
بسم الله الرحمن الرحيم

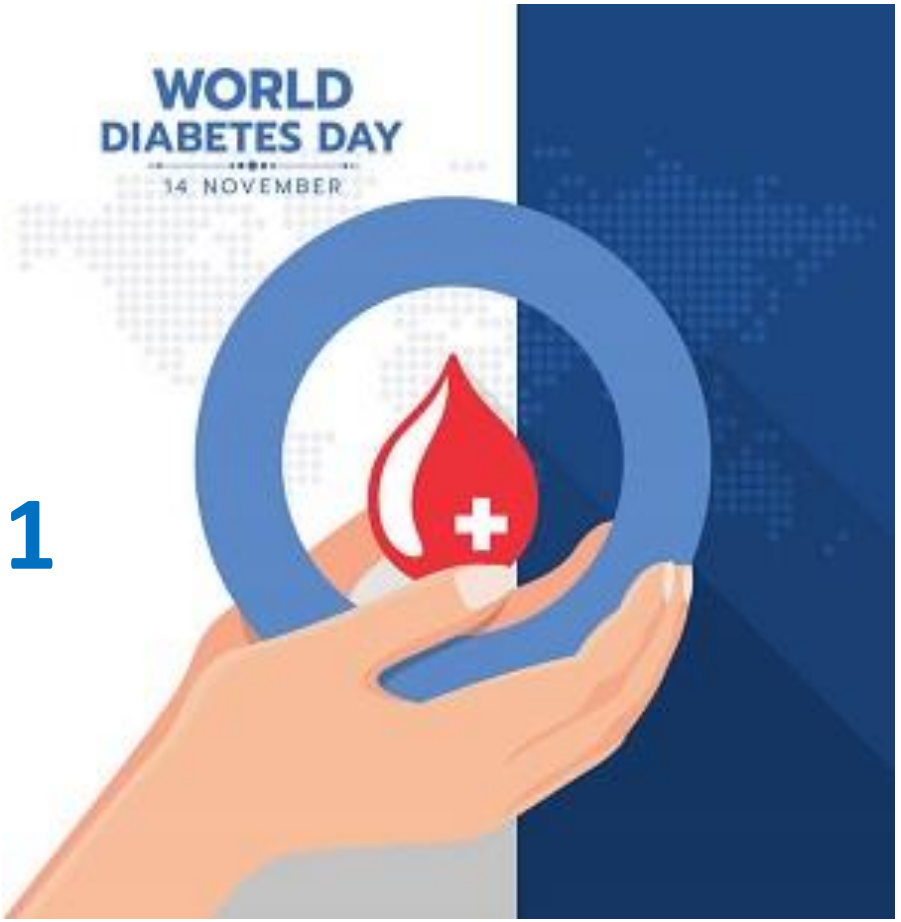
اثر داروهای DPP4 I و SGLT I 2 بر کنترل قند خون و وزن

Dr. Farzad Najafipour

Endocrine Research Center, Tabriz University of Medical Sciences

ACCESS TO DIABETES CARE: IF NOT NOW, WHEN?

2021



دسترسی به مراقبت از دیابت: اگر اکنون نه، چه زمانی؟

Introduction

Despite advances in options for the treatment of diabetes, optimal glycemic control is often **not achieved.**

Hypoglycemia and **weight gain** associated with many antidiabetic medications may interfere with the implementation and long term application of "intensive" therapies.

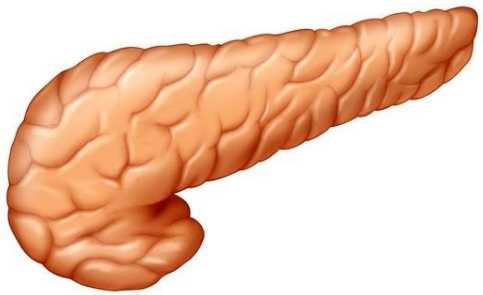
Treatment of Type 2 Diabetes

Insulin

1921

Treatment of Type 2 Diabetes

Sulfonylureas



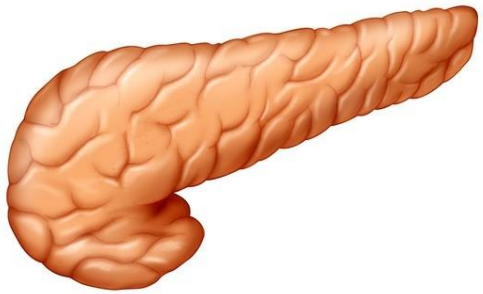
1937

Insulin

1921

Treatment of Type 2 Diabetes

Sulfonylureas

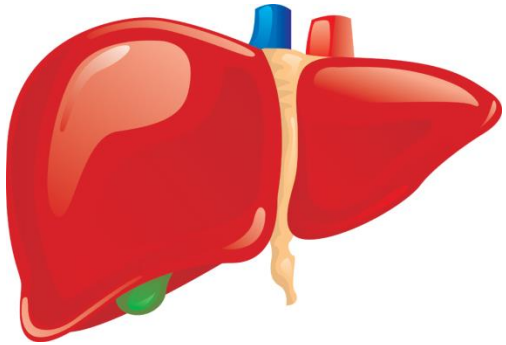


1937

Insulin

1921

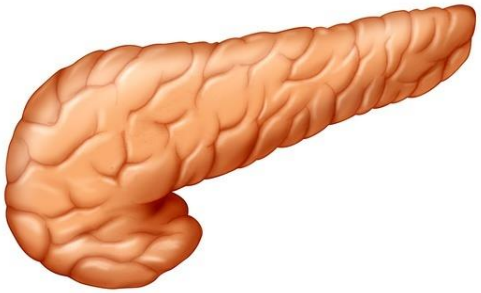
Metformin



1940

Treatment of Type 2 Diabetes

Sulfonylureas

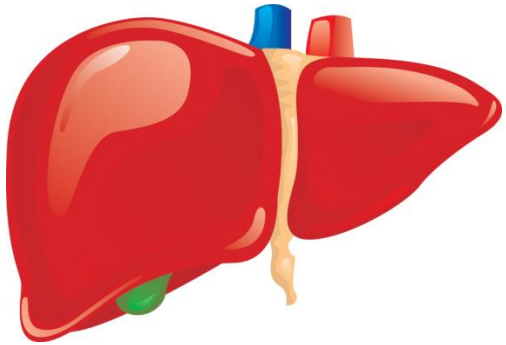


1937

Insulin

1921

Metformin



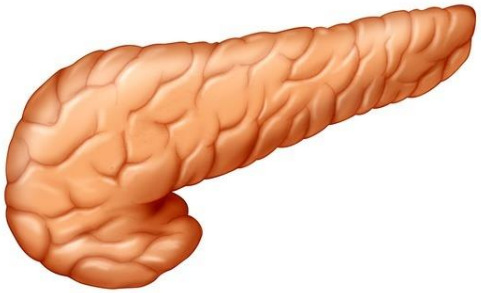
1940

Treatment of Type 2 Diabetes

Thiazolidinediones

1996

Sulfonylureas

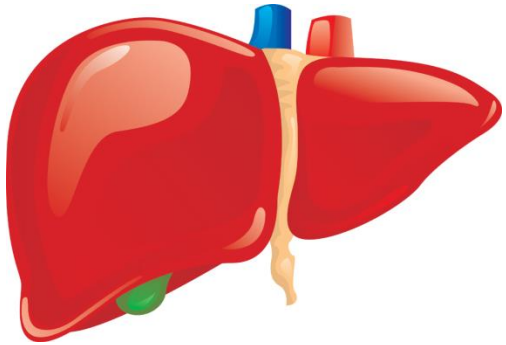


1937

Insulin

1921

Metformin

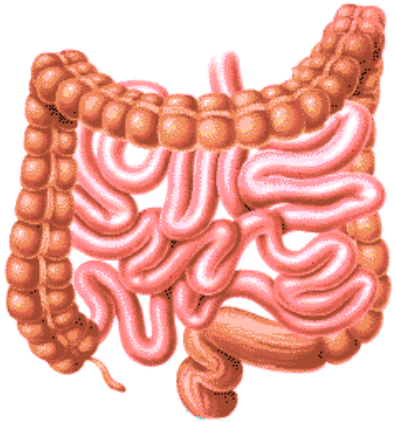


1940

Treatment of Type 2 Diabetes

Thiazolidinediones

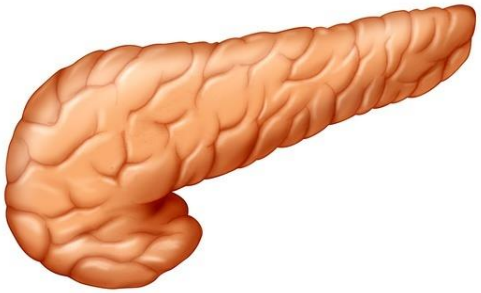
1996



GLP-I analogs & DPP IV inhibitors

2006

Sulfonylureas

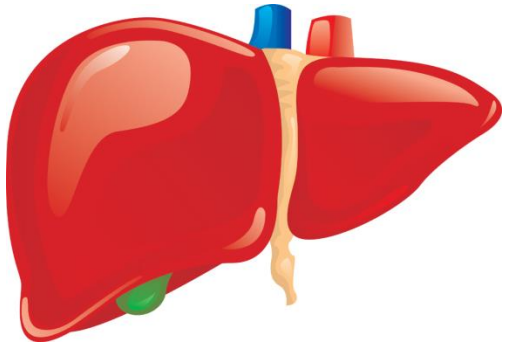


1937

Insulin

1921

Metformin

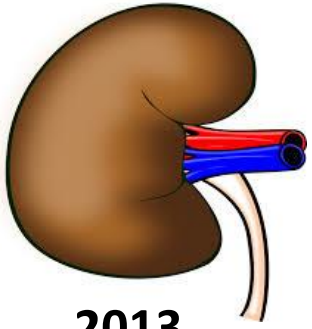


1940

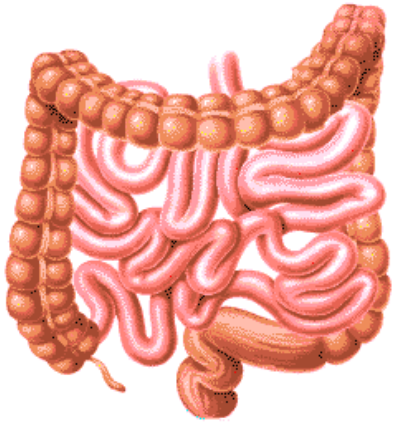
Treatment of Type 2 Diabetes

Thiazolidinediones

1996



2013
SGLT2 inhibitors



GLP-I analogs & DPP IV inhibitors

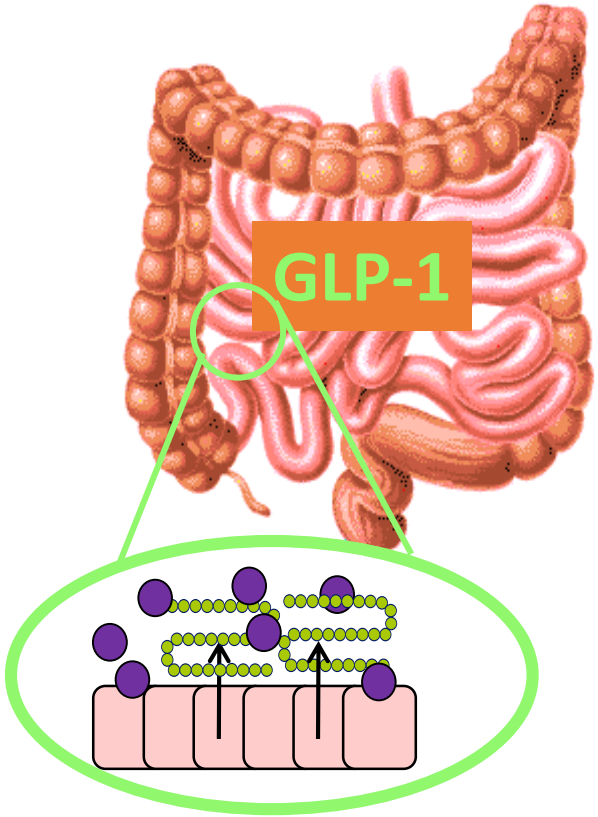
2006

Historical perspectives of incretins and evolution of incretin based therapy

Year	Development
1932	La Barre et al coined the term (Incretin) and defined its effect
1964	Incretin effect (Significant Insulin release on oral ingestion than Intravenous injection)
1966	DPP–4 enzyme first described
1970	GIP demonstrated
1985	GLP 1 demonstrated
1995	GIP & GLP 1 were demonstrated to be degraded by DPP-4 enzyme
2006	Sitagliptin introduced for the use of T2DM

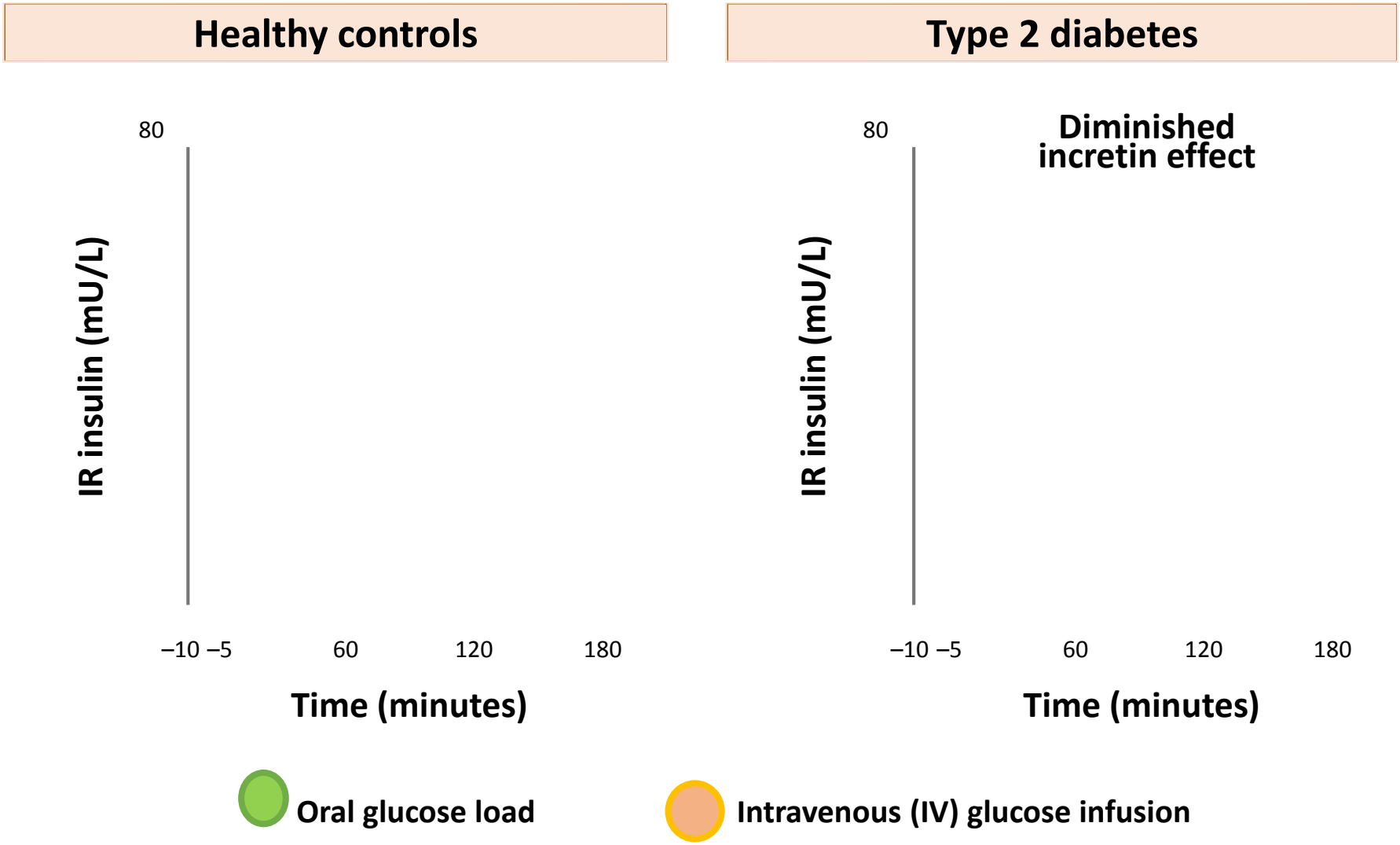
Glucagon-like Peptide 1

GLP-1 is produced from the proglucagon gene in L cells of the small intestine and is secreted in response to nutrients.



