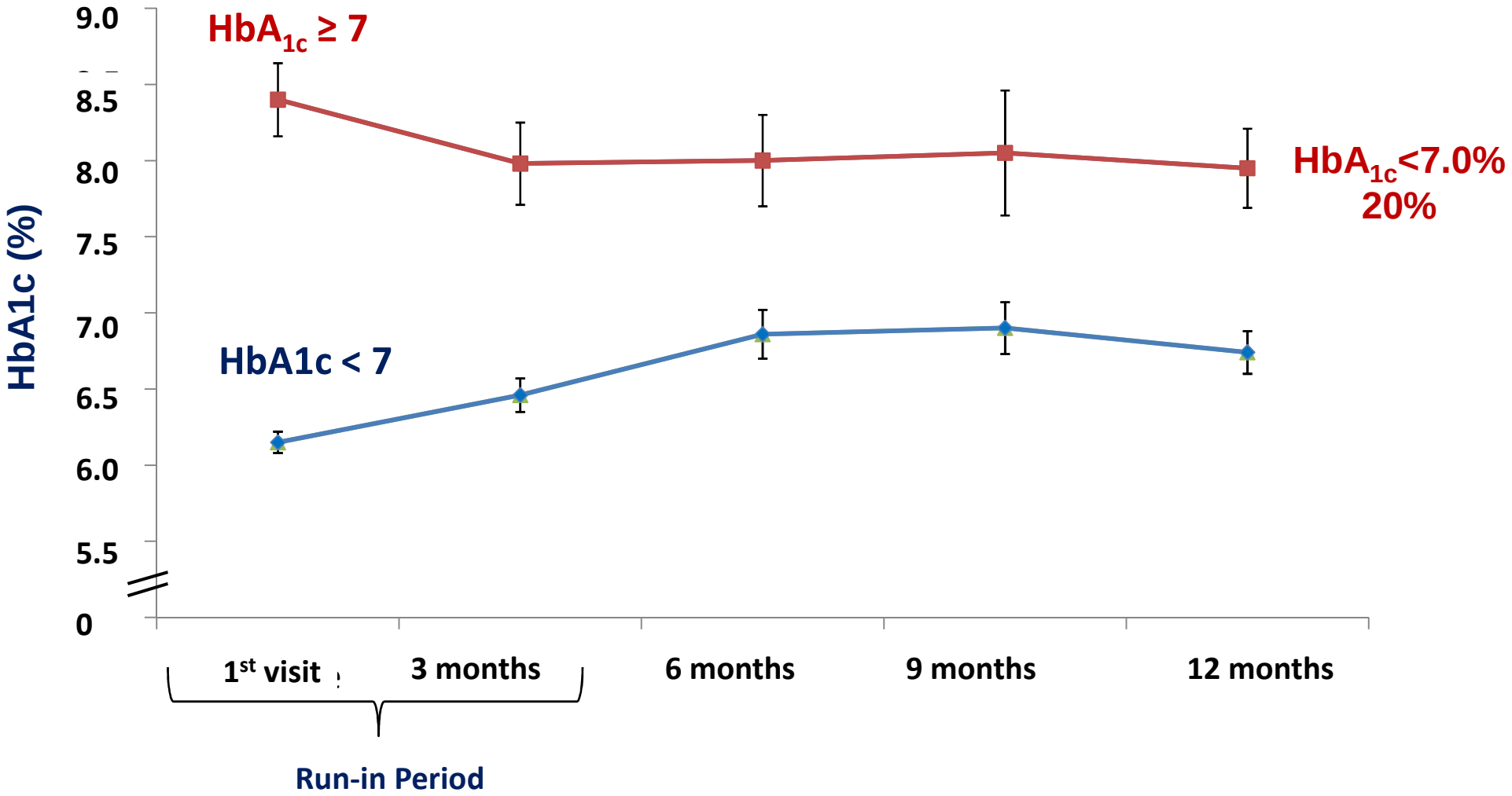


	Baseline	3 months	6 months	9 months	12 months
Patients number	90	90	82	61	90
Insulin use (%)	19 (21)	19 (21)	26 (32)	16 (14)	32 (37)
Number of ADO	2.64 ± 1.89	2.74 ± 1.89	3.11 ± 2.25	3.60 ± 2.34	3.96 ± 2.02

Run-in Period

HbA_{1c} Change

Patients divided according baseline HbA_{1c}



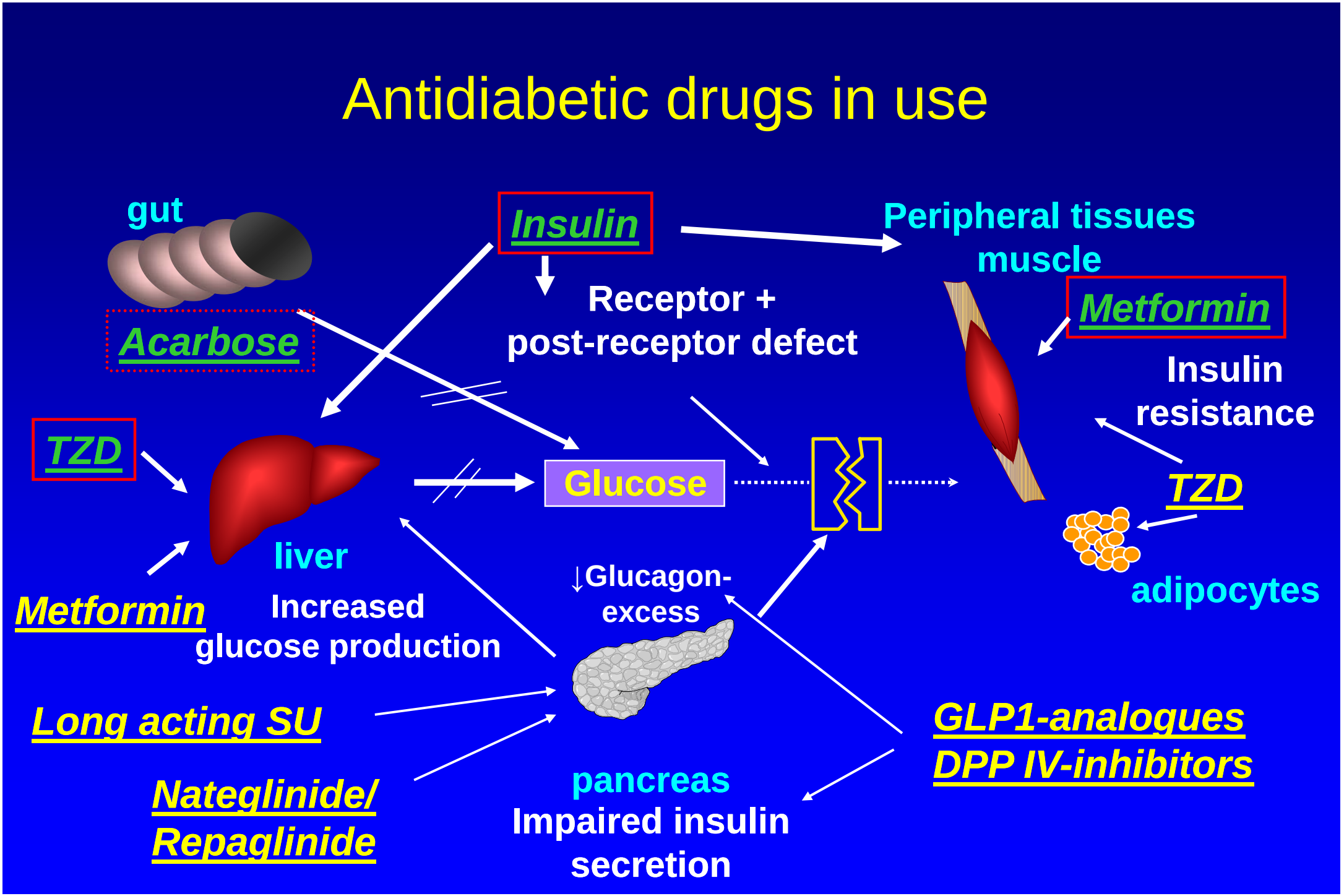
Conclusion

Despite the efforts to obtain and maintain HbA1c <7% with the addition of the medication available in the primary care unit, there was a deterioration in diabetes control during this 1-year study.

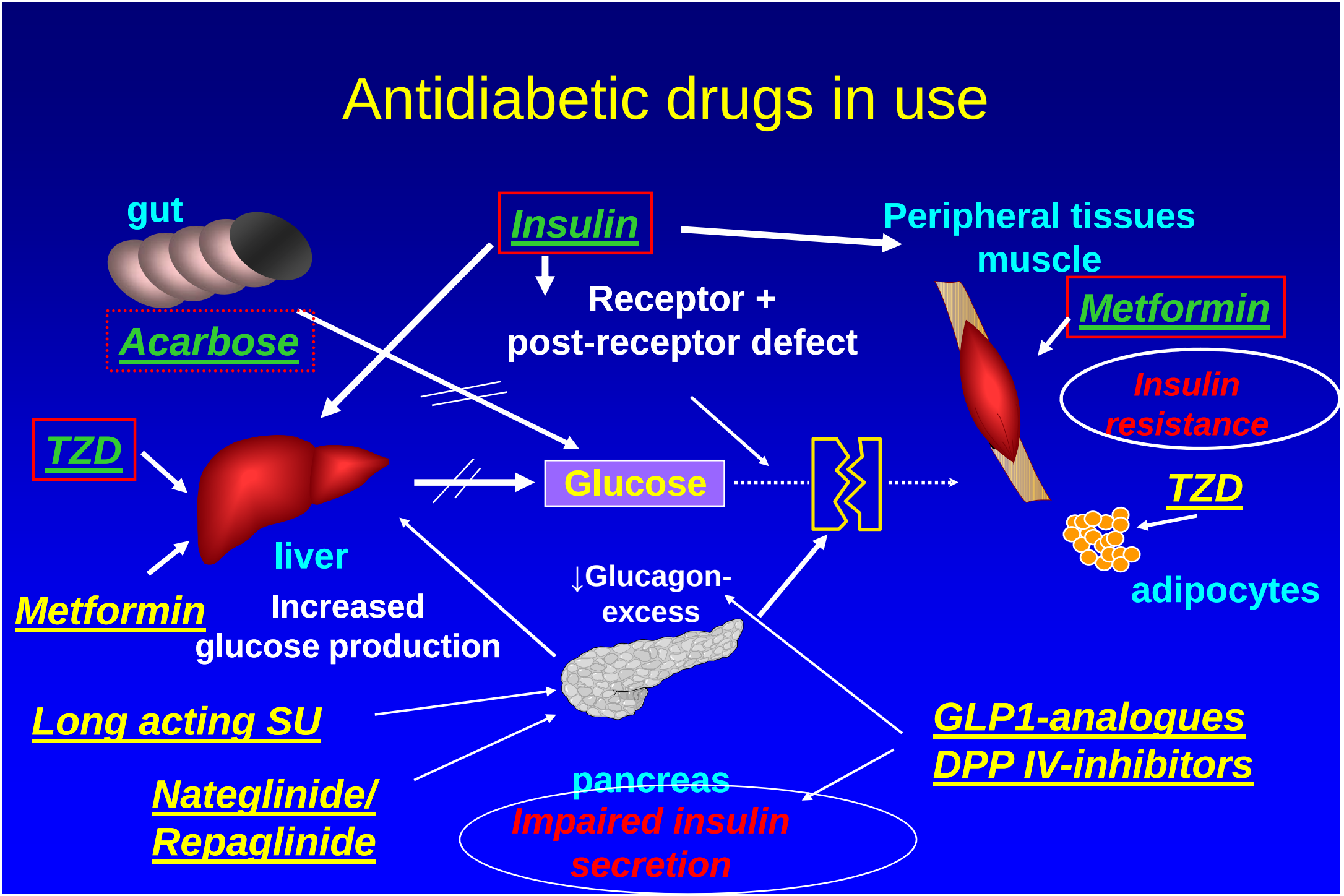
Do we need new treatments for diabetes?

