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38TH ANNUAL MEETING

September 13-15, 2023 MILWAUKEE, WI

Disclosures

No relevant disclosures.

AACVPR ignite 38TH ANNUAL MEETING

Incretin Drugs

New Hope for Weight Loss and Diabetes

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Atlantic Health System

Obesity is a chronic, progressive, relapsing disease.

The treatment of obesity can no longer be reduced to a simplistic view of weight loss.

Metabolic adaptations almost always lead to systematic weight gain following weight-loss.

Incretin drugs offer hope for sustainable weight loss that greatly reduces cardiometabolic risk.

Weight loss that substantial enough to not only improve type 2 diabetes but to put it into remission.

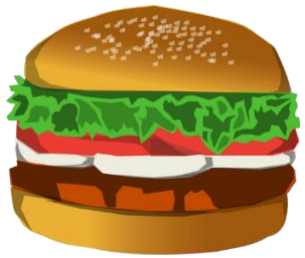
What's On Our Plate Today

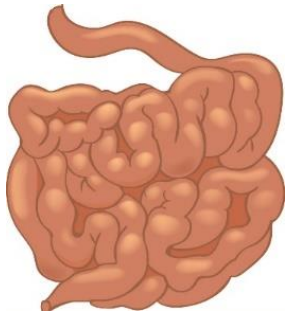
1. Basic Metabolism and Diabetes
2. The Incretin System
3. GLP and GLP/GIP Drugs
4. Diabetes Benefits
5. ASCVD Risk Reduction

What's On Our Plate Today

6. Prescribing Recommendations
7. Contraindications
8. Side Effects
9. General Guidelines / FAQs / Controversies
10. What's coming!

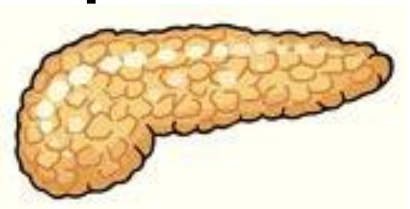
Basic Metabolism and Diabetes





Blood Sugar↑

β cells



↑Insulin

Blood Sugar↓

Insulin

Glucagon

Blood Sugar↑

β cells
↑Insulin

Blood Sugar↓

α cells
↑Glucagon

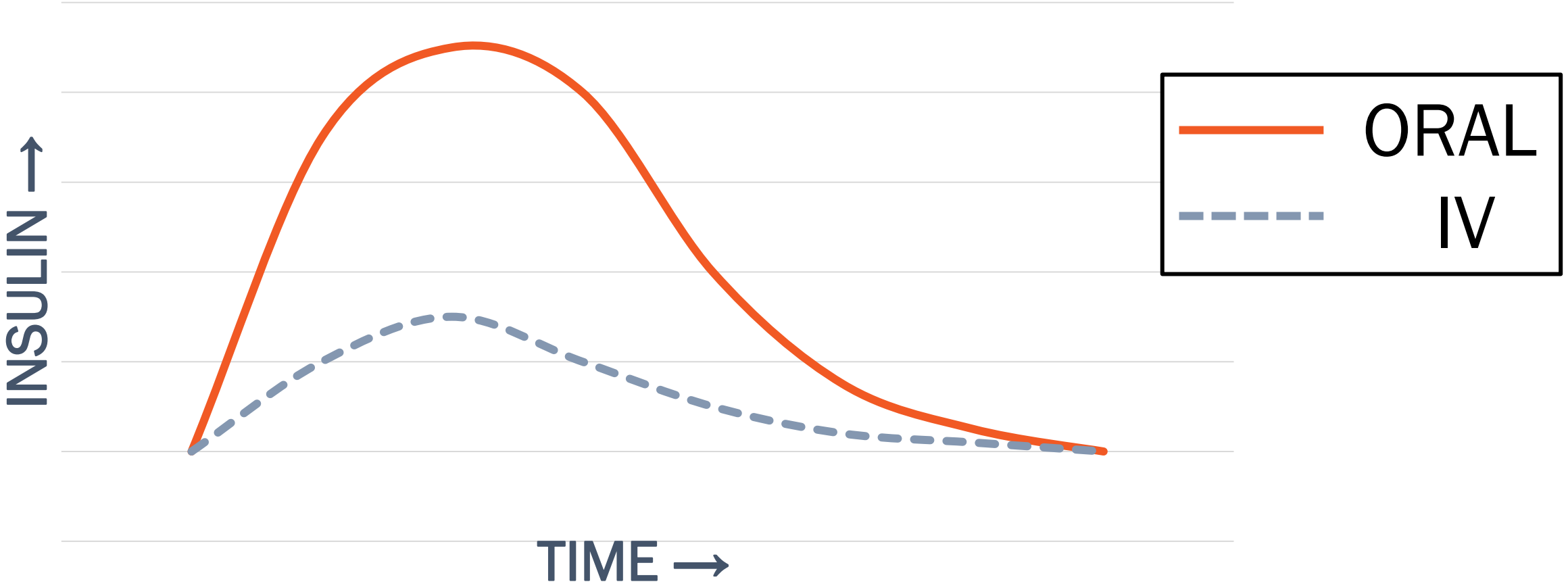
Release glucose

Three Major Defects in Type 2 Diabetes

- Pancreas makes too little insulin
- Insulin doesn't work well - "insulin resistant"
- Pancreas makes too much glucagon

The Incretin System

Normal



This family of hormones was named...

Incretins

Incretins…

Gut hormones that increase insulin production by a glucose-dependent mechanism

Incretins…

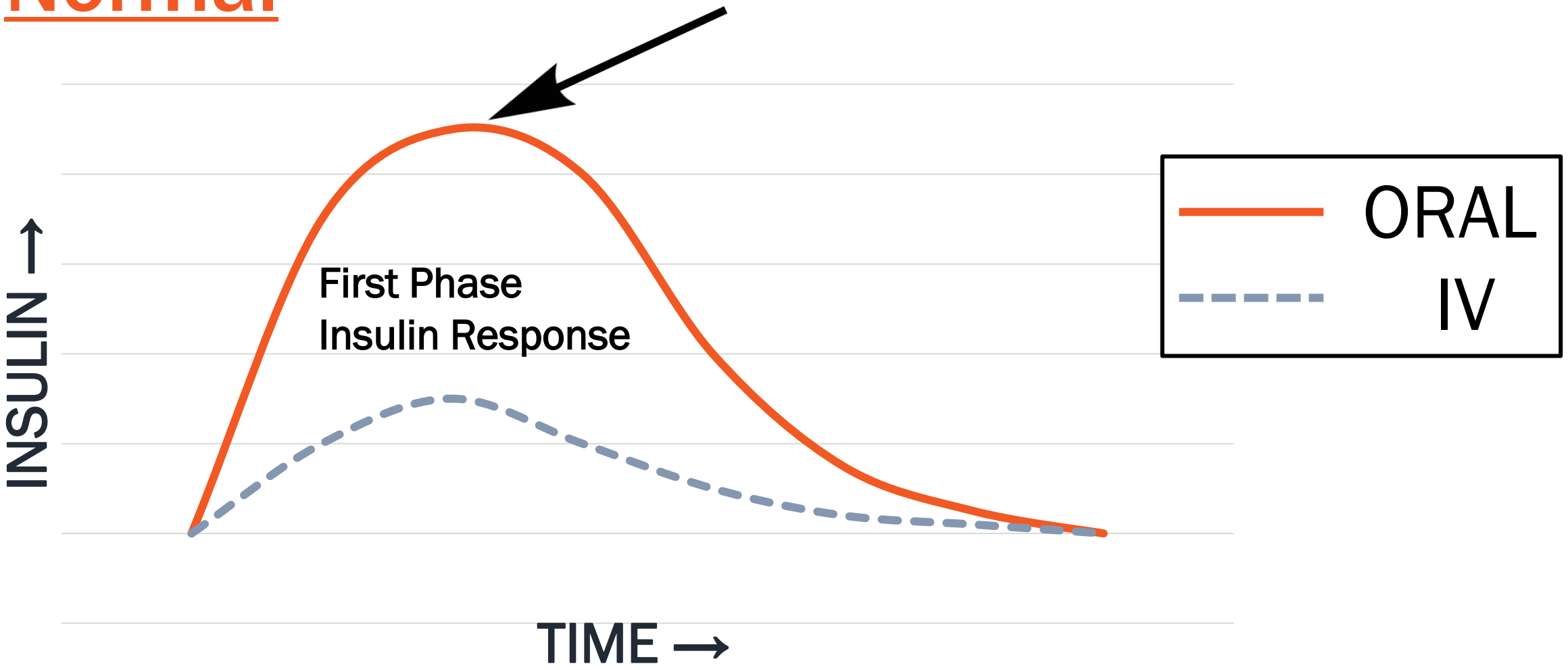
Gut hormones that increase insulin production by a glucose-dependent mechanism

