
بسم الله الرحمن الرحيم

Incretin Base Therapy

GLP 1 Agonist

DPP4 Inhibitor

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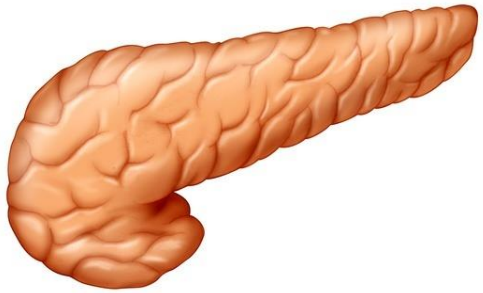
Introduction

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

Sulfonylureas (and insulin)



Treatment of Type 2 Diabetes

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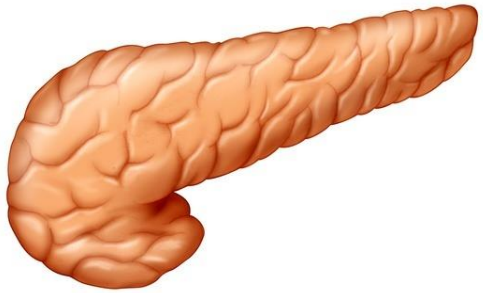
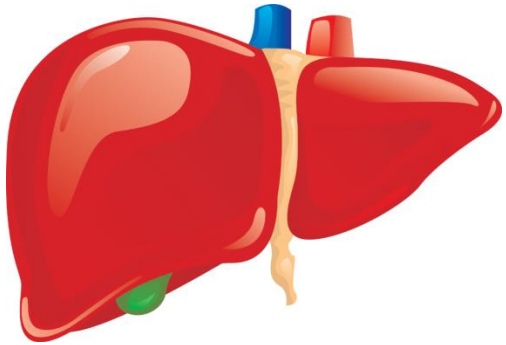
Metformin





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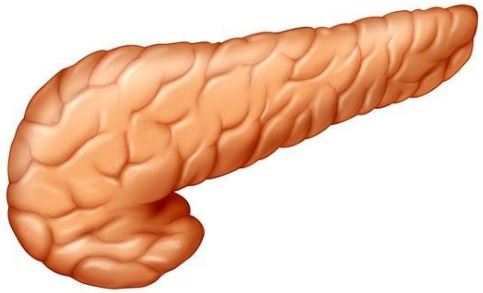

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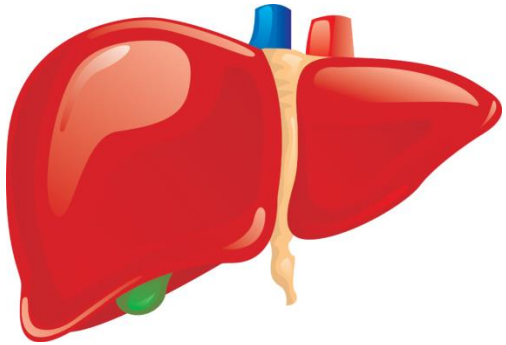

Treatment of Type 2 Diabetes

Thiazolidinediones

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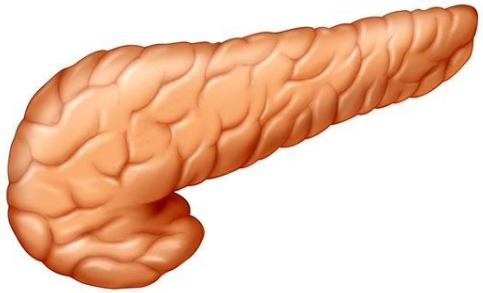

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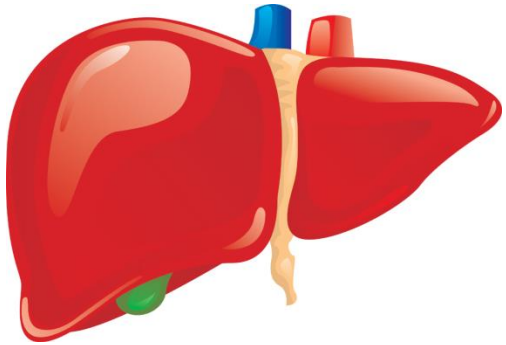

Treatment of Type 2 Diabetes

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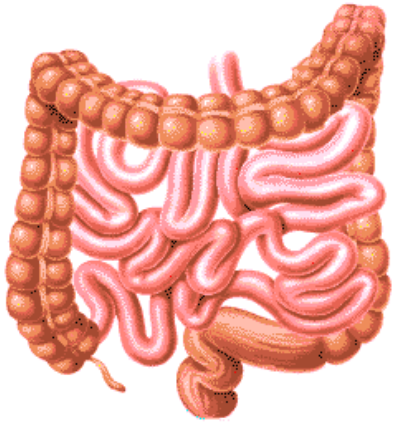
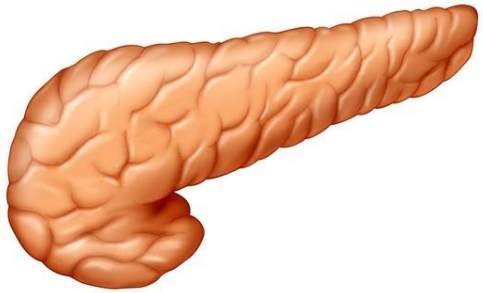


GLP-I analogs & DPP IV inhibitors

Sulfonylureas (and insulin)



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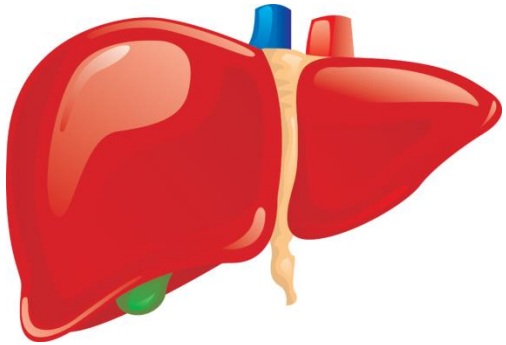

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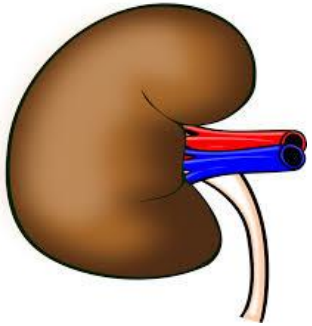
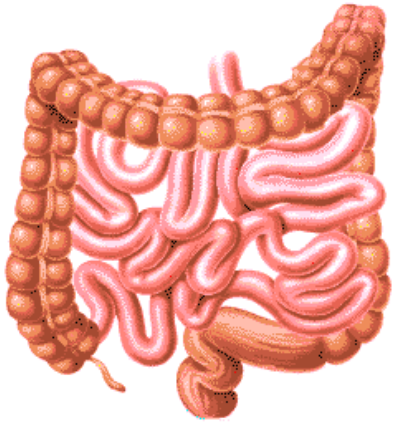


SGLT2 inhibitors



GLP-I analogs & DPP IV inhibitors

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.

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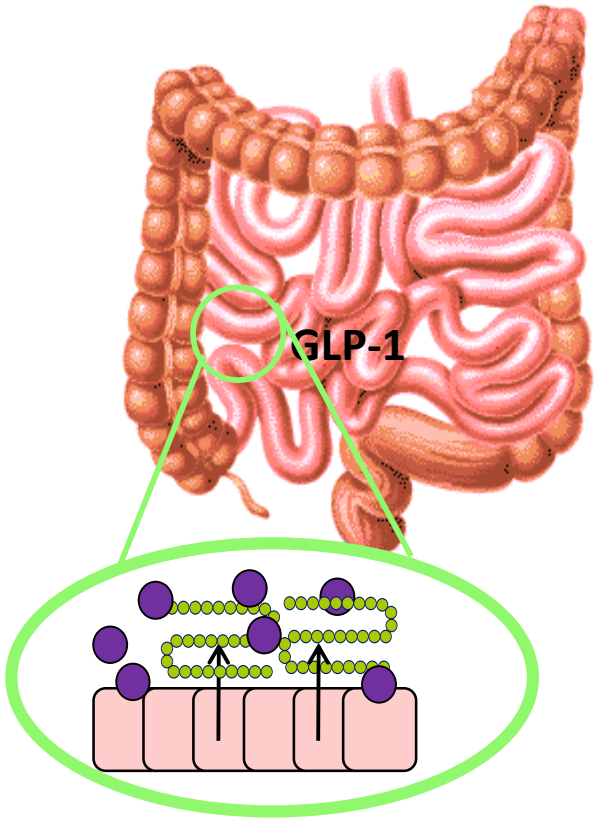
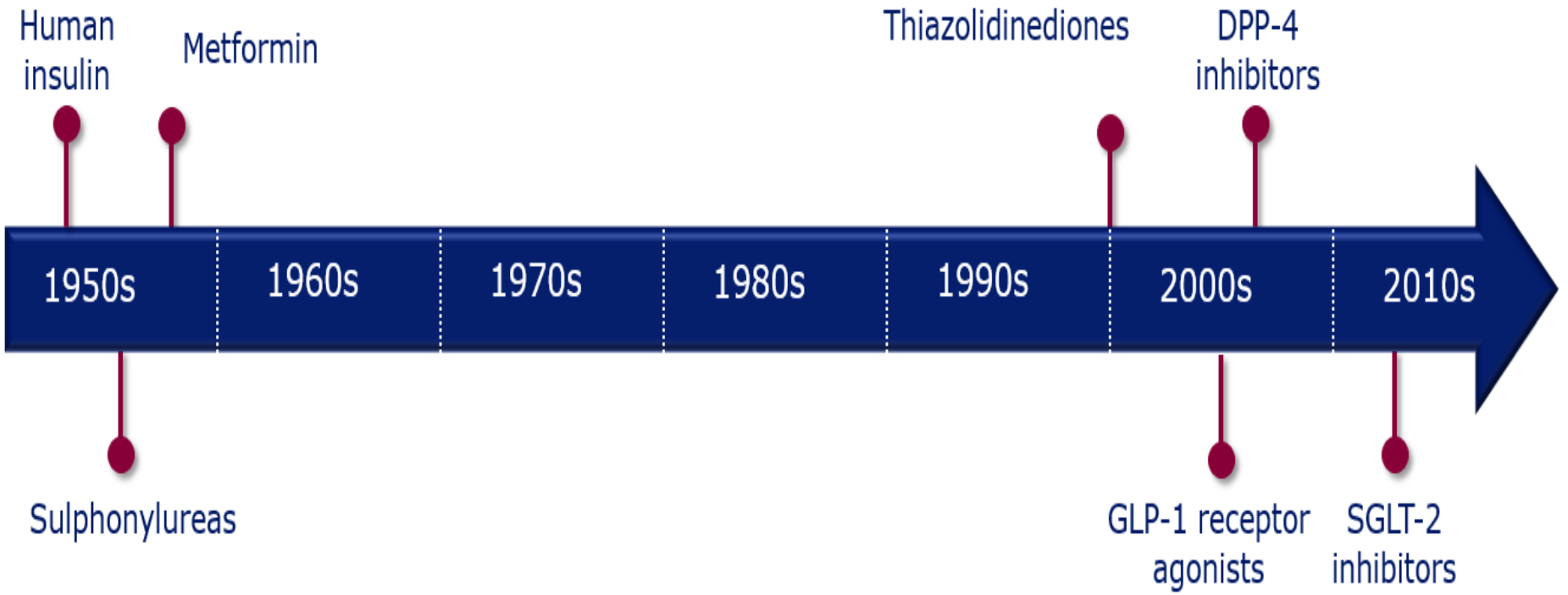


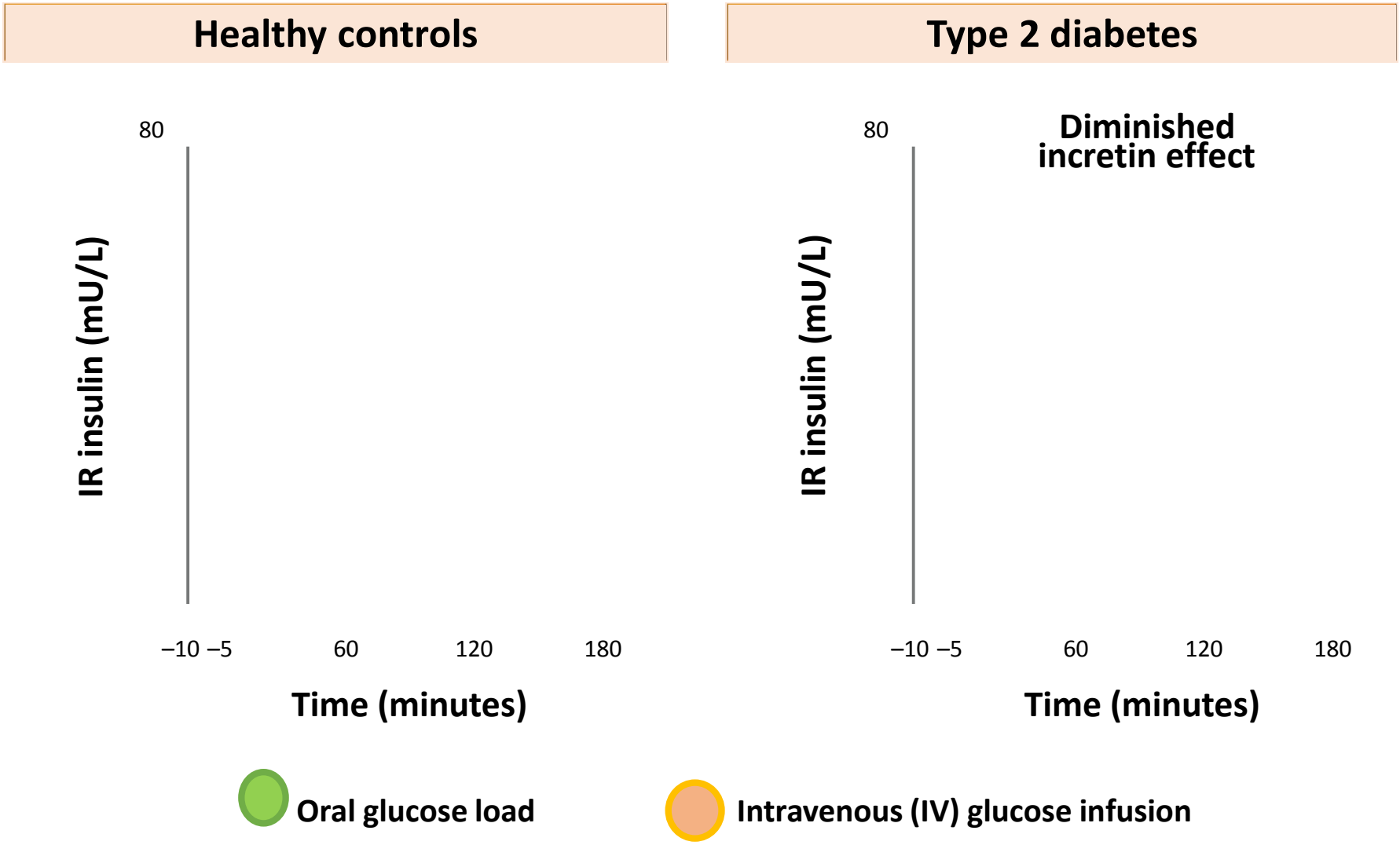
L-cells secrete GLP-1

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


Human insulin
Metformin
Thiazolidinediones
DPP-4 inhibitors
1950s
1960s
1970s
1980s
1990s
2000s
2010s
Sulphonylureas
GLP-1 receptor agonists
SGLT-2 inhibitors