Yes. We do need new tools for the treatment of type 2 diabetes

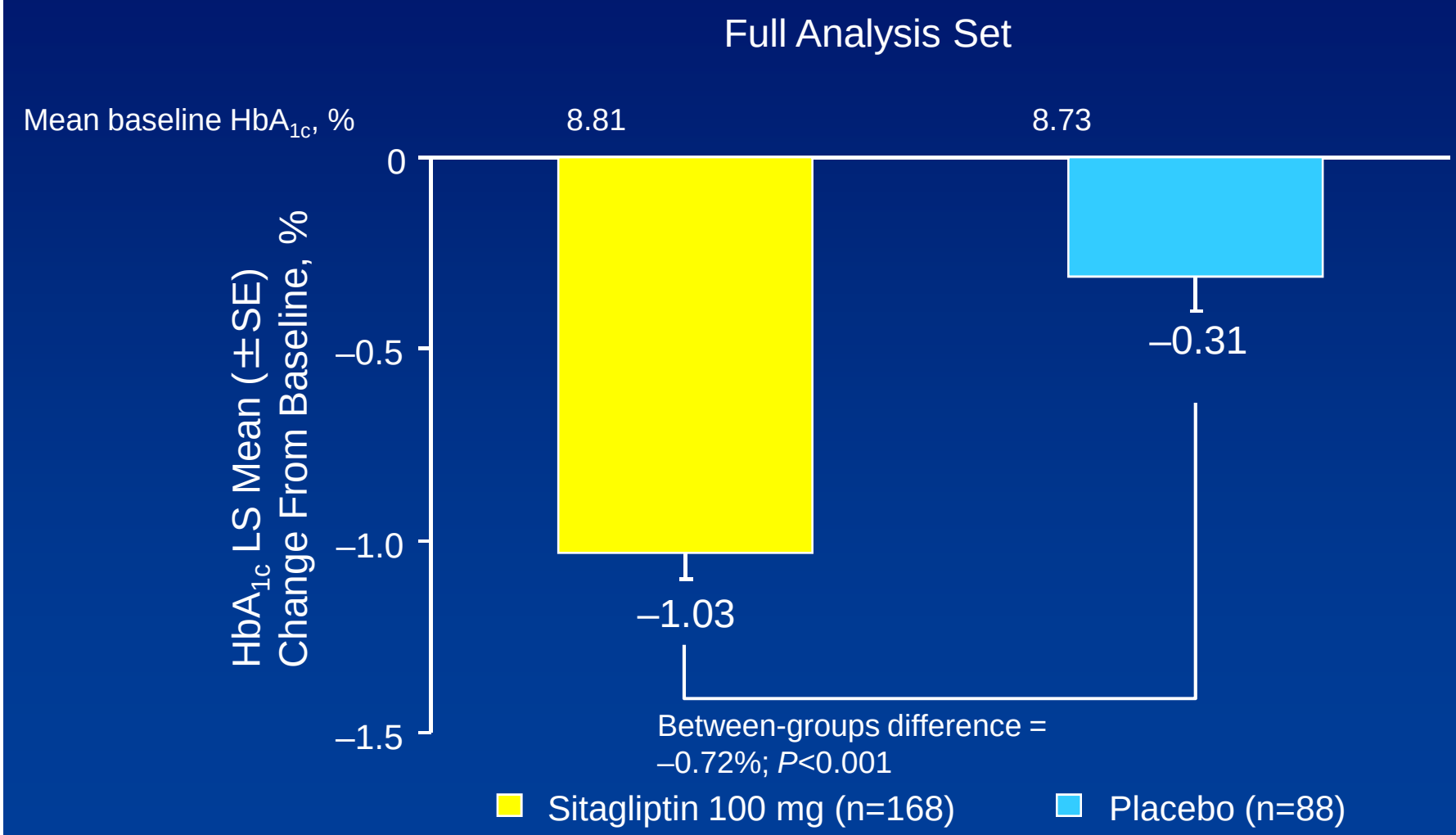
Antidiabetic drugs in use



Antidiabetic drugs in use



Addition of Sitagliptin to Rosiglitazone and Metformin Study: HbA_{1c} Change From Baseline at 18 Weeks



LS=least-squares; SE=standard error.
Data on file, MSD.

Initial Combination Therapy for Type 2 Diabetes Mellitus: Is It Ready for Prime Time?

Bernard Zinman, MD

The American Journal of Medicine (2011) 124, S19–S34

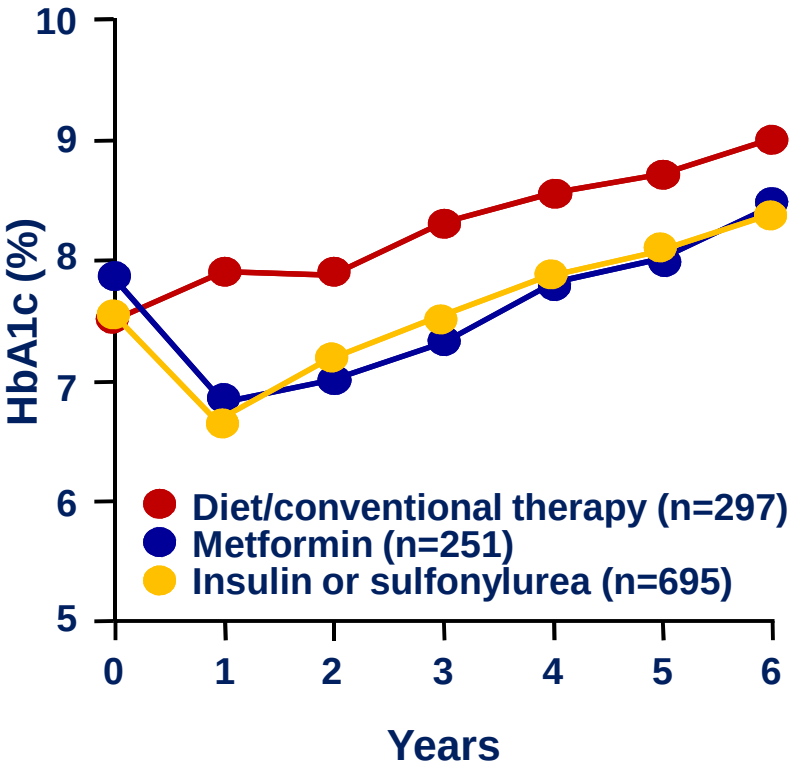
The New IDF Therapeutic Algorithm

NOTE:
The start with a prefixed combination of Metformin plus a DPPVI Inhibitor can be considered.

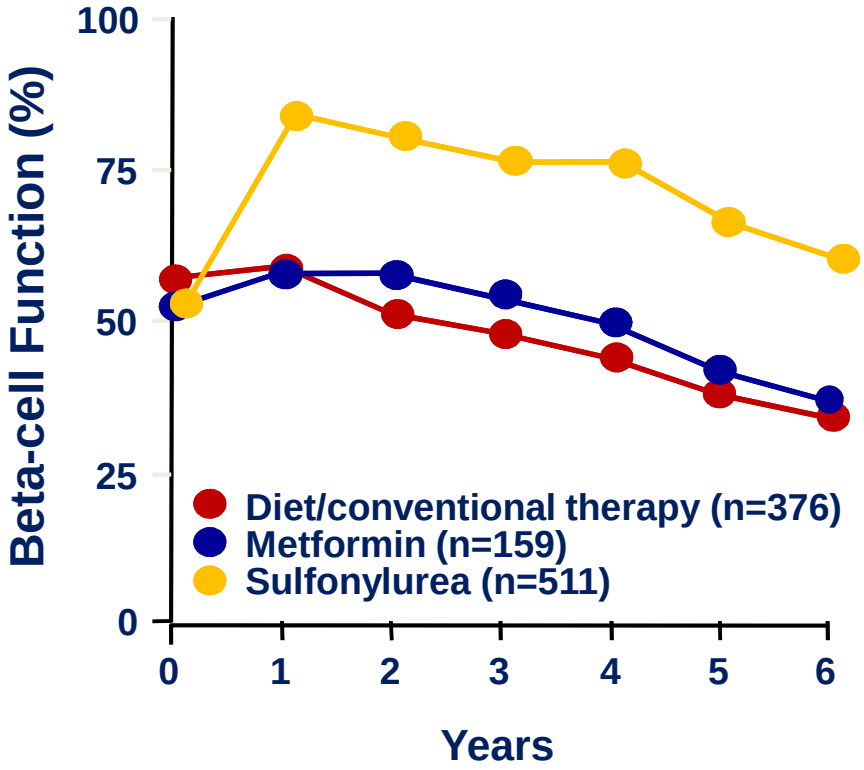
Is the progressive decline in β - cell function inexorable ?

Progressive Deterioration of β-cell function

…Hyperglycemia increases



As β-cell function declines…

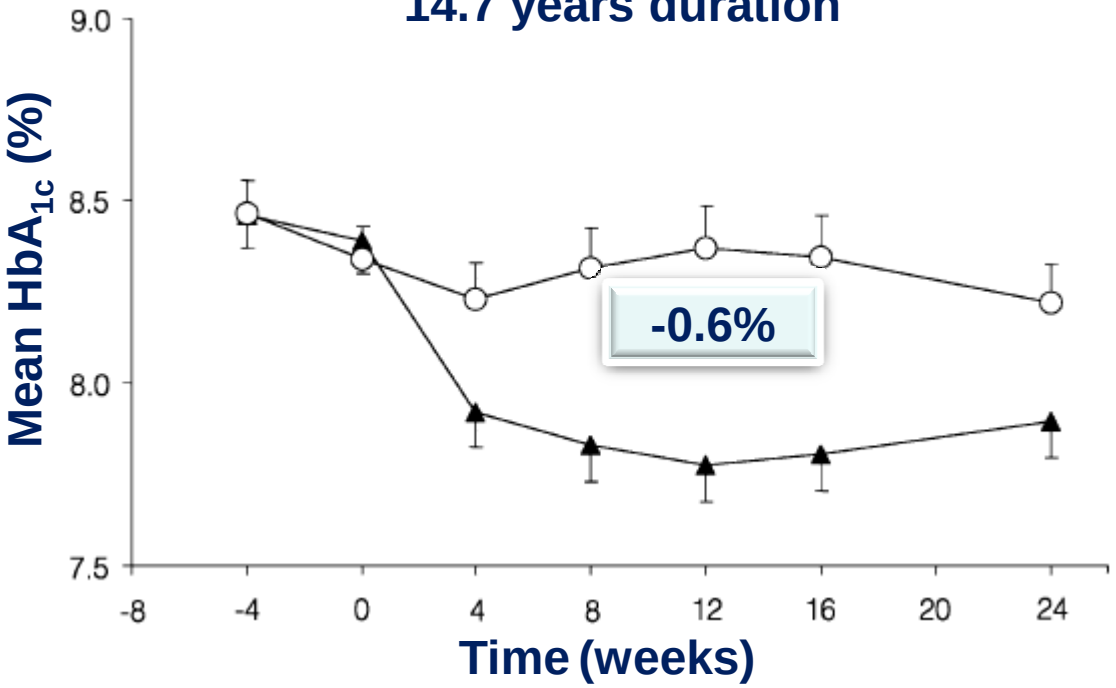


Adapted from UKPDS Group. *Diabetes.* 1995;44:1249–1258.