Incretins…

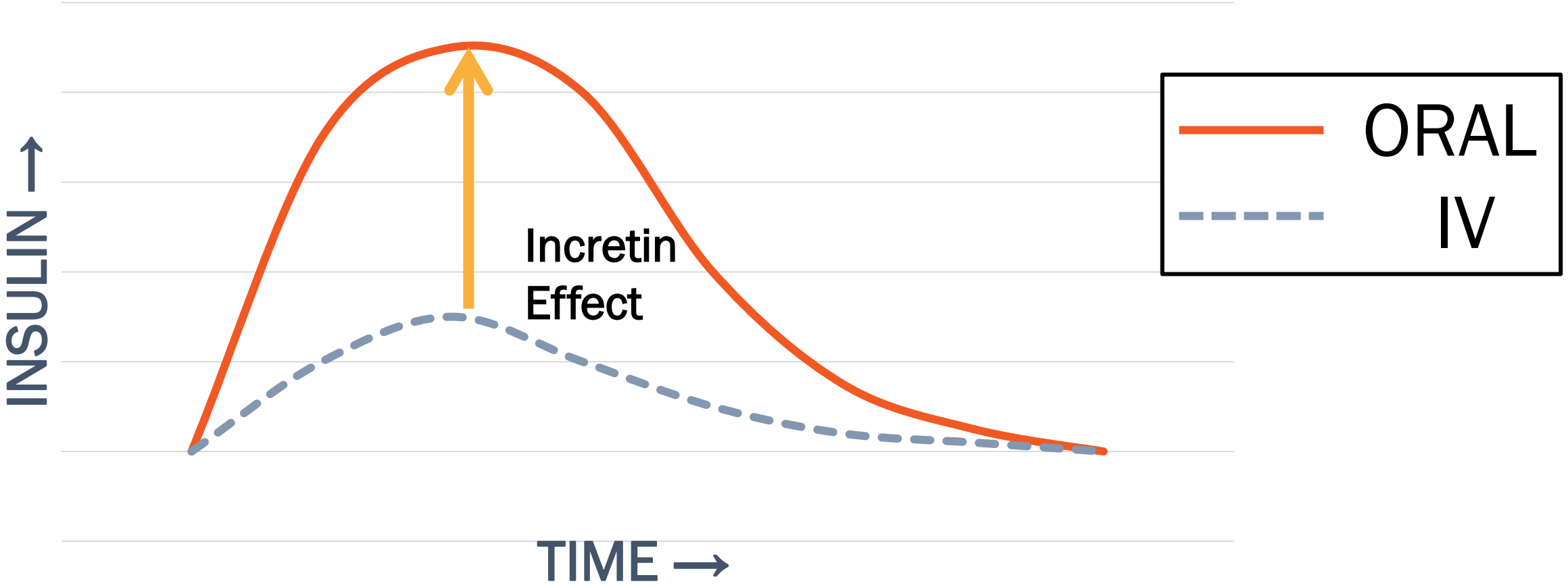
glucose-dependent…

…aka almost no risk of hypoglycemia

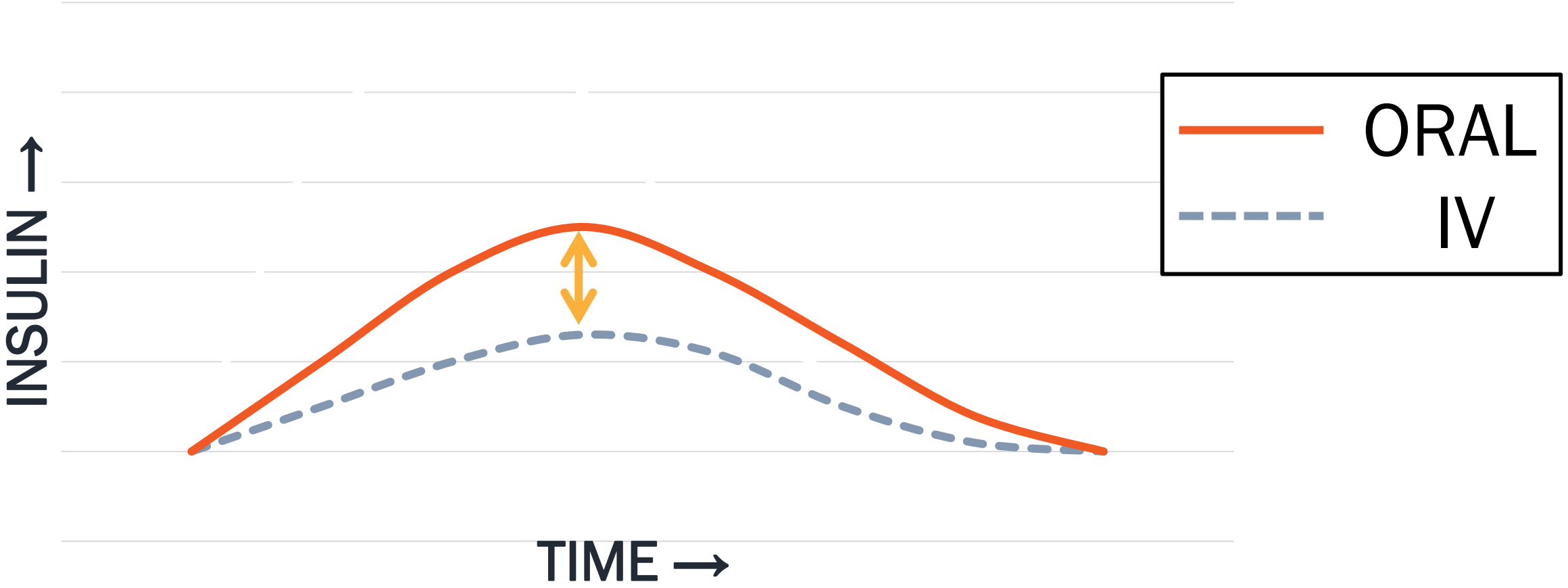
Normal



Normal



Incretin Effect Blunted with Type 2 Diabetes



The Plan

1. Discover incretins

2. Make the incretin system work better to help improve blood sugars for people with diabetes

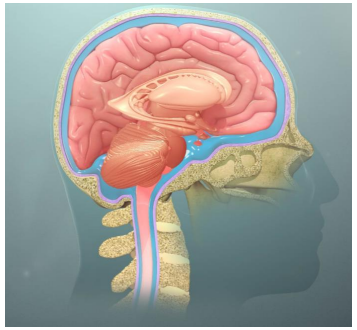
Fast Forward…
We Found 2 Incretins!

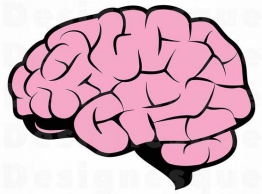
- GLP1

  (glucagon-like peptide 1)

- GIP

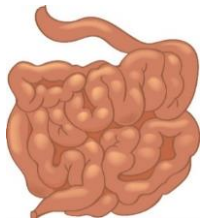
  (glucose-dependent insulinotropic polypeptide)





↓Appetite

↓



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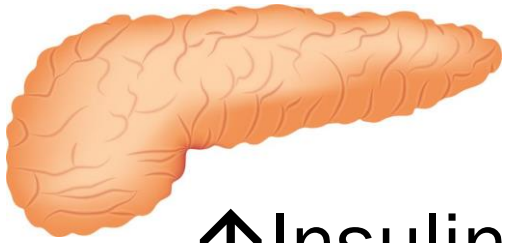
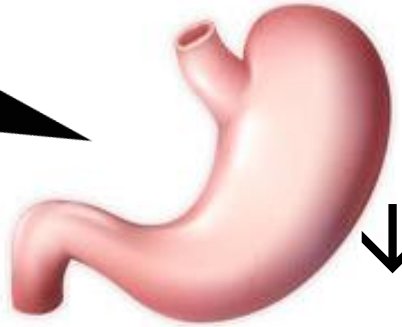
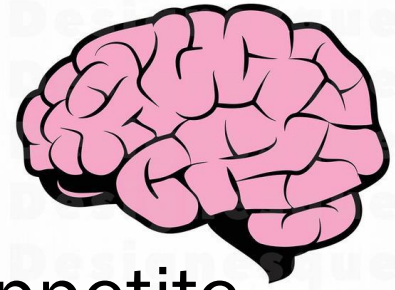
GLP1 & GIP



↑Insulin
↓Glucagon



↓Gastric Emptying



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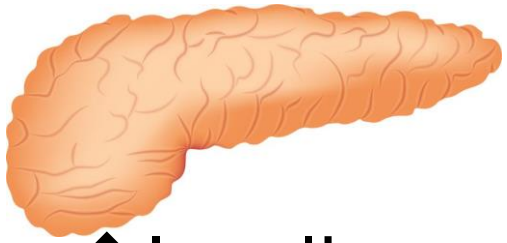
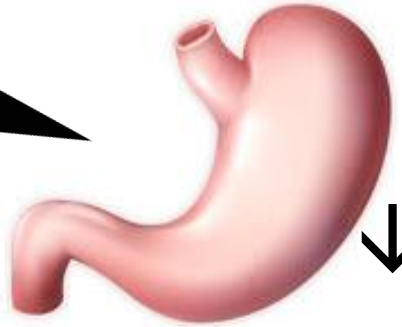