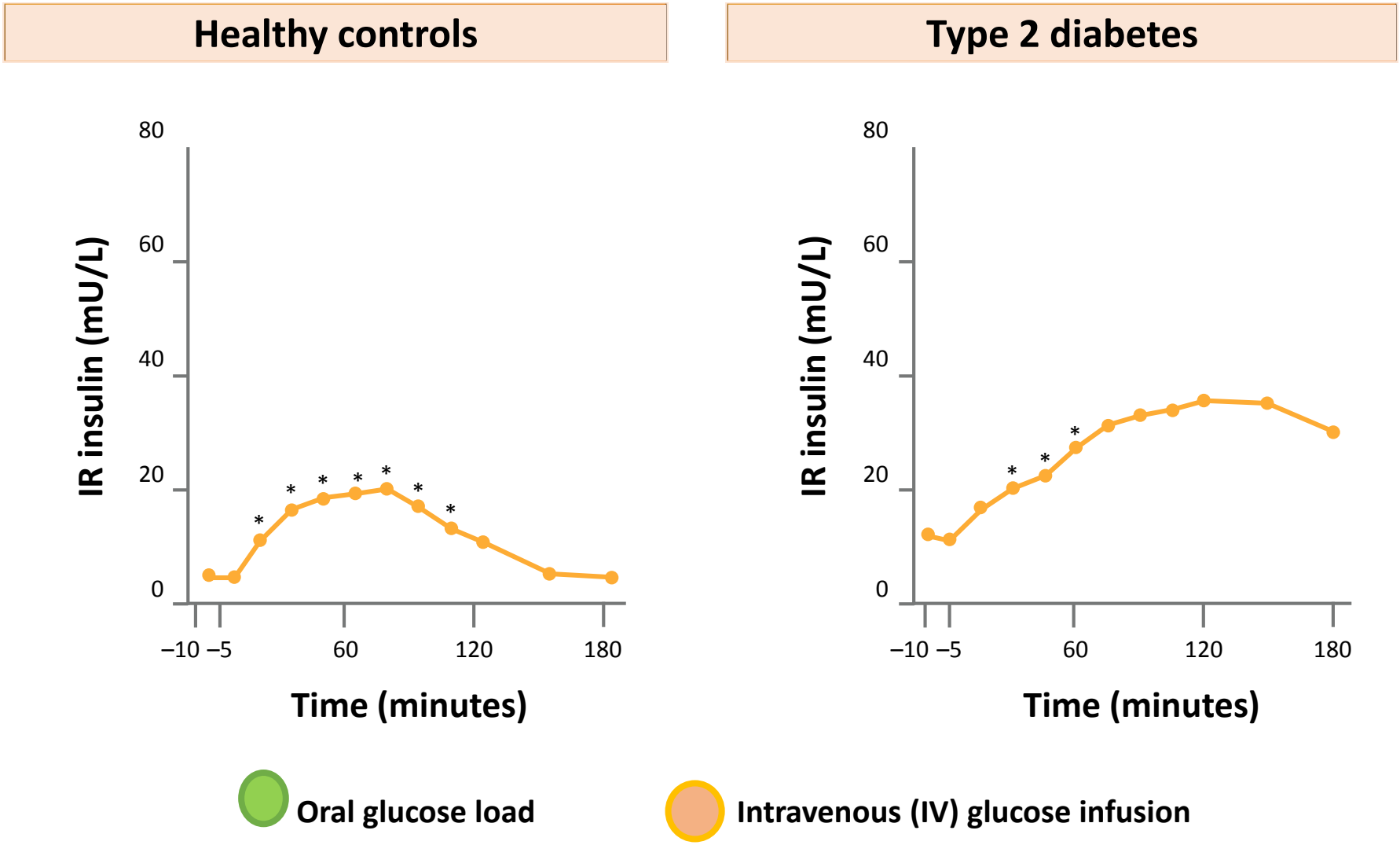
L-cells secrete GLP-1

The Effect of Incretins in Type 2 Diabetes and Non-Diabetes



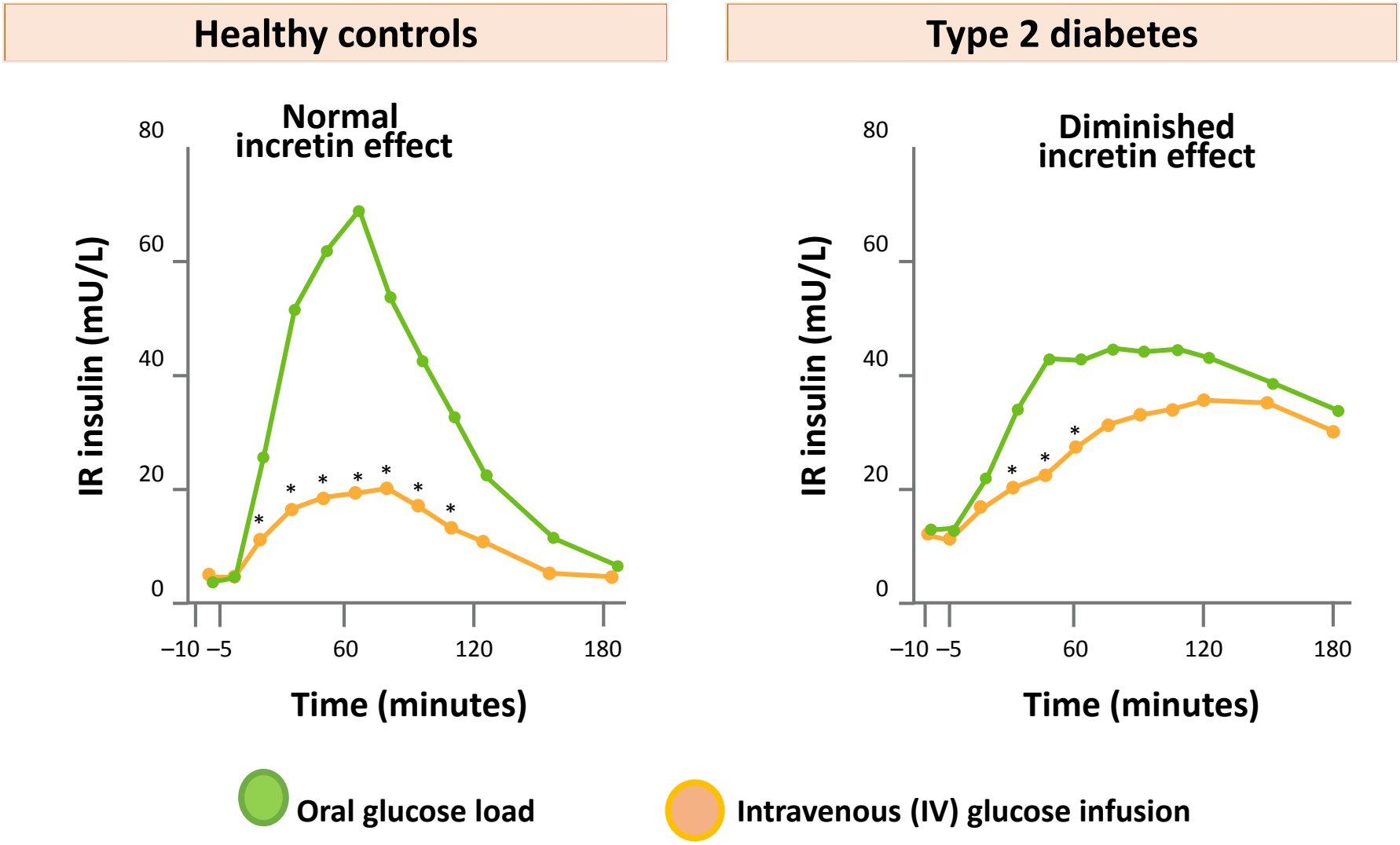
Diabetologia. 1986 ;29(1):46-52.

The Effect of Incretins in Type 2 Diabetes and Non-Diabetes



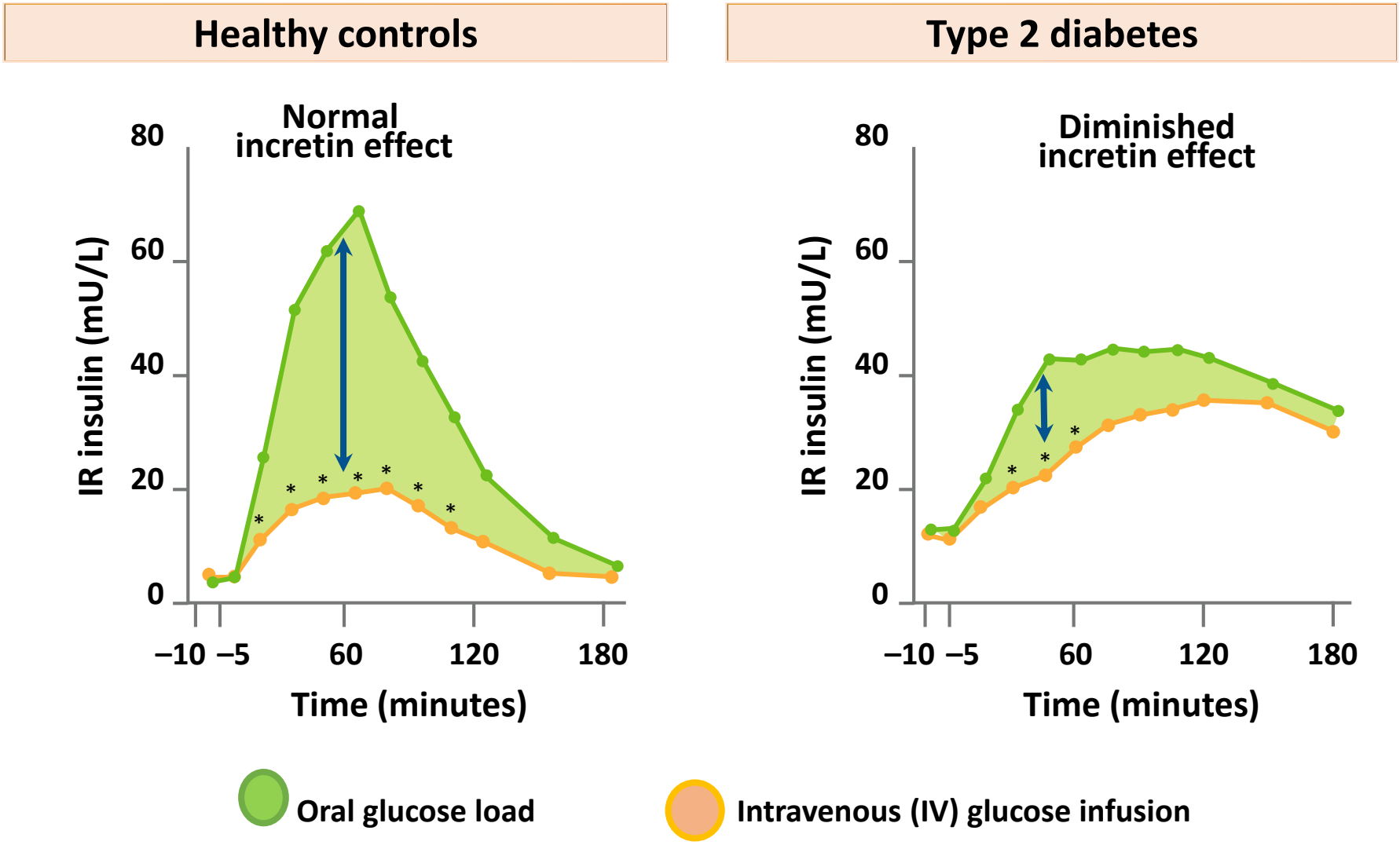
Diabetologia. 1986 ;29(1):46-52.

The Effect of Incretins in Type 2 Diabetes and Non-Diabetes



Diabetologia. 1986 ;29(1):46-52.

The Effect of Incretins in Type 2 Diabetes and Non-Diabetes

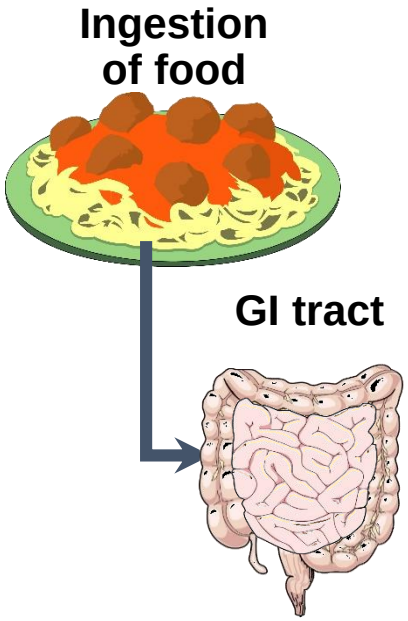


Diabetologia. 1986 ;29(1):46-52.

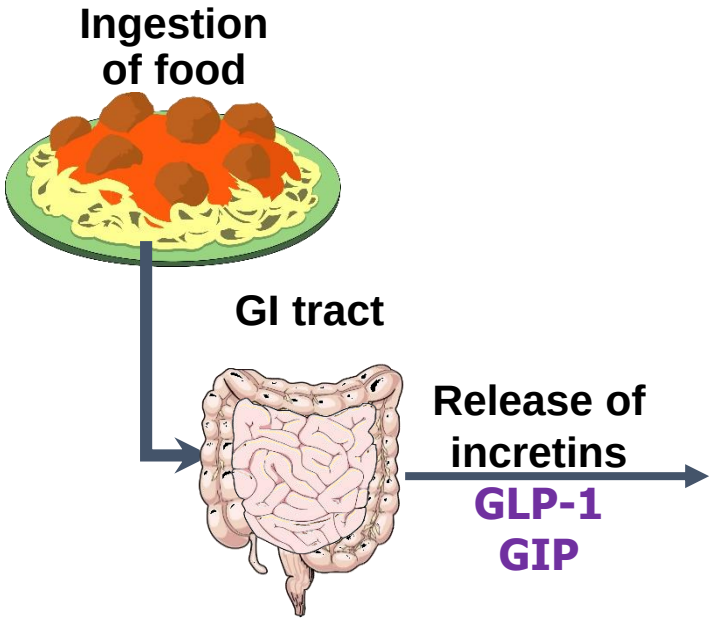
DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes

Ingestion of food

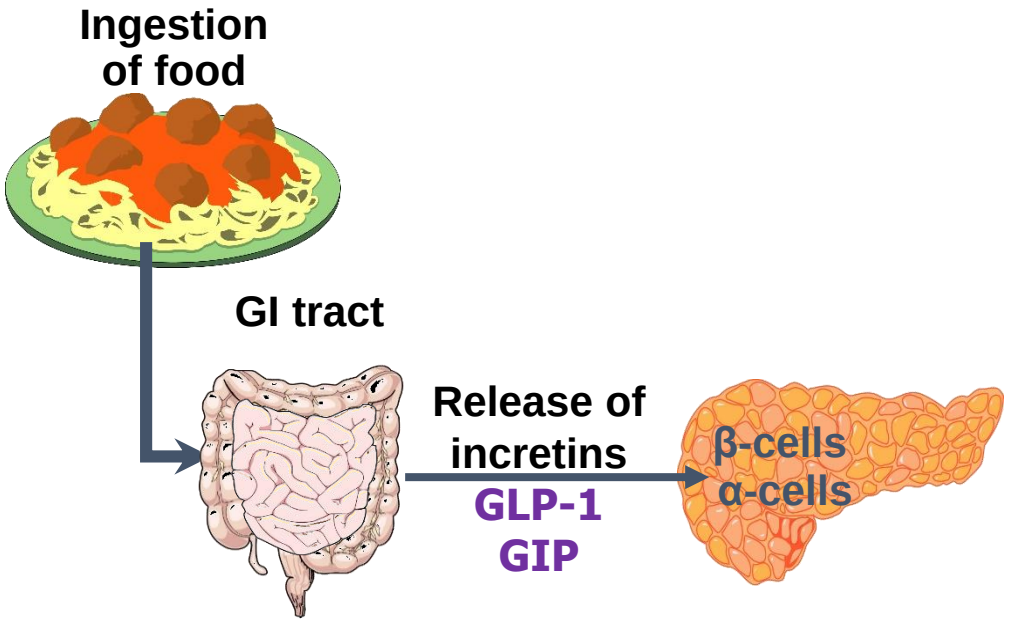
DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



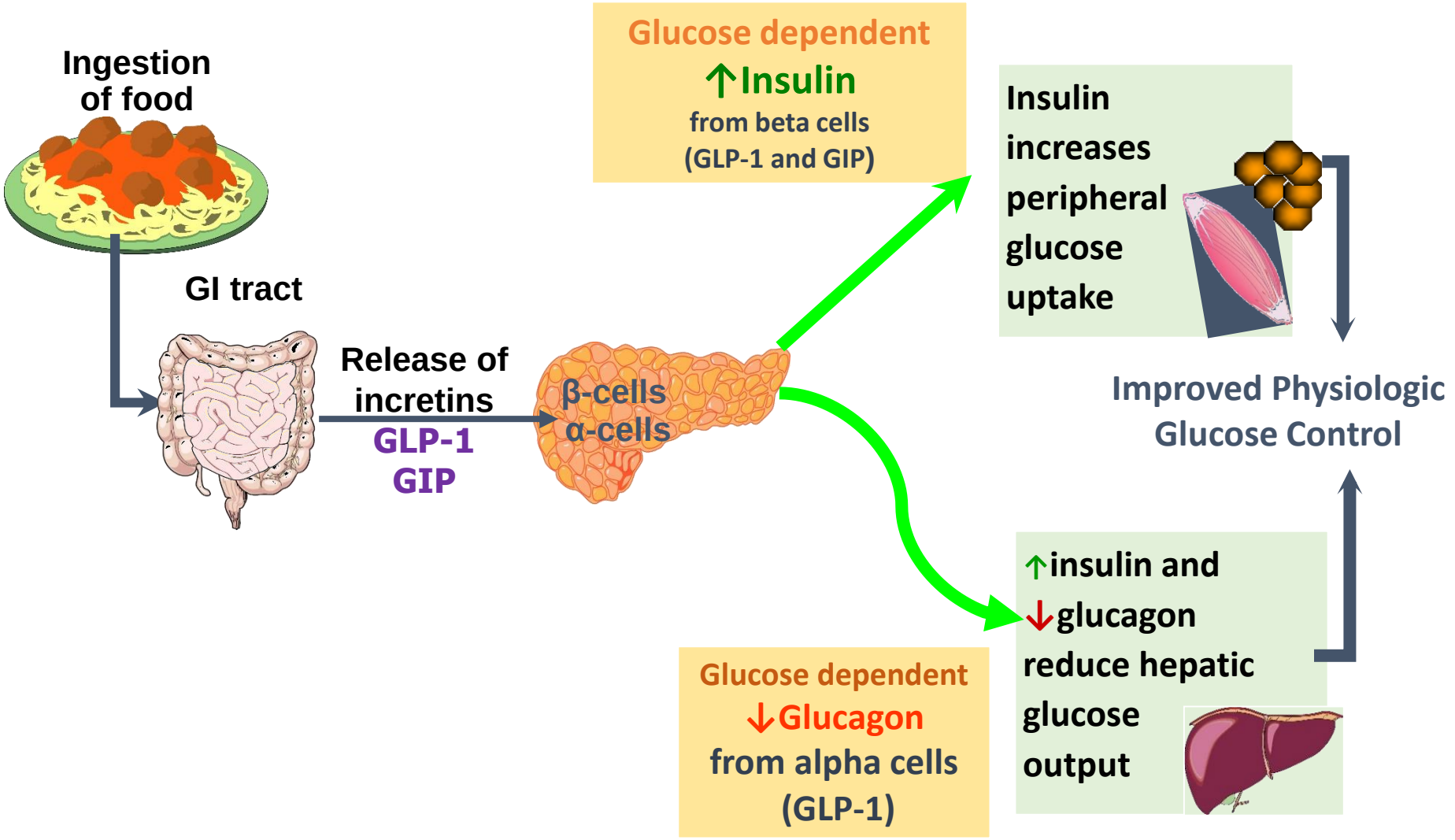
DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes

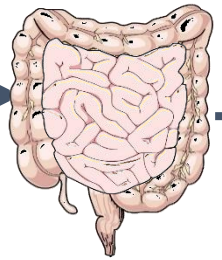


DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



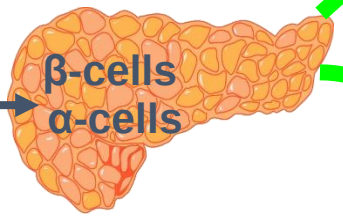
DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes

Ingestion of food



GI tract

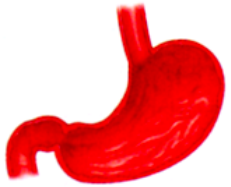
Release of incretins
GLP-1
GIP



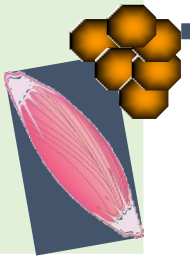
Pancreas

Glucose dependent
↑Insulin
from beta cells
(GLP-1 and GIP)

Stomach
↓Gastric emptying

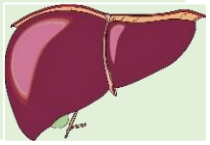


Insulin increases peripheral glucose uptake



Improved Physiologic Glucose Control

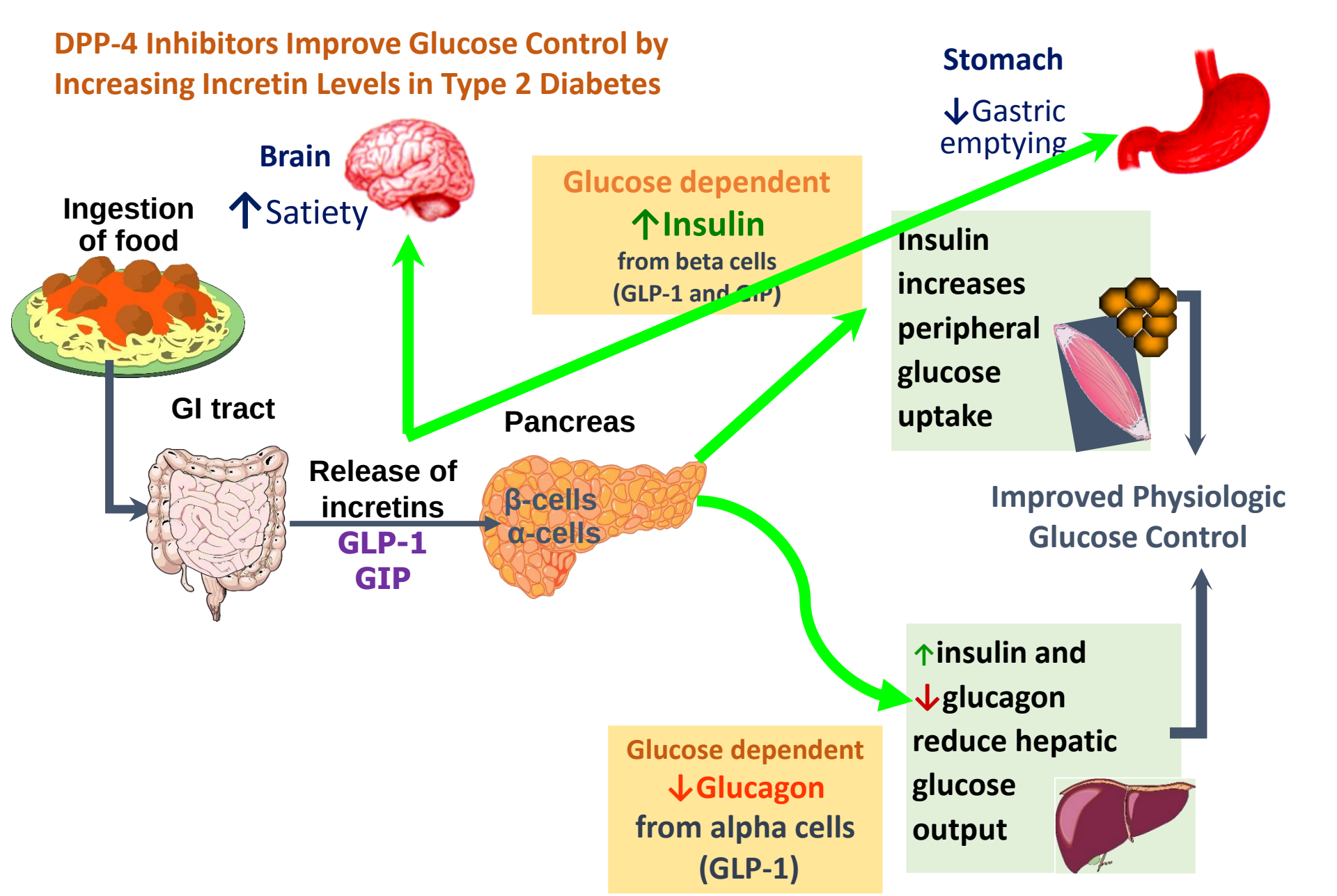
↑insulin and
↓glucagon
reduce hepatic glucose output



Glucose dependent
↓Glucagon
from alpha cells
(GLP-1)

Endocrinology. 2004 ;145(6):2653-9.

DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



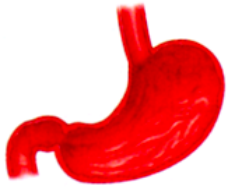
Endocrinology. 2004 ;145(6):2653-9.

DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes

Ingestion of food

Brain

↑Satiety

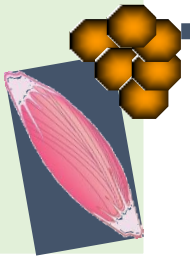


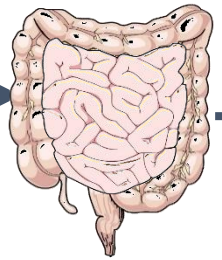
Stomach

↓Gastric emptying

Glucose dependent
↑Insulin
from beta cells
(GLP-1 and GIP)

Insulin increases peripheral glucose uptake





GI tract

Release of incretins
GLP-1
GIP

Pancreas

β-cells
α-cells

Improved Physiologic Glucose Control

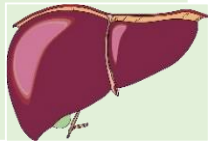
DPP-4 enzyme

Inactive GLP-1

Inactive GIP

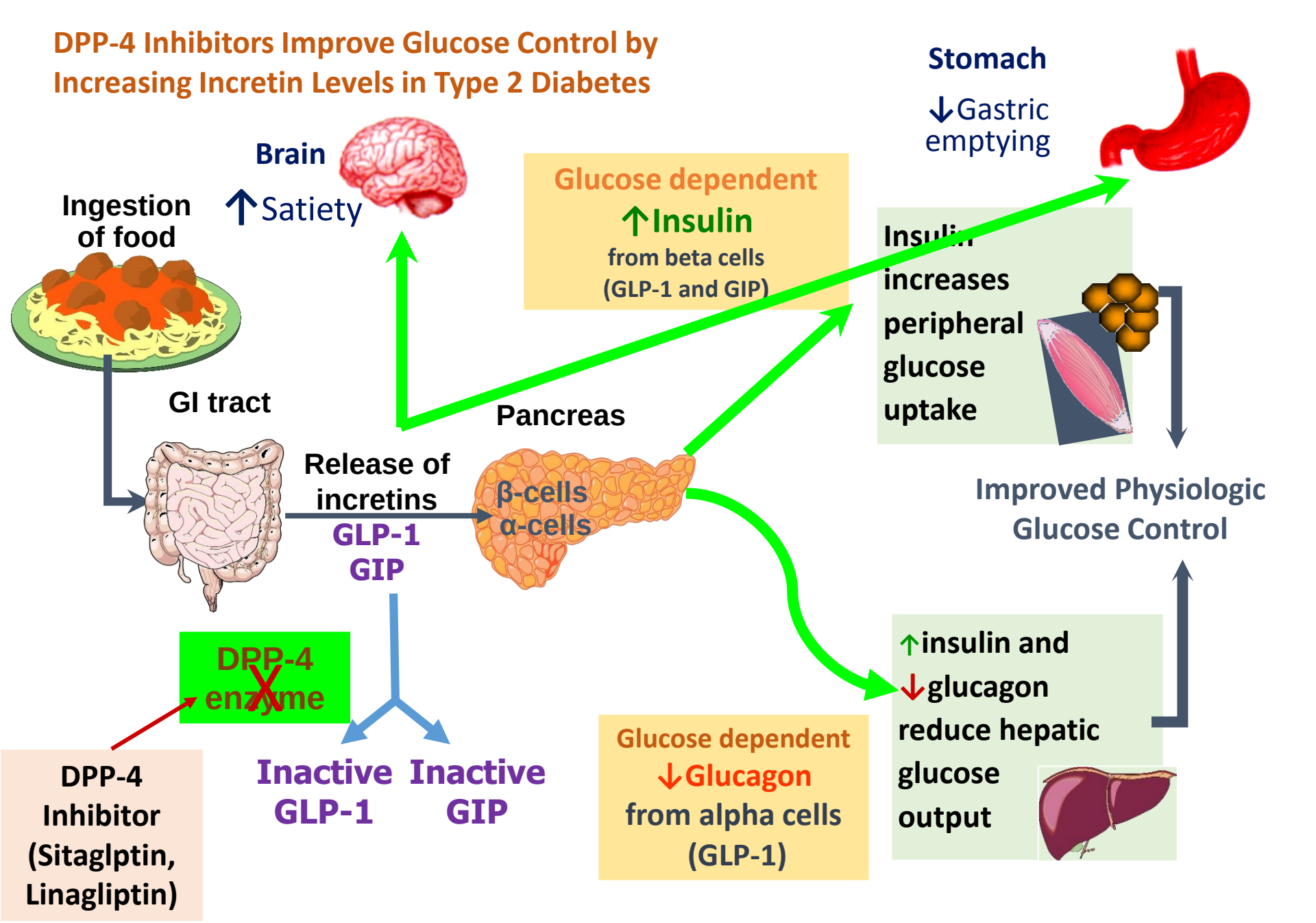
Glucose dependent
↓Glucagon
from alpha cells
(GLP-1)

↑insulin and
↓glucagon
reduce hepatic glucose output



Endocrinology. 2004 ;145(6):2653-9.

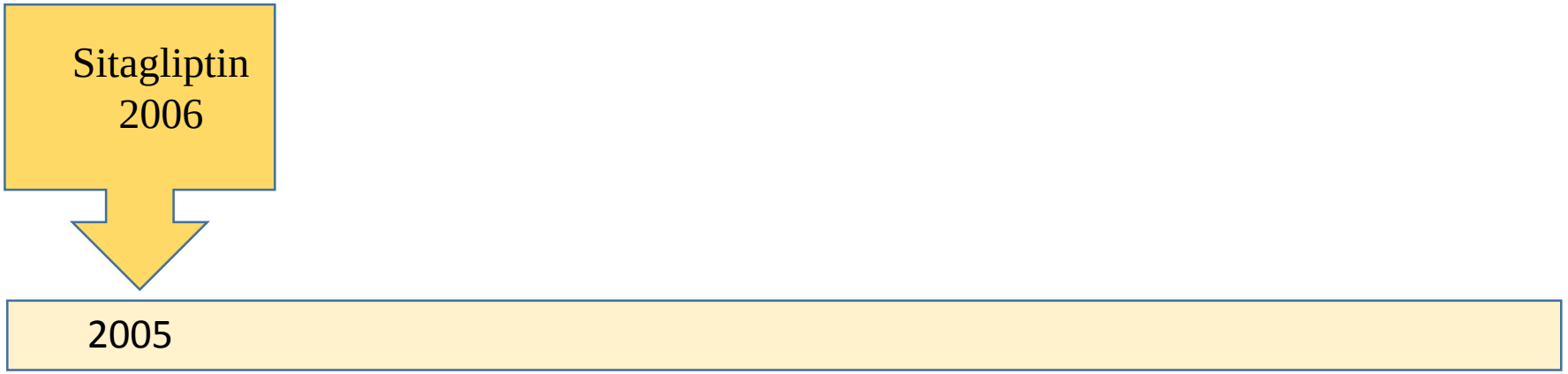
DPP-4 Inhibitors Improve Glucose Control by Increasing Incretin Levels in Type 2 Diabetes



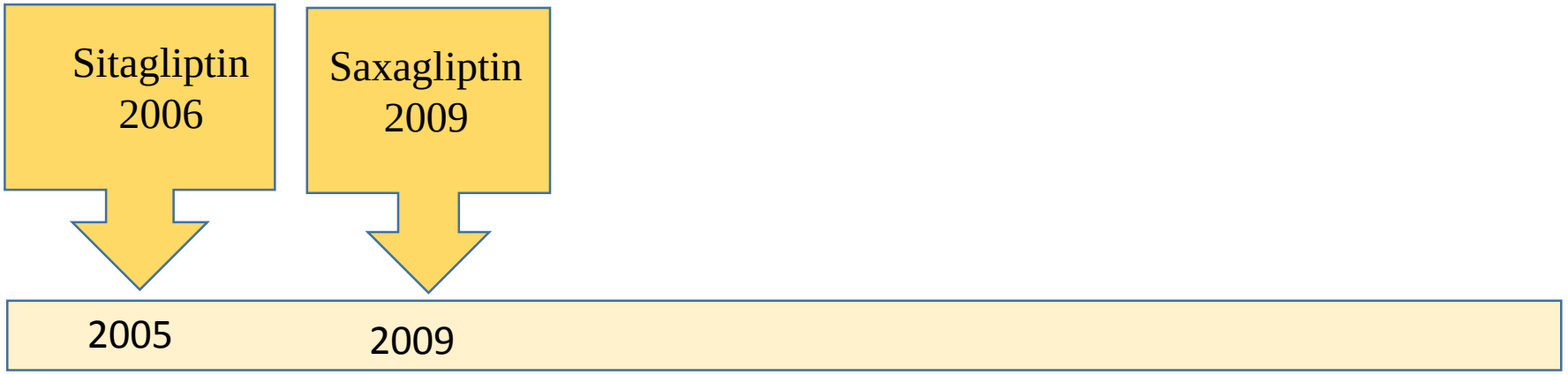
Endocrinology. 2004 ;145(6):2653-9.