Incretin Based Therapy

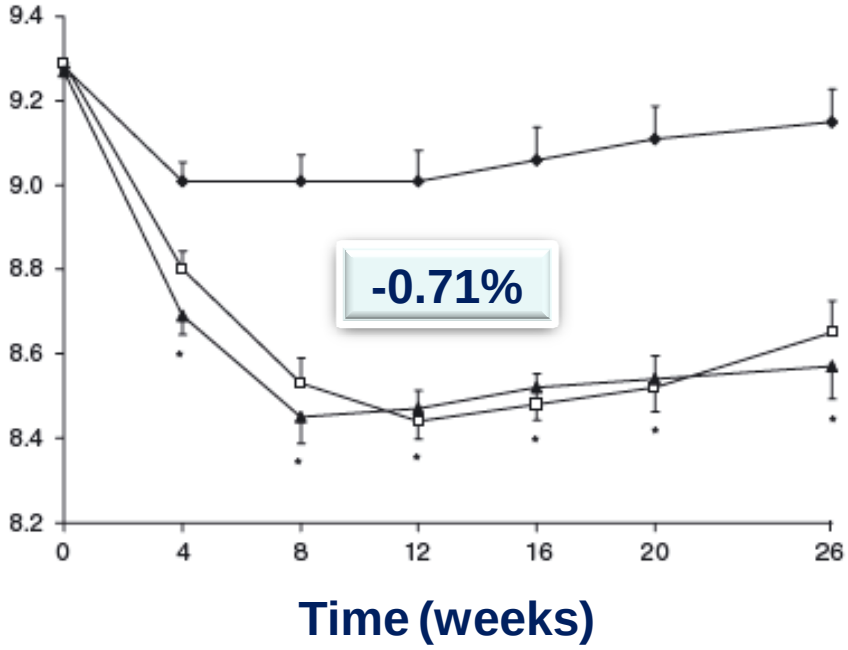
is still effective even in patients with long duration of disease

296 type 2 DM patients insulin only
14.7 years duration



Fonseca et al. Diabetologia 50:1148, 2007

390 type 2 DM patients insulin only
12.5 years duration



Rosenstock et al. DMO 11:1145, 2009

New Incretins

DPP-IV inhibitors

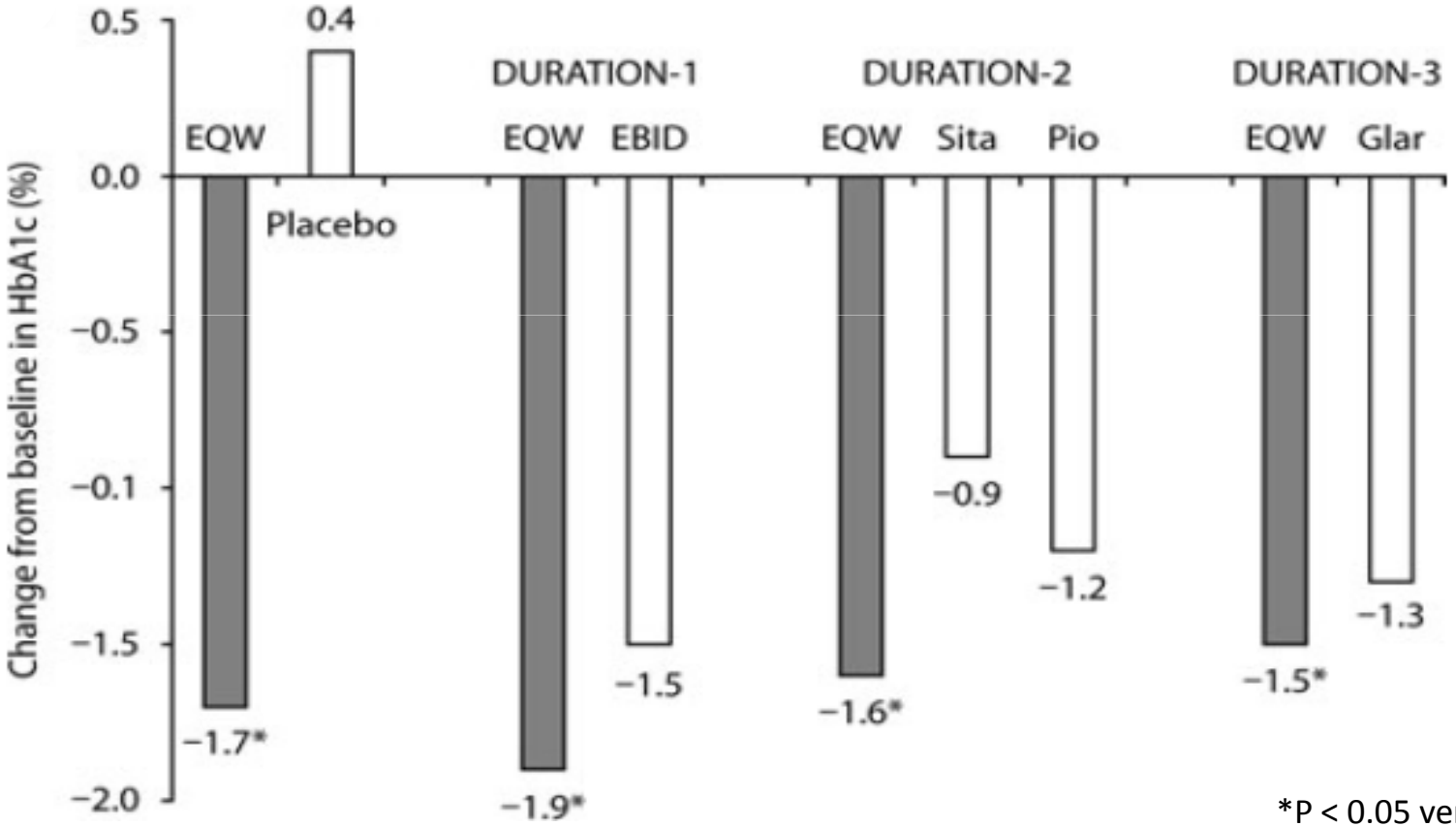
- *Sitagliptin*
- *Vildagliptin*
- *Saxagliptin*
- Alogliptin
- Linagliptin
- Dutogliptin

GLP-1 agonists

- *Exenatide*
- *Liraglutide*
- Exenatide LAR
- Albiglutide

Exenatide once weekly

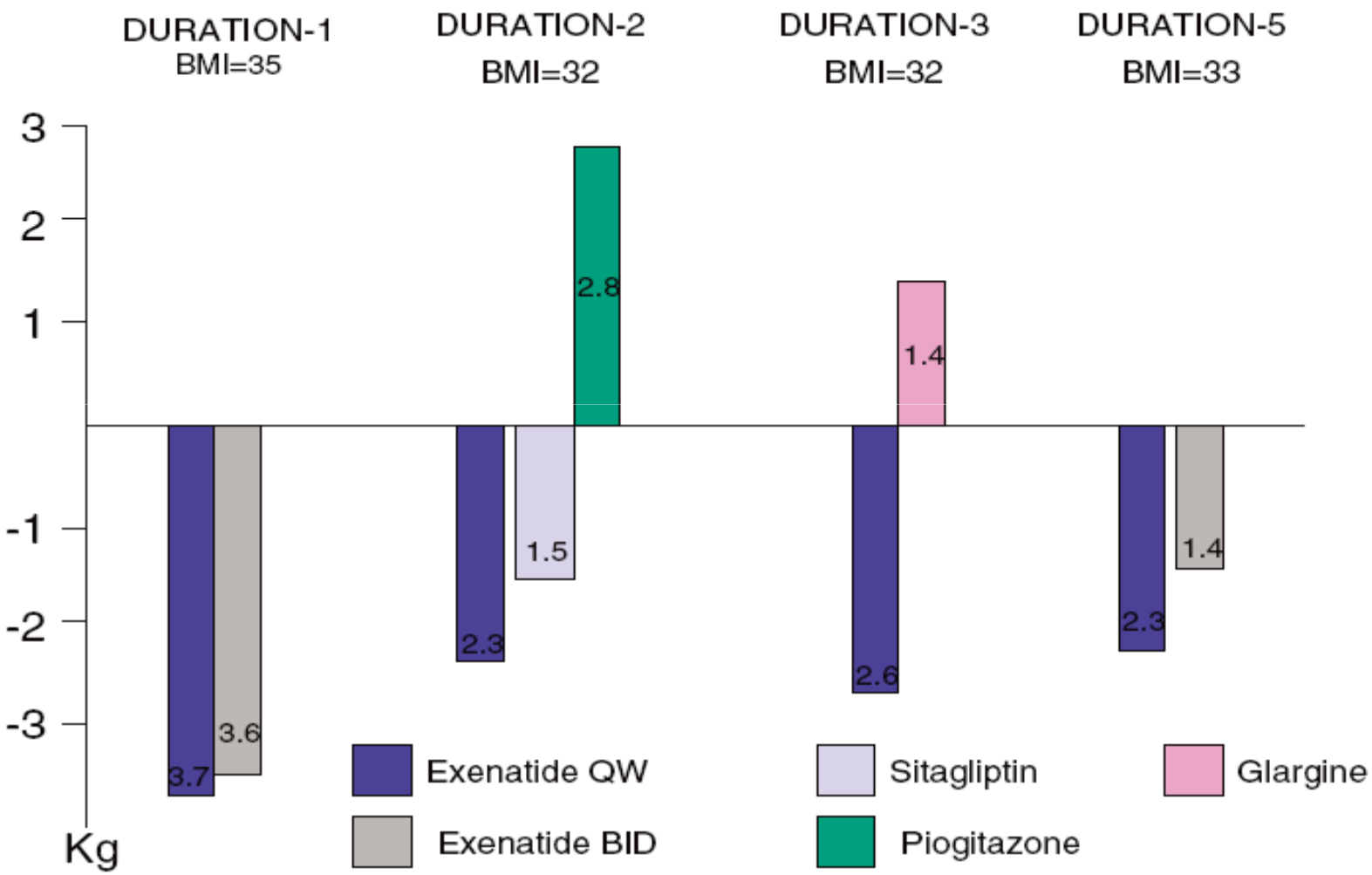
Glucose control mediated by exenatide once-weekly (EQW)



*P < 0.05 versus comparators

DeYoung MB et al. Diabetes Technology & Therapeutics 2011; Kim et al. Diabetes Care 2007; Drucker et al. Lancet 2008; Bergenstal et al. Lancet 2010; Diamant et al. Lancet 2010