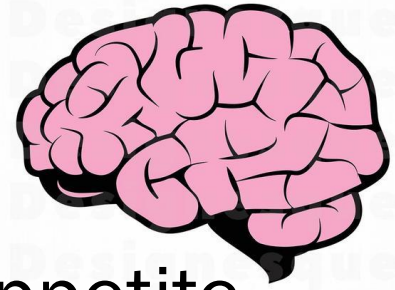
↑Insulin
↓Glucagon

GLP1
RA

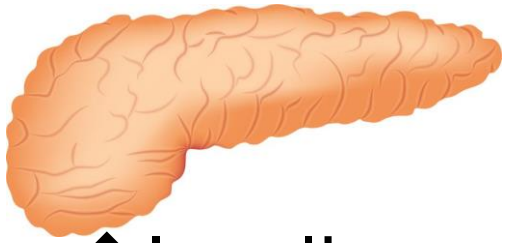


↓Gastric
Emptying

GLP1-RA – works at supraphysiologic level

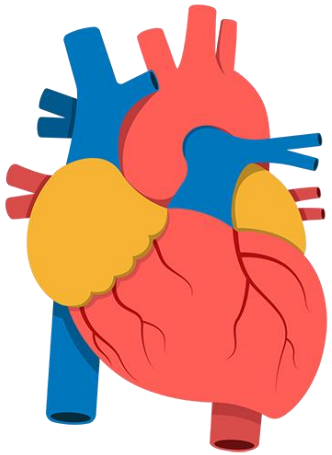


↓Appetite

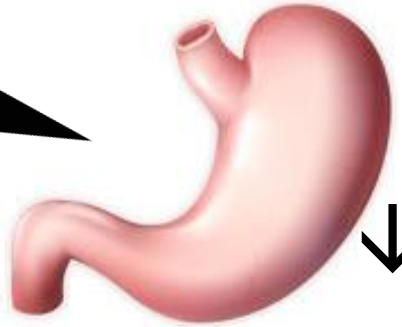


↑Insulin
↓Glucagon
↑β-cell proliferation
↓β-cell apoptosis

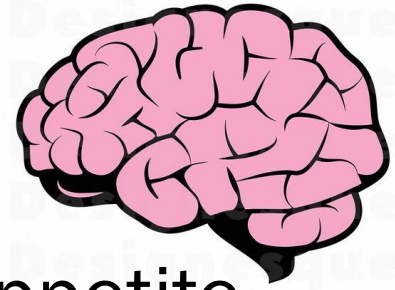
GLP1 RA



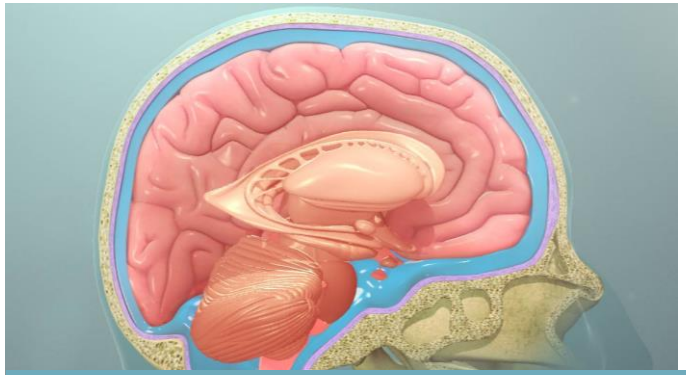
↑ Cardio-protection

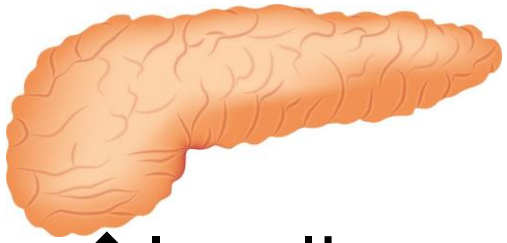


↓Gastric Emptying



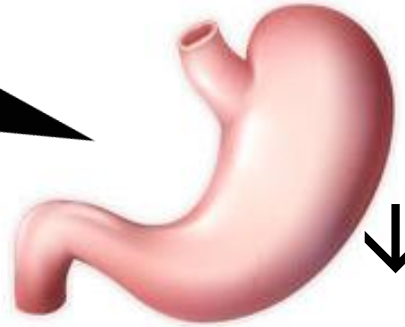
↓Appetite





↑Insulin
↓Glucagon
↑β-cell proliferation
↓β-cell apoptosis

GIP RA



↓Gastric Emptying

GIP RA don't seem to be effective on their own – but boosts effectiveness when added to GLP1 RA

GLP1 Receptor Agonists

Glucagon Like Peptide 1 Receptor Agonists

GLP1-RA

GLP1

GLP

Incretin Mimetics

GIP Receptor Agonists

Glucose-dependent insulinotropic polypeptide

GIP RA

GIP

GLP1 and GLP1/GIP-RA

Let's Meet The Diabetes GLP1-RA and GLP1/GIP RA

- Bydureon BCise (exenatide)
- Victoza (liraglutide)
- Trulicity (dulaglutide)
- Ozempic (semaglutide)
- Rybelsus (semaglutide)
- Mounjaro (tirzepatide)

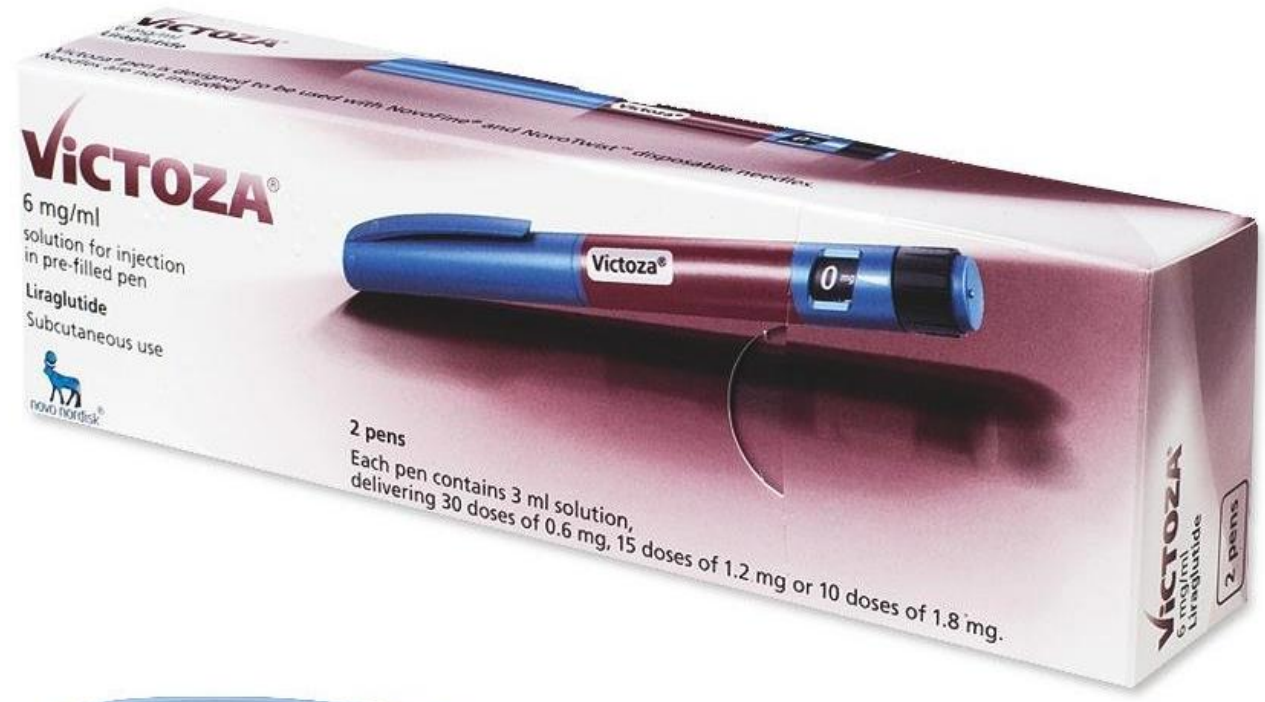
Once-weekly

BYDUREON® BCise™

exenatide extended-release injectable suspension 2 mg

VICTOZA®

liraglutide injection 1.2 mg | 1.8 mg



Daily Injection

trulicity™

dulaglutide once-weekly injection

ONCE-WEEKLY

OZEMPIC®

semaglutide injection 0.5mg, 1mg, 2mg

ONCE-DAILY

RYBELSUS®

semaglutide tablets 7mg | 14mg

once weekly

mounjaro®

(tirzepatide) injection 0.5 mL

2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

Let's Meet the Weight Loss GLP1-RA

- Saxenda (liraglutide)
- Wegovy (semaglutide)

Saxenda®

liraglutide (rDNA origin) injection

Daily Injection

Same exact drug as Victoza – higher max dose

ONCE-WEEKLY

wegovy™

semaglutide injection 2.4 mg

Same exact drug as Ozempic – higher max dose

Glycemic Benefits

Diagnosis	A1C Level
Normal	<5.7%
PreDiabetes	5.7-6.4%
Diabetes	≥6.5%

A1C to Estimated Average Glucose (eAG)