DPP 4 Inhibitors

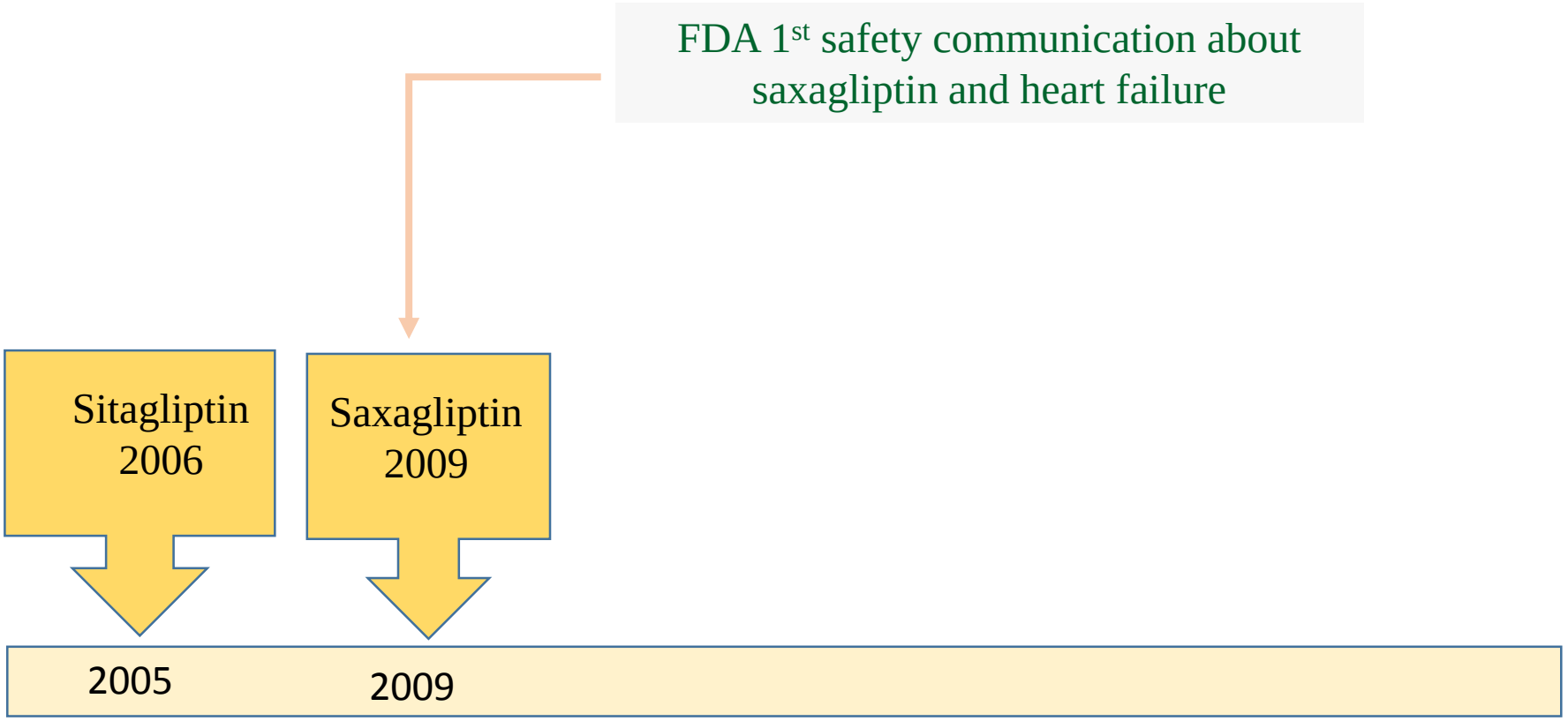
DPP 4 Inhibitors



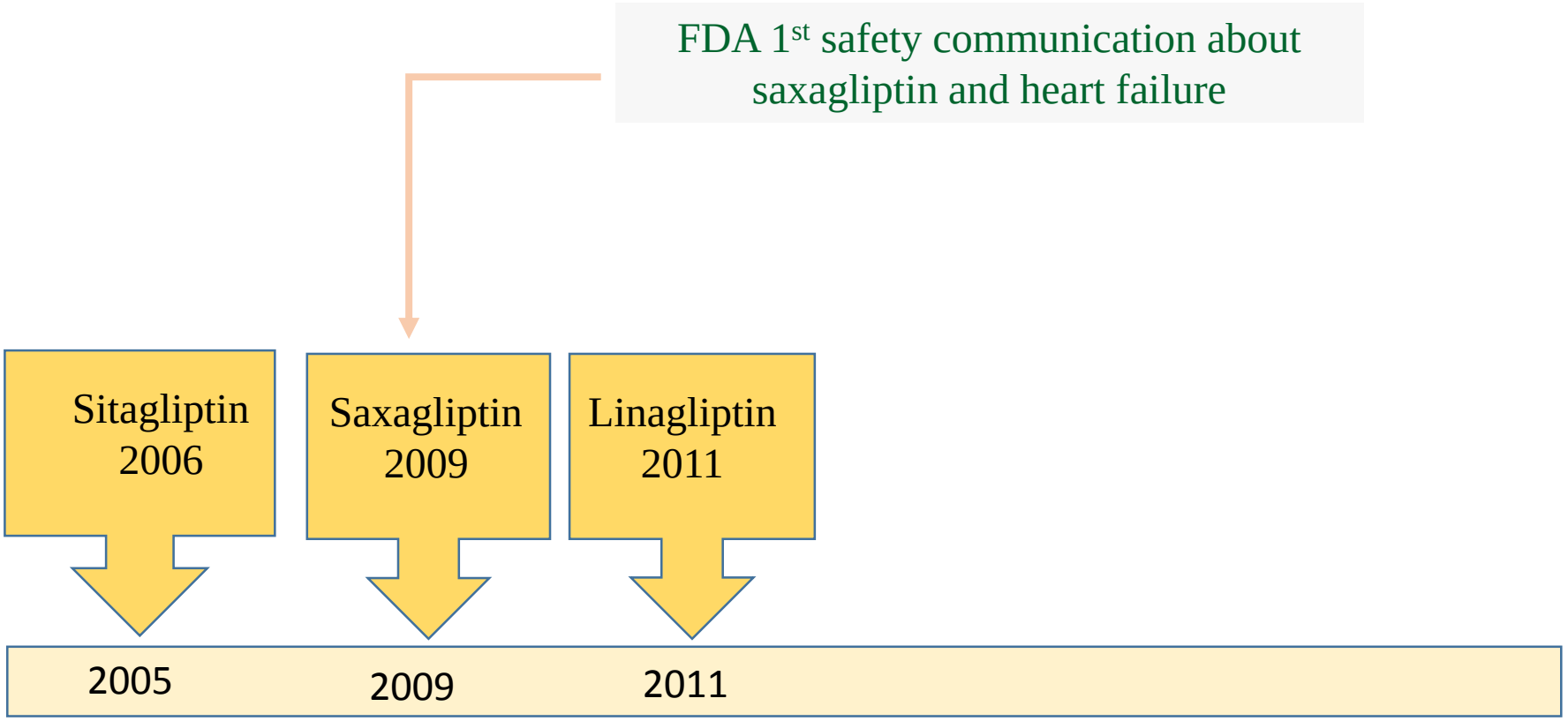
DPP 4 Inhibitors



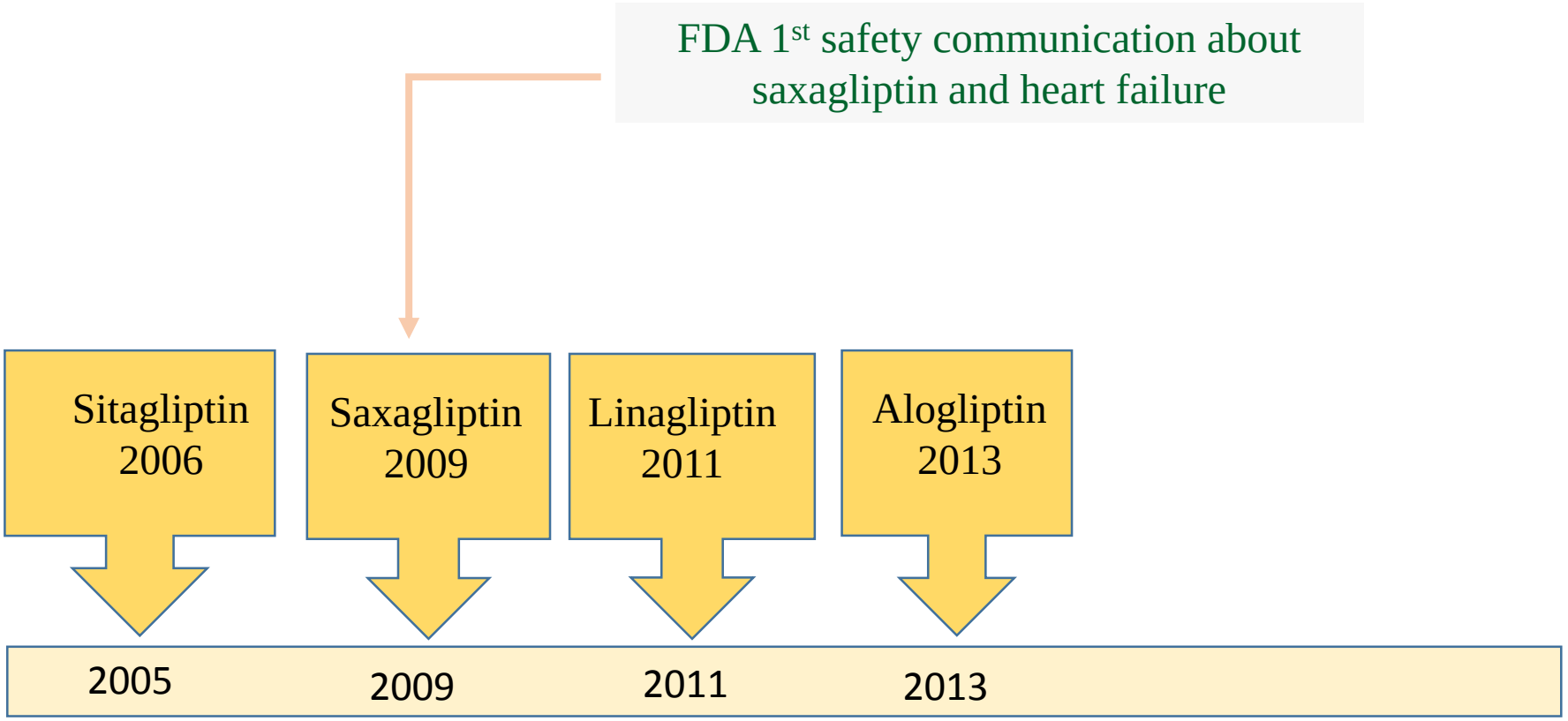
DPP 4 Inhibitors



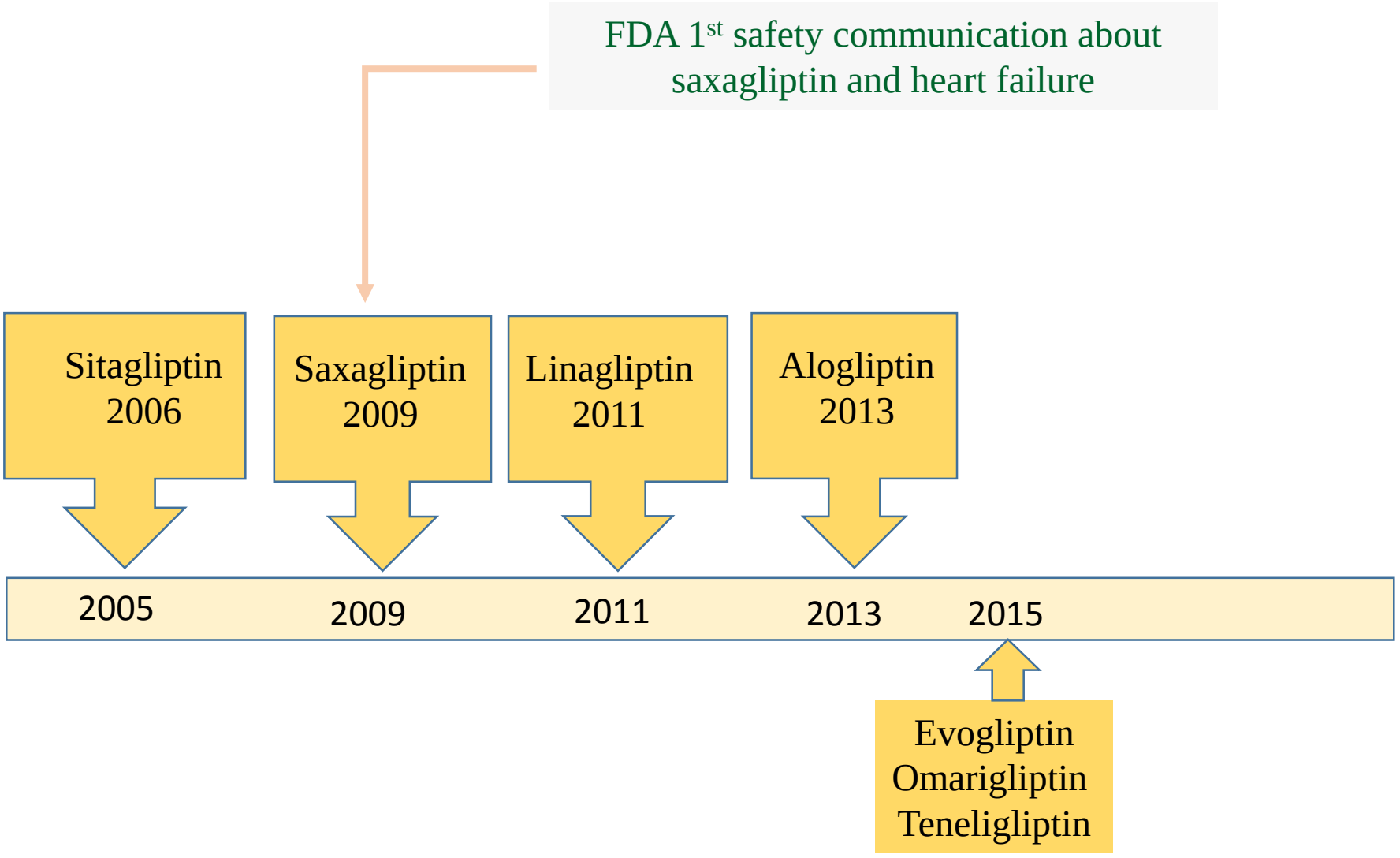
DPP 4 Inhibitors



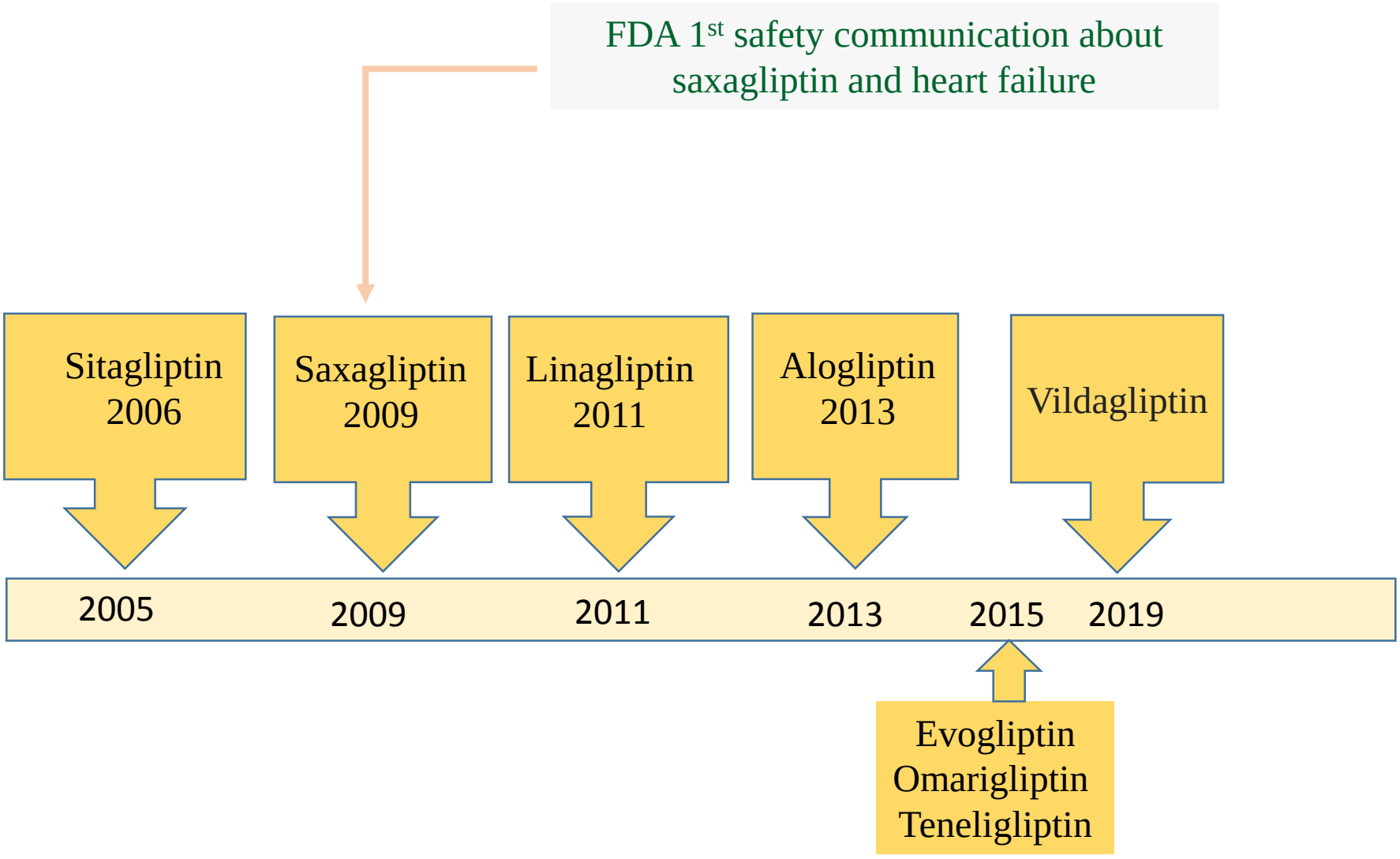
DPP 4 Inhibitors



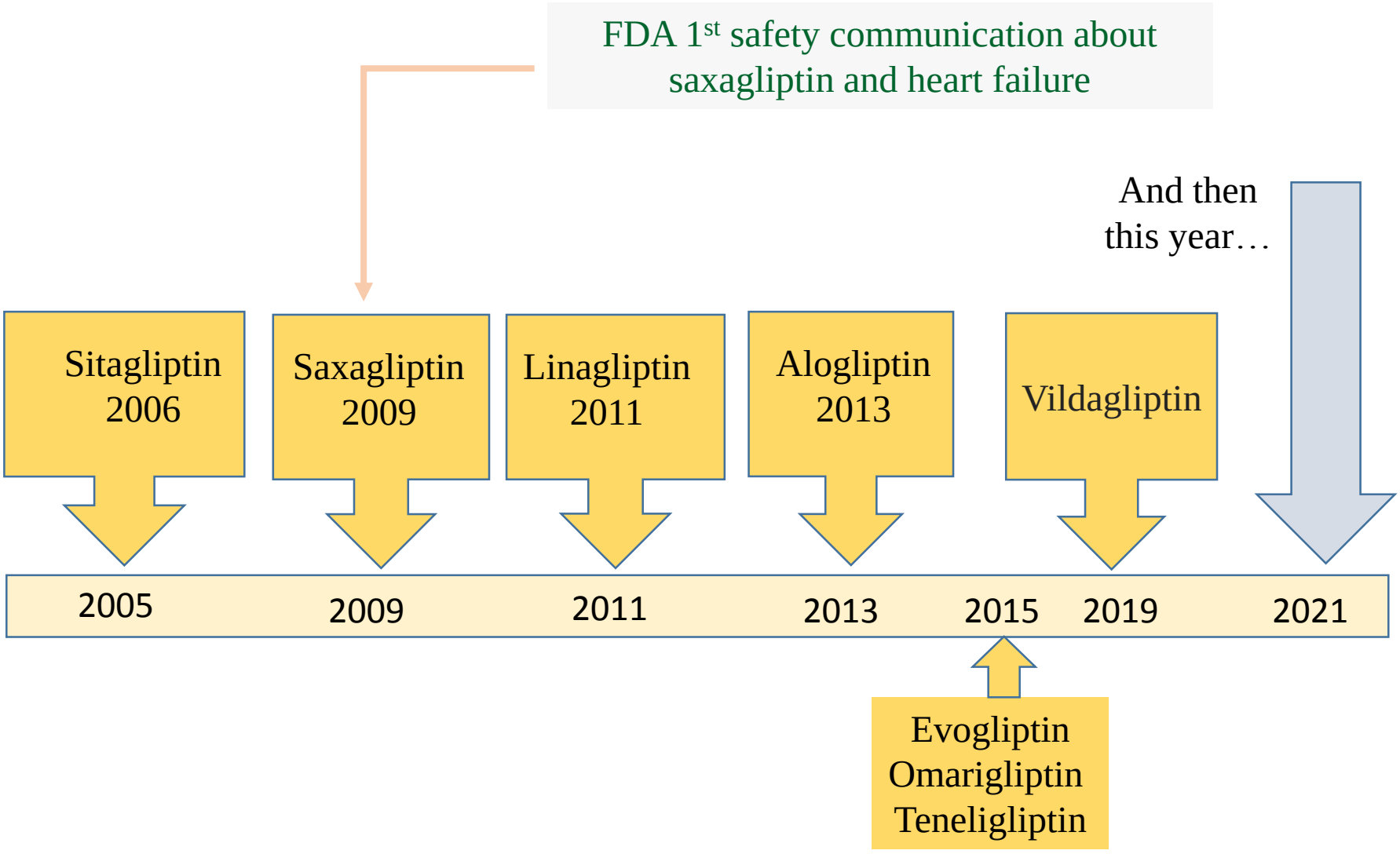
DPP 4 Inhibitors



DPP 4 Inhibitors



DPP 4 Inhibitors



FDA added warnings about the risk of hospitalization for heart failure to the labels of **Saxagliptin** and **Alogliptin** containing type 2 diabetes medicines.

Will the DPP-4 inhibitors replace GLP-1 mimetics?

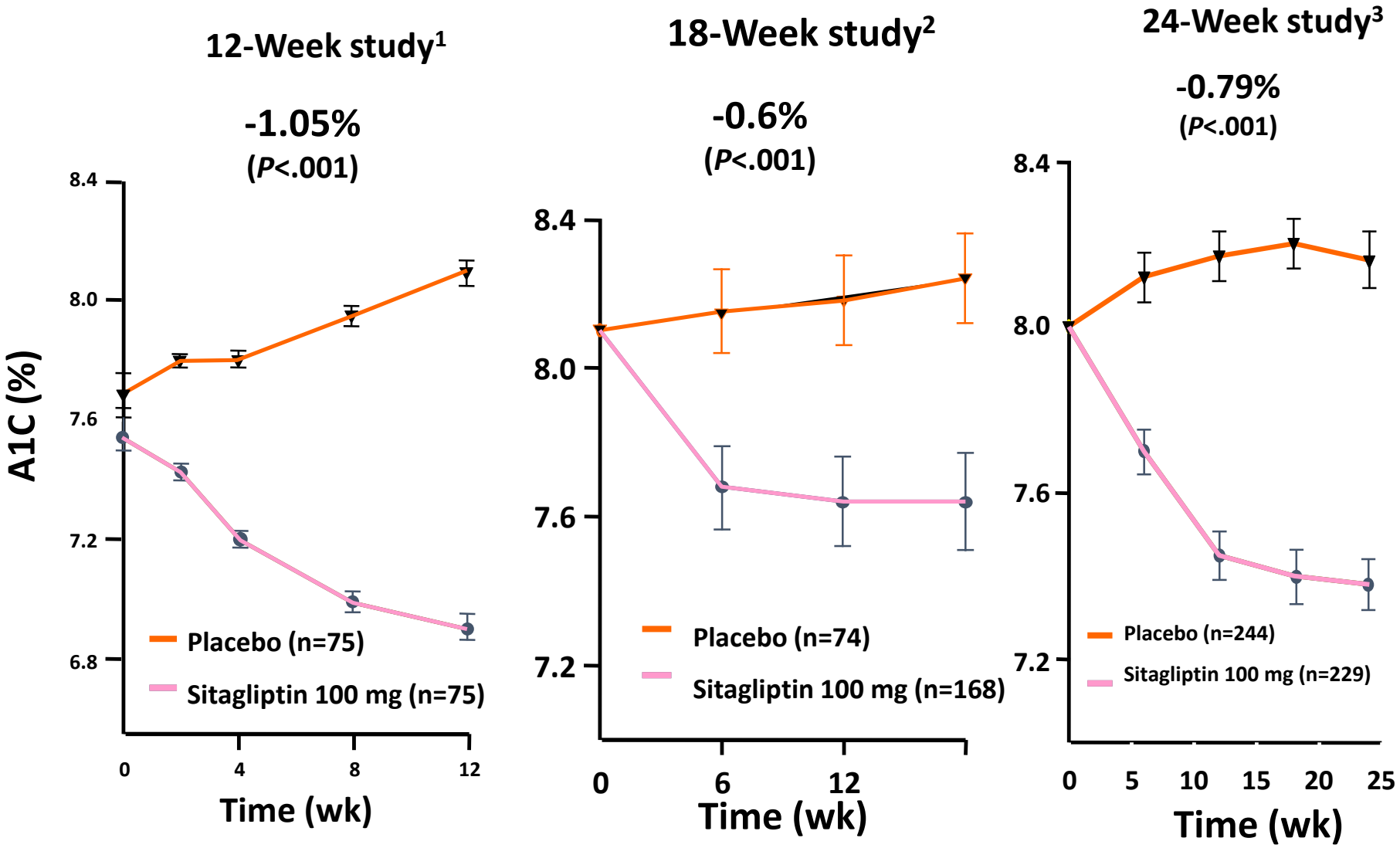
DPP-4 inhibitors have similar action to GLP-1 agonists but **do not result in weight loss**; therefore, for patients in whom weight loss is needed, GLP-1 agonists are indicated.

Lack of weight loss with DPP-4 inhibition is thought to be due to lesser increase in GLP-1 levels (3x) compared with that of GLP-1 mimetic (10x).

Sitagliptin: Once-daily Dosing Administration

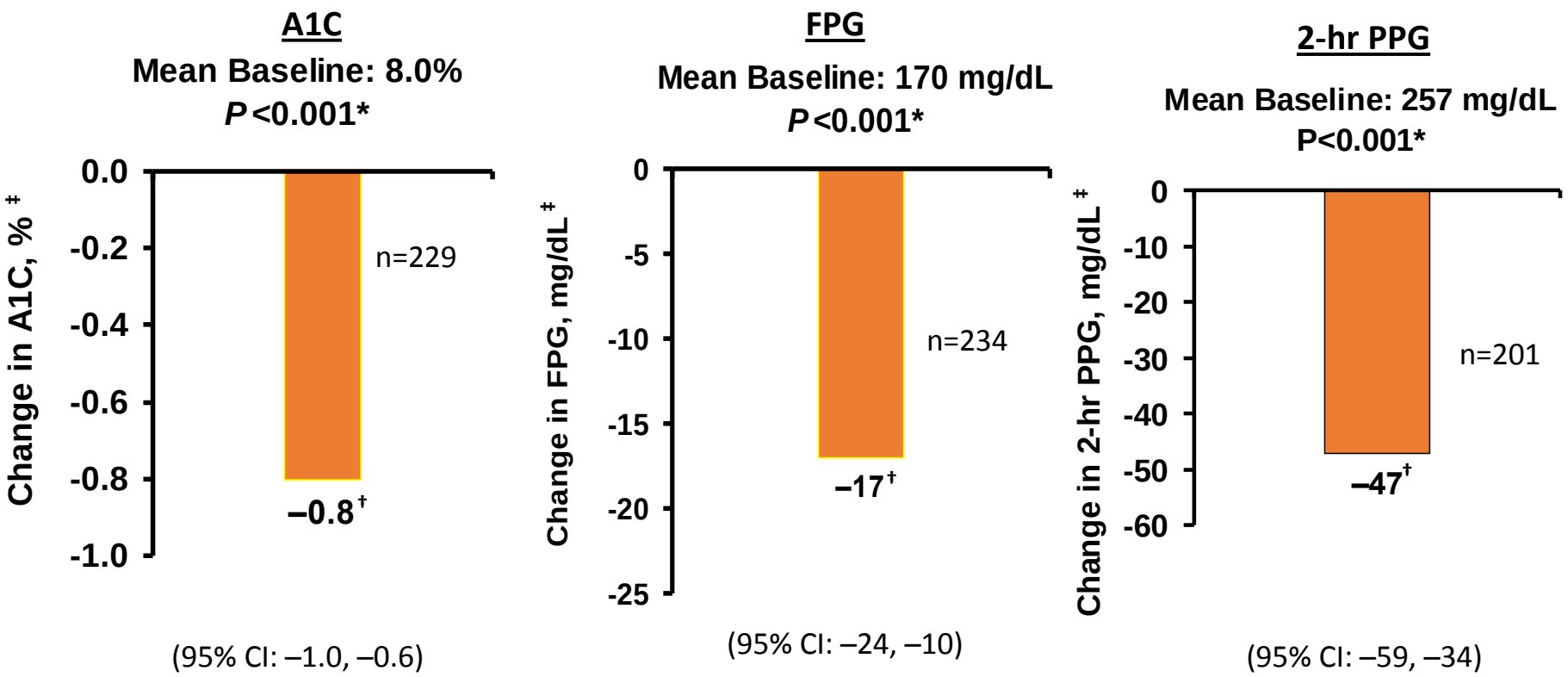
The recommended dose of Sitagliptin is 100 mg once daily as monotherapy or as combination therapy with metformin or others drugs.

Sitagliptin Consistently and Significantly Lowers A1C With Once-Daily Dosing in Monotherapy



Diabetes Care. 2006;29(12):2632-7. 2- Diabetes Res Clin Pract. 2008 ;79(2):291-8 . 3. Diabetologia. 2006 ;49(11):2564-71.

A1C, FPG, and 2-hour PPG placebo-adjusted results in a 24-week study of sitagliptin



Diabetes Care. 2006;29(12):2632-7. 2- Diabetes Res Clin Pract. 2008 ;79(2):291-8 . 3. Diabetologia. 2006 ;49(11):2564-71.

Although DPP-4 inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes, they can be used as monotherapy or add on therapy in patients with type 2 diabetes who are intolerant of, have contraindications to, or who are inadequately controlled on metformin or other glucose-lowering agents.

In particular, linagliptin might be a good choice as initial therapy in a patient with chronic kidney disease at risk for hypoglycemia.

Linagliptin Efficacy

Linagliptin achieves HbA1c decrease of up to 1.2% in poorly controlled patients.

Linagliptin is the only DPP-4 inhibitor which is primarily excreted by gut.

Linagliptin is the first only DPP-4 inhibitor that does not require dose adjustment.