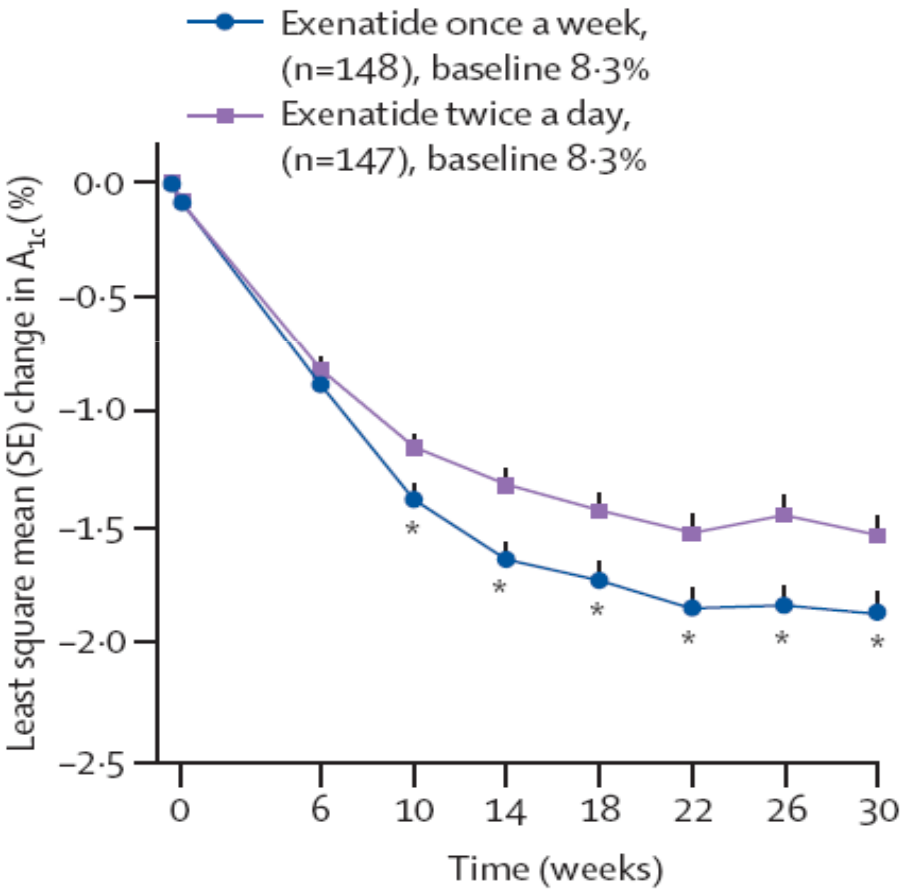
Exenatide once weekly

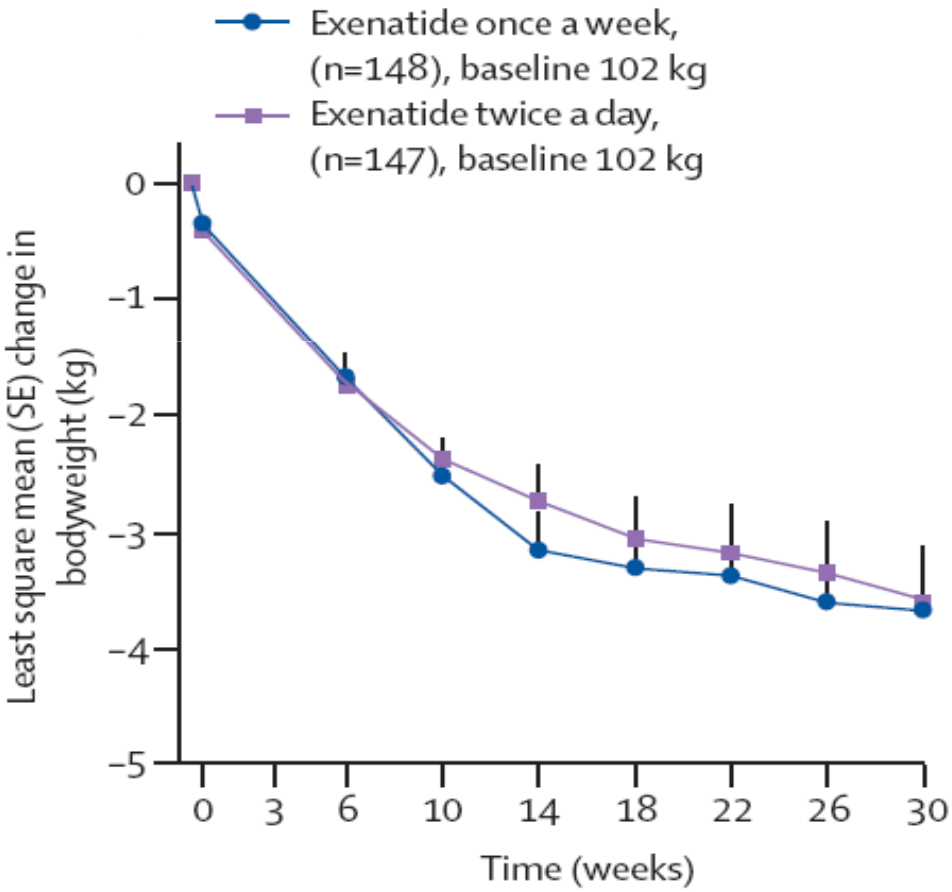


Masbad et al. Diabetes Obesity & Metabolism 2011

Exenatide once weekly

Change in HbA1c and bodyweight from baseline over 30 weeks

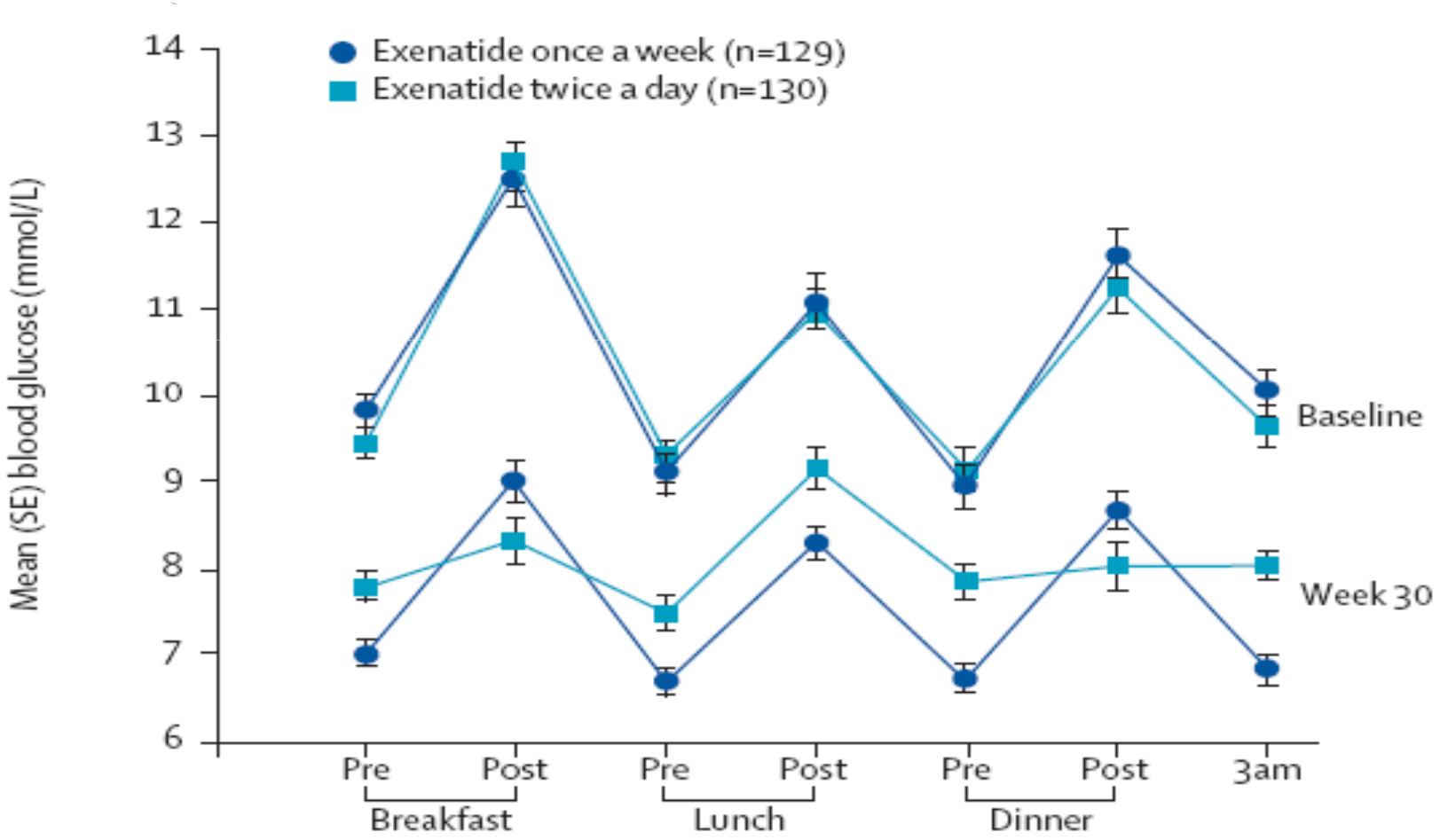




Drucker et al. Lancet 372 October 4, 2008

Exenatide once weekly

7-point self-monitored blood glucose profiles at baseline and week 30

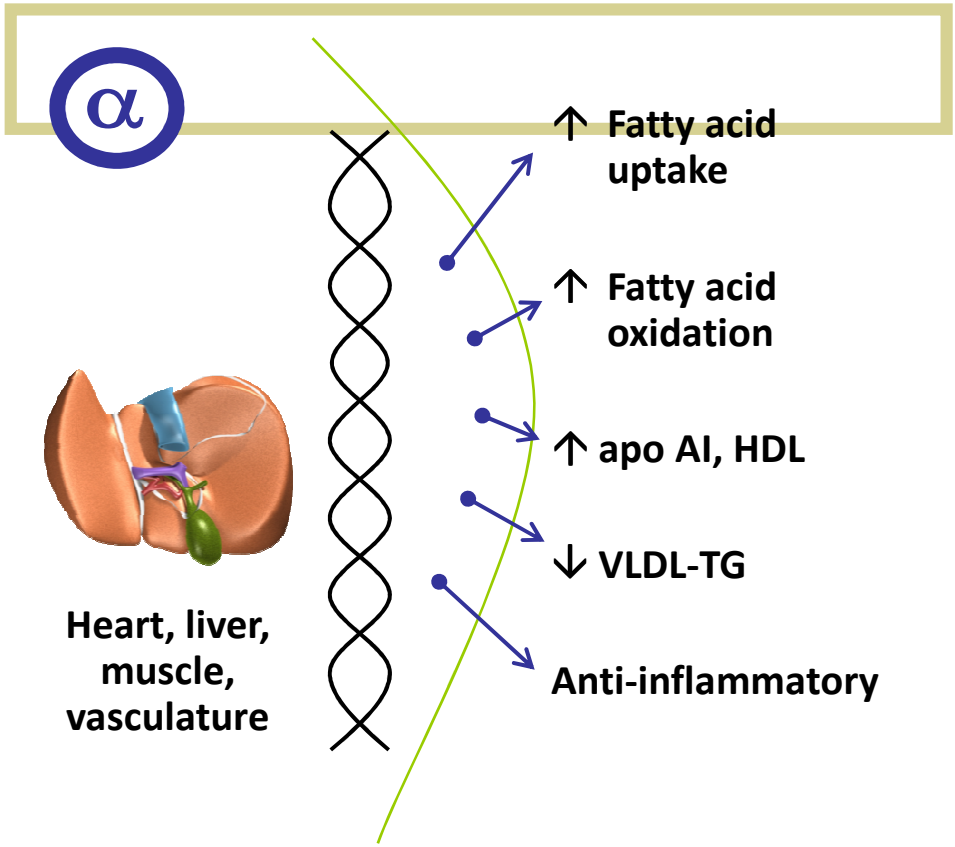


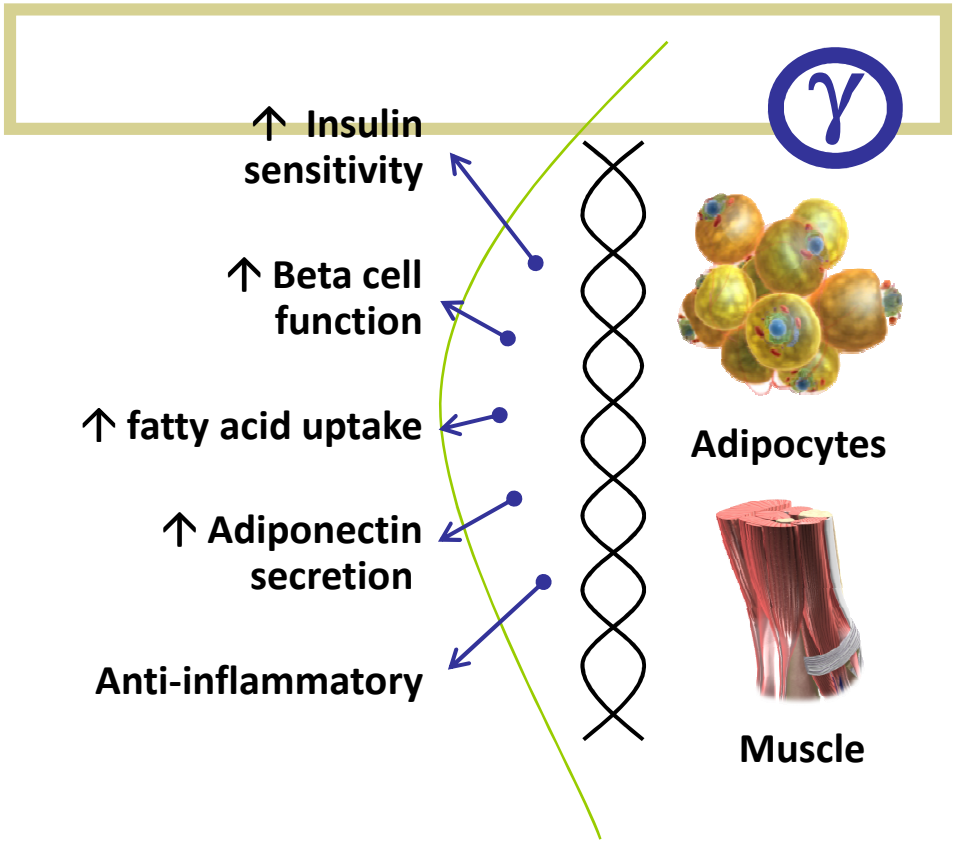
Drucker et al. Lancet 372 October 4, 2008

New Classes of Antihyperglycemic Agents

- **Dual Peroxisome Proliferator-Activated Receptor-α/γ Agonists (PPAR α/γ Agonists)**
- **Inhibitor of 11-β-hydroxysteroid dehydrogenase**
- **Inhibitors of sodium-dependent glucose transporter 2**
- **Ultra long acting insulins**