A1C%	eAG
9	212
8.5	197
8	183
7.5	169
7	154
6.5	140
6	126

From the American Diabetes Association https://professional.diabetes.org/diapro/glucose_calc

A1C goals (general)

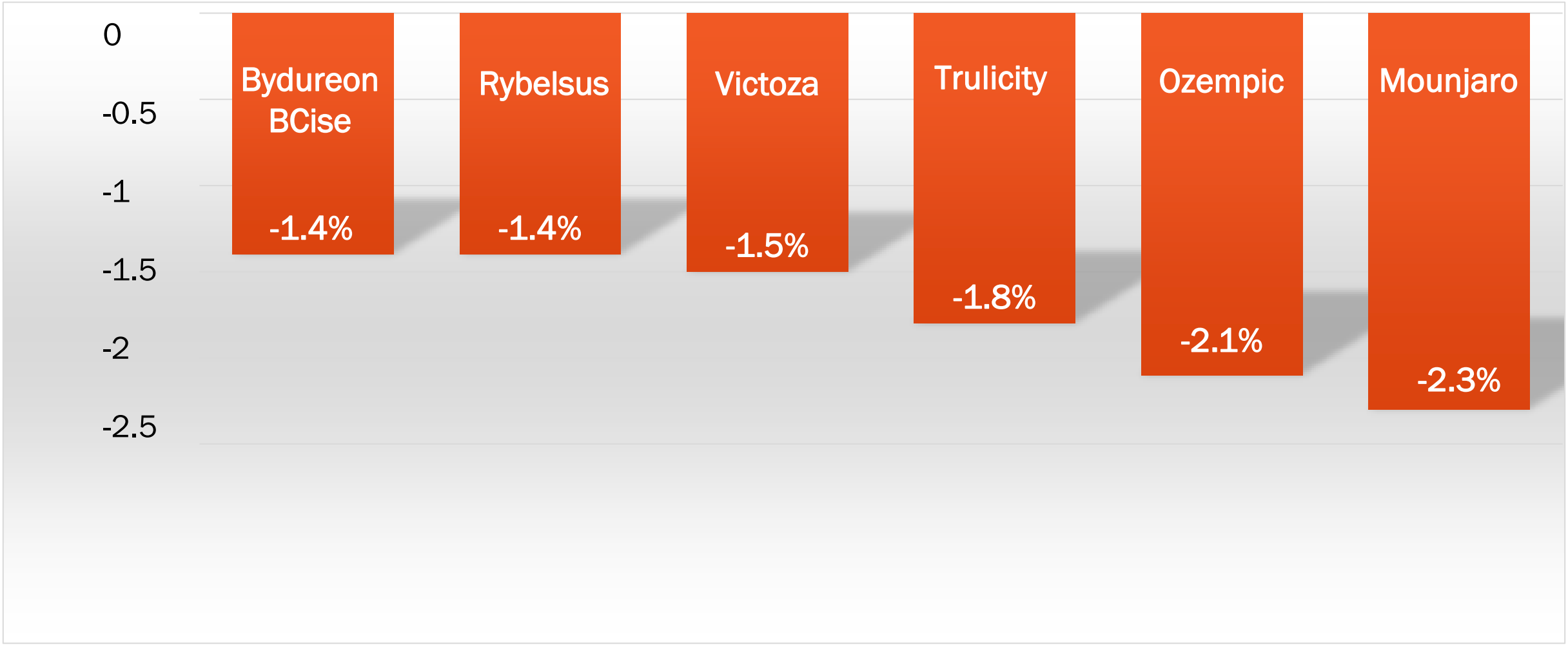
ADA – Less than 7%

AACE - 6.5% or less

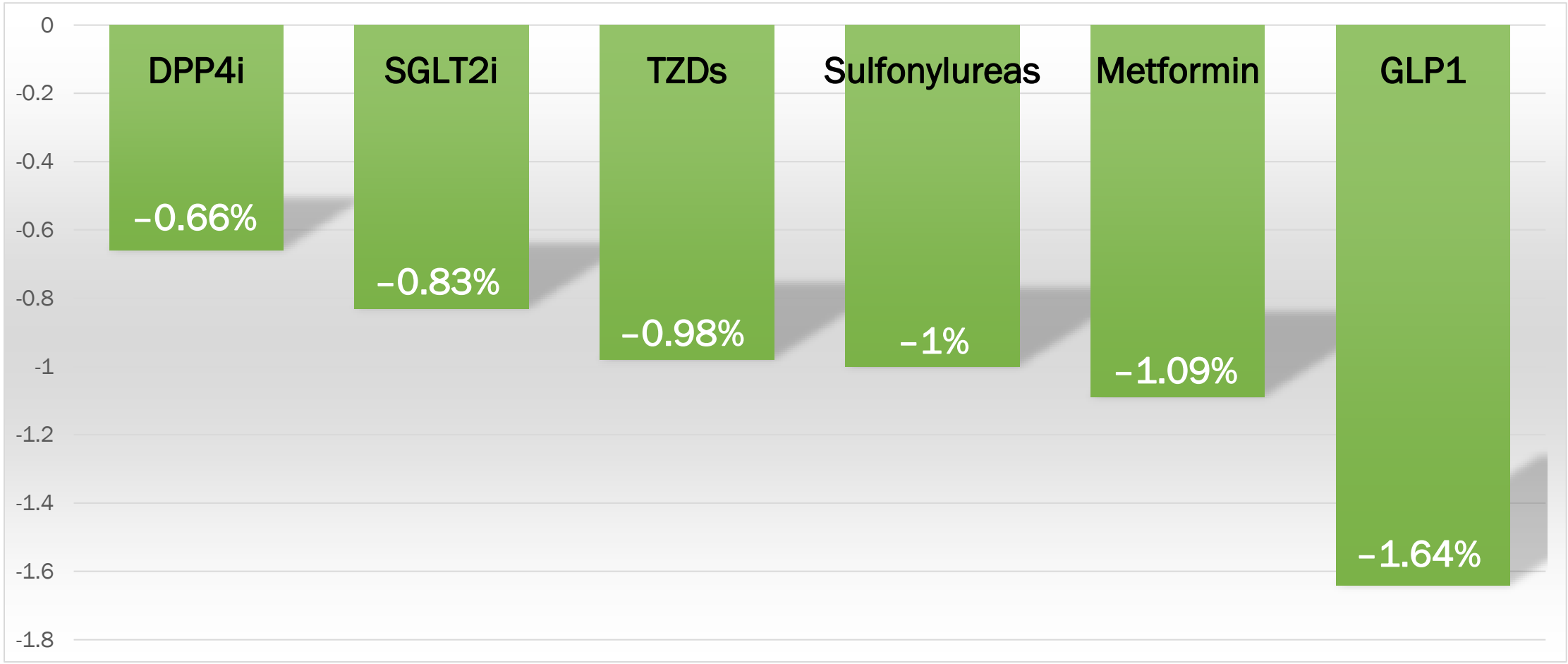
A1C%	eAG
9	212
8.5	197
8	183
7.5	169
7	154
6.5	140
6	126

ADA – American Diabetes Association AACE – American Association of Clinical Endocrinologists