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



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

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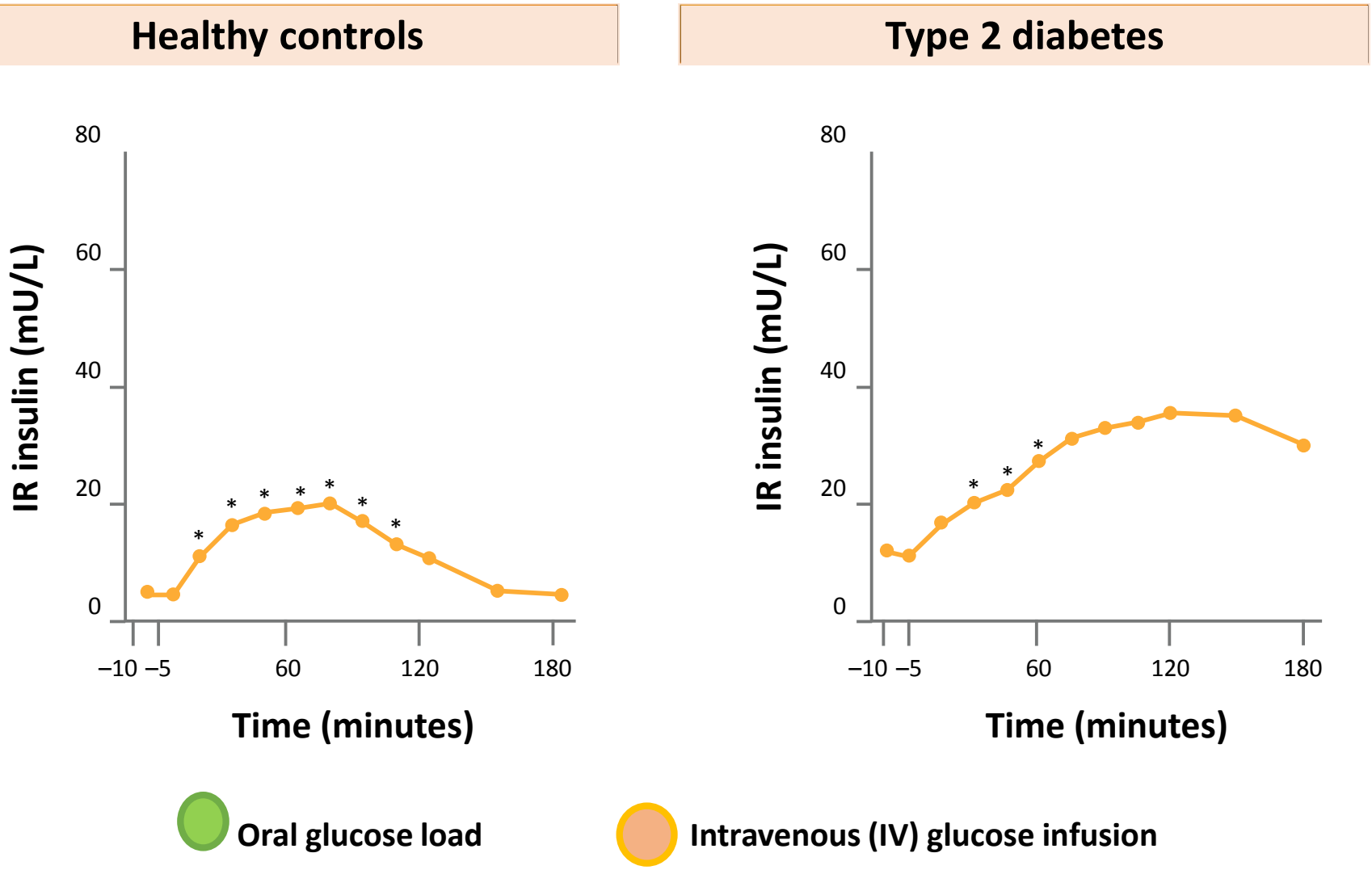

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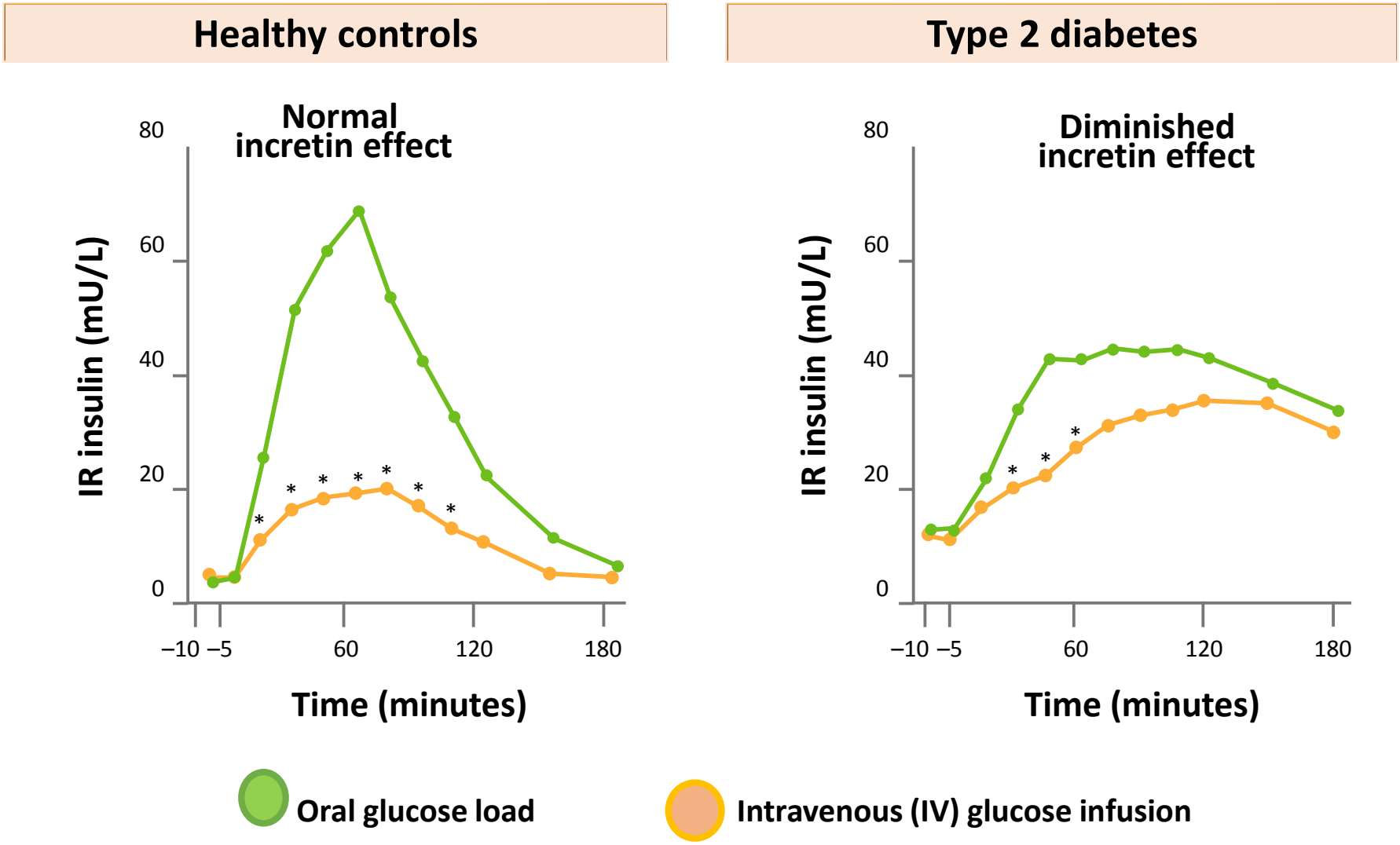

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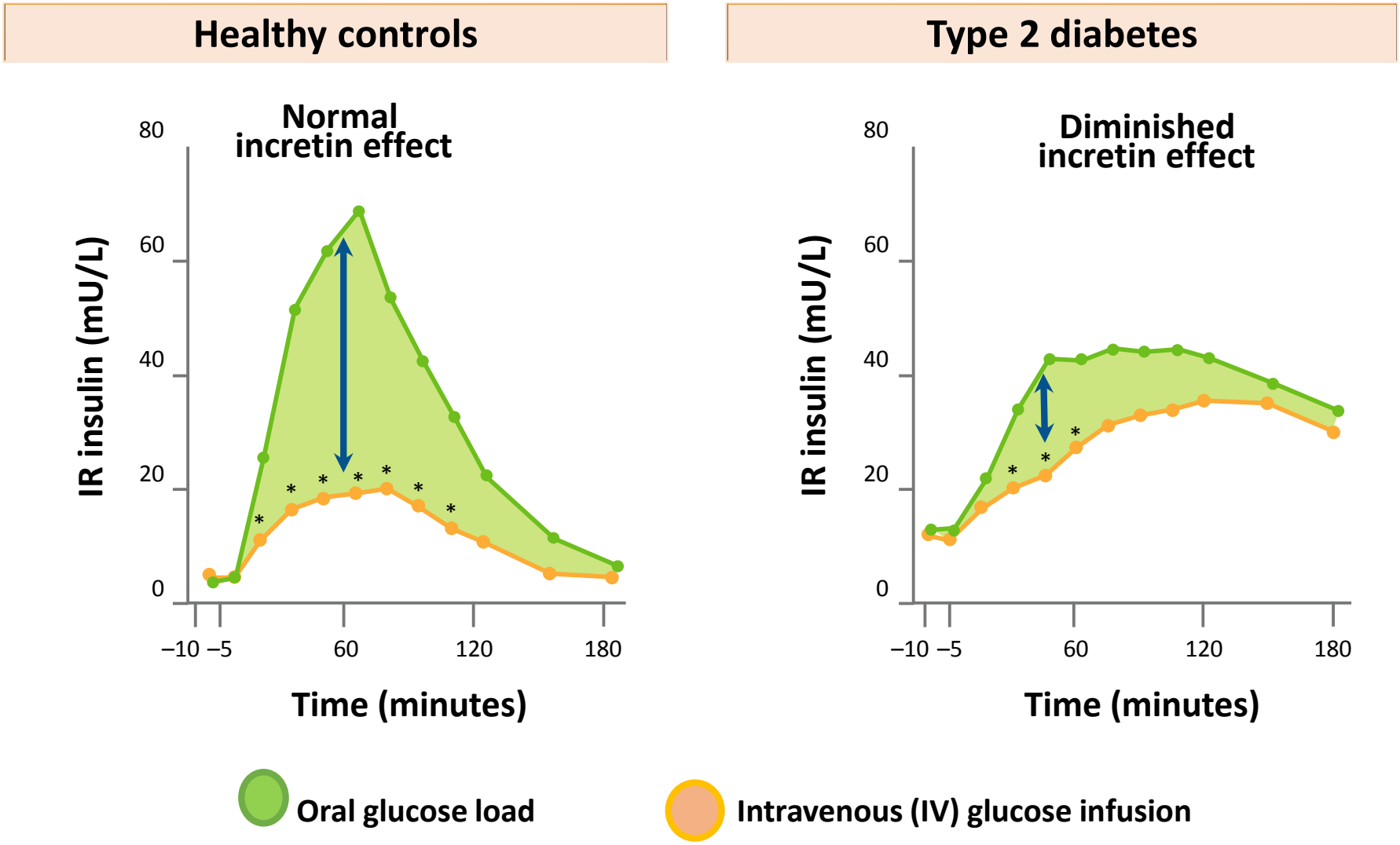

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همه موارد زیر صحیح است به جزء؟

تجویز خوراکی گلوکز باعث افزایش بیشتر انسولین و C-Peptid در مقابل تجویز وریدی گلوکز میشود

اثر Incretin بعلت افزایش GLP-1 است.

داروهای مهارکننده DPP4 باعث افزایش اثر GLP-1 می شود.