Effects of α/γ PPAR activation





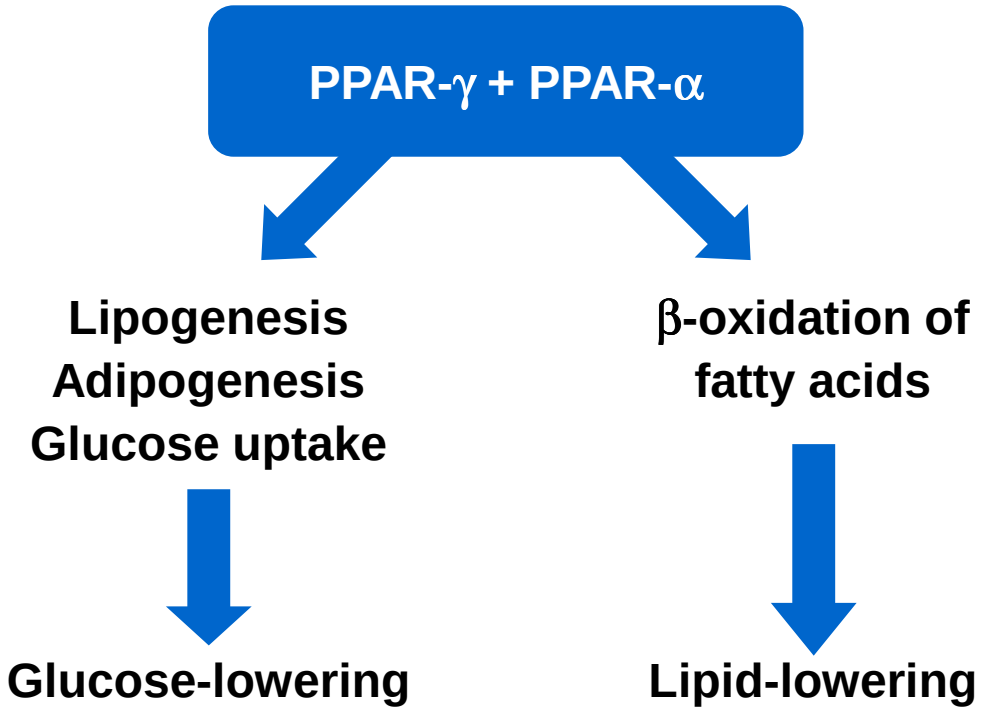
Primary α effect is to improve plasma lipid profile

Primary γ effect is to improve insulin sensitivity

Dual PPAR agonists

A Promising Approach

- ***B*oth dyslipidemia and insulin resistance appear to promote atherosclerosis in diabetics**
- **Likewise, improving lipid profile and insulin resistance both promise to improve clinical outcomes**



Dual Peroxisome Proliferator-Activated Receptor-α/γ Agonists

- MK 767
- Ragaglitazar[NN]
- Tesaglitazar[AZ]
- Naveglitazar[Lilly]
- Muraglitazar[BMS]

- Malignant tumours in mice
- Tumors in rats and mice
- Subcutaneous fibrosarcomas
- Cardiotoxicity, sarcomas
- MI, stroke, TIA

Dual PPAR agonists: muraglitazar & tesaglitazar

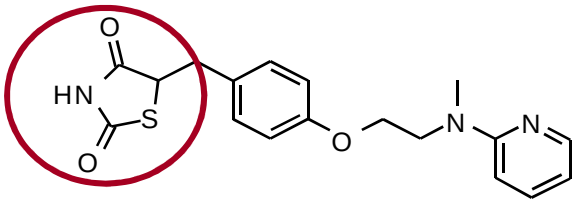
- Muraglitazar
  - Higher incidence of edema vs placebo[1]
  - Body weight increased up to 2.5 kg with 5 mg dose vs 1.5 kg with pioglitazone 30 mg[2]
  - Increased heart failure (0.55% with 5 mg dose vs 0.07% with pioglitazone)[3]
  - Elevated risk of CV death[3]
- Tesaglitazar
  - Higher incidence of edema and weight gain vs placebo[4]
  - Increased serum creatinine by up to ~17%, which stabilized by 12 weeks but was not reversed fully upon discontinuation[4]
  - Considered not to provide adequate benefit vs risk[4]

1. Rubin CJ, *et al. Diabetes Vasc Res* 2009; 6:120–132.
2. Kendall DM, *et al. Diabetes Care* 2006; 29:1016–1023.
3. Nissen SE, *et al. JAMA* 2005; 294:2581–2586.
4. Goke B, *et al. Diabetes Vasc Dis Res* 2007; 4:204–213.

Aleglitazar: structurally distinct from TZDs & fibrates

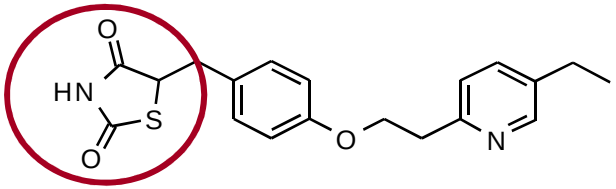
Aleglitazar (a balanced PPAR-α/γ agonist)

Thiazolidinediones (PPAR-γ agonists)



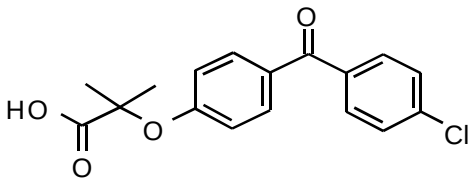
Rosiglitazone

Thiazolidinedione moiety

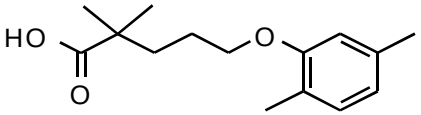


Pioglitazone

Fibrates (PPAR-α agonists)



Fenofibric acid



Gemfibrozil

Benardeau A, *et al. Bioorg Med Chem Lett* 2009; 19:2468–2473.

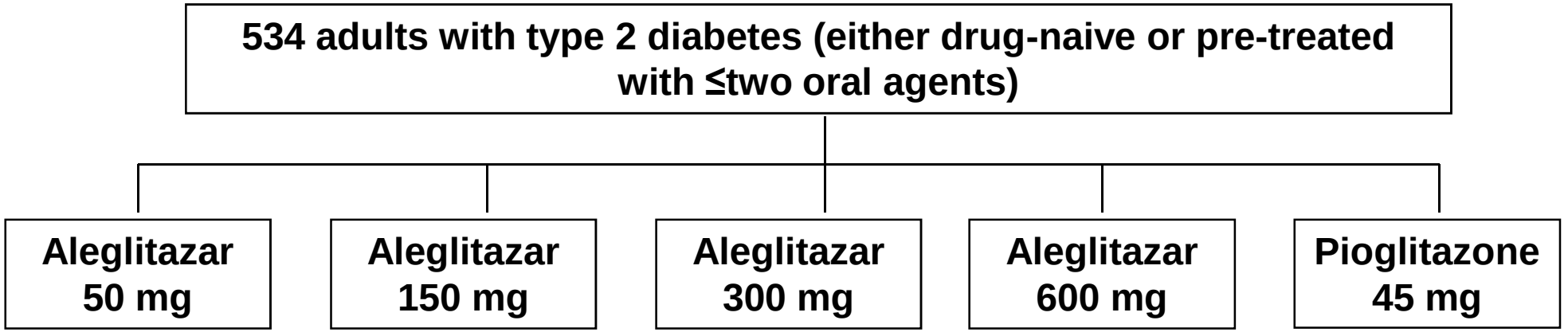
Aleglitazar

- Potent and balanced activity of PPAR-α versus PPAR-γ[1]
- Structurally distinct from TZDs[1]
- Unique gene signature profile compared with pioglitazone + fenofibrate in human cardiac myocytes and hepatocytes[2,3]
- Evidence for desired impact on genes involved in lipid synthesis[3] and inflammatory pathways[2]
  - Reduced expression of genes in LDL synthesis
  - Increased expression of genes in HDL pathway
  - Suppression of genes involved in tissue damage and inflammation in human cardiac myocytes

1. Benardeau A, *et al. Bioorg Med Chem Lett* 2009; 19:2468–2473.
2. Dzyakanchuk A, *et al. Circulation* 2010; 122:A10854.
3. Blander G, *et al. Diabetes* 2009; 58(suppl 1):A295.

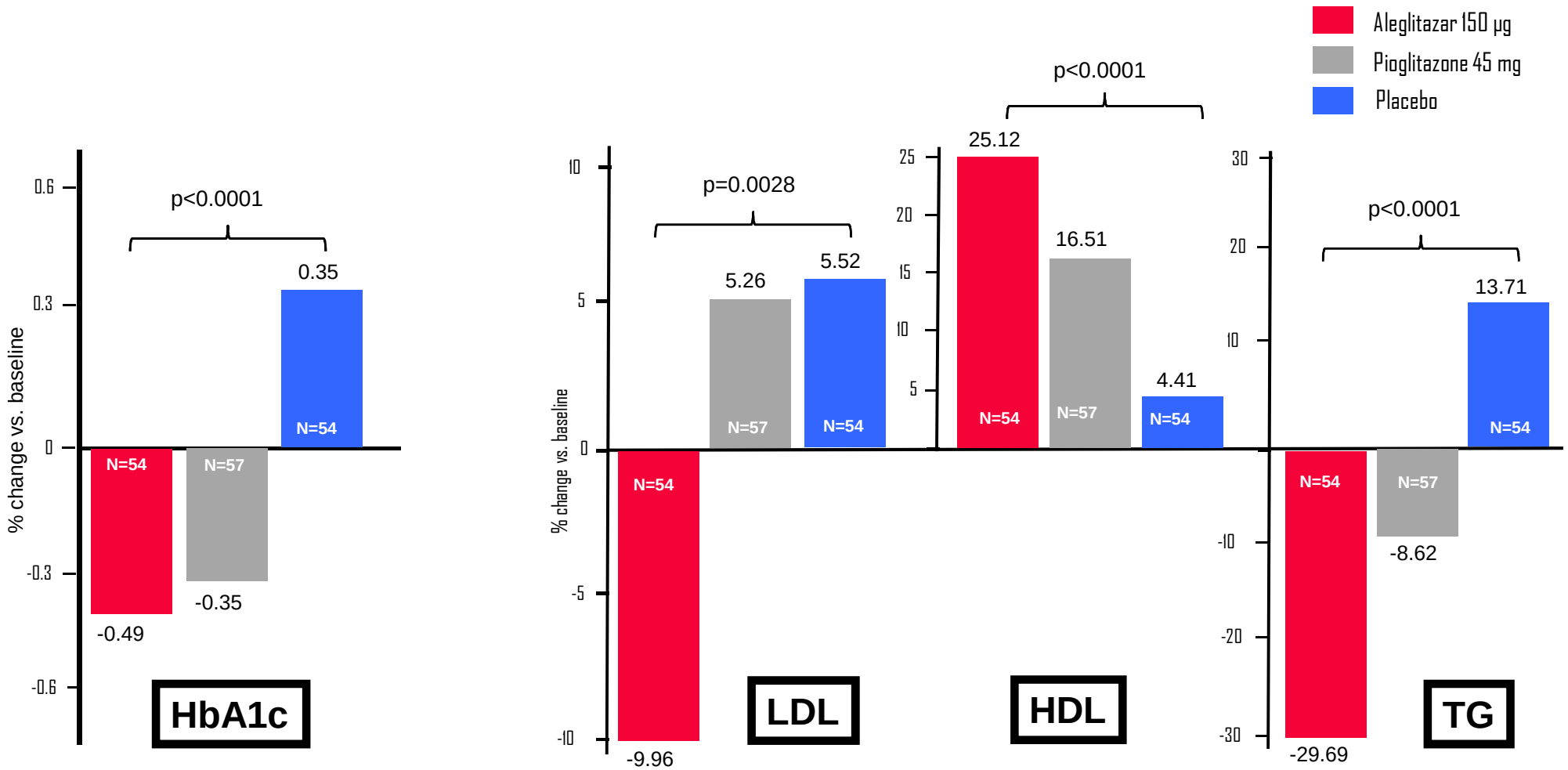
Effect of the dual peroxisome proliferator-activated receptor-α/γ agonist aleglitazar on risk of cardiovascular disease in patients with type 2 diabetes (SYNCHRONY): a phase II, randomised, dose-ranging study

Robert R Henry, A Michael Lincoff, Sunder Mudaliar, Michael Rabbia, Cathy Chognot, Matthias Herz