Average A1C Reduction on Highest Dose of Each Medication

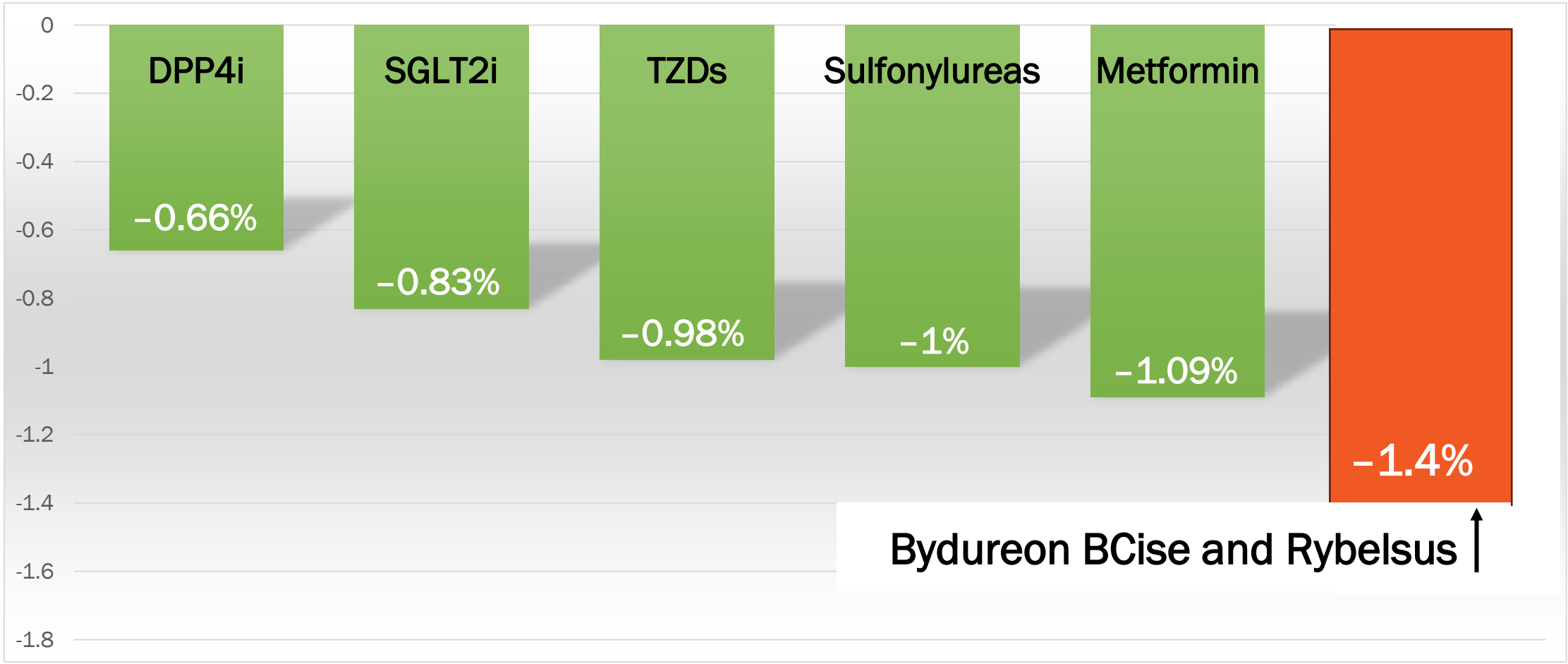


Average A1C Reduction for Highest Dose in Each Drug Category



The weakest GLP1 is stronger than all other diabetes medication categories.

Average A1C Reduction for Highest Dose in Each Drug Category Compared to Weakest GLP1



And remember

Incretins are…

glucose-dependent…

…aka almost no risk of hypoglycemia

ASCVD Risk Reduction

MACE

Major Adverse Cardiac Events

MACE include…

Non-fatal stroke

Non-fatal MI

CV Death

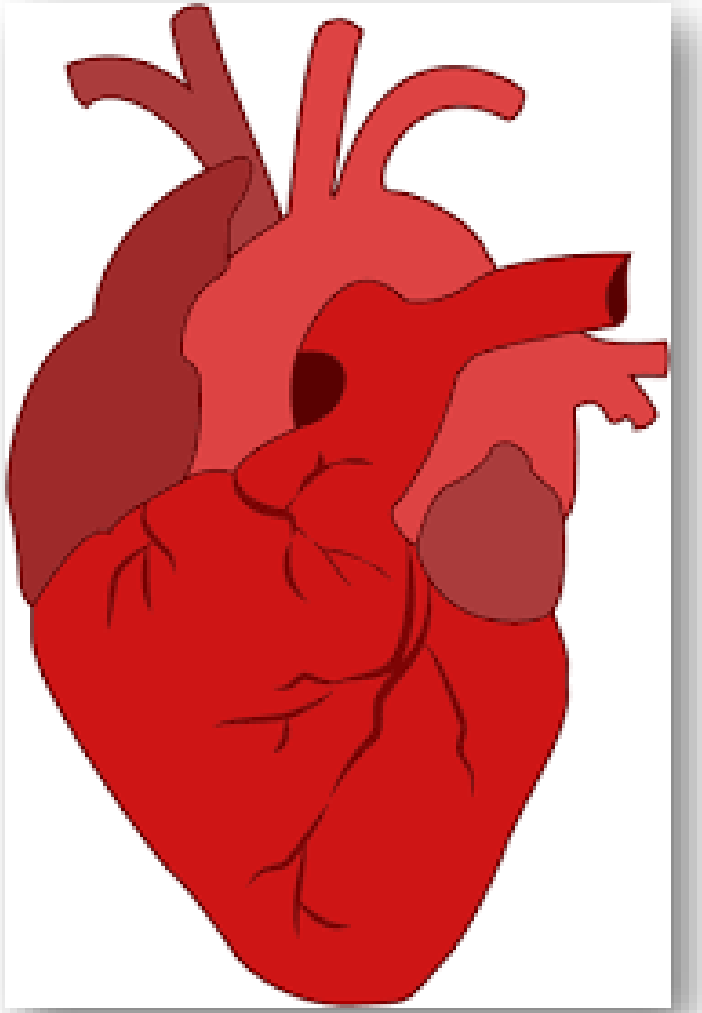
Shown to Be Cardioprotective?

YES

Victoza

Trulicity

Ozempic



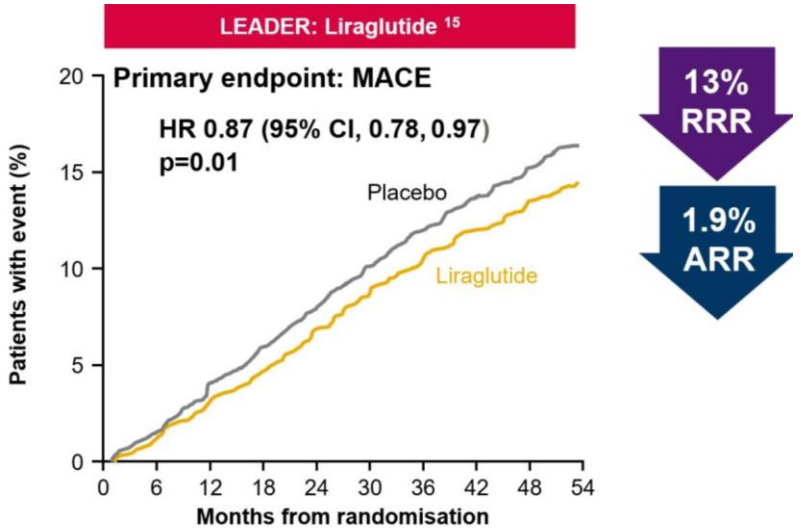
NO

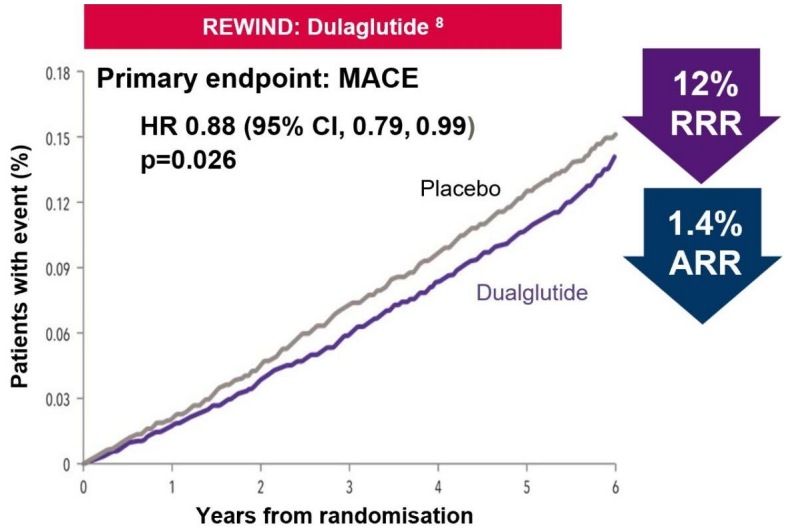
Bydureon BCise

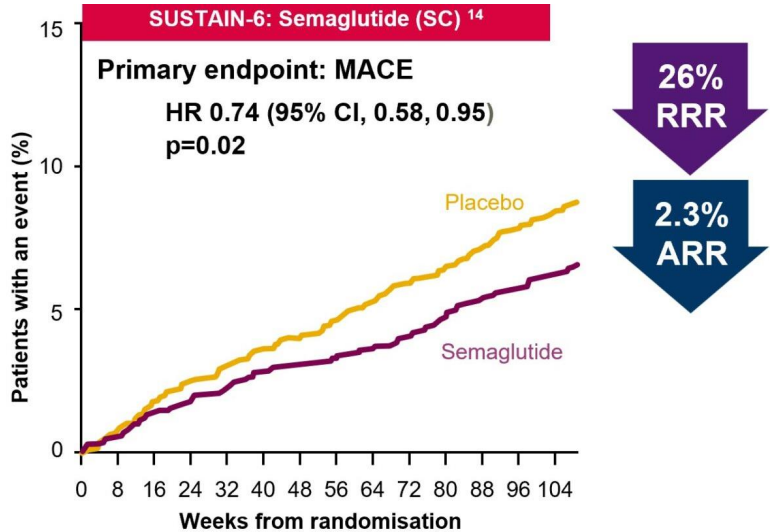
Rybelsus

Mounjaro

Three GLP-1 CVOTs reduced MACE in a T2DM patient cohort







Semaglutide (SC only), Dulaglutide & Liraglutide are recommended to reduce MACE in patient with e-CVD (secondary prevention).

https://local.clinicalpathways.io/nwl-diabetes-guidelines/frame/

ARR and RRR

Actual Risk Reduction (ARR)

and

Relative Risk Reduction (RRR)

ARR

The actual reduction of one thing versus another

4% vs 3%

ARR is 1%

(3% is 1% less than 4%)