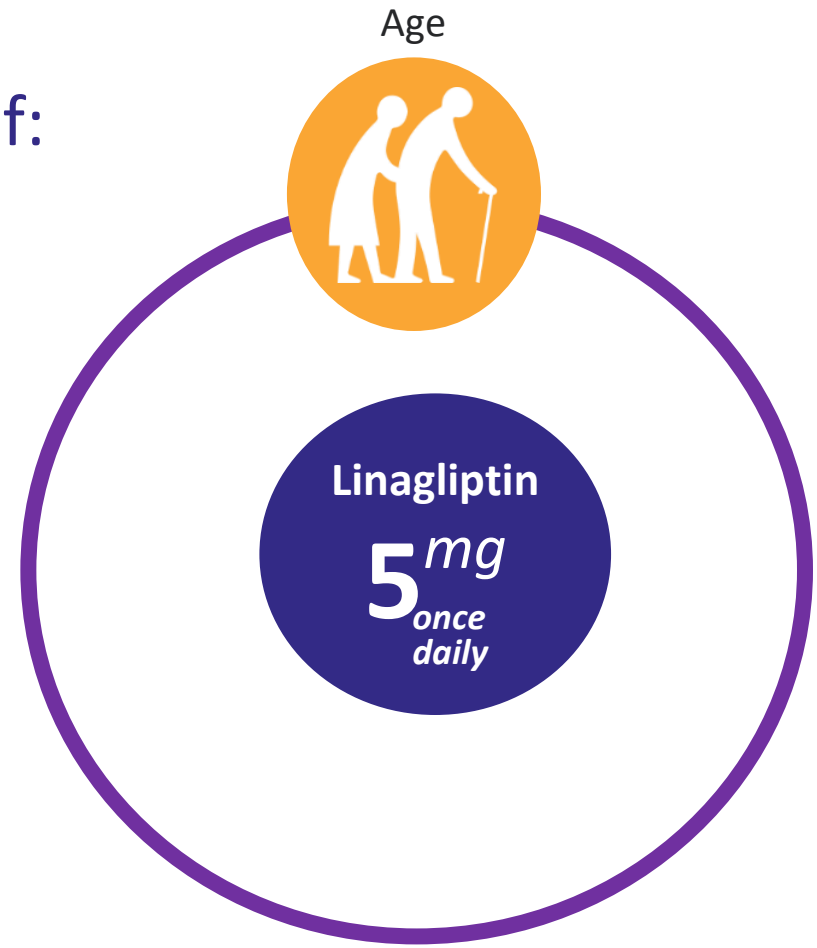
Linagliptin Has Broad Therapeutic Indication

Independent of:

Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication

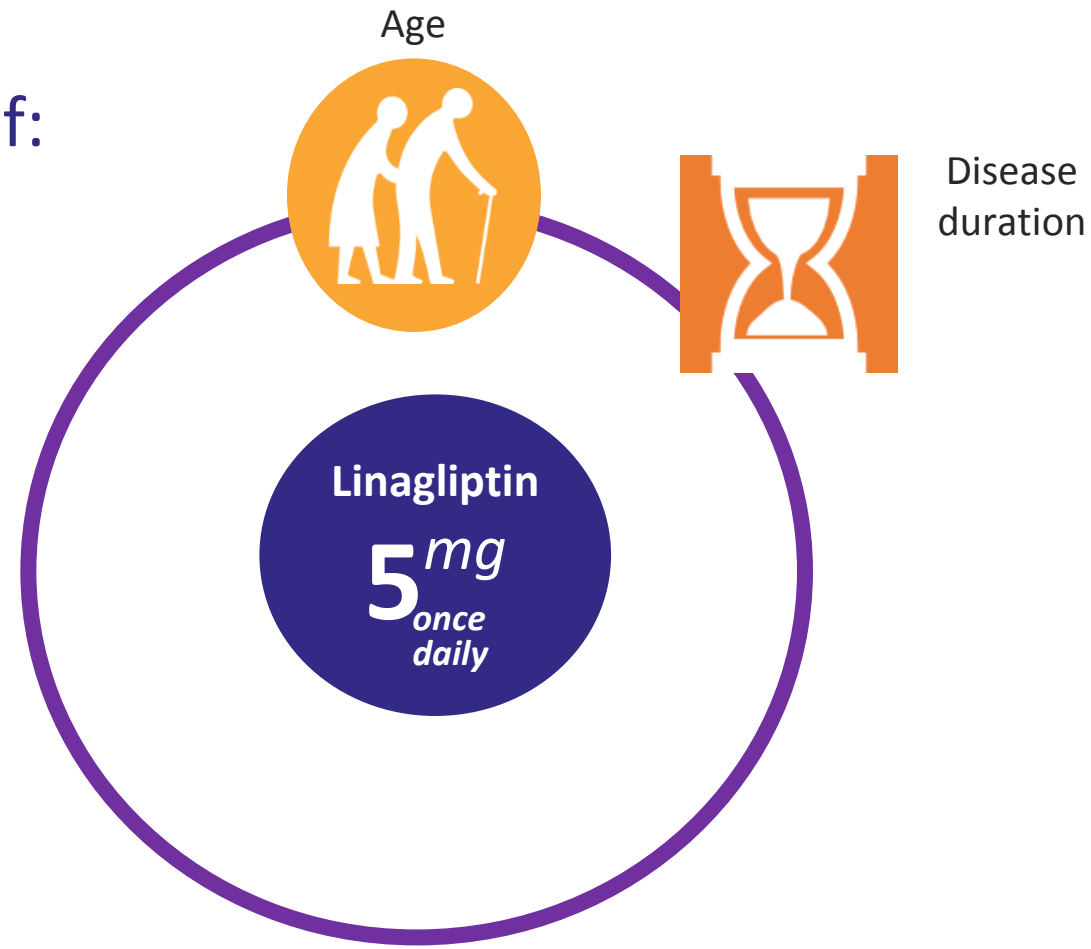
Independent of:



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication

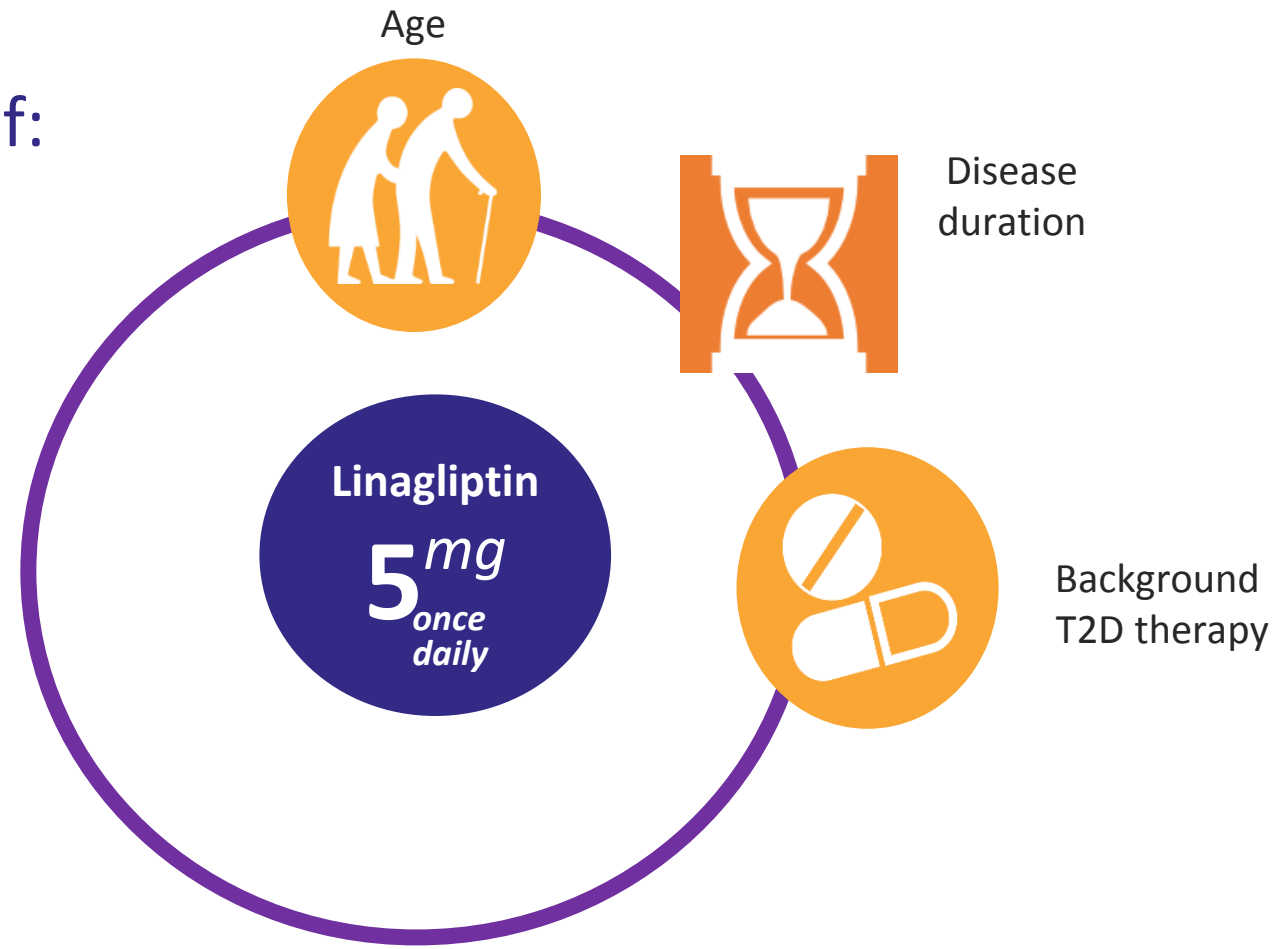
Independent of:



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication

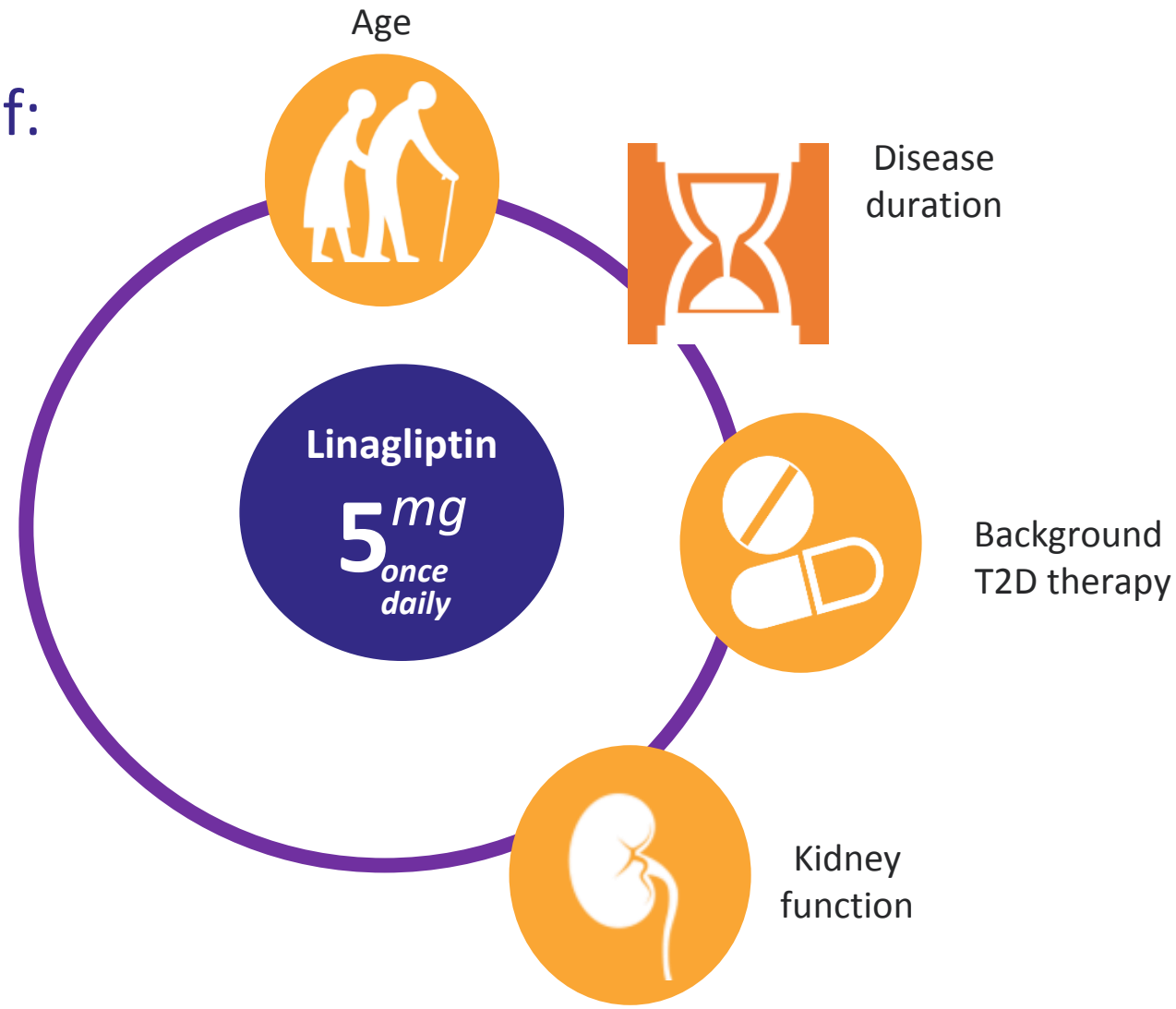
Independent of:



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication

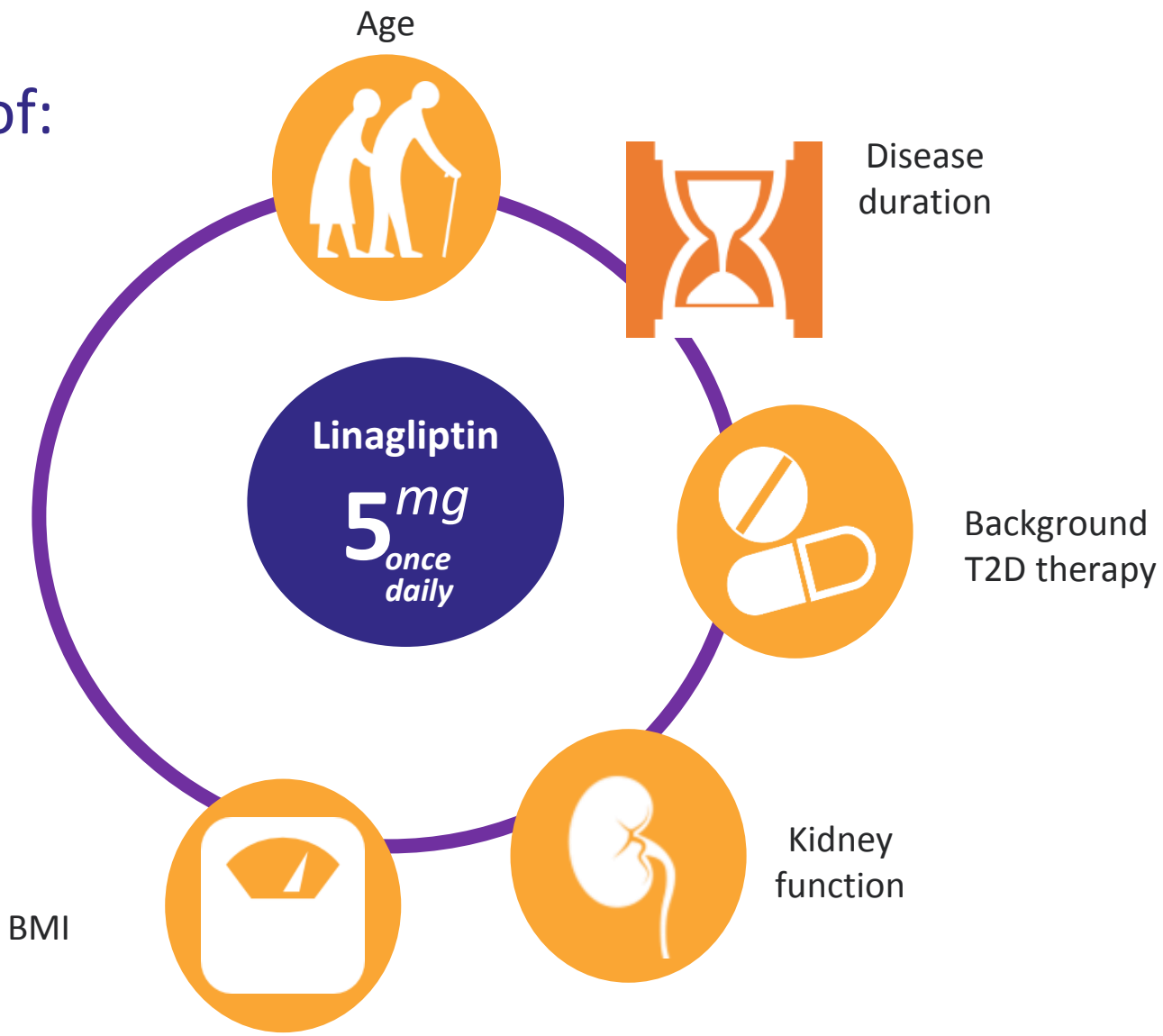
Independent of:



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

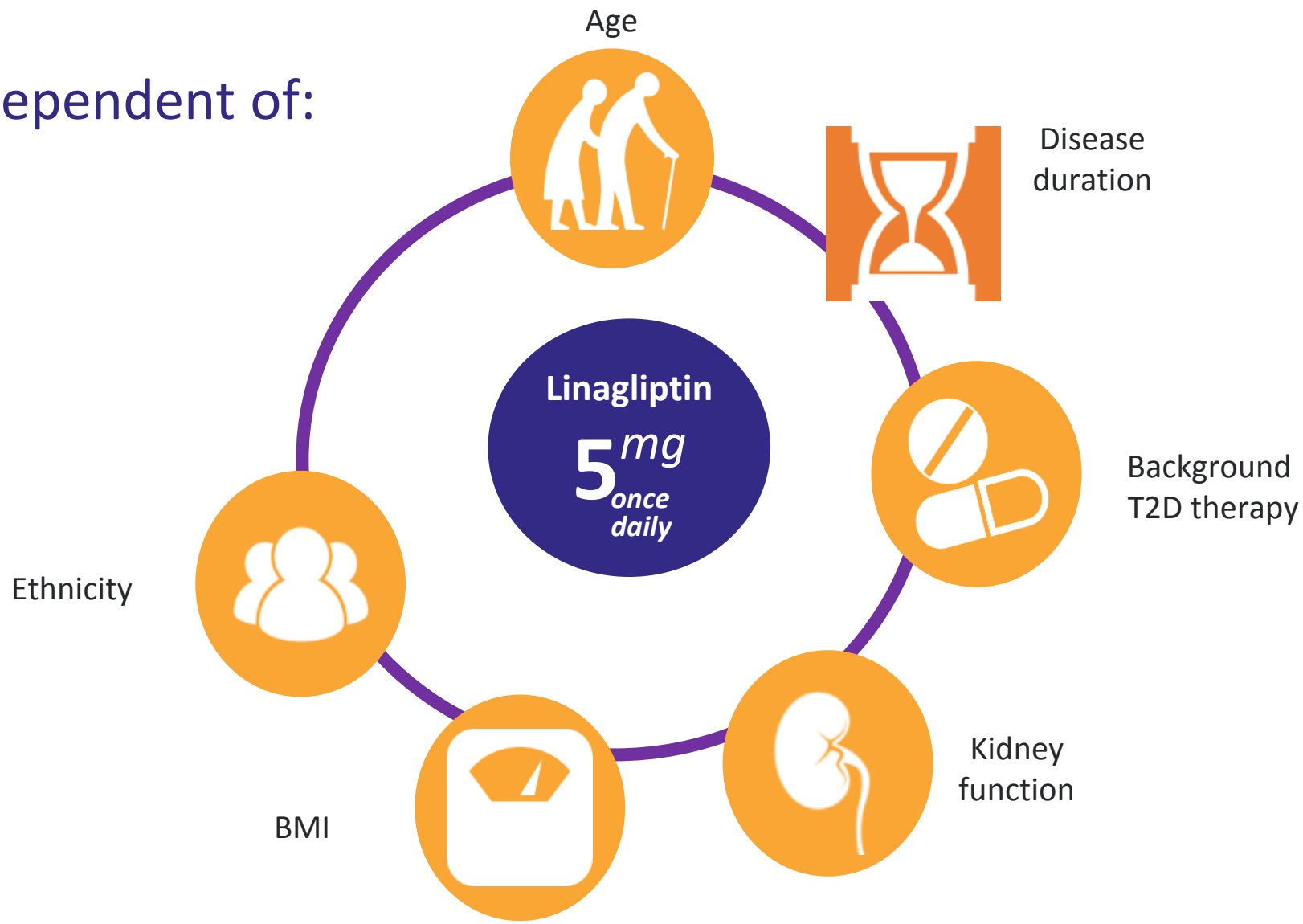
Linagliptin Has Broad Therapeutic Indication

Independent of:



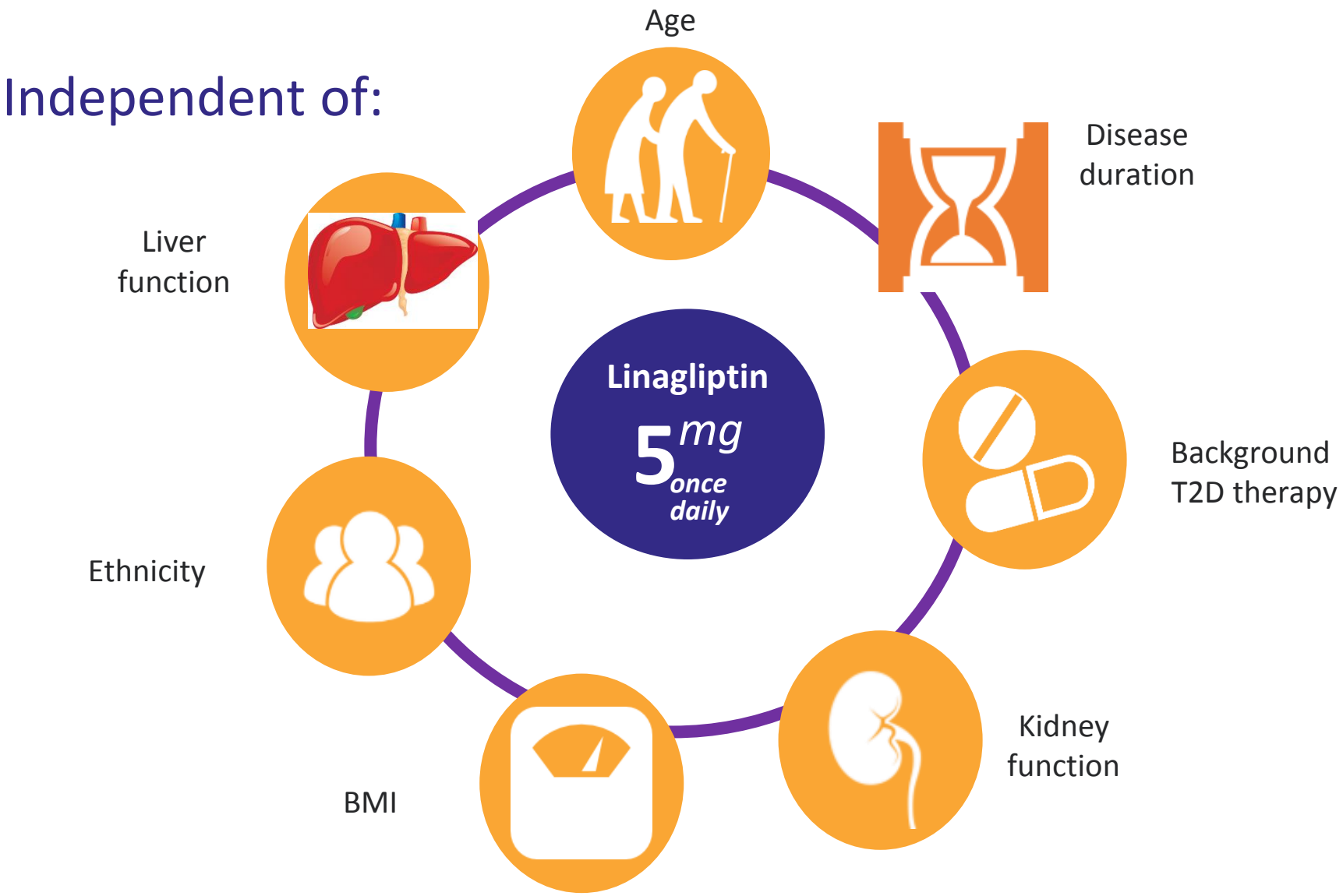
Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin Has Broad Therapeutic Indication



Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

Linagliptin

No dose adjustment is necessary in patients with renal or hepatic impairment.