آگونیست GLP-1 باعث کاهش ترشح انسولین می شود.

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

Ingestion of food

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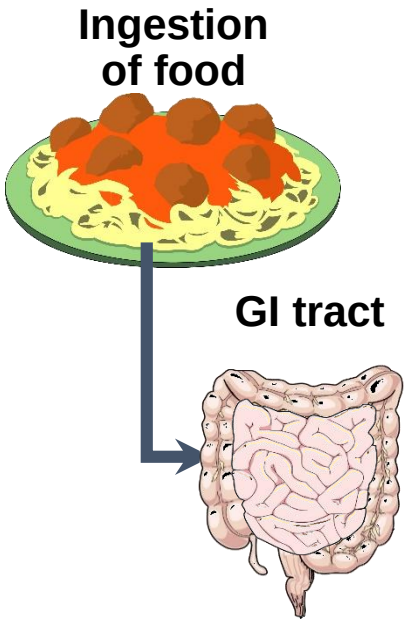

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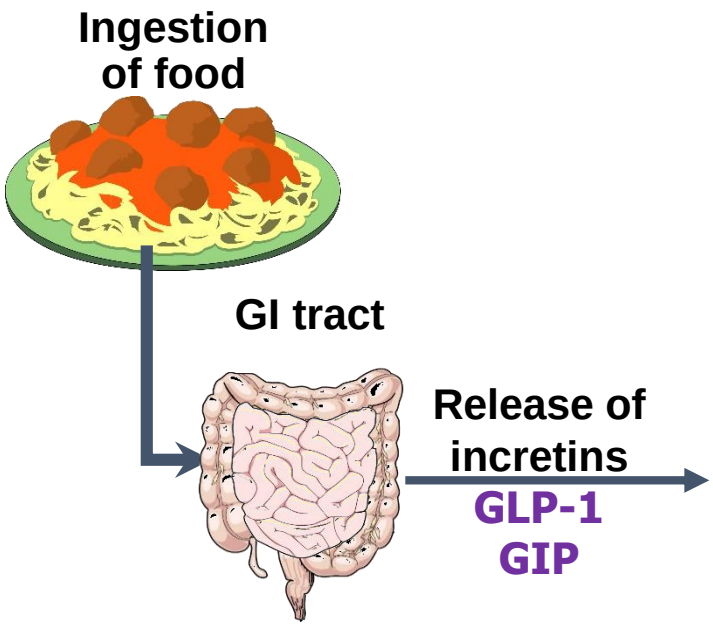

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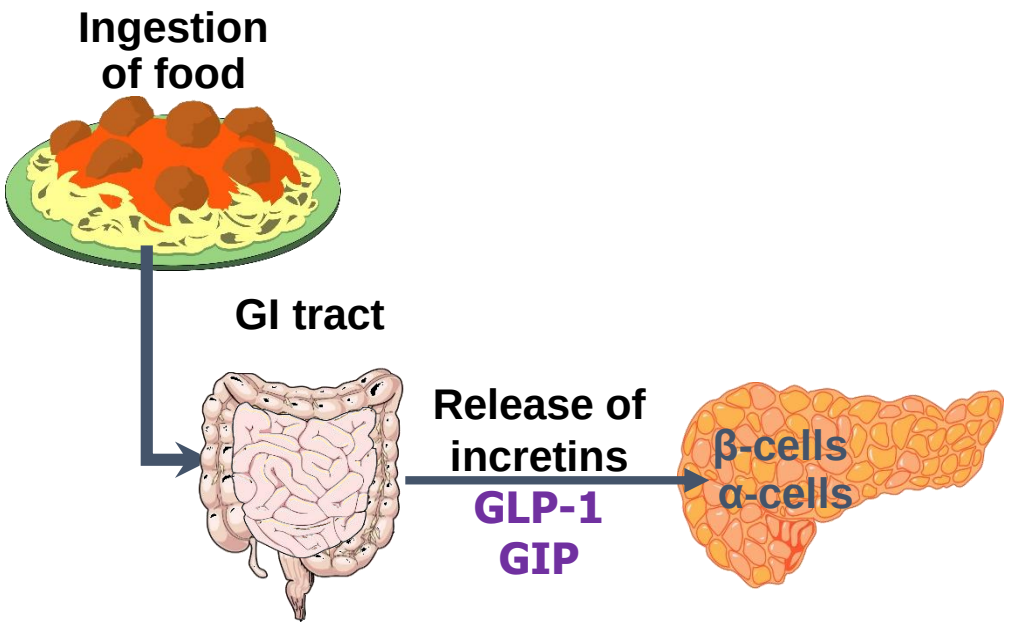

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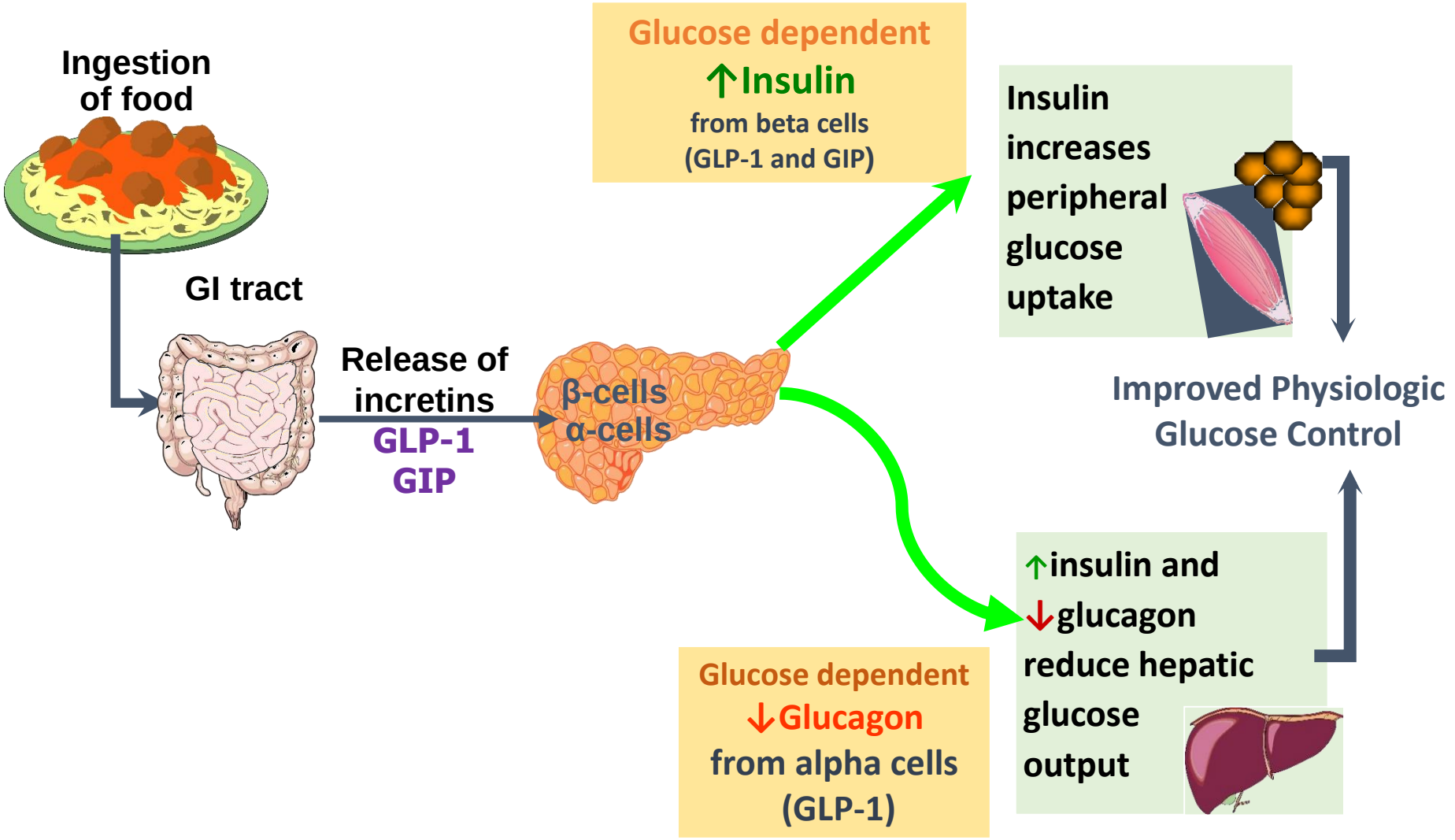

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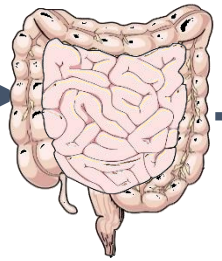
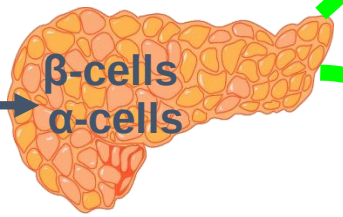


GI tract

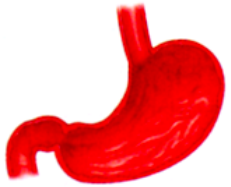
Release of incretins
GLP-1
GIP



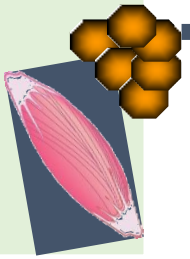
Pancreas

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

Stomach
↓Gastric emptying



Insulin increases peripheral glucose uptake



Improved Physiologic Glucose Control

↑insulin and
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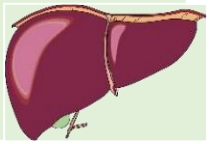
reduce hepatic glucose output



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

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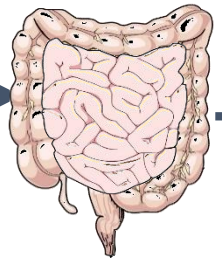

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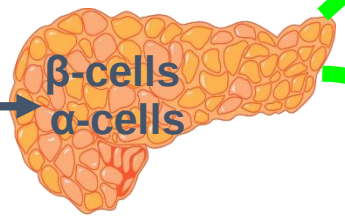
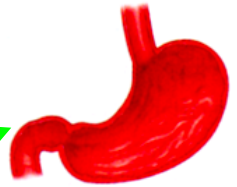


Pancreas

Brain
↑Satiety

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

Stomach
↓Gastric emptying



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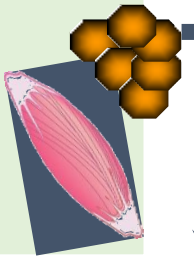

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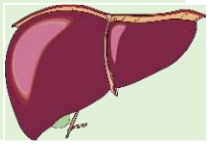

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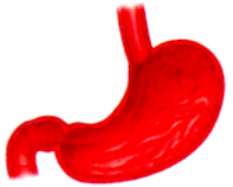

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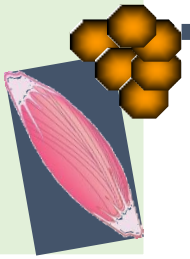
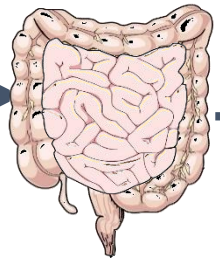


GI tract

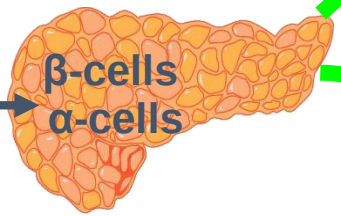


Release of incretins

GLP-1

GIP

Pancreas



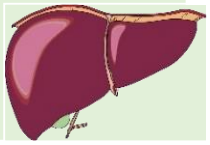
Improved Physiologic Glucose Control

DPP-4 enzyme

Inactive GLP-1

Inactive GIP

↑insulin and ↓glucagon reduce hepatic glucose output



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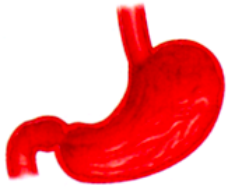

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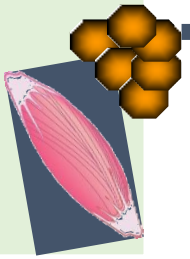

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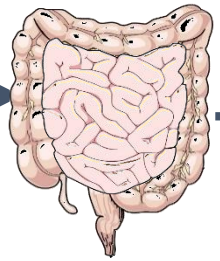

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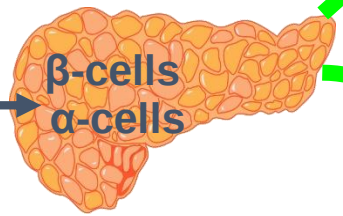


Improved Physiologic Glucose Control

DPP-4 enzyme

DPP-4 Inhibitor (Sitaglptin, Linagliptin)

Inactive GLP-1

Inactive GIP

Glucose dependent

↓Glucagon

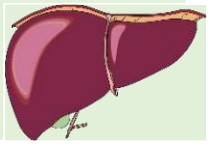
from alpha cells

(GLP-1)

↑insulin and

↓glucagon

reduce hepatic glucose output



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GLP-1 Receptor agonists

GLP-1 exhibits a short half-life of one to two minutes due to N-terminal degradation by the enzyme DPP-4.

Synthetic GLP-1 receptor agonists are variably **resistant** to degradation by the enzyme **DPP-4** and therefore have a longer half-life, facilitating clinical use.