RRR

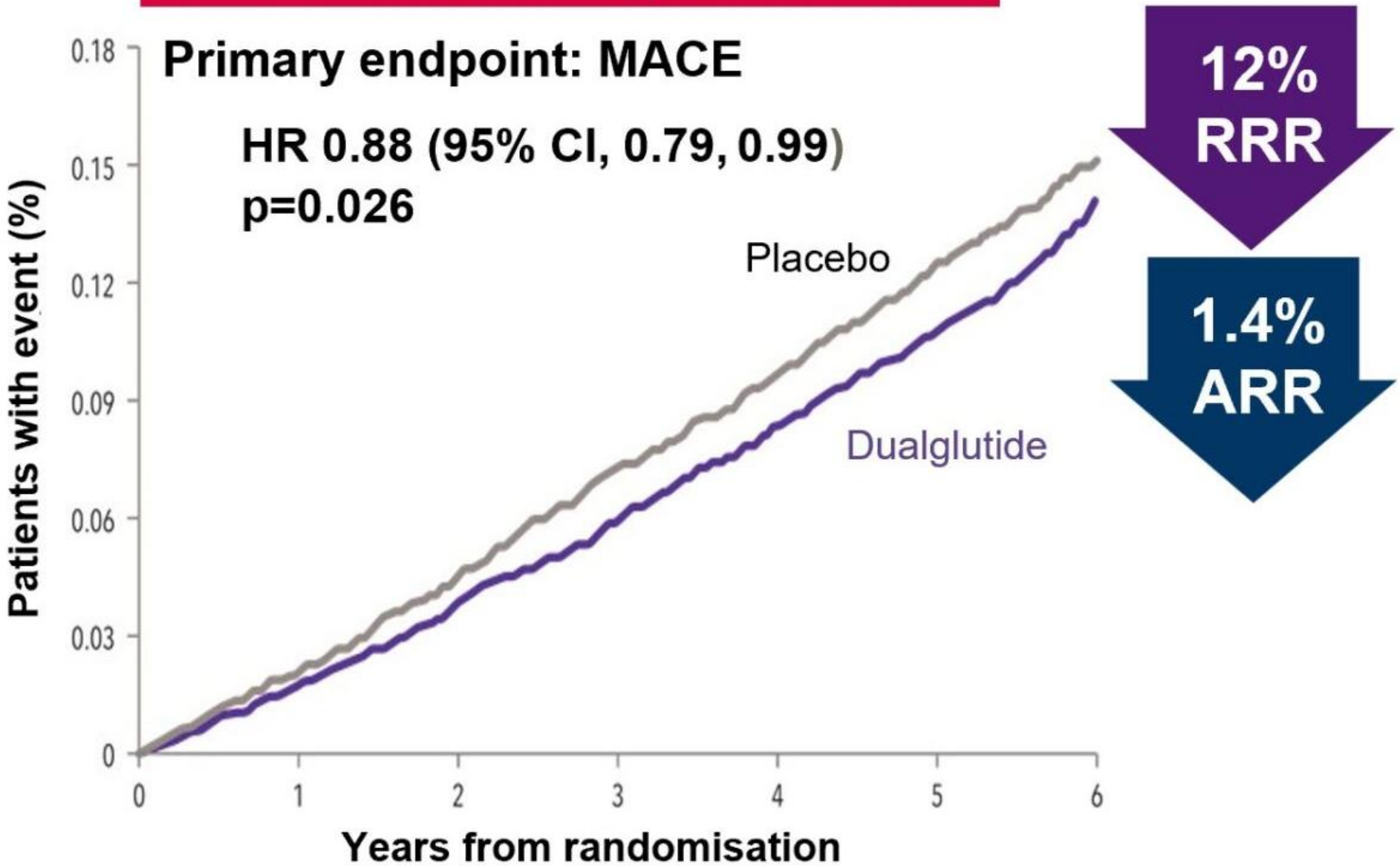
The reduction of one risk *compared* to another.

4% vs 3%

RRR is 25%

(3% is 25% less than 4%)

REWIND: Dulaglutide [8]

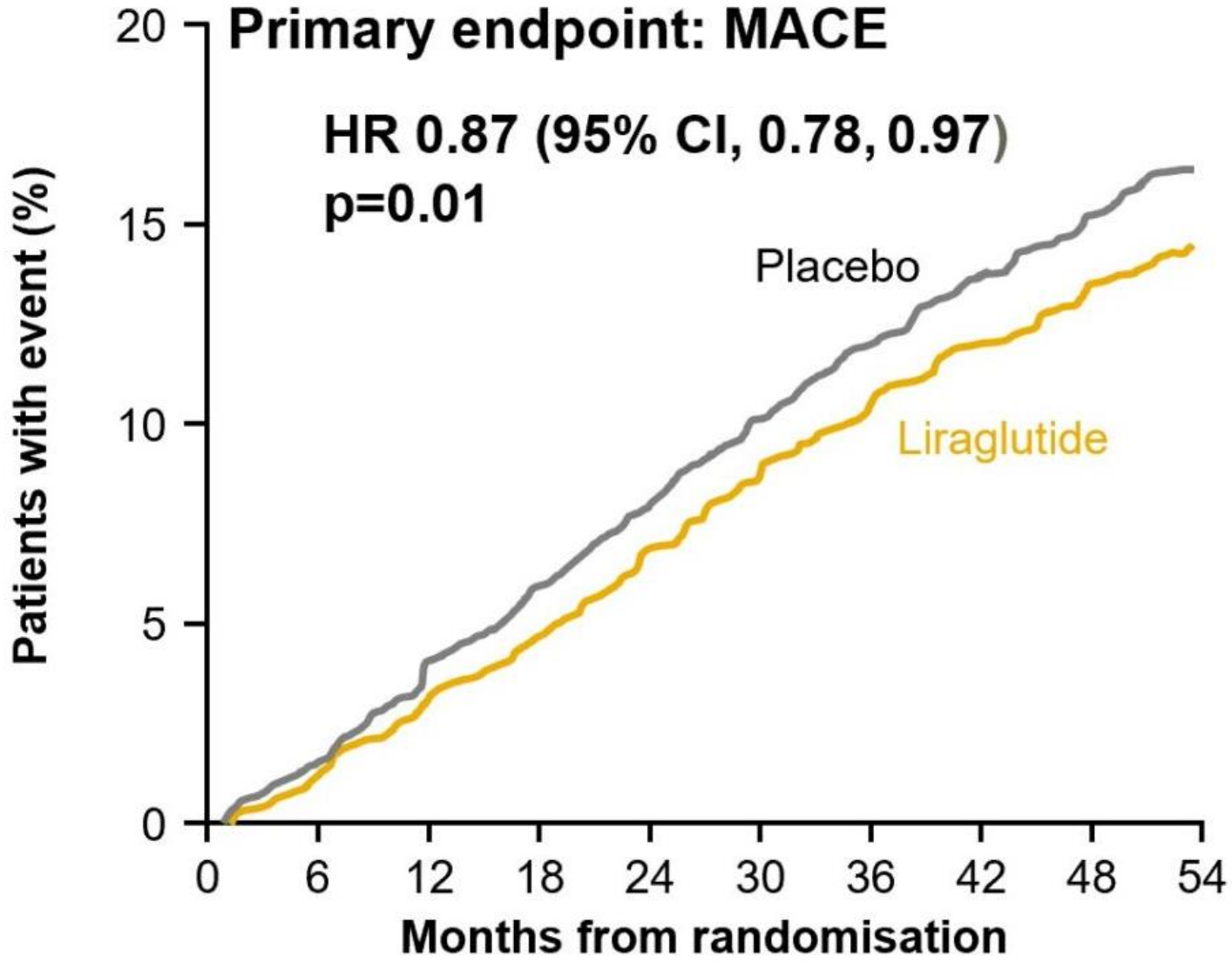


12% RRR

1.4% ARR

Trulicity

LEADER: Liraglutide [15]