Linagliptin-metformin is available in a single tablet

Empagliflozin-linagliptin is available as a combination pill (10 mg/5 mg and 25 mg/5 mg).

There are inadequate data to support the use of DPP-4 inhibitors in combination with **prandial insulin**.

Combination therapy with GLP-1 receptor agonists and DPP-4 inhibitors does not provide additive glucose lowering effects, and thus, the combination should be avoided.

Because they do not cause hypoglycaemia, they do not require dose titration and can be taken at **any time of day**, independently of meal times.

They are also generally **free of drug–drug interactions** and can mostly be used with other medications without the need for dose adjustment of either agent.

Cardiovascular effects

DPP-4 inhibitors have generally **neither reduced nor increased** cardiovascular events (or the development or progression of kidney disease).

Sitagliptin Cardiovascular Outcomes Study (TECOS)

Main inclusion criteria

1. Patients aged ≥ 50 years with T2D
2. HbA_{1c} 6.5–8.0% receiving stable oral glucose-lowering therapy and/or insulin*
3. Pre-existing vascular disease

+ Usual care for T2D

Sitagliptin 100 mg daily vs Placebo

N = 14,671; median follow-up 3.0 years

Primary endpoint: time to first occurrence of:

- CV-related death
- Unstable angina requiring hospitalisation
- Non-fatal stroke
- Non-fatal MI

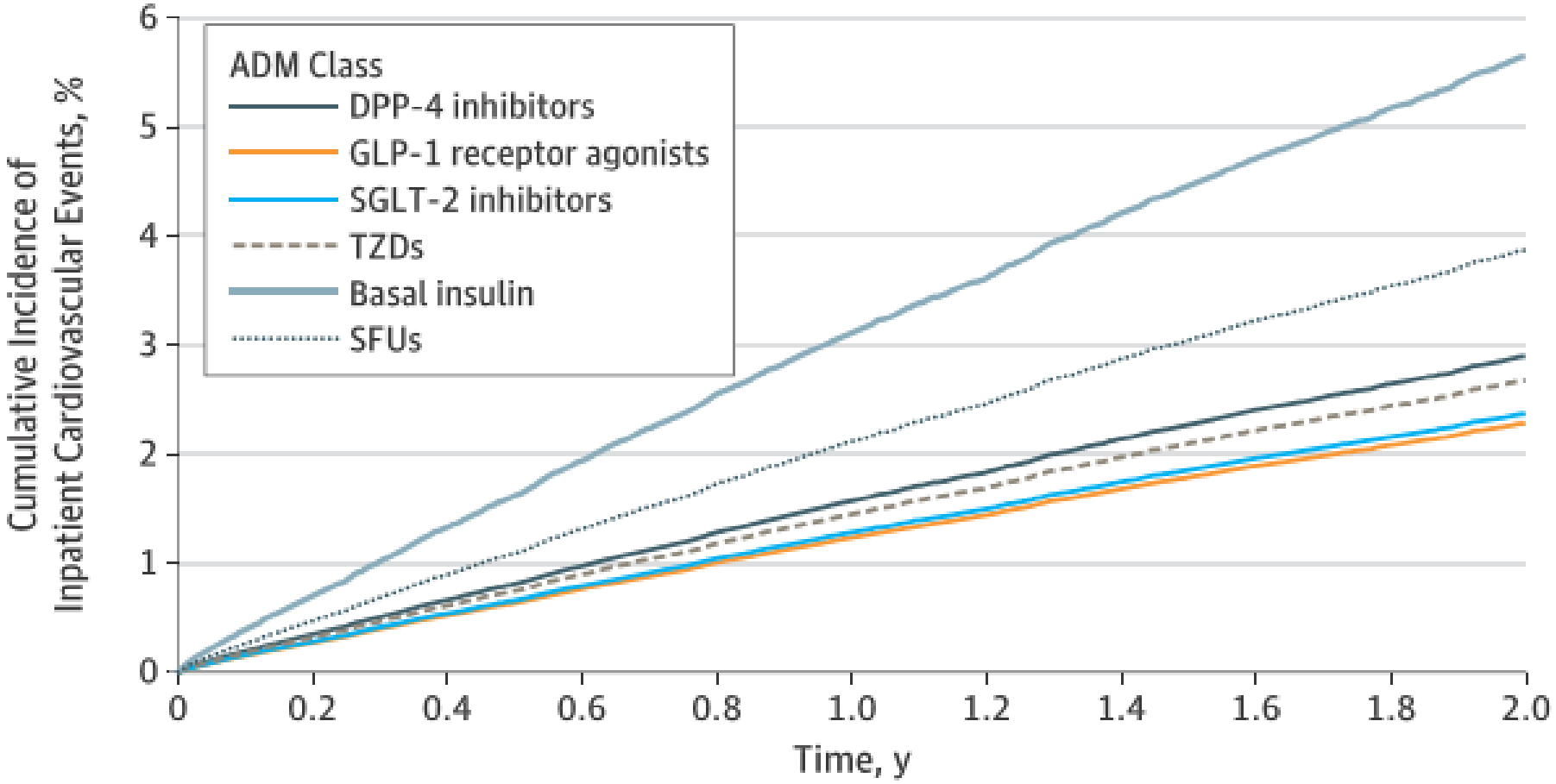
N Engl J Med. 2015.16;373(3):232-42

Conclusion:

Among patients with type 2 diabetes and established cardiovascular disease, adding **sitagliptin** to usual care **did not** appear to **increase** the risk of major adverse cardiovascular events, hospitalization for heart failure, or other adverse events.

N Engl J Med. 2015. 16;373(3):232-42

Association of second-line antidiabetic medications with cardiovascular events among insured adults with type 2 diabetes



JAMA Network Open. 2018;1(8):e186125

Side effects:

The incidence of side effects and hypoglycemia are **very low.**

In clinical trials, the most common reported side effects of DPP4 inhibitors include **nasopharyngitis**, **upper respiratory tract infection**, **urinary tract infection** and **headache.**

Adverse Effects

Musculoskeletal

Some DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin) have been associated with **severe joint pain**. Other reported musculoskeletal side effects include myalgias, muscle weakness, and muscle spasms.

Symptoms have been reported from two days to five months after initiating DPP-4 inhibitors.

Adverse Effects

Skin

In postmarketing reports, sitagliptin, saxagliptin, linagliptin, and alogliptin have been associated with **hypersensitivity reactions**, including anaphylaxis, angioedema, and blistering skin conditions, including Stevens-Johnson syndrome.

DPP-4 inhibitors are contraindicated in patients with a history of a serious hypersensitivity reaction after previous exposure.

Adverse Effects

Pancreas

Acute pancreatitis has been reported in association with DPP-4 inhibitors. At the current time, there are insufficient data to know if there is a causal relationship.

If pancreatitis is confirmed, a DPP-4 inhibitor should not be restarted.

In addition, DPP-4 inhibitors should not be initiated in a patient with a history of pancreatitis.

Incretin based drugs and risk of cholangiocarcinoma among patients with type 2 diabetes: population based cohort study.

Compared with use of other second or third line antidiabetic drugs, use of DPP-4 inhibitors, and possibly GLP-1 receptor agonists, might be associated with an increased risk of **cholangiocarcinoma** in adults with type 2 diabetes.

BMJ. 2018 Dec 5;363:k4880

Association of Diabetes Mellitus and Cholangiocarcinoma: Update of Evidence and the Effects of Antidiabetic Medication

The association between incretin-based therapy and the risk of CCA needs further clarification, as metformin is being studied in an ongoing clinical trial.

Canadian Journal of Diabetes 17 September 2020

Mortality

DPP-4 inhibitors do not appear to have any effect on overall mortality.

Toxicity

Clinical trials showed no adverse drug reactions using very high doses of saxagliptin, alogliptin, linagliptin.

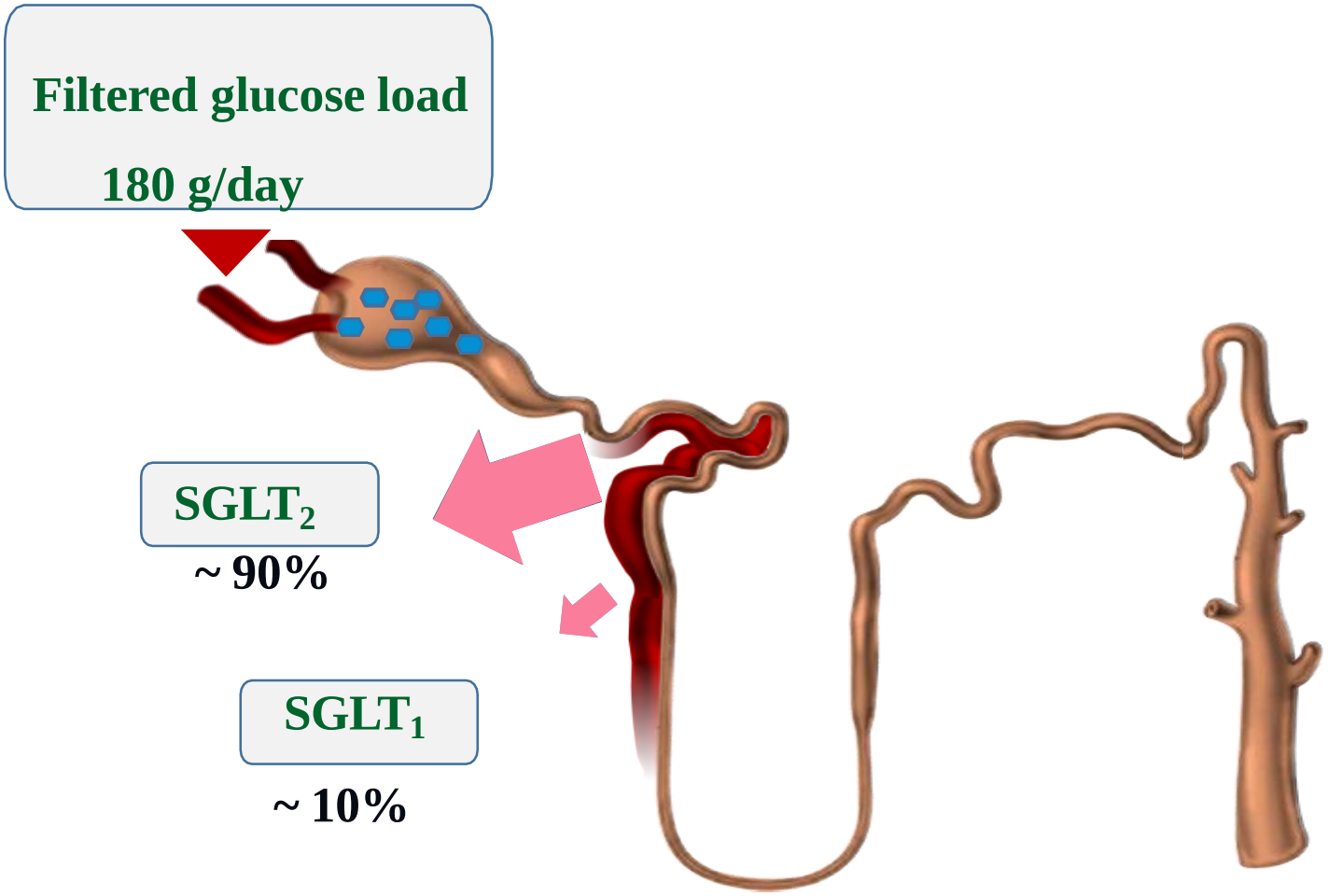
However, high doses of sitagliptin were associated with an 8.0-millisecond mean increase in QTc in controlled clinical trials as labeled by the FDA.

In case of overdose, hemodialysis removes approximately 13% of sitagliptin and approximately 23% of saxagliptin but did not affect alogliptin or linagliptin.

Treasure Island (FL): StatPearls Publishing; 2021 Jan-.

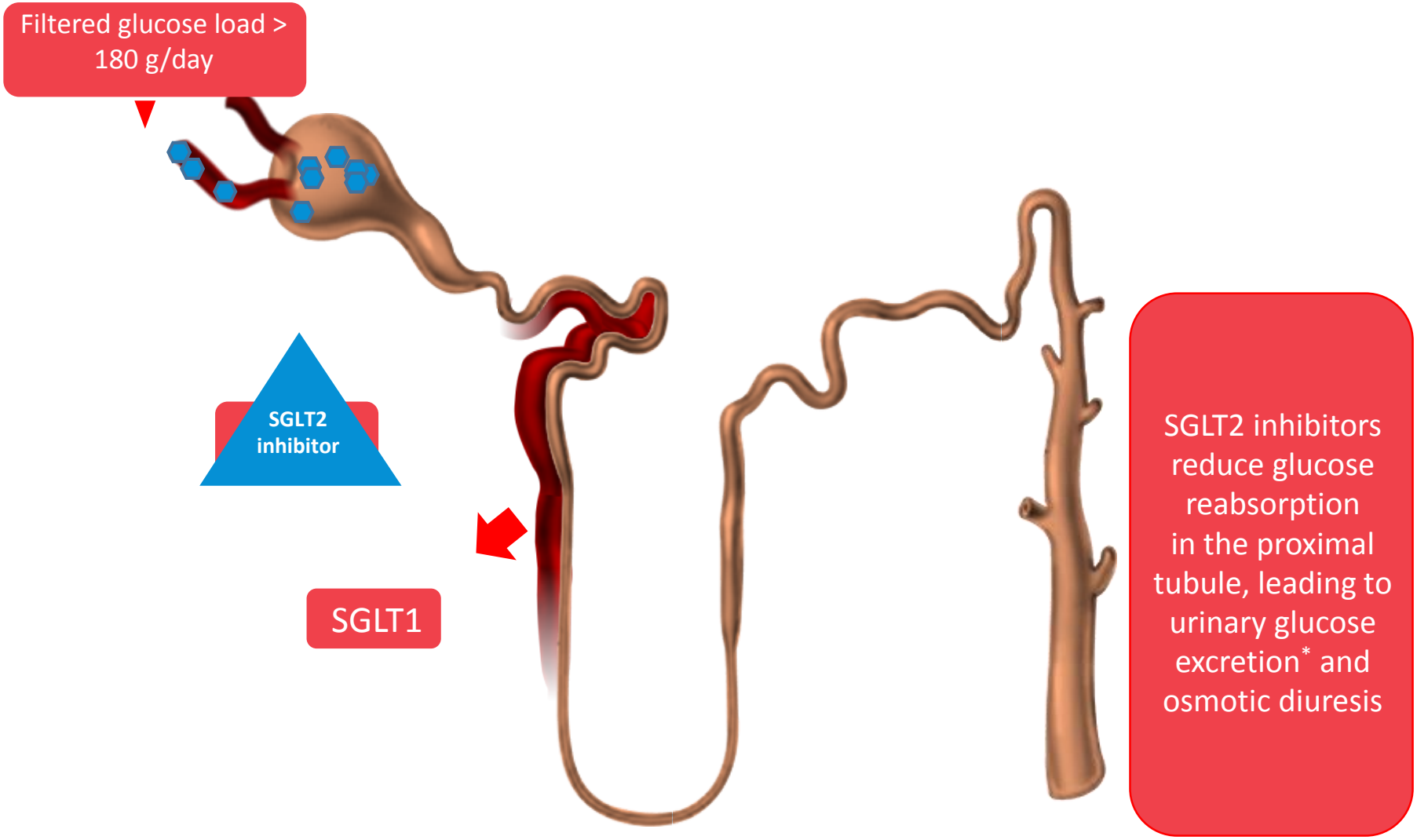
SGTI 2

Renal glucose re-absorption in healthy individuals



Gerich JE. Role of the kidney in normal glucose homeostasis and in the hyperglycaemia of diabetes mellitus: therapeutic implications. Diabetic Medicine. 2010; 27(2): 136-42.

Urinary glucose excretion via SGLT2 inhibition



. Bakris et al. Kidney Int 2009;75;1272–7.

Efficacy

Promotes glucose excretion in the kidney and not only **improve FPG** but reduce absolute **HbA1c** levels.

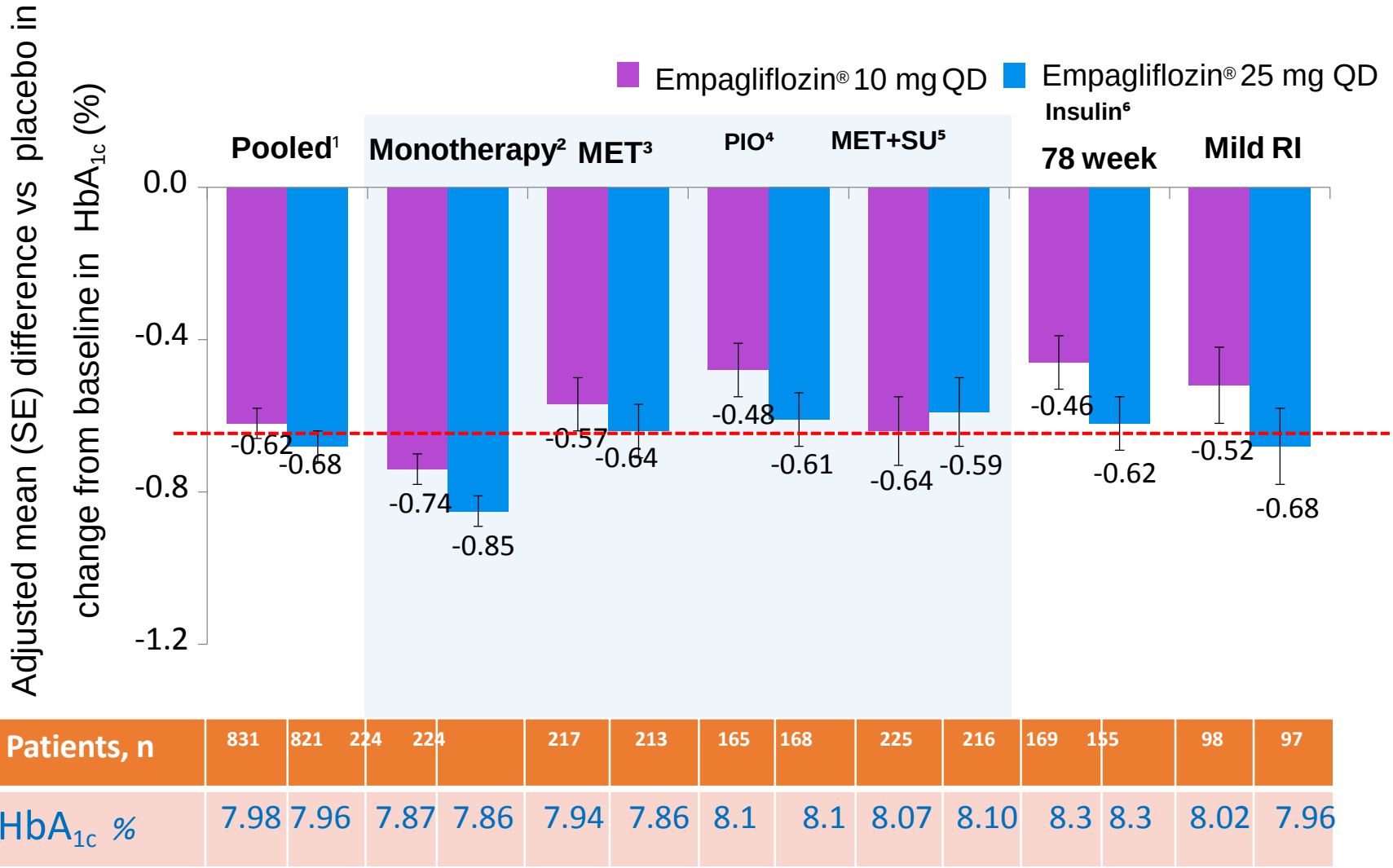
They also induce **blood pressure reductions** and **weight loss.**

To improve **cardiovascular** and **renal outcomes** along with all-cause mortality in diabetic patients.