Exenatide, Liraglutide, Albiglutide, Taspoglutide, Lixisenatide, Dulaglutide, **oral and subcutaneous** Semaglutide

GLP-1 RA vs. Sulphonylurea

Outcome	Liraglutide (n=241)	Liraglutide (n=242)	Glimepiride (n=244)
HbA_{1c} change from baseline (%)	−1.0	−1.0	-1.0
HbA_{1c} <7.0% (% patients)	35.3	42.4	36.3
Weight change from baseline (kg)	− 2.8*	−2.6*	+1.0

*Significant vs. glimepiride

Nauck *et al. Diabetes Care* 2009;32:84–90 (LEAD-2)

GLP-1 RA vs. Thiazolidinedione

Outcome	Liraglutide (n=228)	Liraglutide (n=234)	Glitazone (n=232)
HbA_{1c} change from baseline (%)	−1.1*	−1.1*	−0.4
HbA_{1c} <7.0% (% patients)	35	42	22
Weight change from baseline (kg)	+0.32*	-0.23*	+2.11

*Significant vs. rosiglitazone

Marre *et al. Diabetic Med* 2009;26:268–78 (LEAD-1)

GLP-1 RA vs. DPP-4 Inhibitor or TZD

Outcome	Liraglutide (n=170)	Sitagliptin 100 mg (n=172)	Pioglitazone 45 mg (n=172)
HbA_{1c} change from baseline (%)	-1.5*	-0.9	-1.2
HbA_{1c} <7.0% (% patients)	~60*	~30	~45
Weight change from baseline (kg)	-2.3*	-0.8	+2.8

*Significant vs. both sitagliptin and pioglitazone

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

GLP-1 RA vs. Basal Insulin

Outcome	Liraglutide (n=233)	Insulin glargine once-daily (n=223)
HbA_{1c} change from baseline (%)	−1.5*	−1.3
HbA_{1c} <7.0% (% patients)	60*	48
Weight change from baseline (kg)	−2.6*	+1.4

*Significant vs. insulin glargine

Diamant *et al. Lancet* 2010;375:2234–43

GLP 1 RA

In patients with type 2 diabetes, a GLP 1 receptor agonist is preferred to insulin when possible.

Type 2 Diabetes Treatment Efficacy

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

Type 2 Diabetes Treatment Efficacy

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SUs	High	Gain

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Inzucchi *et al. Diabetologia* 2012;55:1577–96

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Weight loss **is common** with GLP-1 receptor agonists

Inzucchi *et al. Diabetologia* 2012;55:1577–96

کدام دسته دارویی زیر بیشترین کاهش وزن را ایجاد می کند؟

آگونیست GLP-1

مهارکننده DPP4

مهار کننده SGLT2

سولفونیل اور

GLP-1 receptor agonists and **DPP4 inhibitors** are **not considered as initial therapy** for the majority of patients with type 2 diabetes.

Initial therapy in most patients with type 2 diabetes should begin with diet, weight reduction, exercise, and metformin.

Basal Insulin Plus GLP-1 RA

When used in combination with basal insulin, patients using GLP-1 receptor agonists compared with placebo achieved glycemic targets at **reduced insulin doses** and less hypoglycemia or weight gain.

Basal Insulin Plus GLP-1 RA

Liraglutide has been evaluated for use in combination with basal insulin therapy.

Degludec-liraglutde (IDegLIRA)

Cardiovascular Effects

The GLP-1 receptor agonists proved to be effective in **reducing cardiovascular disease**, in particular liraglutide, semaglutide, and dulaglutide may be preferred in patients with existing ASCVD.

Liraglutide had **no effect on heart failure** outcomes in patients with established heart failure.

For patient with established ASCVD or indicators of high ASCVD risk (such as patients ≥ 55 years of age with coronary, carotid, or lower-extremity artery stenosis ≥ 50% or left ventricular hypertrophy), heart failure, or CKD, an SGLT2 inhibitor or GLP-1 RA with demonstrated CVD benefit.

Adverse Effects

The side effects of GLP-1 receptor agonists are predominantly **gastrointestinal**, particularly nausea, vomiting, and diarrhea, and occur consistently in trials in 10 to 50 percent of patients.

Adverse Effects

Immunogenicity

Antibodies to GLP-1 receptor agonists may develop. In the majority of patients, the titer of antibodies decreases over time and does not affect glycemic control. However, some patients develop high titers of antibodies that may attenuate the glycemic response.

Precautions

Acute pancreatitis has been reported in association with GLP-1 agonist treatment and should not be used in patients with a history of pancreatitis.

In addition, GLP-1 receptor agonists are not approved by FDA for use in those with **type 1 diabetes.**

GLP-1 receptor agonists should be used with caution in patients with **renal impairment**.

should not be used in patients with a personal or family history of **medullary thyroid cancer** or multiple endocrine neoplasia 2A or 2B.

Mortality

The effect of GLP-1 receptor agonists on overall mortality is uncertain.

In a systematic review and meta-analysis of 189 trials, there was **no difference in all-cause mortality** between any incretin drug and control.

DPP4 Inhibitors

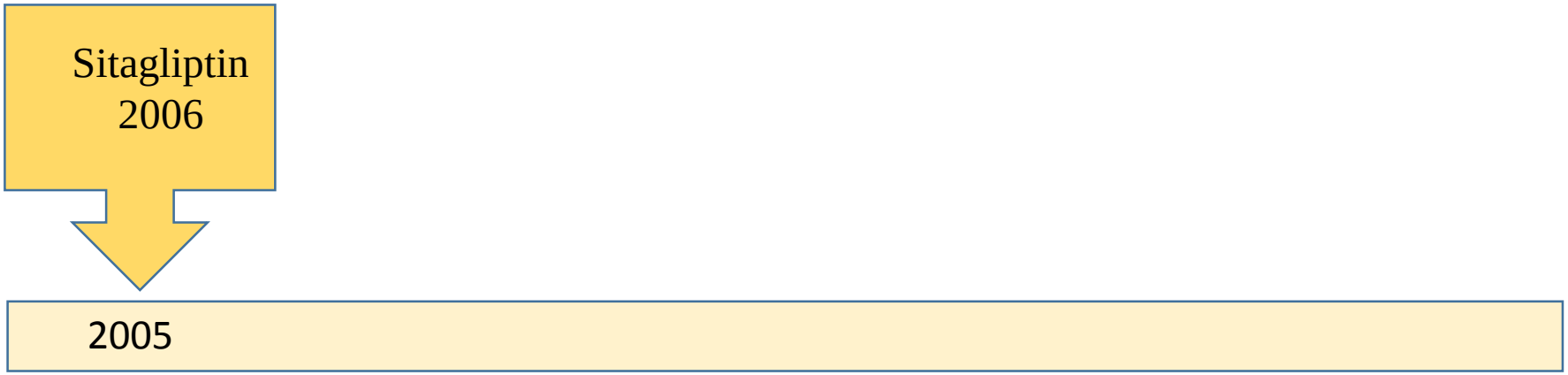
Will the DPP-4 inhibitors replace GLP-1 mimetics?

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).

DPP 4 Inhibitors

DPP 4 Inhibitors



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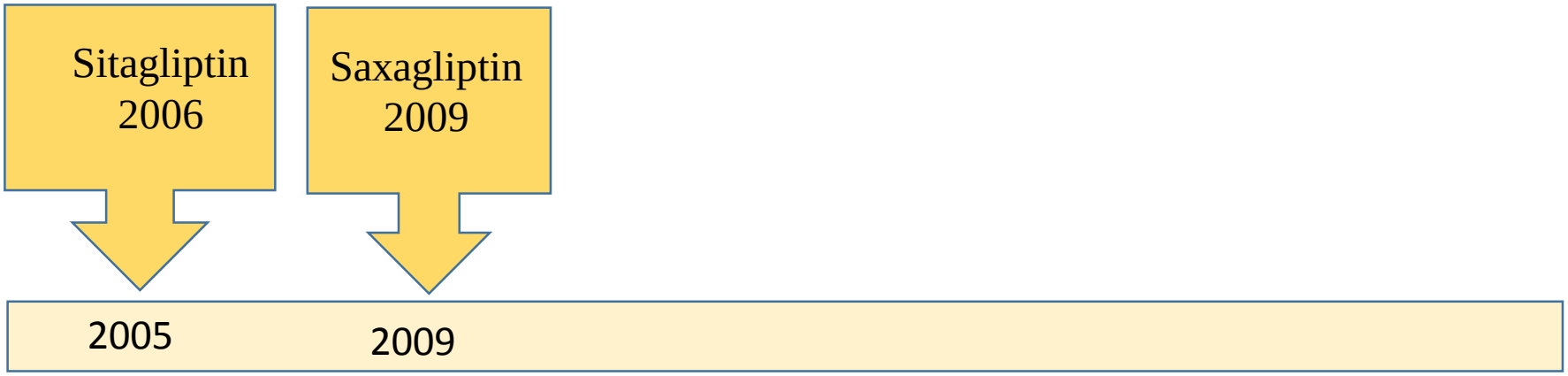

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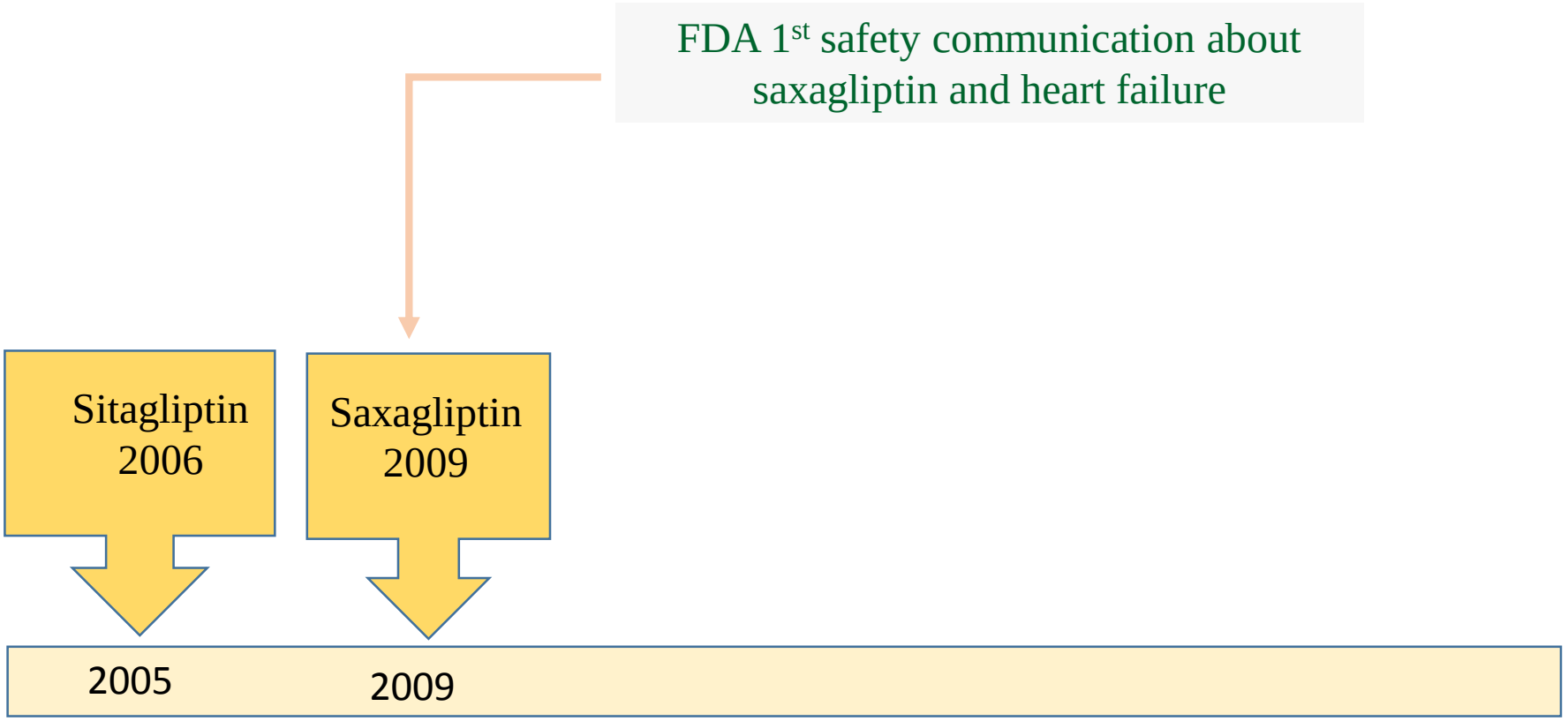