13% RRR

1.9% ARR

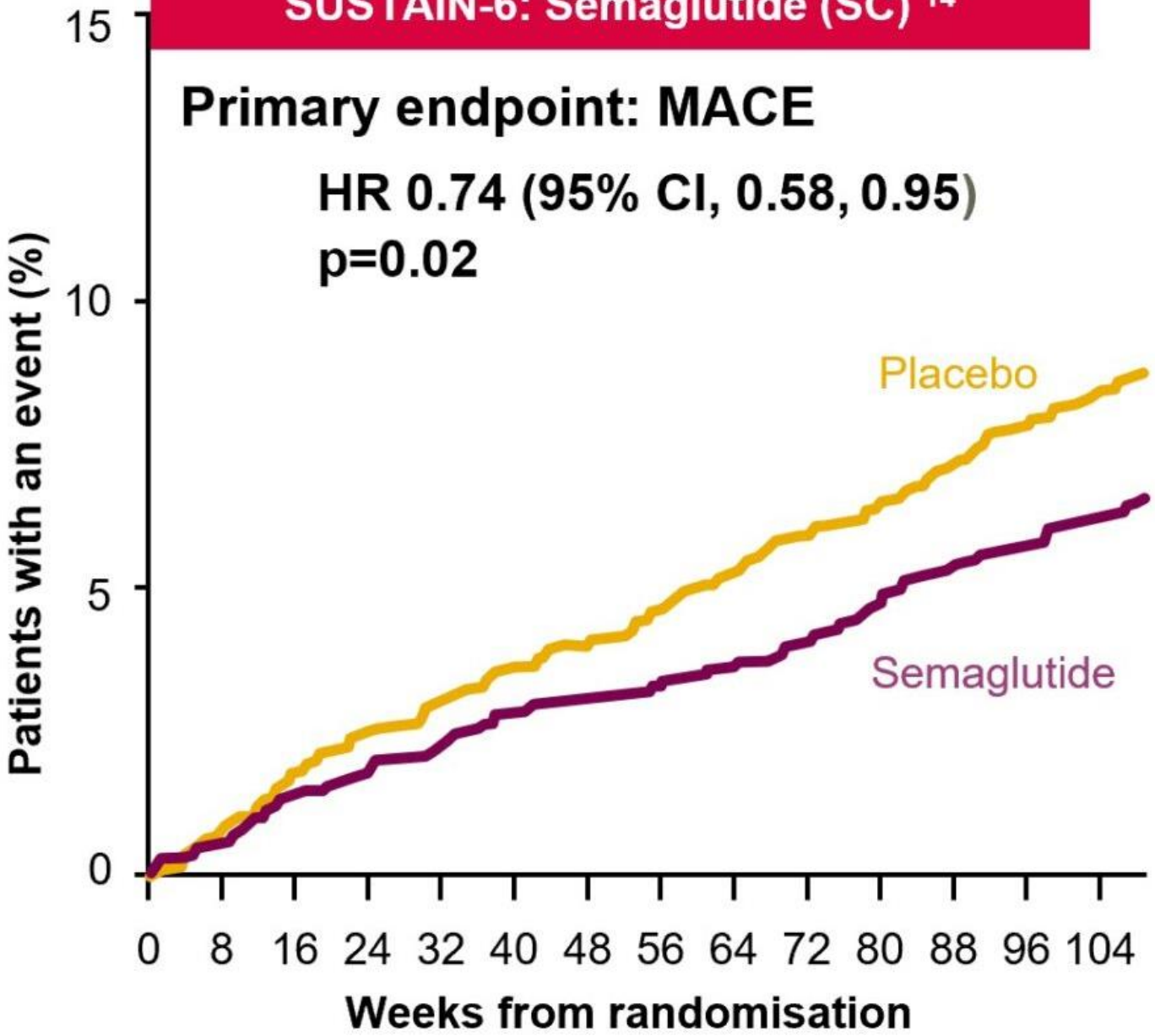
Victoza

SUSTAIN-6: Semaglutide (SC) [14]

Primary endpoint: MACE

HR 0.74 (95% CI, 0.58, 0.95)

p=0.02



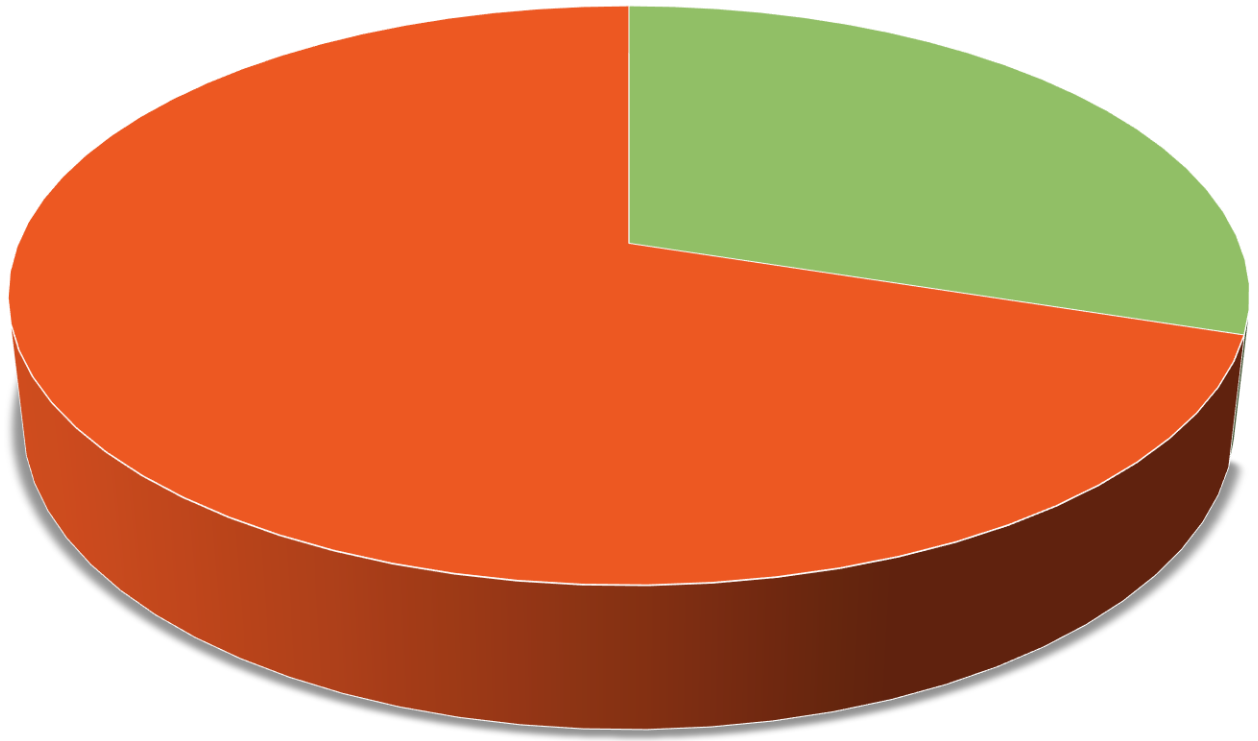
26% RRR

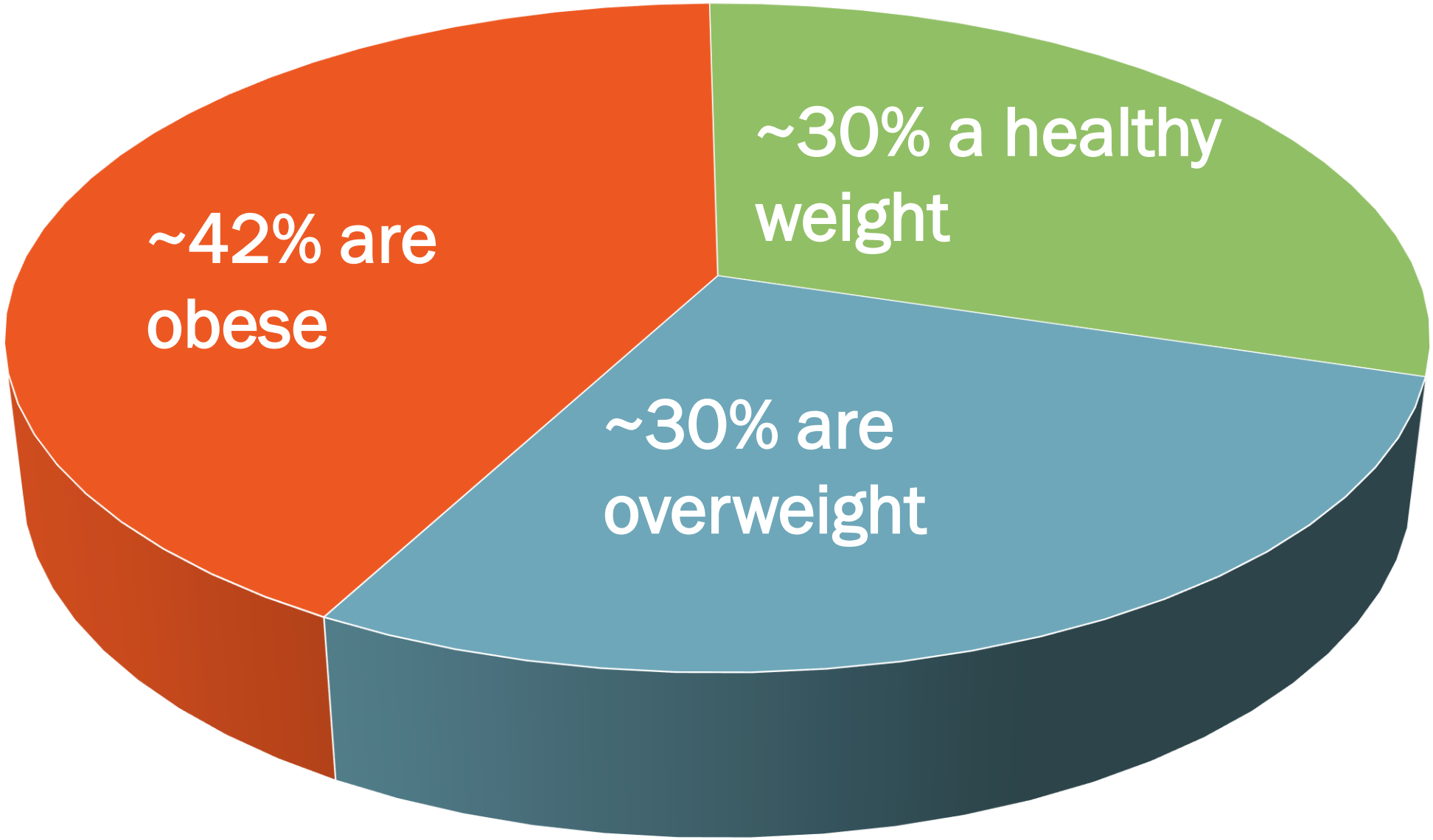
2.3% ARR

Ozempic

Weight Loss

Over 70% of us are overweight or obese




~42% are obese
~30% a healthy weight
~30% are overweight

Why is it so hard?