Lancet 374: 2009

SYNCHRONY: Effects on HbA1c and Lipids



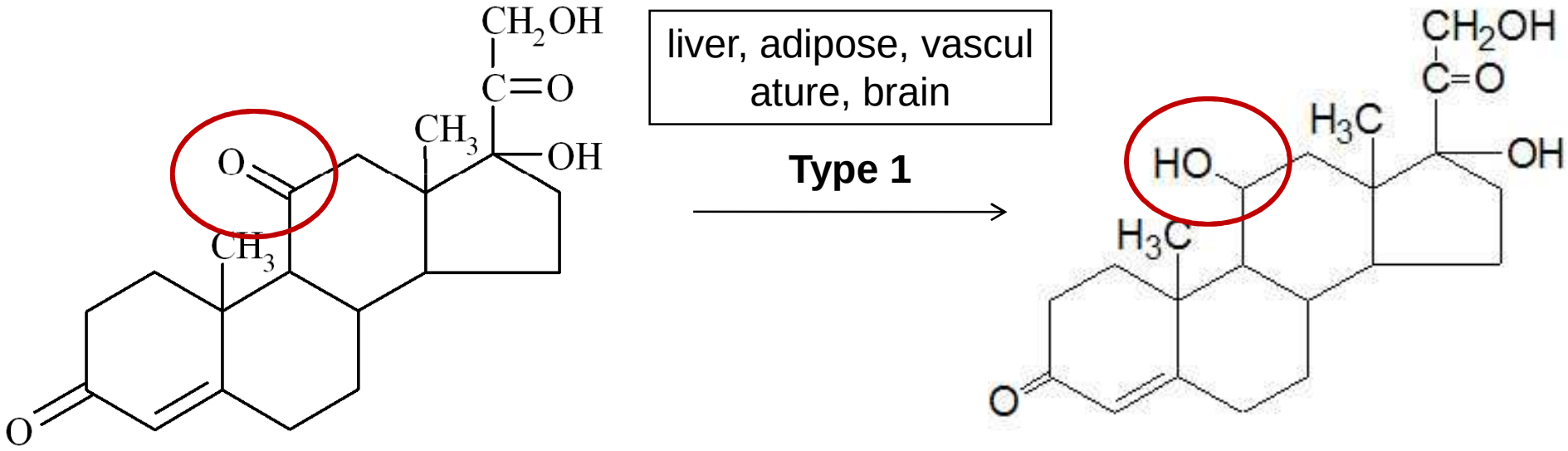
No statistical comparisons were made between aleglitazar 150 µg and pioglitazone 45 mg
Henry R et al. *Lancet* 2009;374:126

Aleglitazar Clinical Development Program

Study	Objectives
SYNCHRONY trial[1]	• Dose finding, determine efficacy, safety, and tolerability • Primary Endpoint: HbA1c change from baseline at week 16
SESTA-R trial[2]	• Evaluate effect (at 4x therapeutic dose, 600 µg) on GFR, renal plasma flow, and serum creatinine
ALECARDIO trial[3]	• To determine whether aleglitazar reduces CV mortality and morbidity in patients with a recent ACS event and T2DM • Evaluate the effects of aleglitazar on other clinical endpoints of CV risk • Evaluate the effects of aleglitazar on glycemic control, the lipoprotein profile, blood pressure, and biomarkers of CV risk • Evaluate the tolerability and long-term safety profile of aleglitazar (e.g. fluid retention, heart failure, fractures, renal function, musculoskeletal adverse events and liver enzyme elevation)
ALENEPHRO trial[4]	• Long-term safety data (52-weeks) and reversibility (8-weeks) with aleglitazar at therapeutic dose (150 µg)
Drug-drug interaction studies (ACE-I, ARBs, ASA, NSAIDs)	• PK/PD effects of concomitant treatment of aleglitazar and another agent on renal function in controlled setting
Renal Mechanistic Study	• Examination of renal effects in comparison to fibrate and pioglitazone

[1]Henry R et al. *Lancet* 2009;374:126; [2]ClinicalTrials.gov NCT00461006; [3]ClinicalTrials.gov NCT01042769; [4]ClinicalTrials.gov NCT01043029;

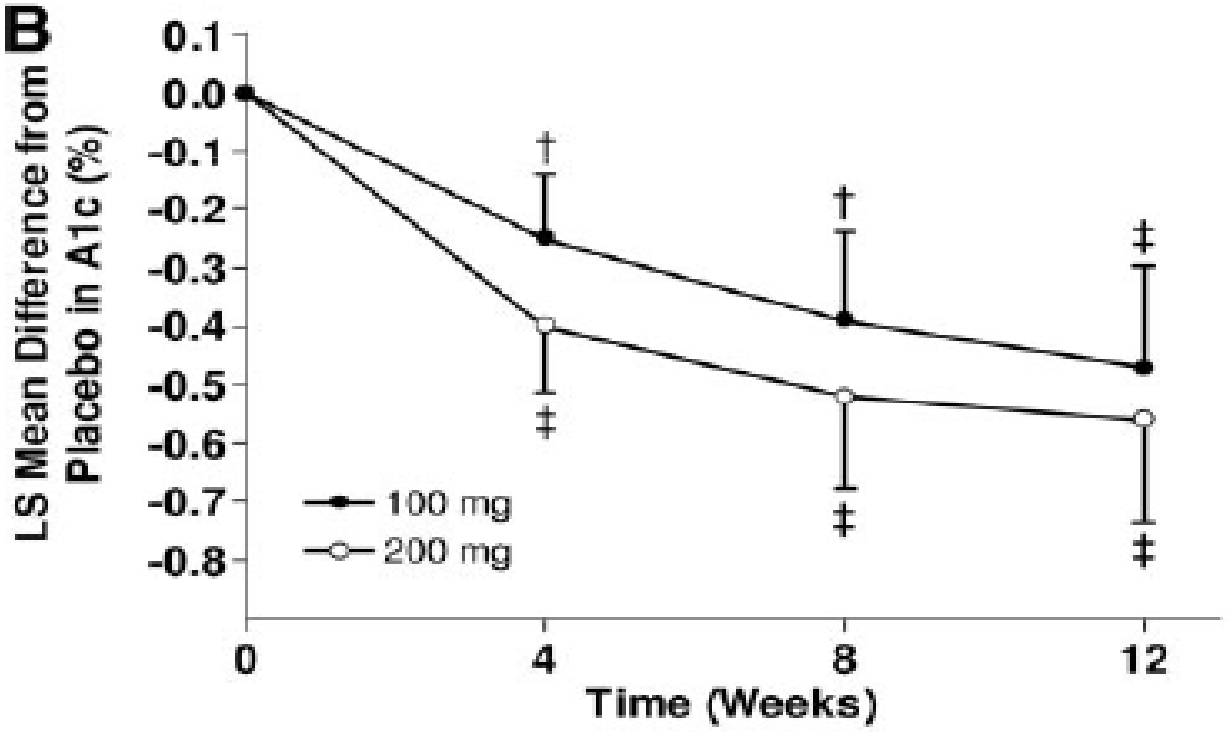
11-β-hydoxysteroid-dehydrogenase type 1 inhibitor



cortisone

cortisol

The 11-β-Hydroxysteroid Dehydrogenase Type 1 Inhibitor INCB13739 Improves Hyperglycemia in Patients With Type 2 Diabetes Inadequately Controlled by Metformin Monotherapy

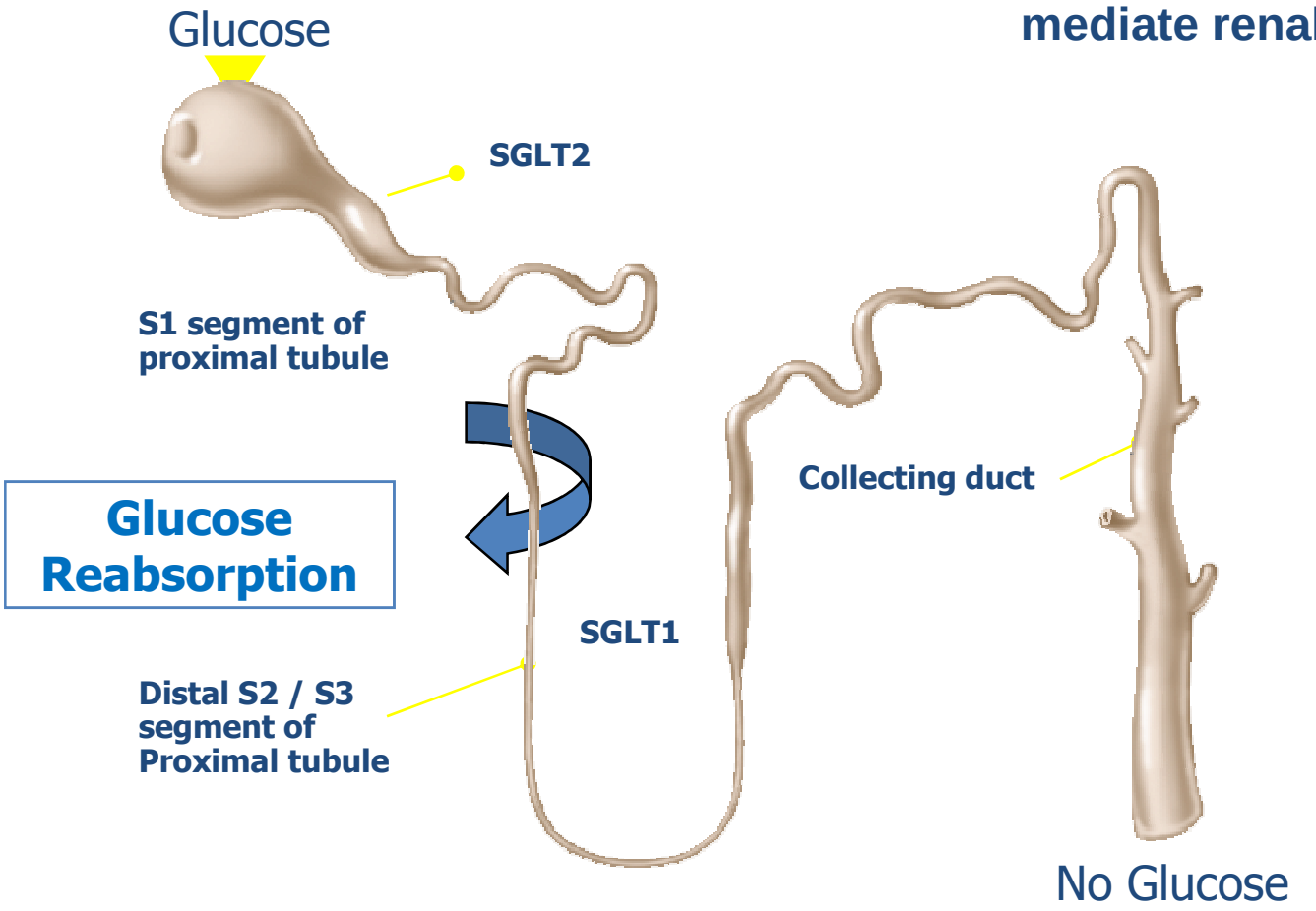


Diabetes Care 33:1516–1522, 2010

Inhibitors of SGLT2

- Dapaglifozin
- Canaglifozin
- Seglifozin
- Remoglifozin
- ISIS 388626

Renal Handling of Glucose, Non-Diabetic Individual

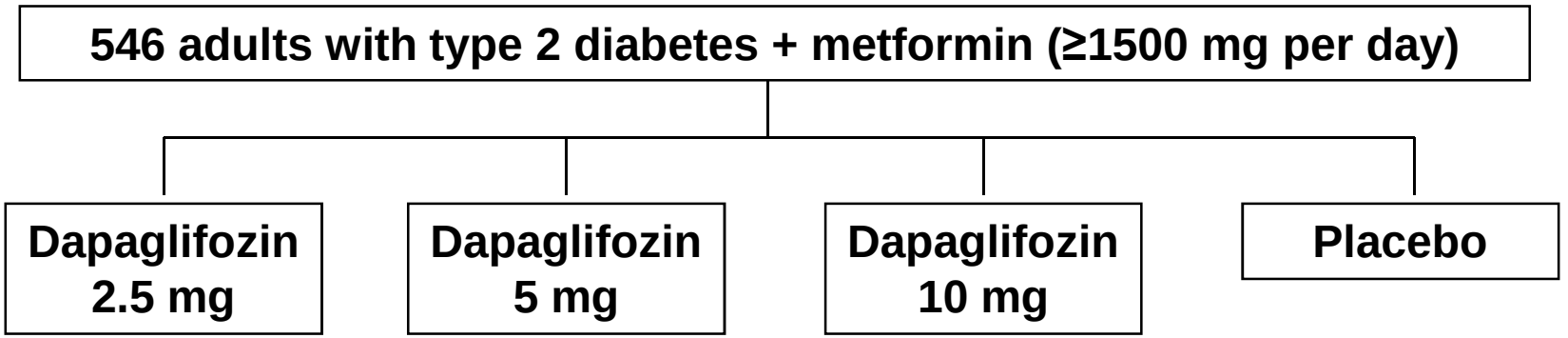


- Sodium-dependent glucose transporters mediate renal glucose reabsorption

- Volume of plasma kidney filters/day = 180 L
- Normal glucose concentration = 1000 mg/L (100 mg/dL)
- Glucose filtered/day = (180 L/day) (1000 mg/L) = 180 g