Based on recent preclinical and clinical data, they could play an important role in the stabilization of cellular metabolic stress, glucose-mediated toxicity and inflammation in key organs such as the kidneys and the heart.

HbA1c Across Different Background Therapy Empagliflozin vs. Placebo

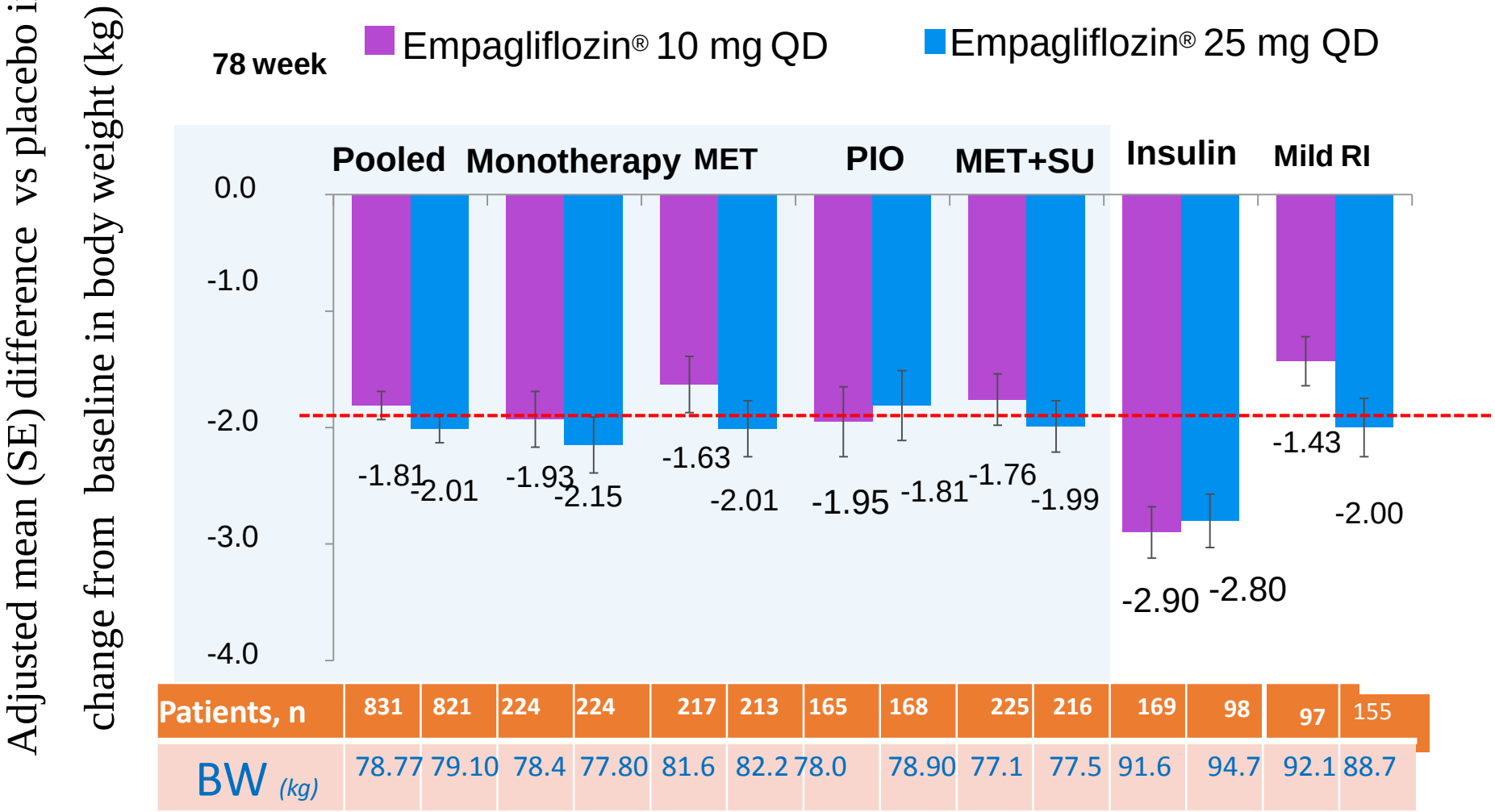
Phase III pooled efficacy analysis



Patients, n	831	821	224	224	217	213	165	168	225	216	169	155	98	97
HbA_{1c} %	7.98	7.96	7.87	7.86	7.94	7.86	8.1	8.1	8.07	8.10	8.3	8.3	8.02	7.96

1-Hach T, et al. *Diabetes*. 2013;62(suppl 1A);A21 (P69-LB); 2-Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208–219;

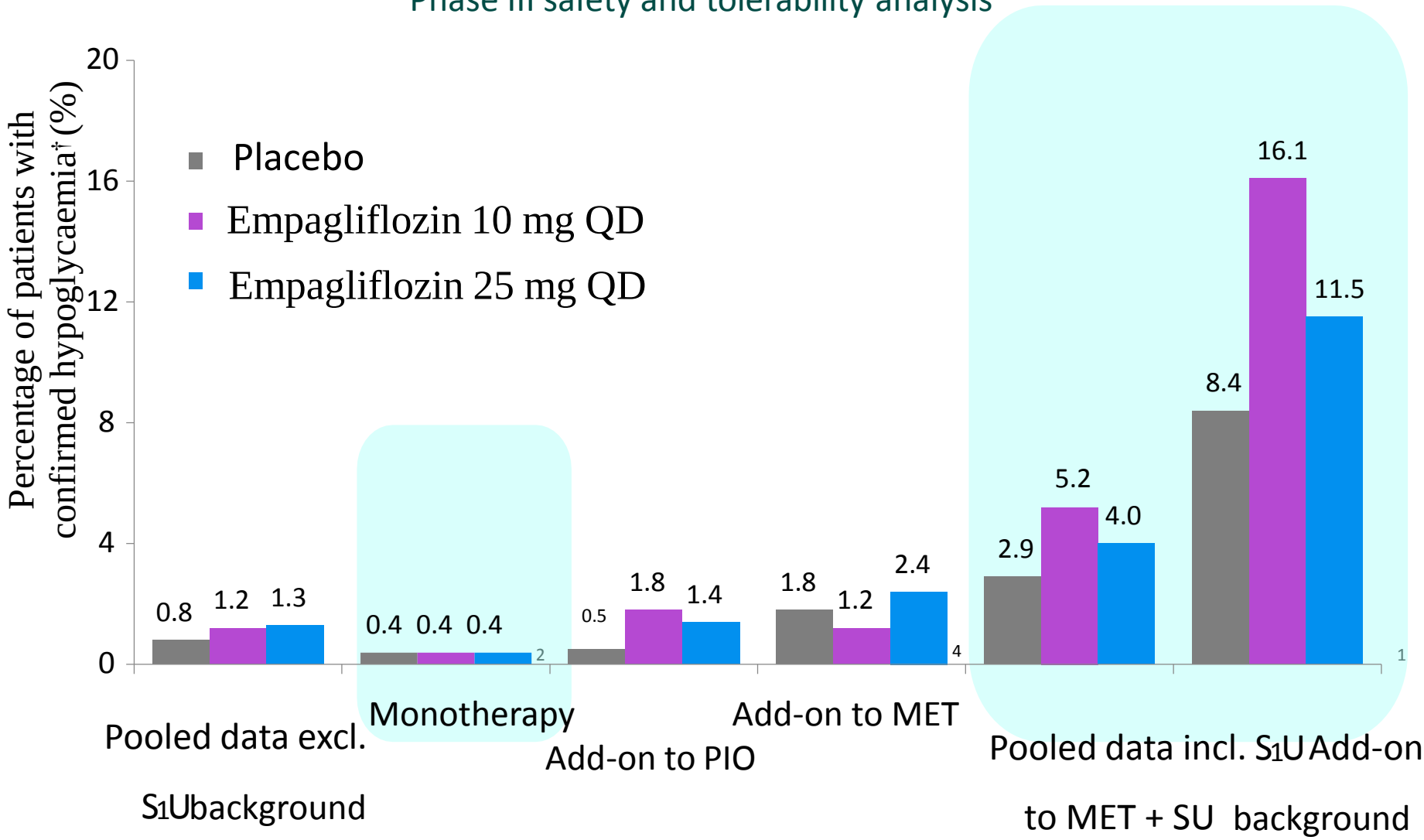
Body Weight Across Different Background Therapy Empagliflozinvs. Placebo



1-Hach T, et al. *Diabetes*. 2013;62(suppl 1A);A21 (P69-LB); 2-Roden M, et al. *Lancet Diabetes Endocrinol*. 2013;1(3):208–219;

Hypoglycemic Events

Phase III safety and tolerability analysis

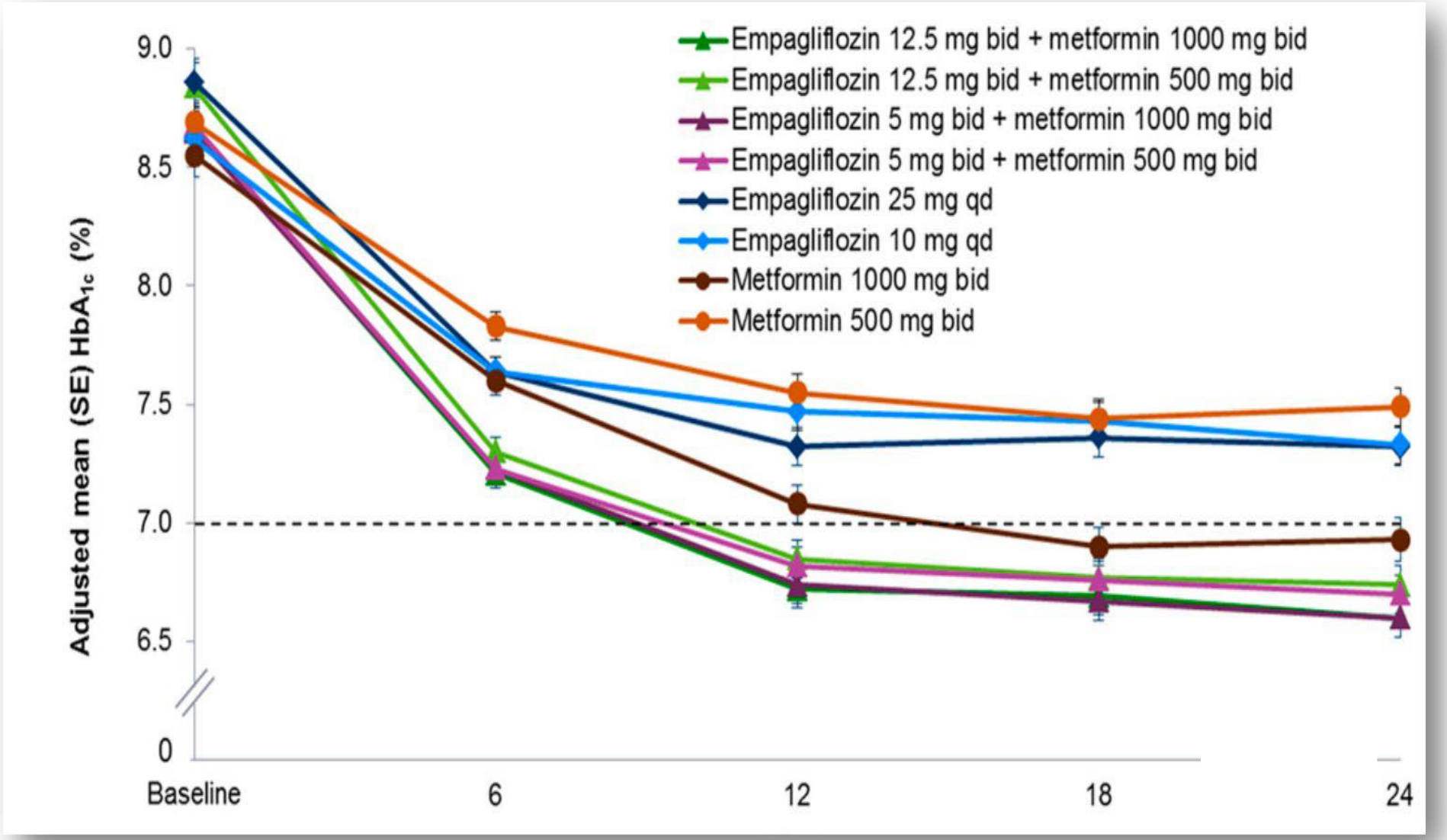


Roden M, et al. Lancet Diabetes Endocrinol. 2013;1(3):208–219

Initial combination therapy of

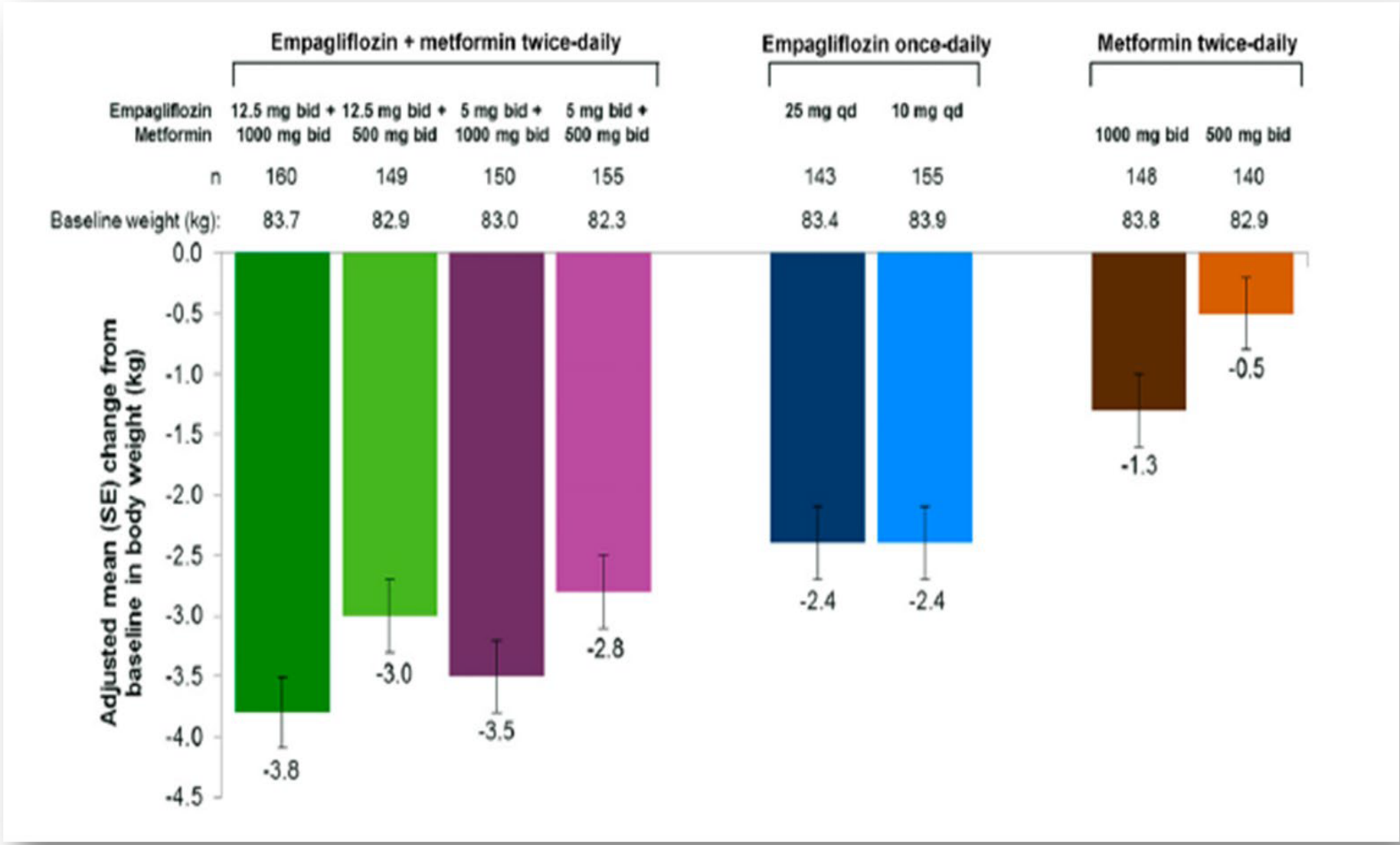
Empagliflozin and Metformin

Change from Baseline in HbA1c



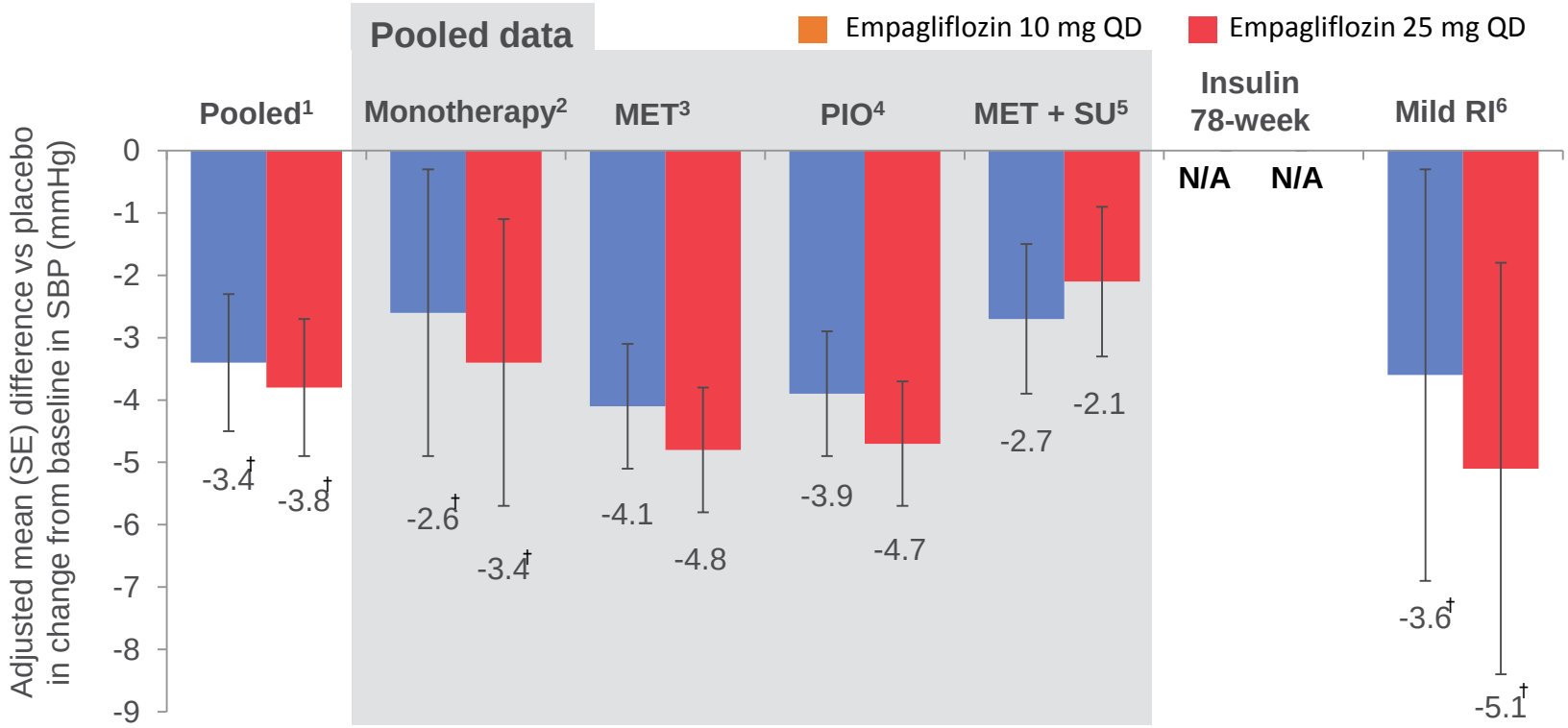
1-Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change from Baseline in Weight