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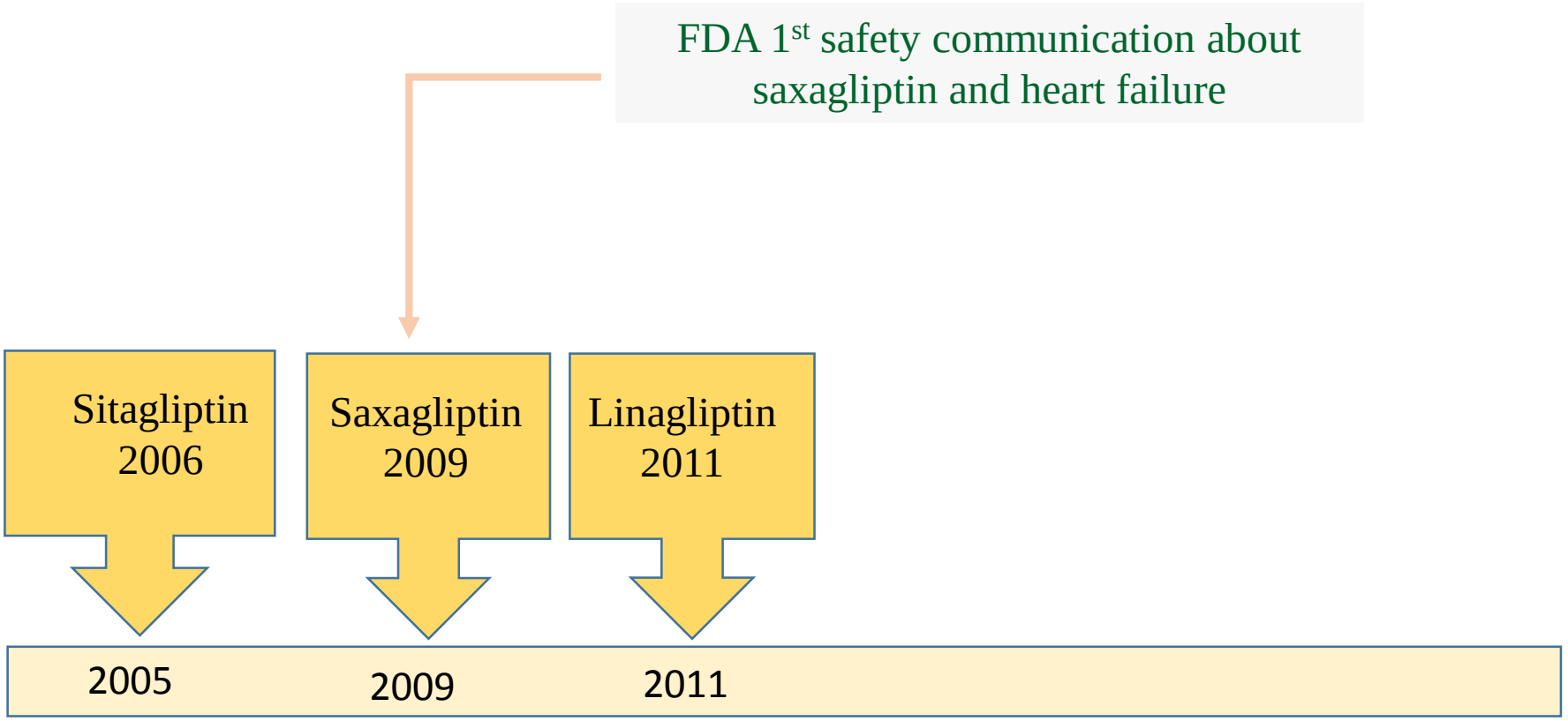

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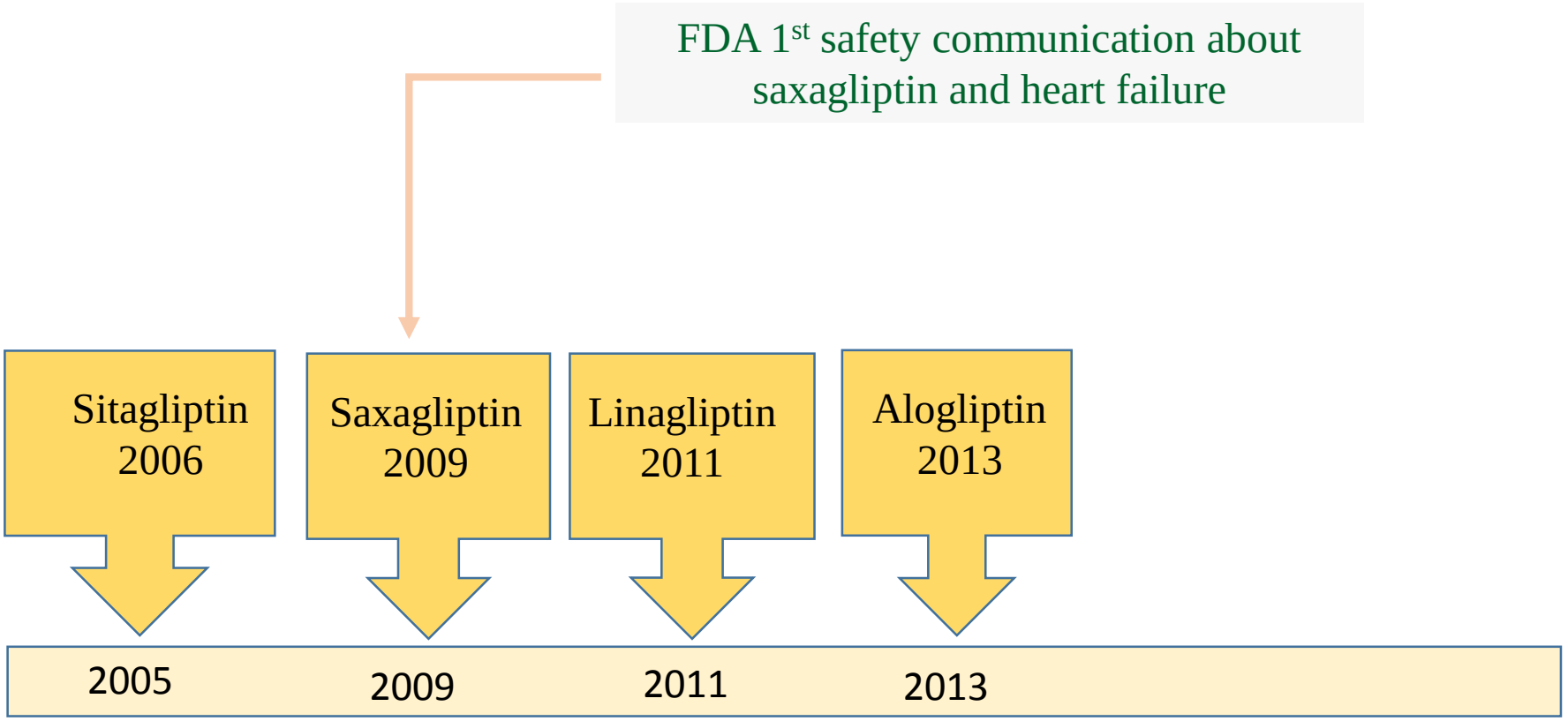

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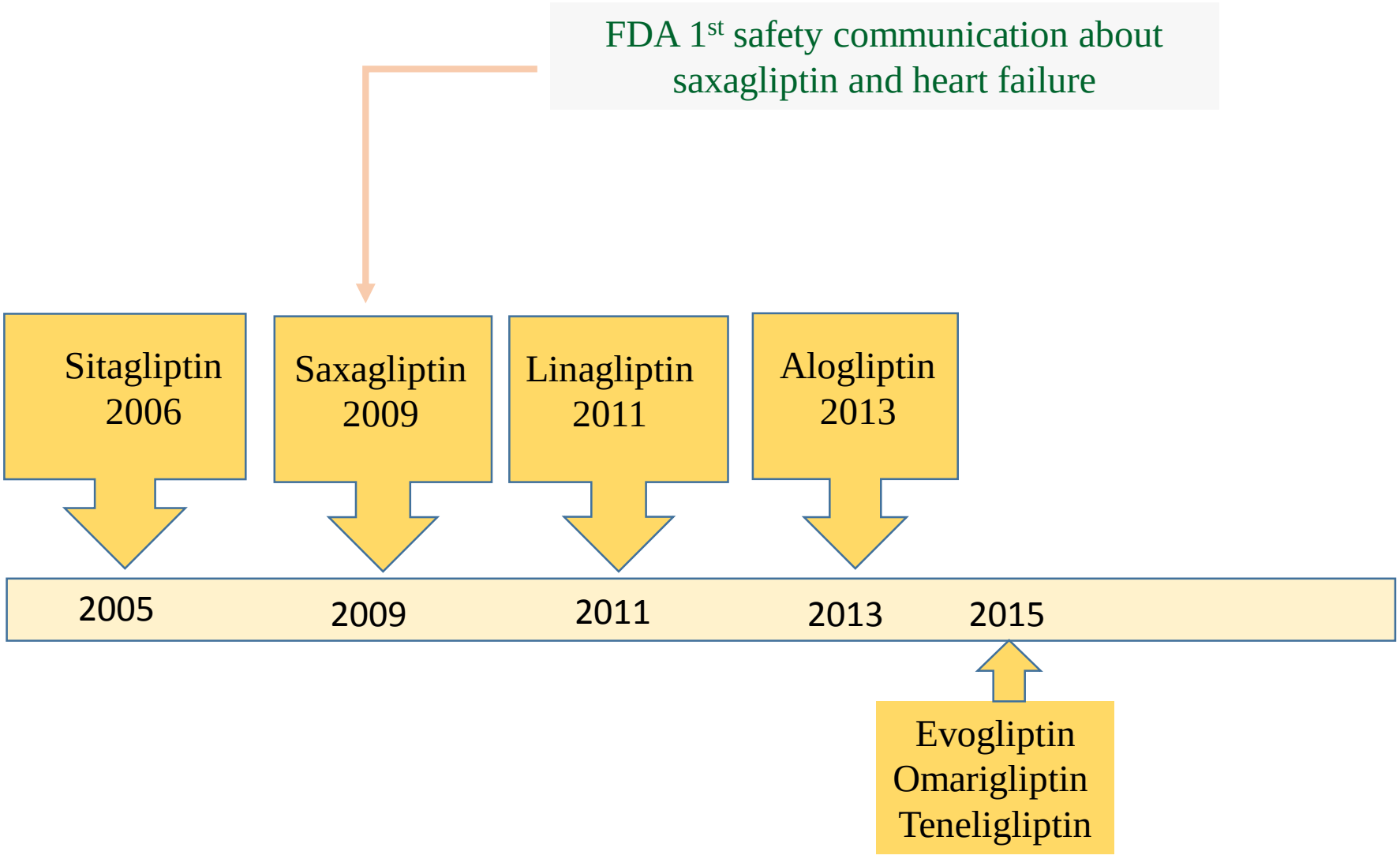

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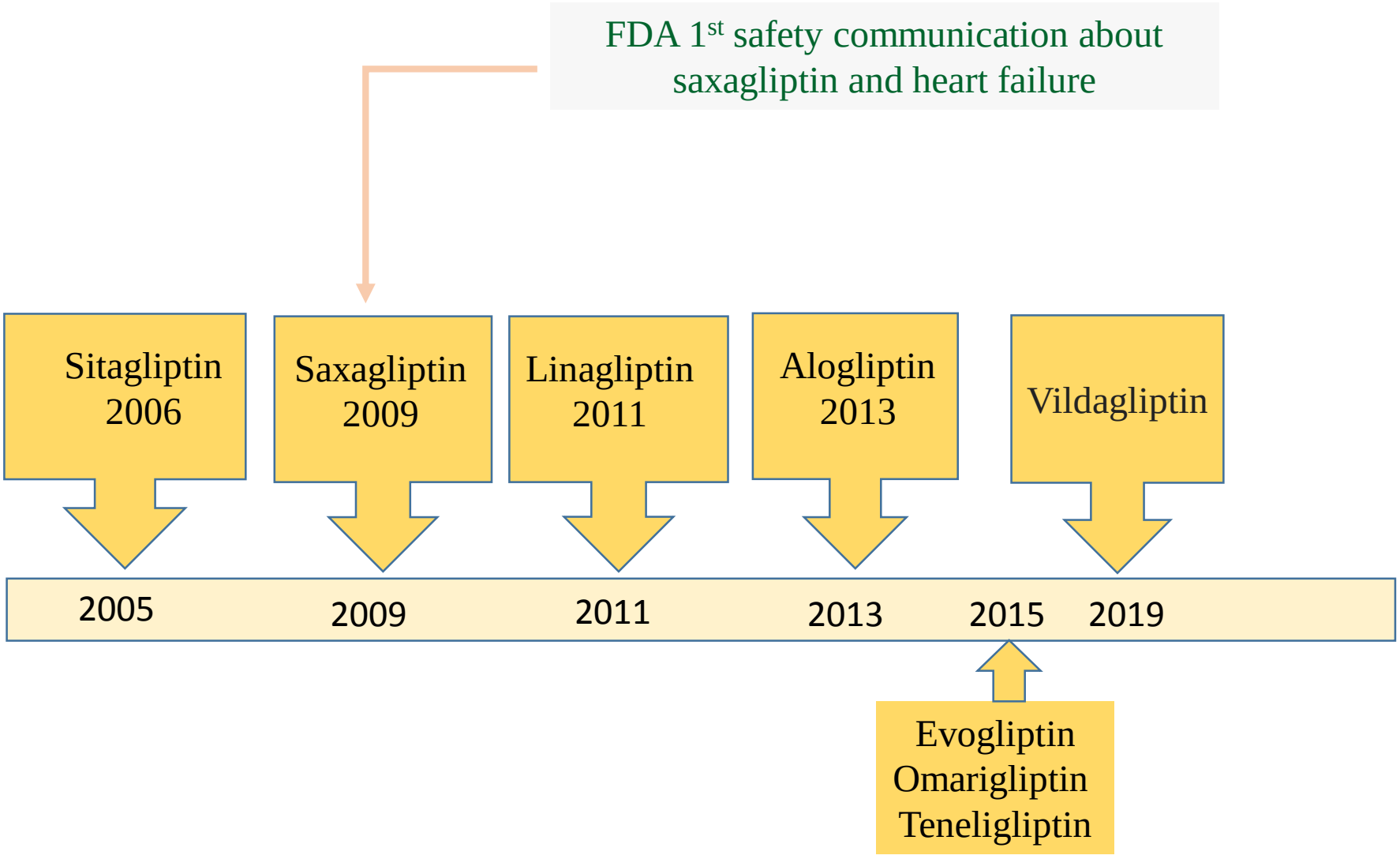