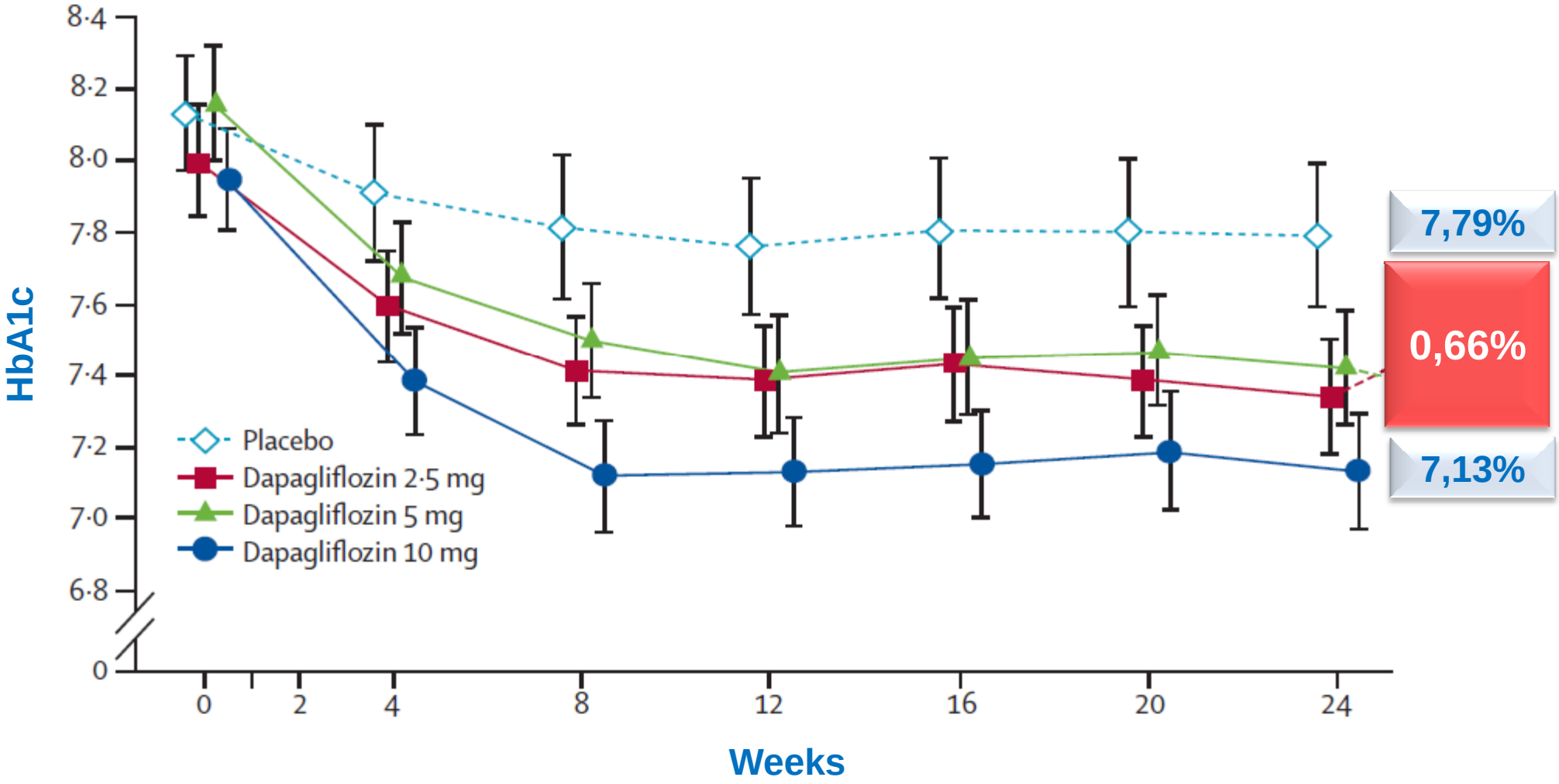
Effect of dapagliflozin in patients with type 2 diabetes who have inadequate glycaemic control with metformin: a randomised, double-blind, placebo-controlled trial

Clifford J Bailey, Jorge L Gross, Anne Pieters, Arnaud Bastien, James F List



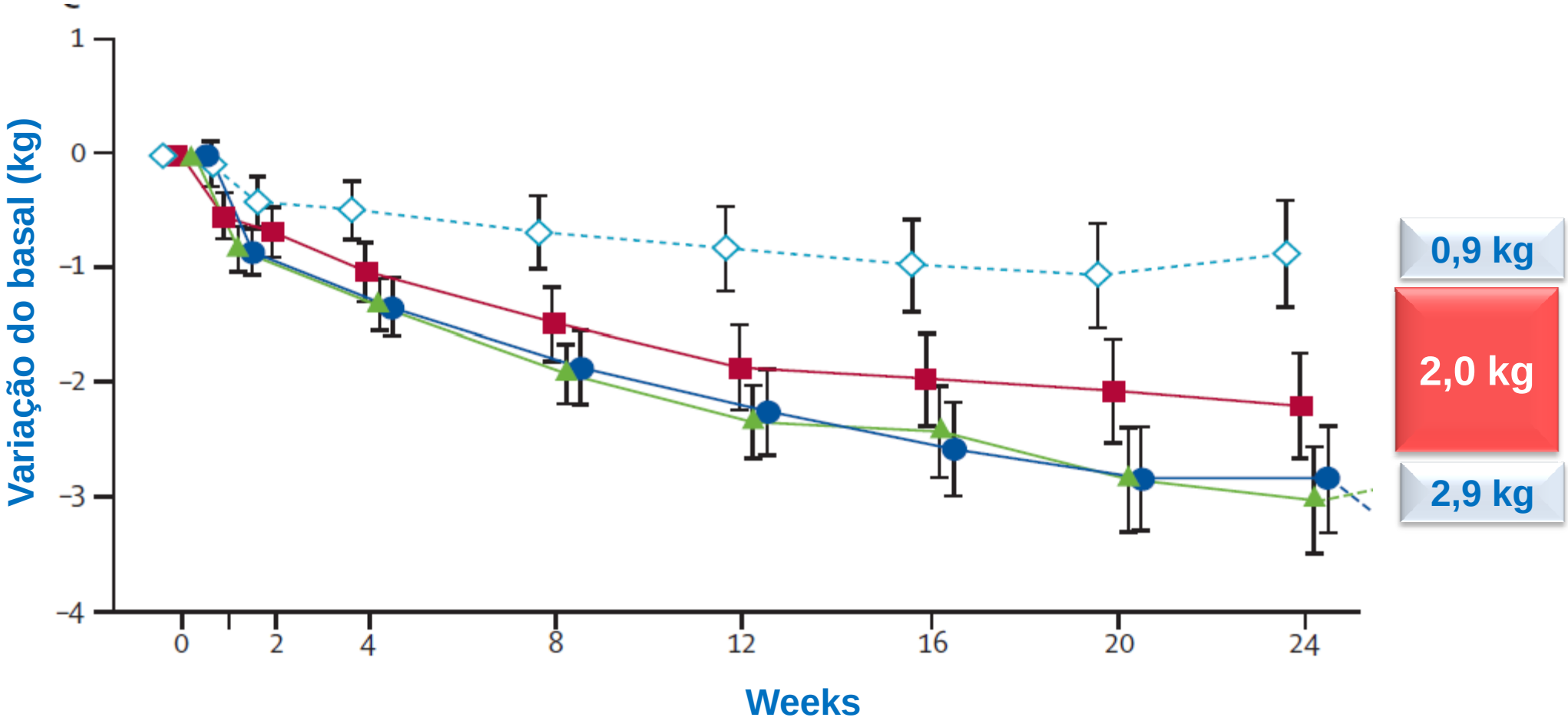
Lancet 375:2223, 2010

Efficacy – HbA_{1c}



Lancet 375:2223, 2010

Efficacy – Weight



Lancet 375:2223, 2010

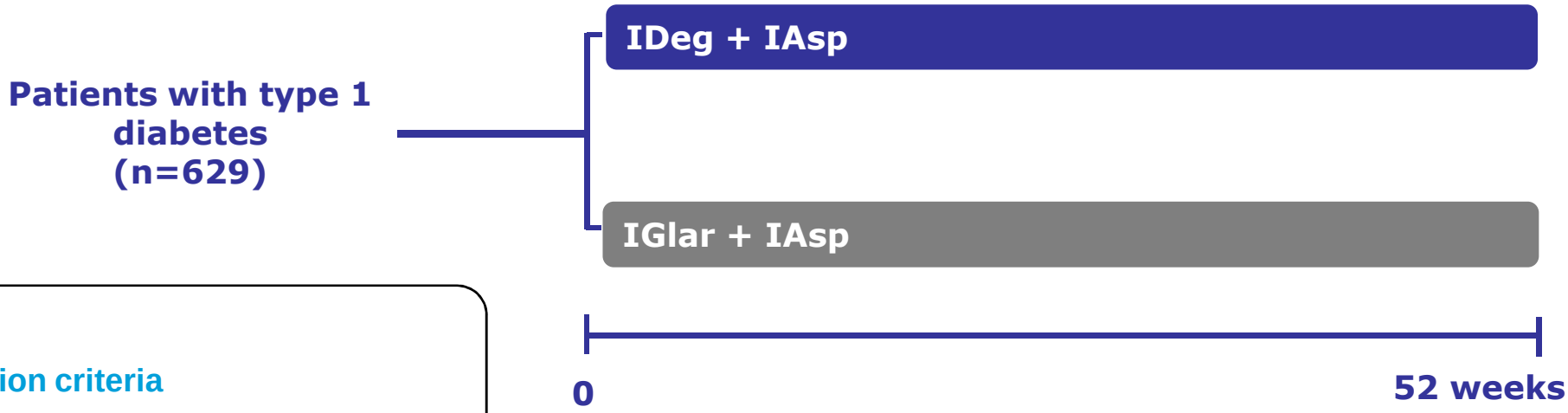
Ultra Long Acting Insulins: Insulin Degludec

A 52-week treat-to-target trial comparing efficacy and safety of insulin degludec and insulin glargine both administered OD in a basal–bolus regimen with insulin aspart as mealtime insulin in patients with type 1 diabetes mellitus

(BEGIN™)

Heller S, Diabetes July 2011; vol 60 (Supplement 1): OP-70

Study design



Inclusion criteria

- Type 1 diabetes ≥12 months
- Previously treated with basal–bolus ≥12 months
- HbA_{1c} ≤10%
- BMI ≤35 kg/m^2
- Age ≥18 years

Randomised 3:1 (IDeg:IGlar)
Open label

Heller S, Diabetes July 2011; vol 60 (Supplement 1): OP-70

Conclusions

- Insulin degludec effectively improved HbA1c and is non-inferior to insulin glargine in basal-bolus therapy in type 1 diabetes
- Titration targets were achieved faster for patients treated in the insulin degludec arm
  - On average, patients treated with insulin glargine used 9-10% more insulin than those treated with insulin degludec (0.75 vs 0.82 U/kg)
- Patients treated with insulin degludec had 25% less risk of nocturnal hypoglycaemia than with insulin glargine
- Insulin degludec demonstrated a good safety and tolerability profile