1-Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change From Baseline In SBP



Patients, n	831	821	224	224	217	213	165	168	225	216	N/A	N/A	98	97
BL SBP (mmHg)	129.6	129.0	133.0	129.9	129.6	130.0	126.5	125.9	128.7	129.3	132.4	132.8	137.4	133.7

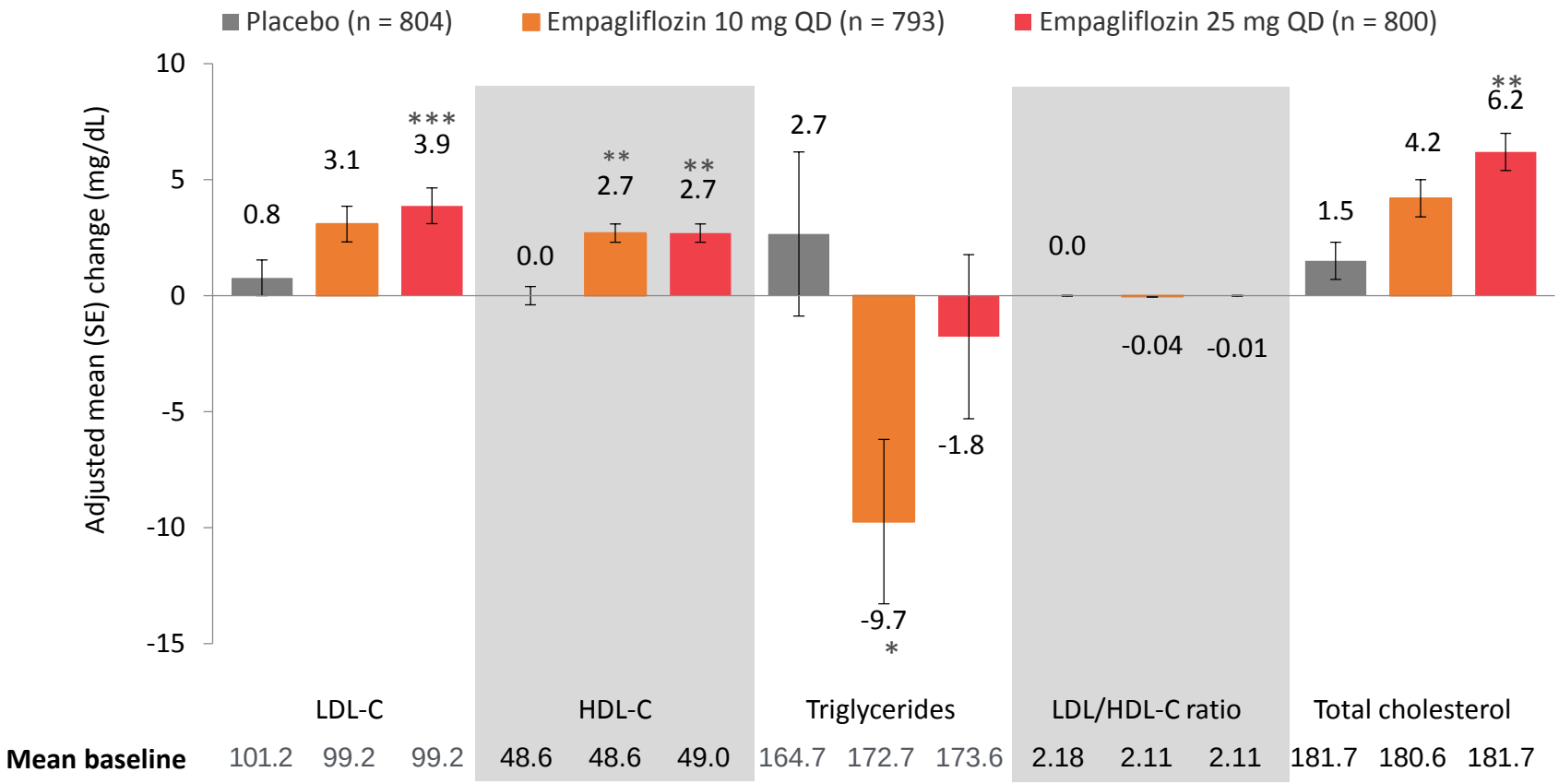
*All statistically significant. †Error bar represents 95% CI. N/A, published data not available.

1. Hach et al. Diabetes 2013;62(suppl 1A):A21(P69-LB). 2. Roden et al. Lancet Diabetes Endocrinol 2013;1:208–19.
3. Häring et al. Diabetes Care 2014;37:1650–9. 4. Kovacs et al. Diabetes Obes Met 2014;16:147–58.
5. Häring et al. Diabetes Care 2013;36:3396–3404. 6. Barnett et al. Lancet Diabetes Endocrinol 2014;2:369–84. .

Initial combinations of empagliflozin + metformin for 24 weeks significantly reduced HbA1c versus empagliflozin once daily and metformin twice daily, without increased hypoglycemia, reduced weight versus metformin twice daily, and were well tolerated.

Hadjadj S et al, Initial combination of empagliflozin and metformin in patients with type 2 diabetes. Diabetes Care. 2016 1;39(10):1718-28.

Change in lipids (mg/dL) from baseline at Week 24



*p < 0.05; **p < 0.001; ***p = 0.008 vs placebo

Hach et al. Diabetes 2013;62(Suppl 1A):A21 (P69-LB).

Convenience of a once-daily oral treatment

Recommended starting dose **Empagliflozin** 10 mg once daily Can be taken with/without food in the morning.

Dose may be increased to 25 mg once daily.

Can be used alone or in combination with other common therapies:

A lower dose of insulin or insulin secretagogues (eg, sulphonylureas) may be needed to reduce the risk of hypoglycaemia when empagliflozin is used in combination with these agents.

Jardiance FDA label 2018. Reference ID: 4367802

Type 2 Diabetes Treatment Efficacy

Change in HbA_{1c} (%)	Change in body weight (kg)

Type 2 Diabetes Treatment Efficacy

	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain

Type 2 Diabetes Treatment Efficacy

	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain
TZDs	Intermediate	Gain

Type 2 Diabetes Treatment Efficacy

	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain
TZDs	Intermediate	Gain
GLP-1RAs	High	Loss

Type 2 Diabetes Treatment Efficacy

	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain
TZDs	Intermediate	Gain
GLP-1RAs	High	Loss
DPP4 I	Intermediate	Neutral

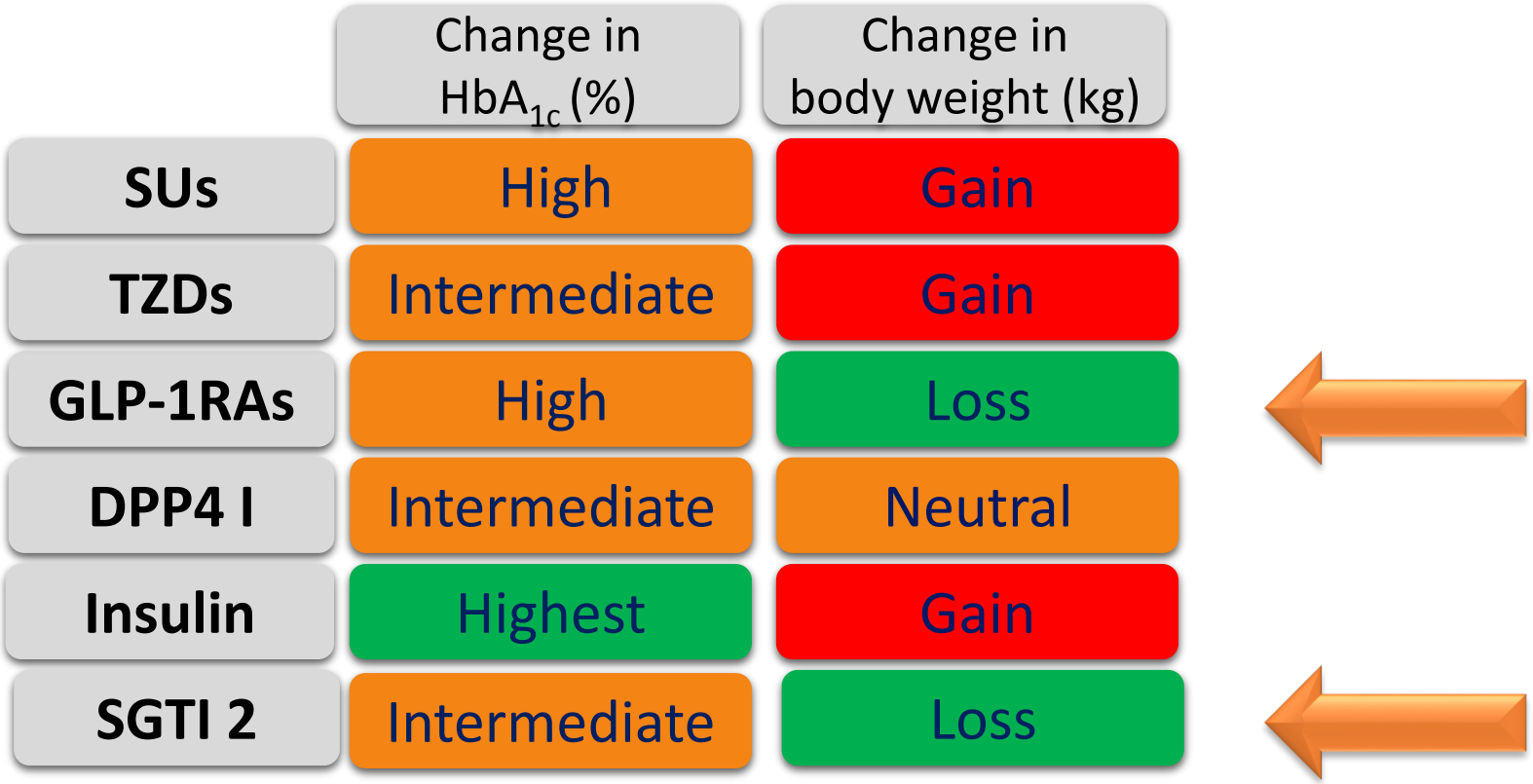
Type 2 Diabetes Treatment Efficacy

	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain
TZDs	Intermediate	Gain
GLP-1RAs	High	Loss
DPP4 I	Intermediate	Neutral
Insulin	Highest	Gain

Type 2 Diabetes Treatment Efficacy

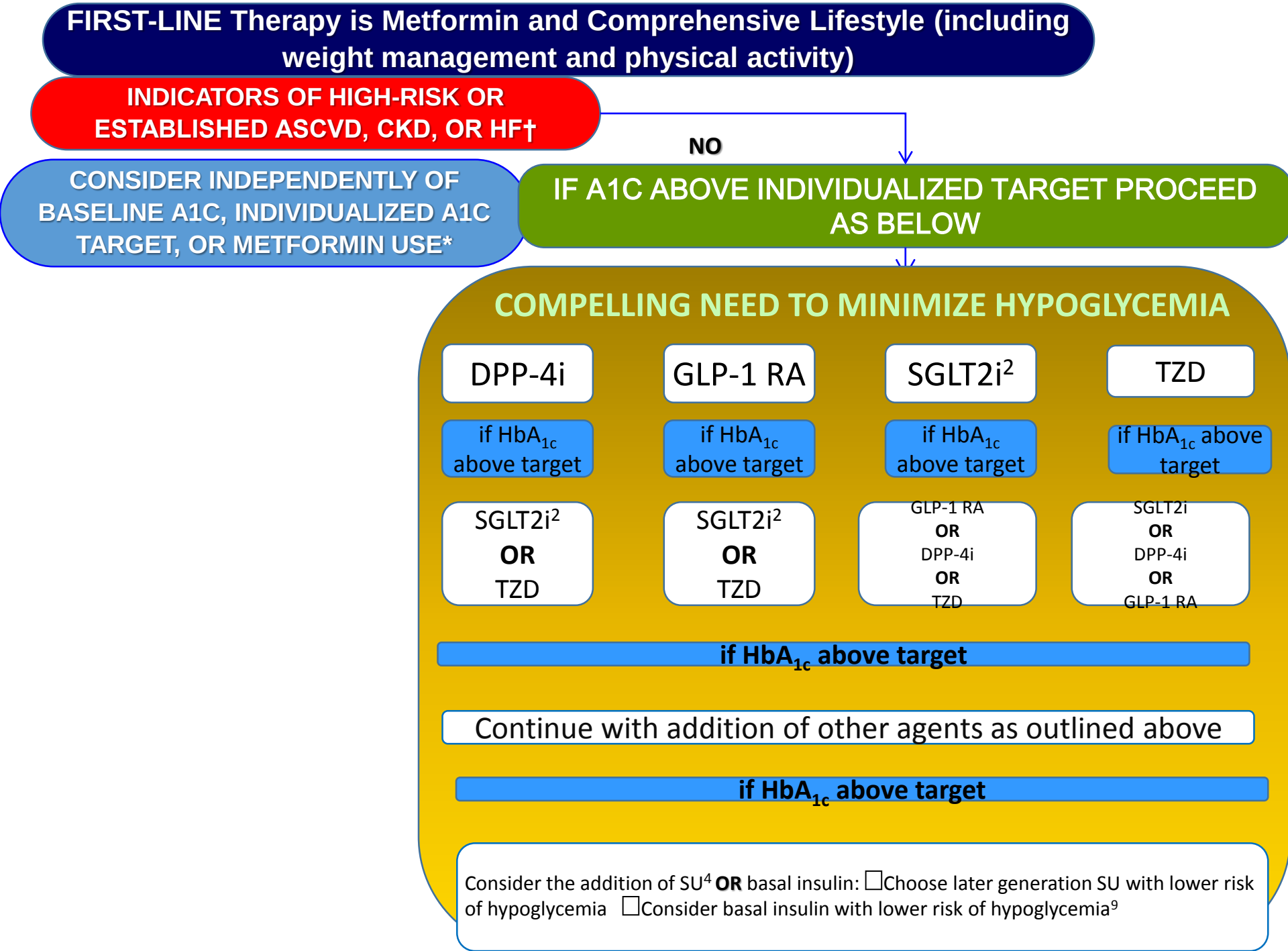
	Change in HbA_{1c} (%)	Change in body weight (kg)
SUs	High	Gain
TZDs	Intermediate	Gain
GLP-1RAs	High	Loss
DPP4 I	Intermediate	Neutral
Insulin	Highest	Gain

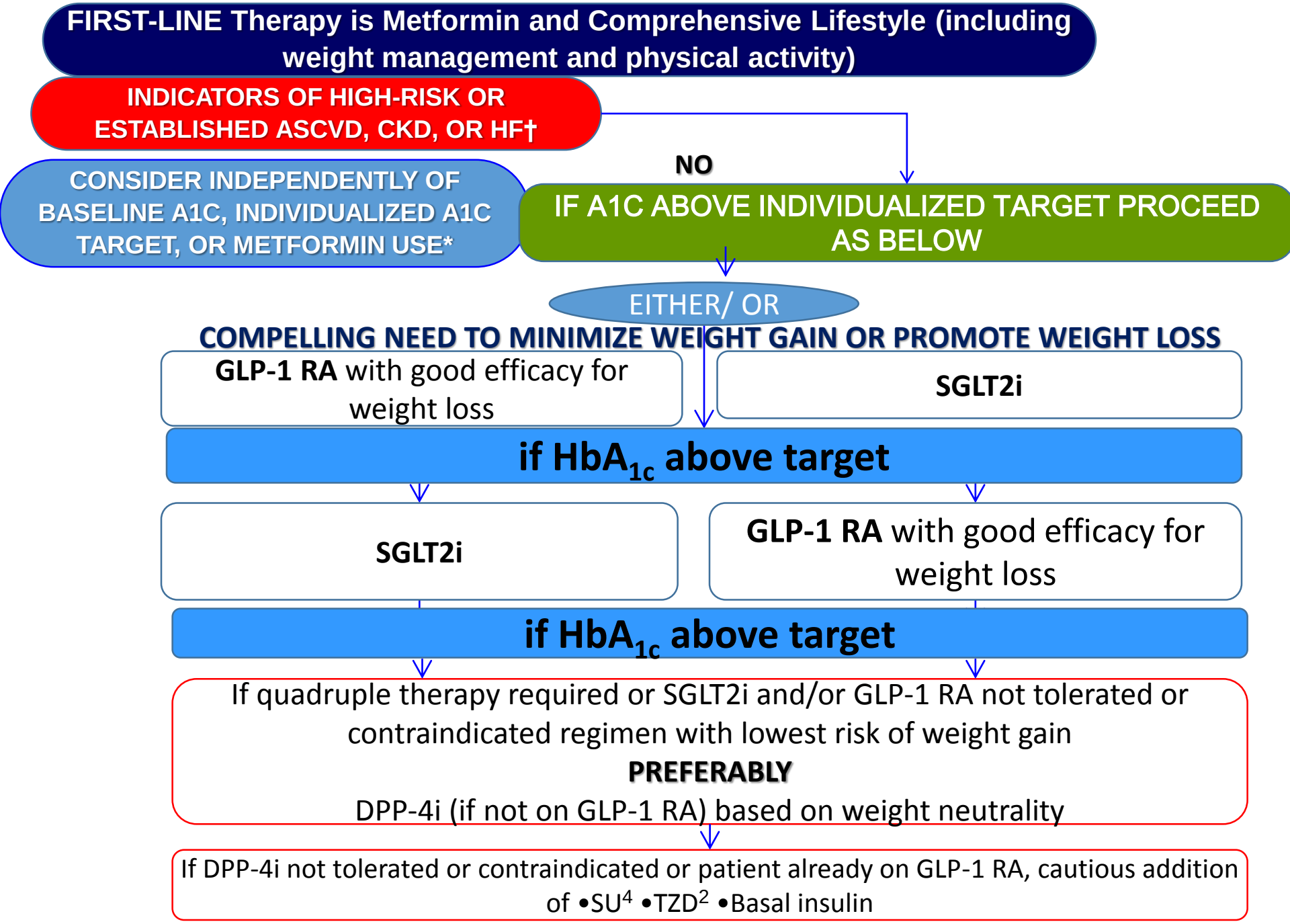
Type 2 Diabetes Treatment Efficacy



Weight loss is common with **GLP-1 receptor agonists** and **SGTI 2**

FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
NO
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
COMPELLING NEED TO MINIMIZE HYPOGLYCEMIA
DPP-4i
GLP-1 RA
SGLT2i2
TZD
if HbA1c above target
if HbA1c above target
if HbA1c above target
if HbA1c above target
SGLT2i2 OR TZD
SGLT2i2 OR TZD
GLP-1 RA OR DPP-4i OR TZD
SGLT2i OR DPP-4i OR GLP-1 RA
if HbA1c above target
Continue with addition of other agents as outlined above
if HbA1c above target
Consider the addition of SU4 OR basal insulin: ☐Choose later generation SU with lower risk of hypoglycemia ☐Consider basal insulin with lower risk of hypoglycemia9


FIRST-LINE Therapy is Metformin and Comprehensive Lifestyle (including weight management and physical activity)
INDICATORS OF HIGH-RISK OR ESTABLISHED ASCVD, CKD, OR HF†
NO
CONSIDER INDEPENDENTLY OF BASELINE A1C, INDIVIDUALIZED A1C TARGET, OR METFORMIN USE*
IF A1C ABOVE INDIVIDUALIZED TARGET PROCEED AS BELOW
EITHER/ OR
COMPELLING NEED TO MINIMIZE WEIGHT GAIN OR PROMOTE WEIGHT LOSS
GLP-1 RA with good efficacy for weight loss
SGLT2i
if HbA1c above target
SGLT2i
GLP-1 RA with good efficacy for weight loss
if HbA1c above target
If quadruple therapy required or SGLT2i and/or GLP-1 RA not tolerated or contraindicated regimen with lowest risk of weight gain
PREFERABLY
DPP-4i (if not on GLP-1 RA) based on weight neutrality
If DPP-4i not tolerated or contraindicated or patient already on GLP-1 RA, cautious addition of •SU4 •TZD2 •Basal insulin

Clinicians may consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors more routinely after metformin rather than sulfonylureas or basal insulin.

JAMA Network Open. 2018;1(8):e186125

Contraindications

The entire class of SGLT2 inhibitors are absolutely contraindicated in patients with an eGFR less than 30 mL/min/1.73m^2.

Summary

Benefits and Risks of Empagliflozin:

Benefits

- Glucose control (without hypoglycemia)
- Weight loss
- BP reduction
- Lower risk of heart failure
- Reduced (CV) mortality
- Better renal outcomes

Risks

- Genital mycotic infections
- Urinary tract infections
- Volume depletion - related AEs
- Rare euglycemic ketoacidosis
- Bone fractures (canagliflozin)
- Rare amputations (canagliflozin)

Gaede et al. *Diabetologia*. 2016: 59;2298-2307; Adapted from Scheen AJ. Curr Diab Rep. 2016;16:92.


Thank you!