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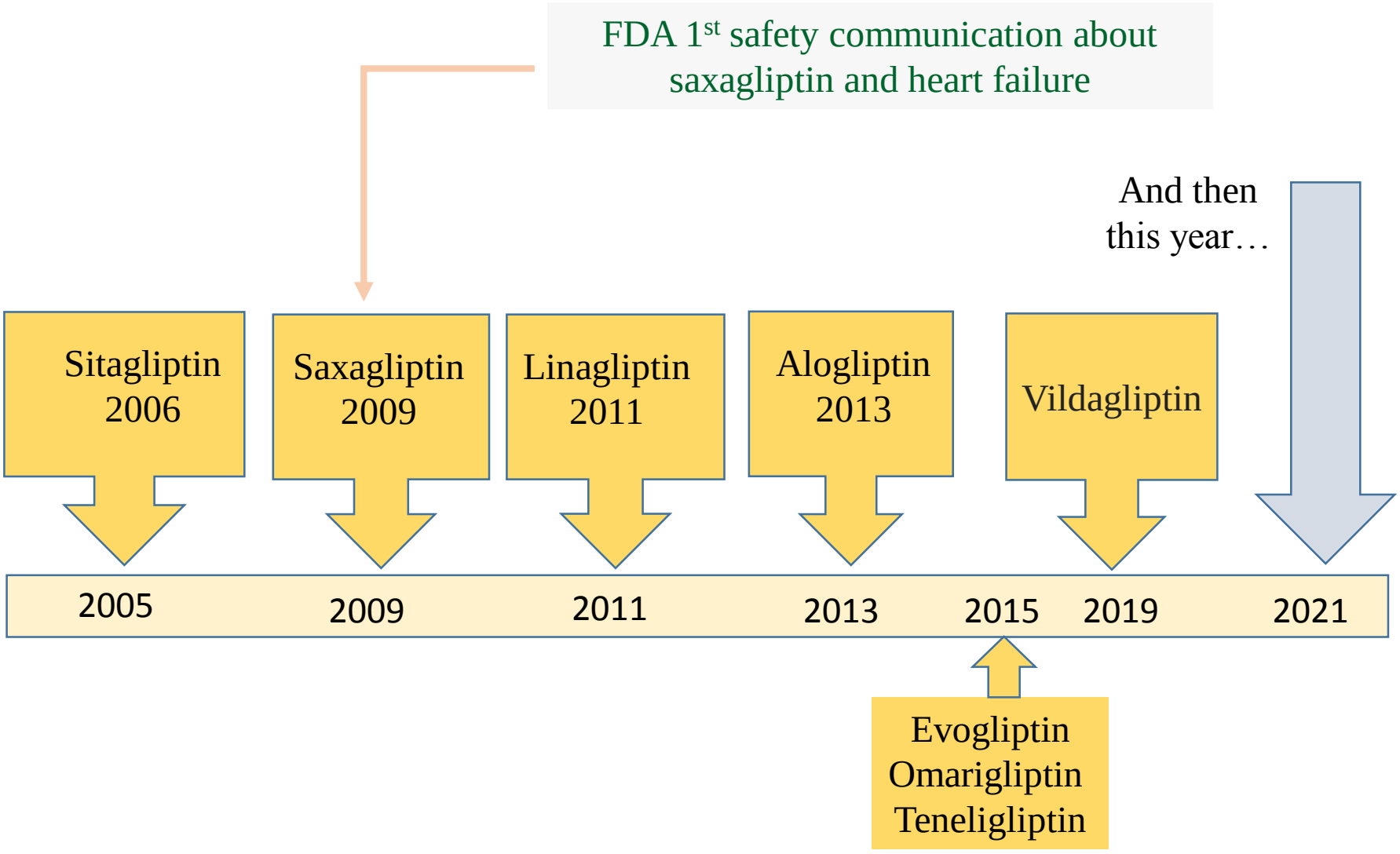


FDA added warnings about the risk of hospitalization for heart failure to the labels of **Saxagliptin** and **Alogliptin** containing type 2 diabetes medicines.

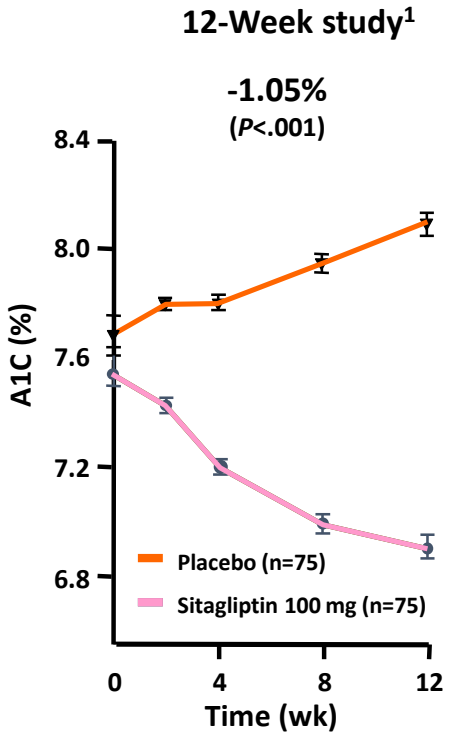
Clinicians may consider prescribing GLP-1 receptor agonists, SGLT-2 inhibitors, or DPP-4 inhibitors more routinely after metformin rather than sulfonylureas or basal insulin.

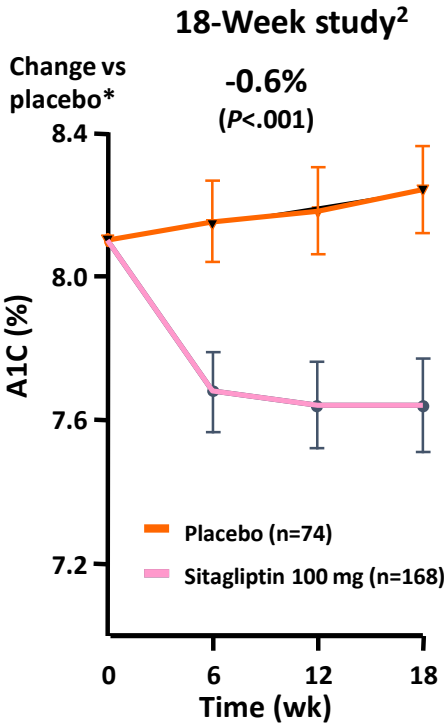
JAMA Network Open. 2018;1(8):e186125

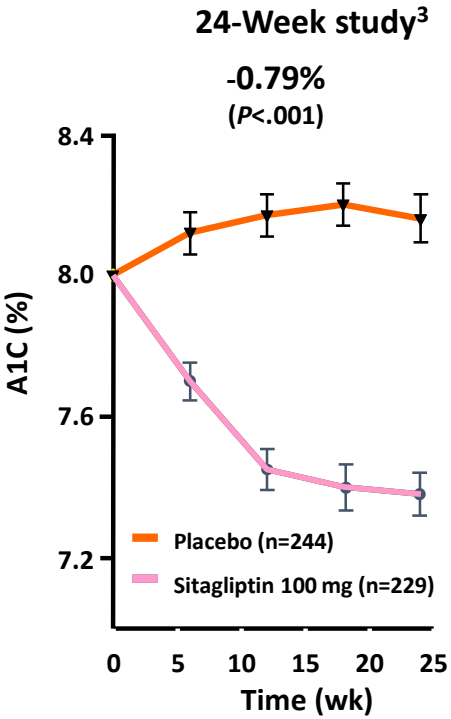
Sitagliptin: Once-daily Dosing Administration

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



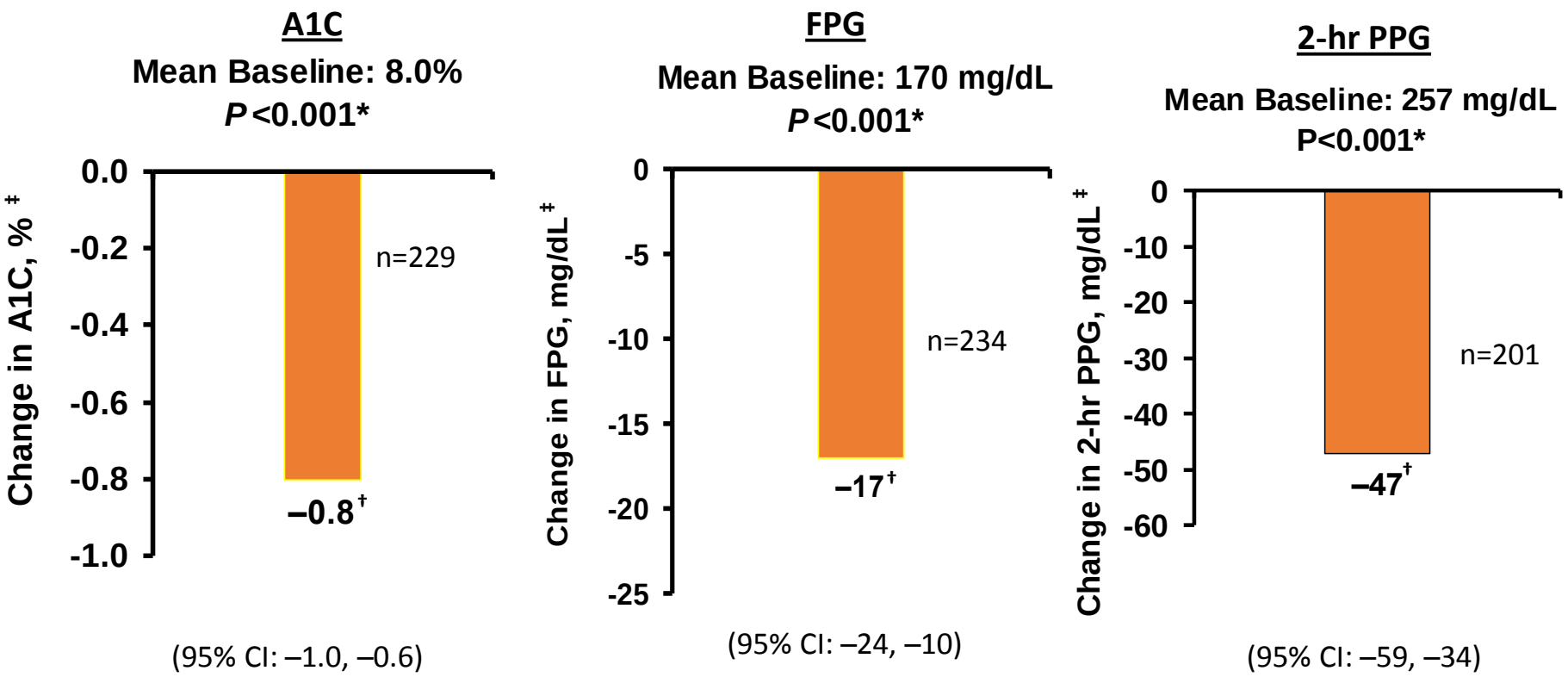




*Between group difference in LS means.

1. 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



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:

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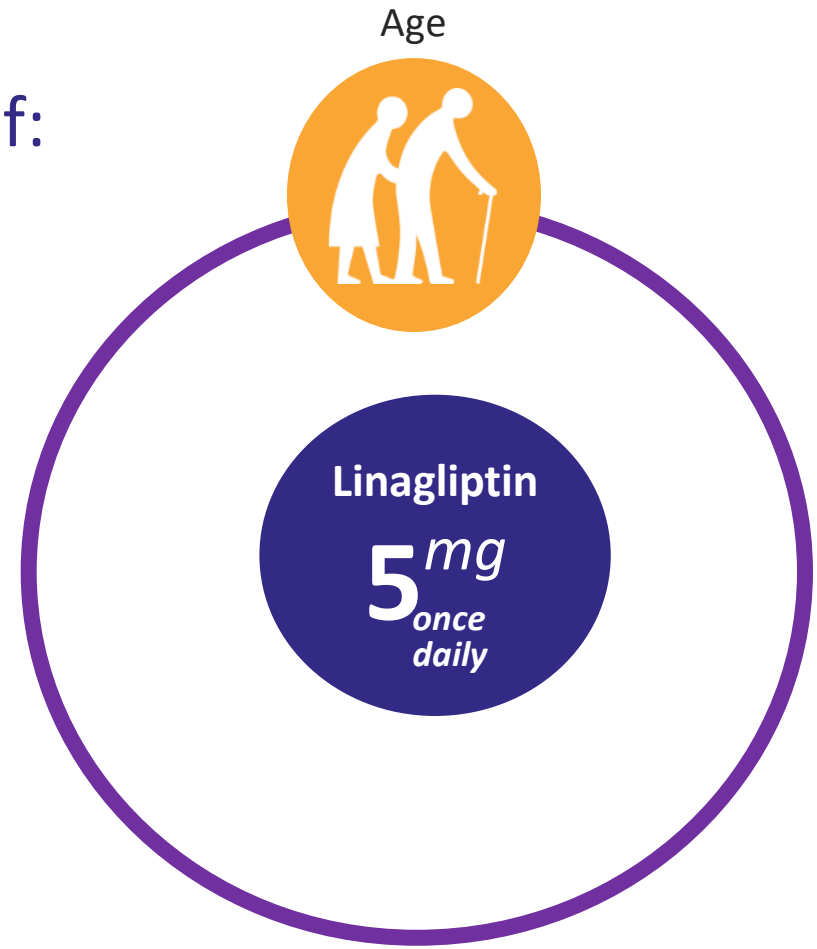