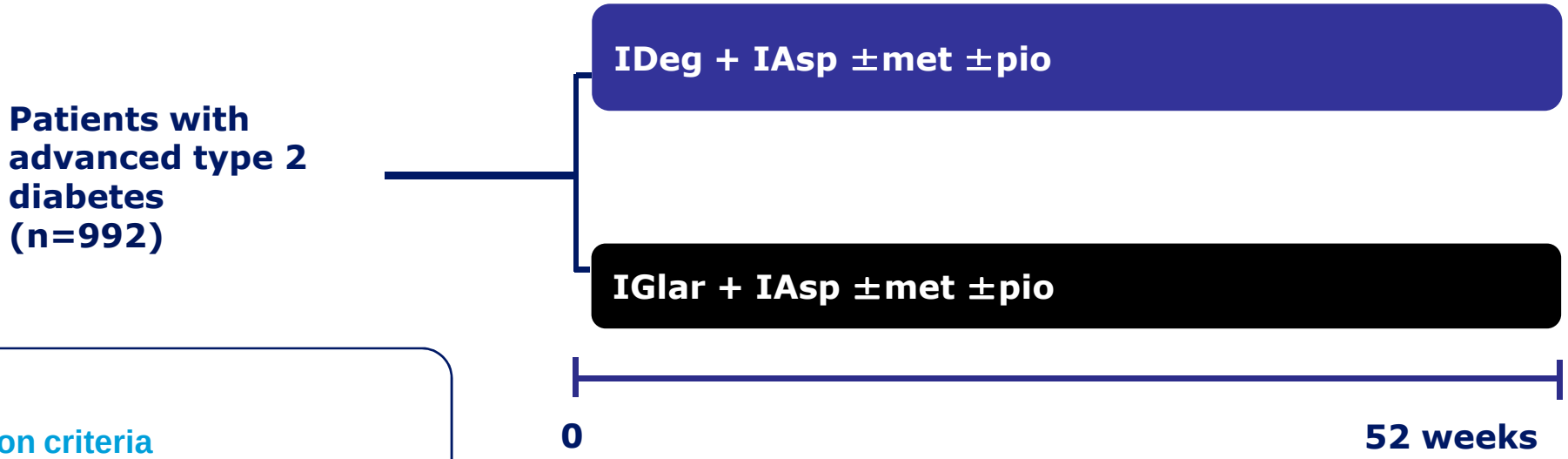
Heller S, Diabetes July 2011; vol 60 (Supplement 1): OP-70

A 52-week treat-to-target trial comparing efficacy and safety of insulin degludec and glargine both administered OD in a basal–bolus regimen with insulin aspart ±metformin ±pioglitazone in patients with type 2 diabetes mellitus previously treated with insulin

(BEGIN™: BB)

Garber AJ, Diabetes July 2011; vol 60 (Supplement 1): OP-74

Study design



Randomised 3:1
Open label

Inclusion criteria

- Type 2 diabetes ≥6 months
- Previously treated with any insulin regimen ≥3 months ± OADs
- HbA_{1c} 7–10%
- BMI ≤40 kg/m^2
- Age ≥18 years

pio: pioglitazone
met: metformin
IGlar: insulin glargine
OD: once daily

Garber AJ, Diabetes July 2011; vol 60 (Supplement 1): OP-74

Conclusions

- Insulin degludec effectively improved HbA1c and is non-inferior to insulin glargine in basal-bolus therapy with insulin aspart in type 2 diabetes
  - Insulin degludec achieved a 1.2%-point HbA1c reduction to 7.1%
- Insulin degludec resulted in significantly less risk of hypoglycaemia than insulin glargine
  - 18% less risk of overall confirmed hypoglycaemia
  - 25% less risk of nocturnal hypoglycaemia
- Overall, insulin degludec demonstrated a good safety and tolerability profile

BBT: basal–bolus therapy

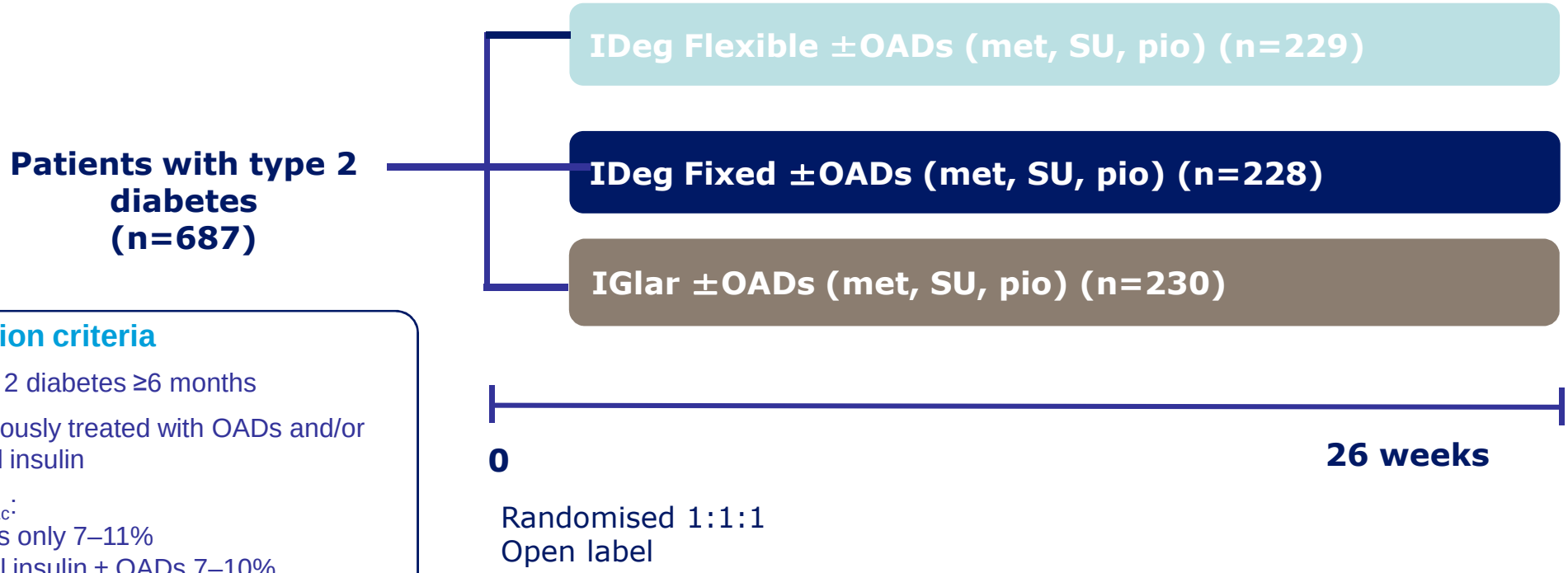
Garber AJ, Diabetes July 2011; vol 60 (Supplement 1): OP-74

A 26-week, treat-to-target trial comparing efficacy and safety of a flexible insulin degludec dosing regimen with fixed insulin degludec dosing and insulin glargine, each given once daily ± OAD therapy, in patients with type 2 diabetes mellitus

(BEGIN™: FLEX)

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Study design



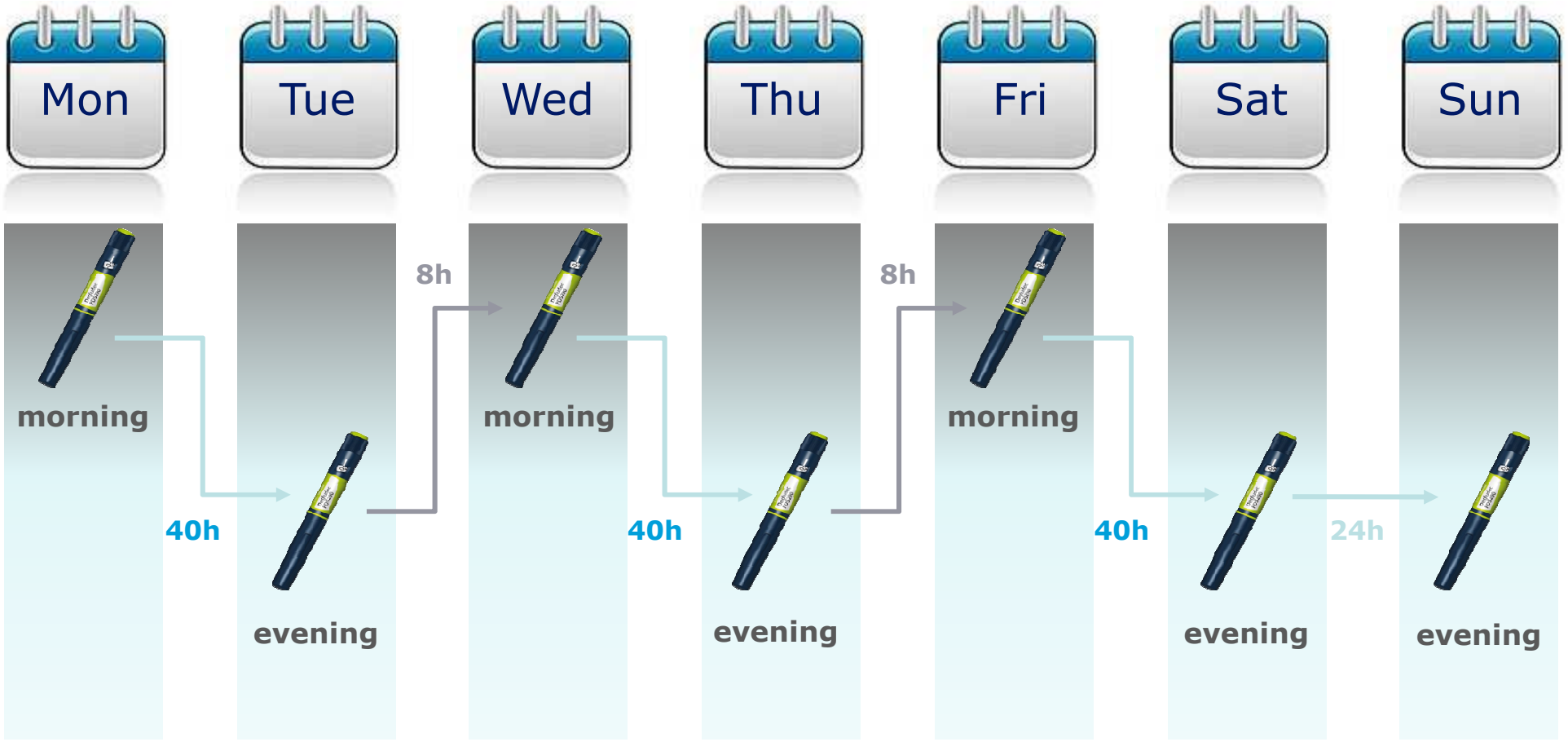
Inclusion criteria

- Type 2 diabetes ≥6 months
- Previously treated with OADs and/or basal insulin
- HbA_{1c}:
  OADs only 7–11%
  Basal insulin ± OADs 7–10%
- BMI ≤40 kg/m^2
- Age ≥18 years

OAD: oral antidiabetic drug
met: metformin
pio: pioglitazone
SU: sulphonylurea
OD: once-daily

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

IDeg vs IGlar in T2: flexible dosing



Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Conclusions

- Insulin degludec can be dosed at any time of the day at a different time from day to day, while effectively improving glycaemic control in patients with type 2 diabetes mellitus
  - FPG is reduced more with insulin degludec dosed flexibly than insulin glargine dosed OD
- The rate of overall hypoglycaemia is unchanged with flexible dosing and there is a trend towards a decrease in nocturnal hypoglycaemia compared with insulin glargine
- With injection intervals ranging from 8 to 40 hours, daily administration of insulin degludec is flexible to the daily life of patients with diabetes and provides 'forgiveness' with regard to delayed or even missed doses

Meneghini L, Diabetes July 2011; vol 60 (Supplement 1): 35-LB

Conclusions

- Metabolic control is far from ideal in some countries
- New tools for the treatment of diabetes are very welcome
- Incretin-based therapy has the potential to restore β-cell function
- New classes are under development and may offer additional benefits

PERSONALIZING TREATMENT IN TYPE 2 DIABETES: AN INNOVATIVE APPROACH

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