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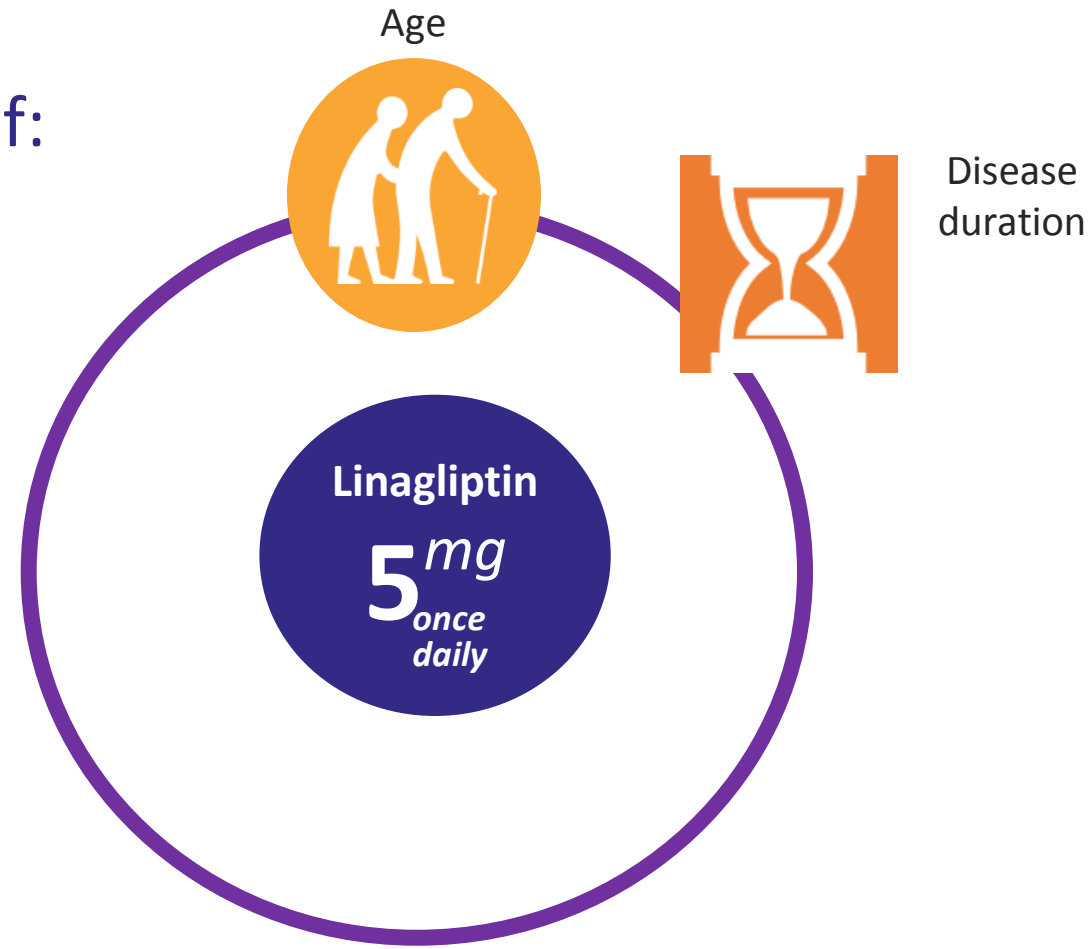

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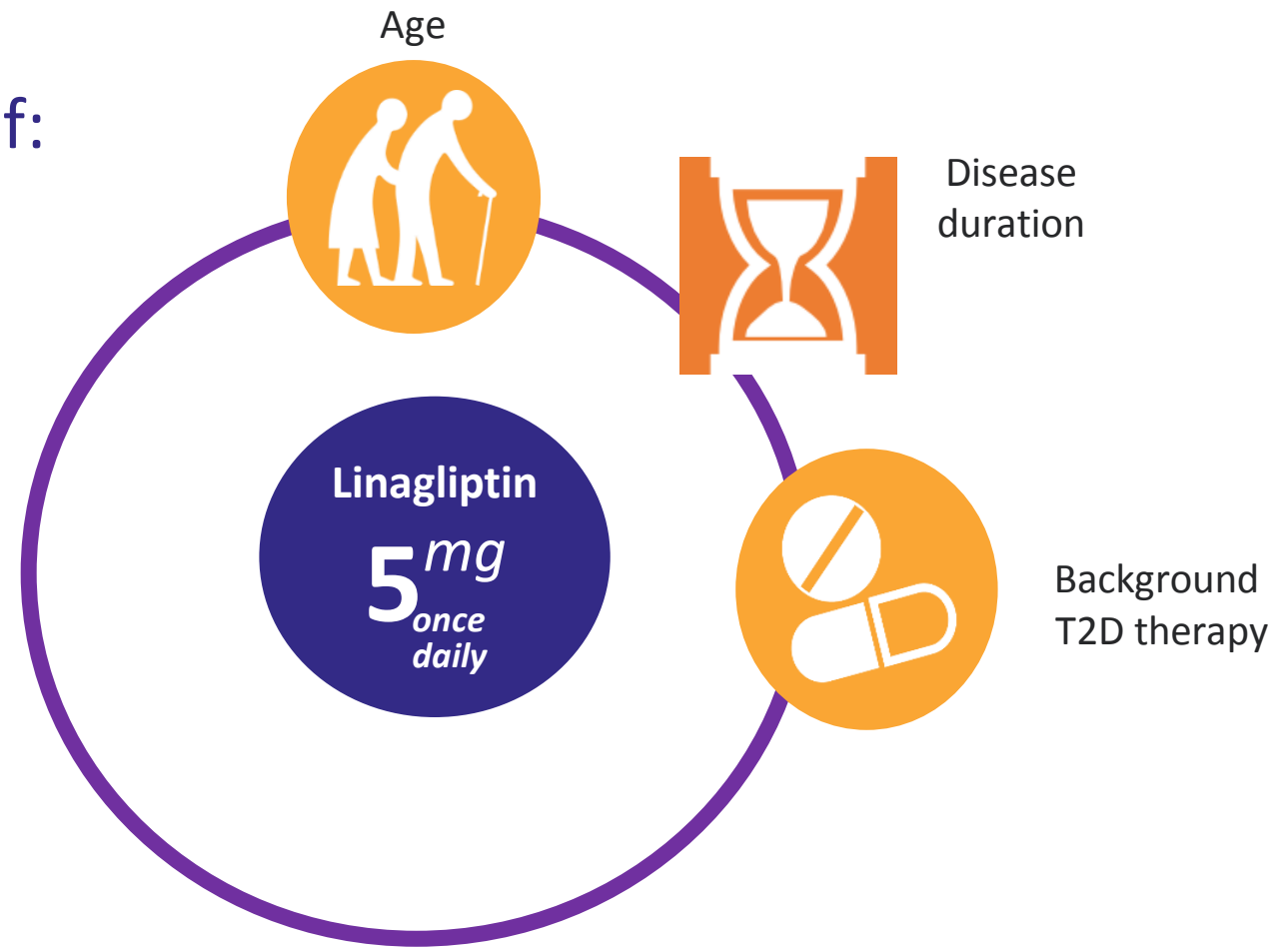

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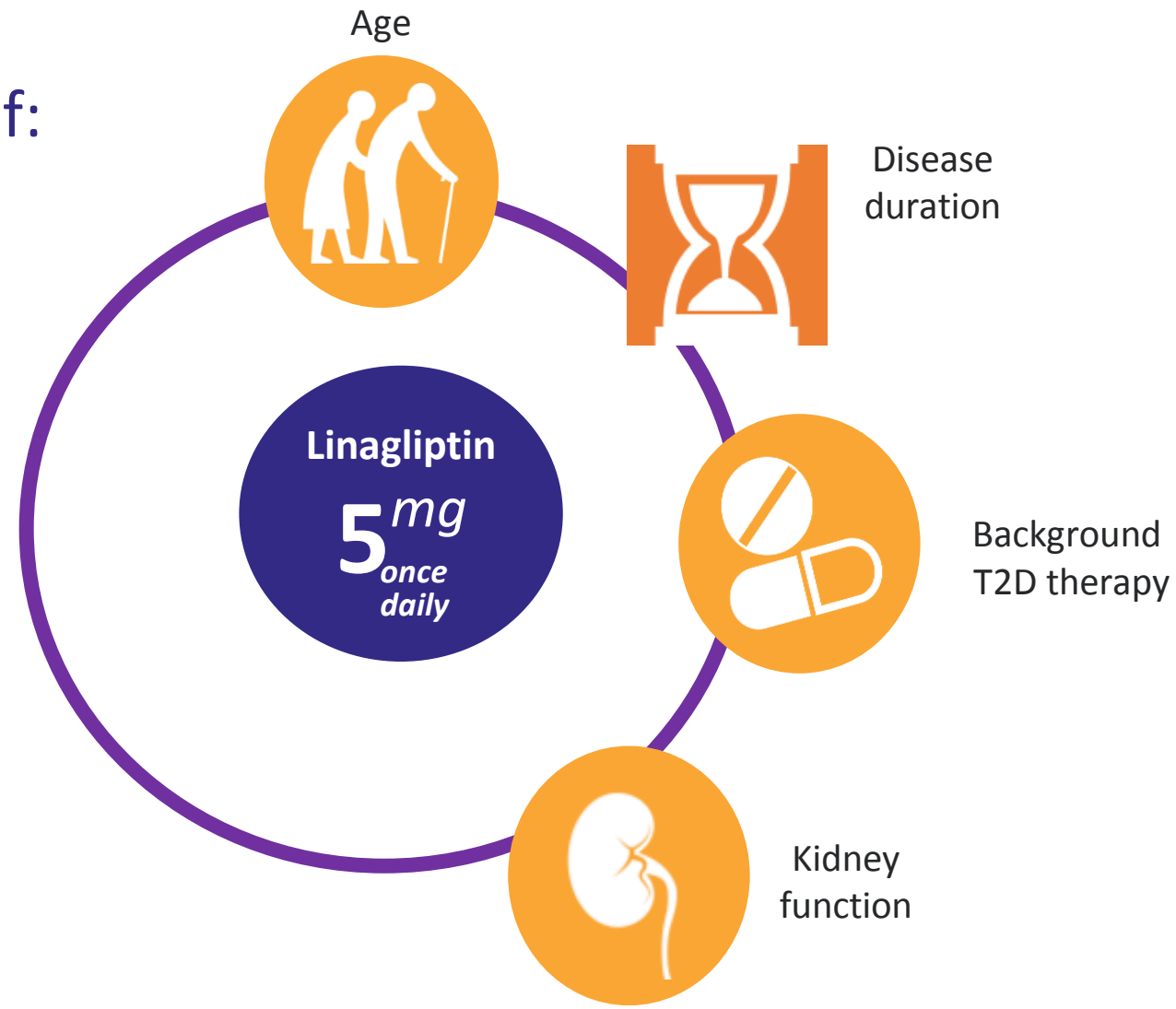

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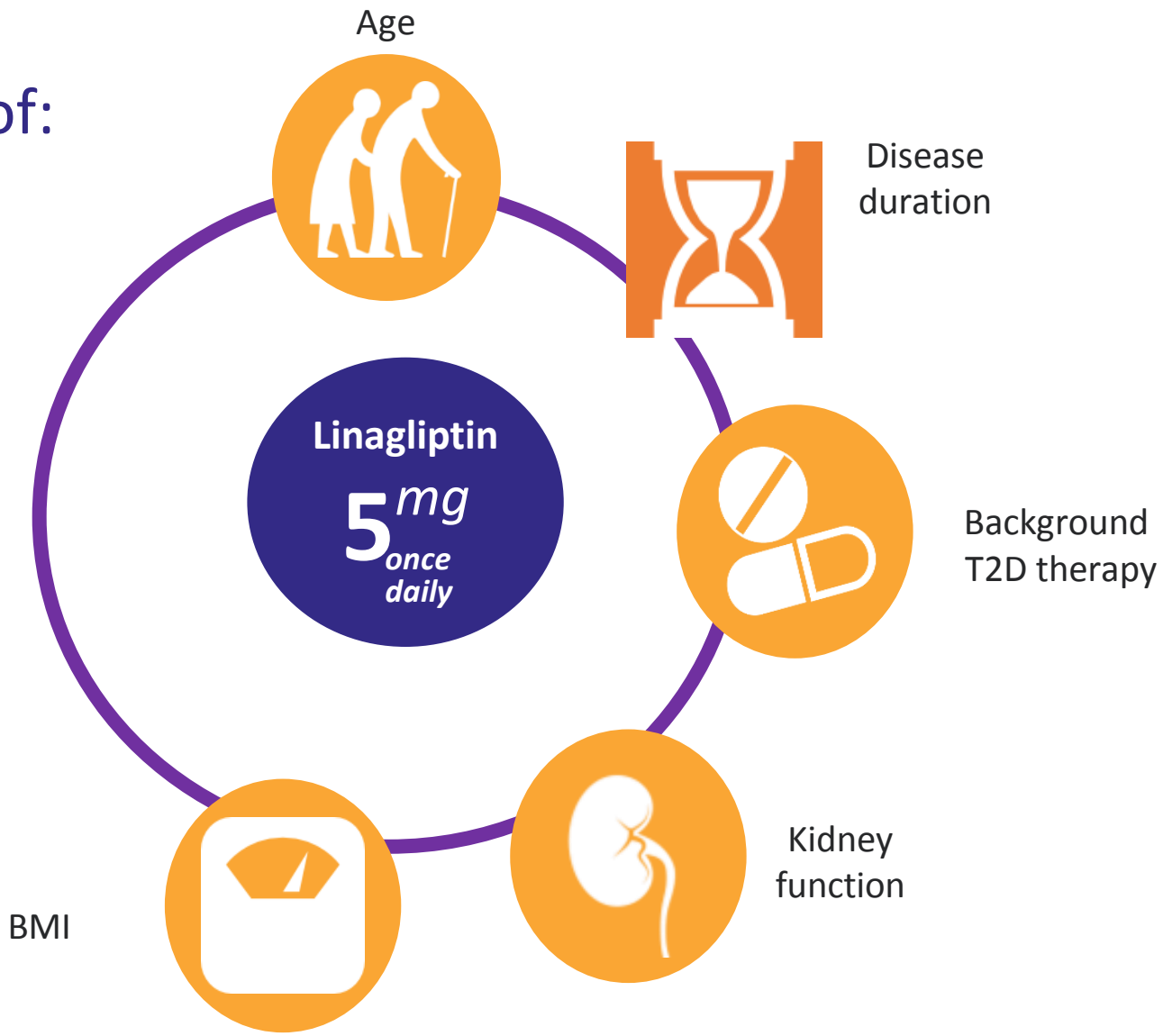

Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

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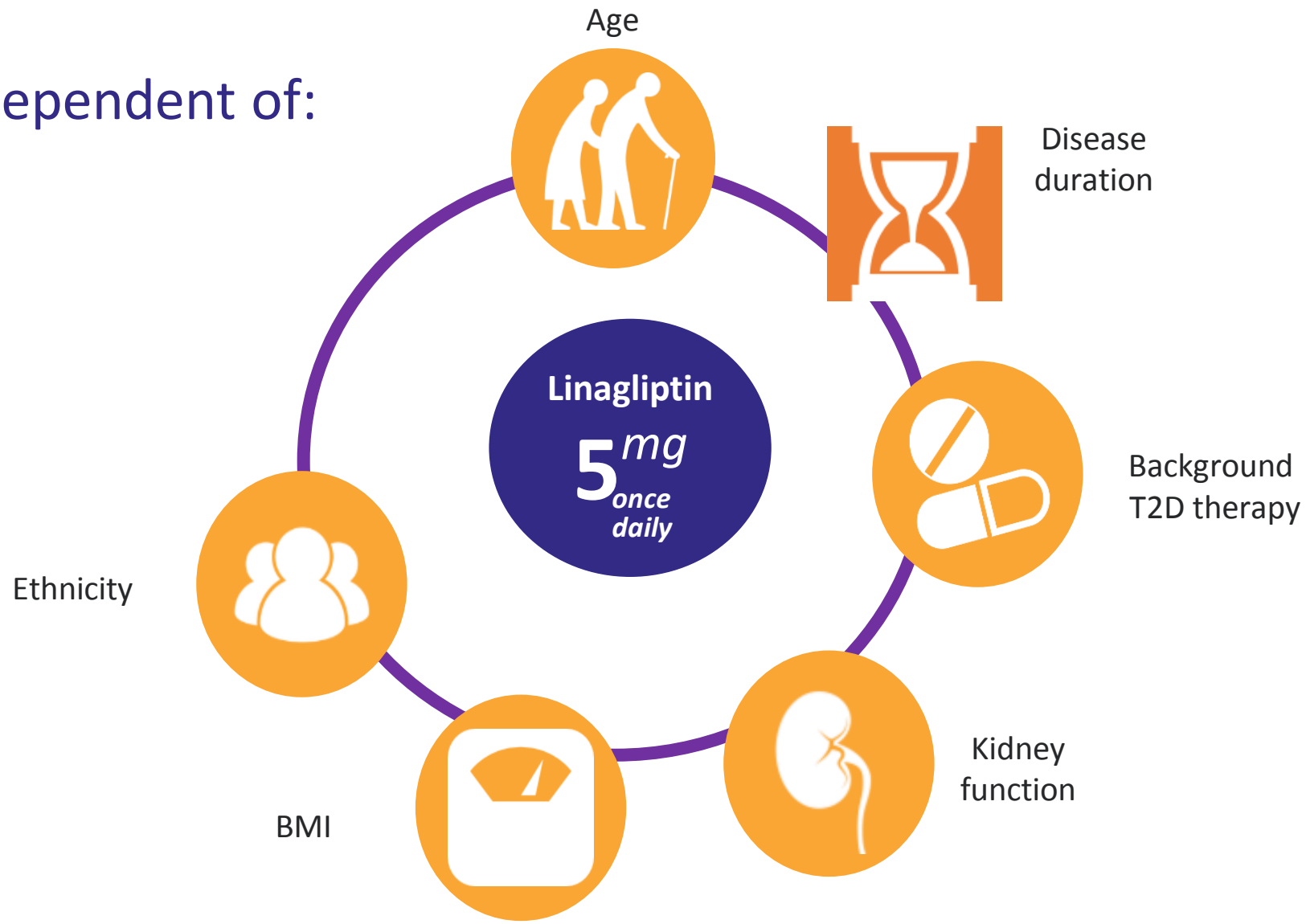

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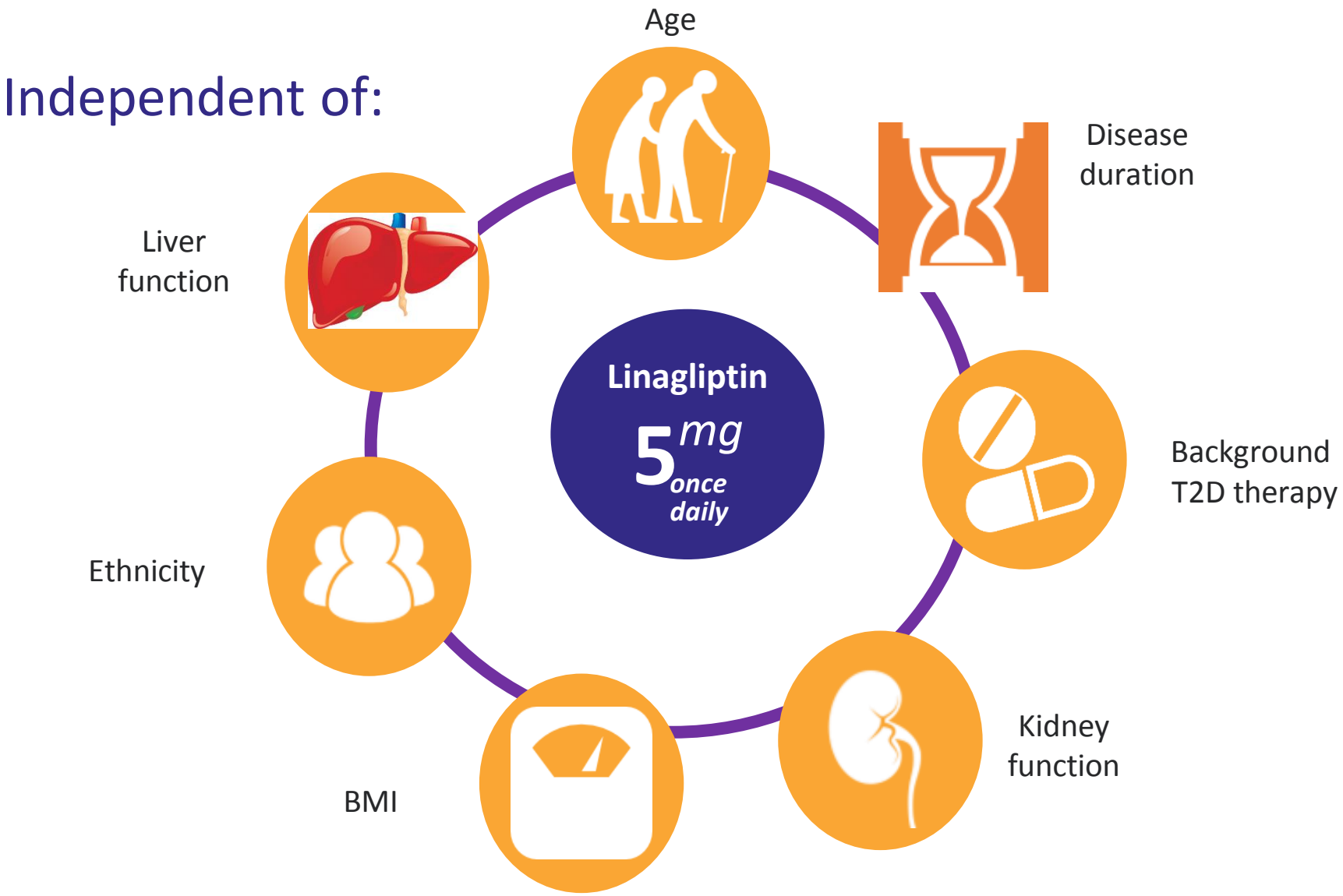


Boehringer Ingelheim and Eli Lilly. Trajenta®(linagliptin) Prescribing Information. 2017

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.

Can DPP-4 inhibitors be used in comorbid conditions ?

Elderly

Renal

Hepatic impairment

Elderly

Age is not a comorbid disease condition per se but usually a constellation that increases the likelihood of comorbid diseases.

In elderly patients with T2DM, reductions in Hb A1c after treatment with a DPP-4 inhibitor were not significantly different from those in younger patients and the use of DPP-4 inhibitors was associated with a **low risk of hypoglycemia** and also **weight neutrality**.

Renal impairment

With reduced GFR, toxicity of the oral drugs increases as the drugs tend to accumulate in the body. Except linagliptin every gliptin dose has to be reduced in case of moderate to severe renal impairment.

Hepatic impairment

No significant changes in liver enzymes were reported with DPP-4 inhibitors alone or in combination with various other glucose-lowering agents.

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) Study Design[1]

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

*50 mg daily if the baseline eGFR was ≥ 30 and < 50 mL per minute per 1.73 m^2.

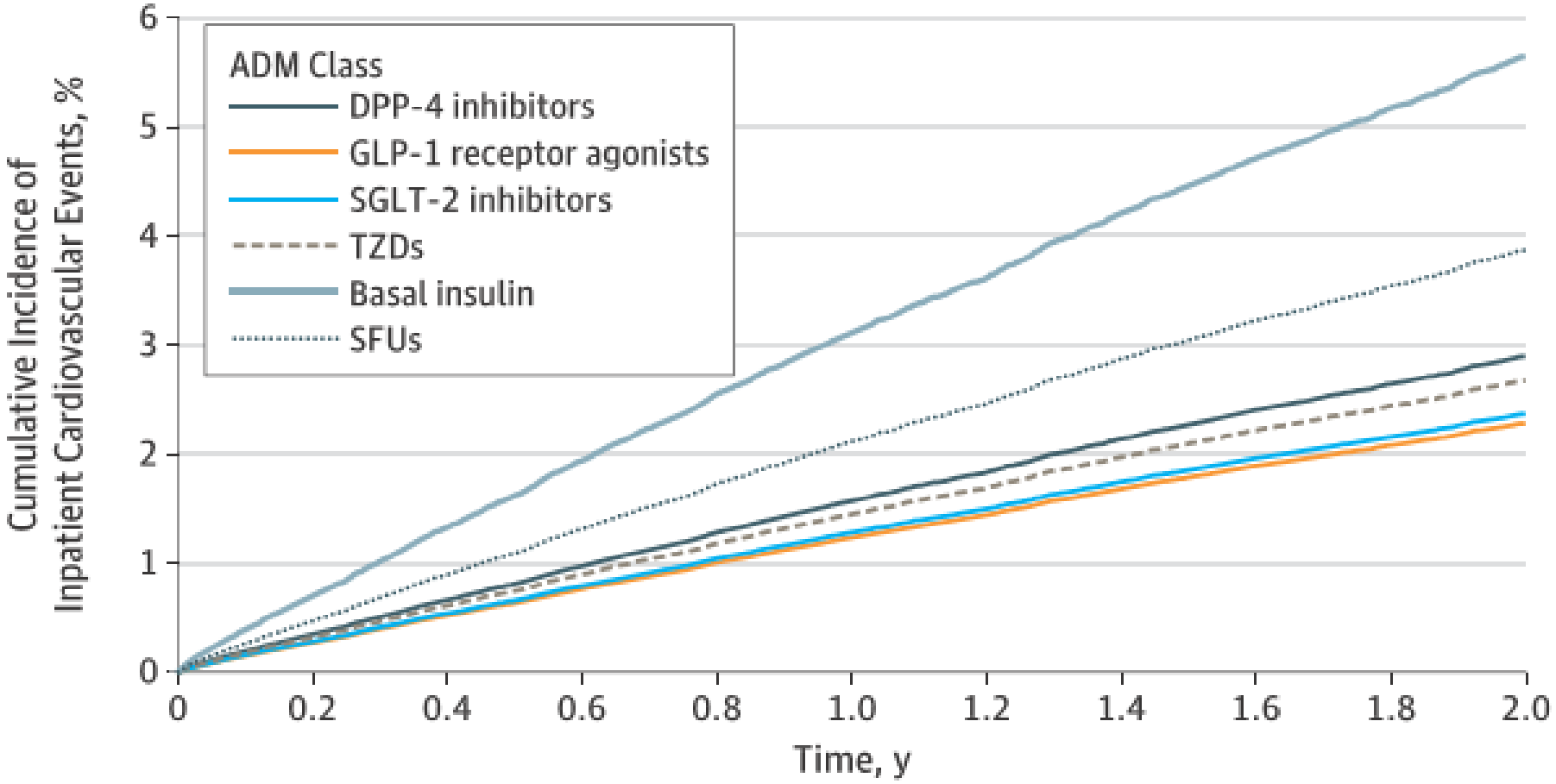
1-N Engl J Med. 2015.16;373(3):232-42

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

The DPP-4 inhibitors were well tolerated in short term studies. The long-term safety with DPP-4 inhibitors has not been established.

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.

بیمار آقای ۵۲ ساله با دیابت تیپ ۲ مراجعه کرده است. وی سالهاست که تحت درمان با انسولین می باشدو با آزمایشات زیر مراجعه کرده است:

FBS=150 mg/dl HbA1C=8.5% Cr=2.9 mg/dl Tg=155 mg/dl

Total cholesterol=180 mg/dl HDL-C=39 mg/dl

تجویز کدام دارو در بیمار ارجحتر است؟

Linagliptin

متفورمین

Sitagliptin

Zip-Met

خانم ۴۵ ساله ای با دیابت نوع ۲ که تحت درمان با متفورمین روزانه ۲۰۰۰ mg می باشد با آزمایشات زیر مراجعه کرده است.

FBS=185 mg/dl BS 2hpp= 230 mg/dl HbA1C= 8.2%

BMI=40 kg/m2 WT=120 kg

کدام درمان داروی در بیمار ارجحتر است؟

اضافه کردن سولفونیل اوره

اضافه کردن انسولین Lantus

اضافه کردن پیوگلیتازون

اضافه کردن آگونیست GLP-1


Thank you