Physiology + Obesogenic Environment = Obesity

“The brain has developed “…Neural pathways specialized in satiety, hunger and energy expenditure…These pathways have been programmed through millennia of human phylogenetic development so that homeostasis maintains a person's weight at the highest possible level”

doi: 10.17925/EE.2022.18.1.35

"Thus, even if people with obesity temporarily succeed in losing weight, they immediately face millennia of adaptation leading to weight regain, often to an even greater level from where they started."

doi: 10.17925/EE.2022.18.1.35

"Given the complex pathophysiology of obesity and the potent counterregulatory neuroendocrine pathways activated to counter weight loss, obesity can no longer be attributed to a lack of willpower."

doi: 10.17925/EE.2022.18.1.35

Obesity is a chronic, progressive, relapsing disease.

Just 5%

- Blood sugars improve
- Blood pressure improves
- Triglycerides improve

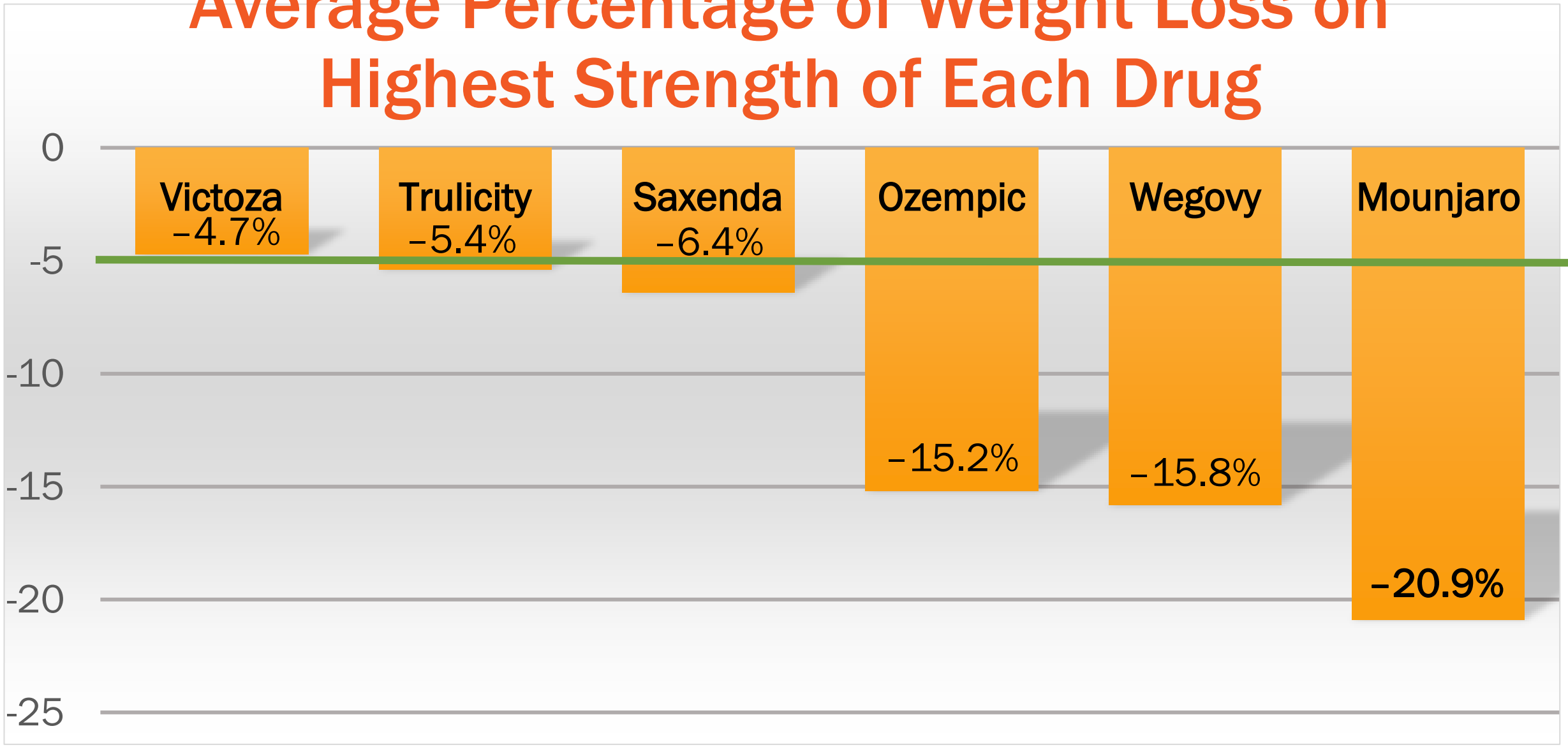
10%

- Can prevent diabetes
- Non-alcoholic fatty liver disease improves
- Dyslipidemia improves

>15%

- Type 2 diabetes – possible for some cases of diabetes to go into remission

Average Percentage of Weight Loss on Highest Strength of Each Drug



Prescribing Recommendations


American
Diabetes
Association®


AACE®
American Association
of Clinical Endocrinology


EASD
European Association
for the Study of Diabetes

Independent of A1C, if…

established or high risk for

ASCVD

…start a GLP1-RA or SGLT2i with proven benefit

Newly Diagnosed?

Newly Diagnosed?

Independent of A1C, if…

established or high risk for

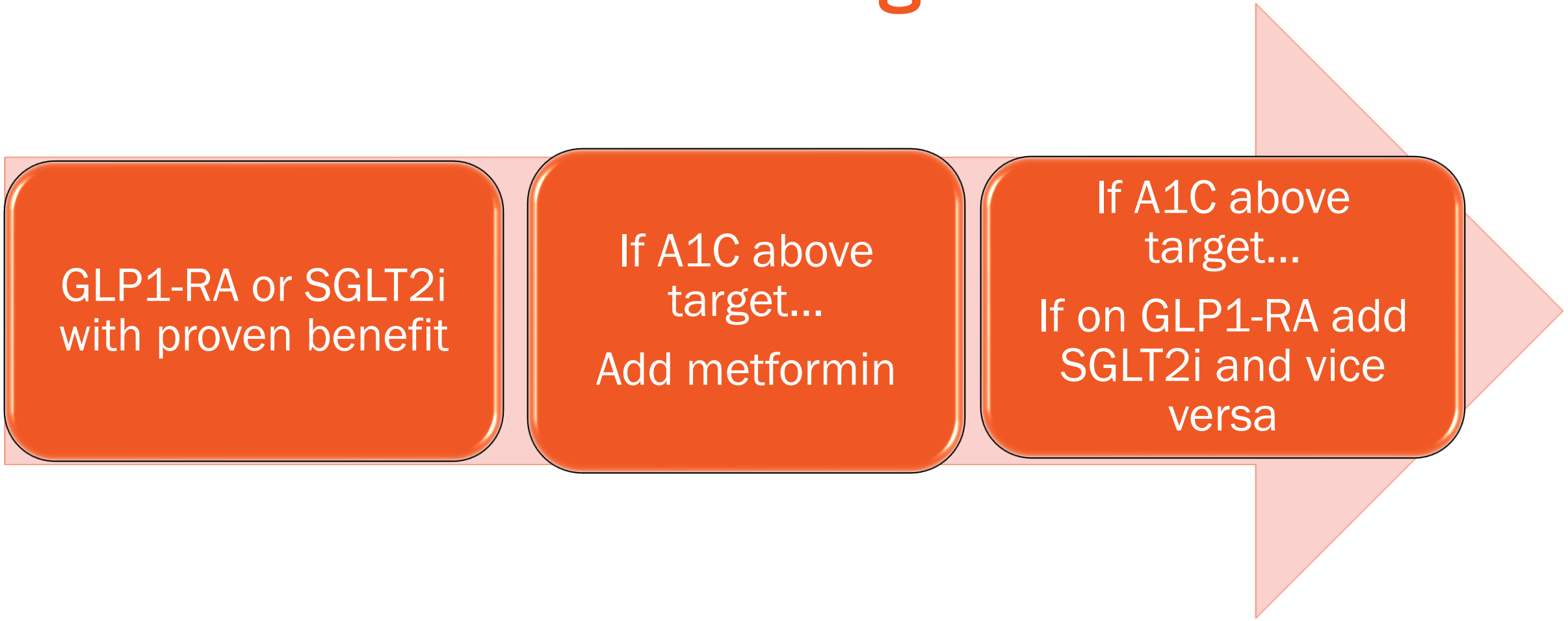
ASCVD

…start a GLP1-RA or SGLT2i

with proven benefit

As First Line Therapy

Recommendations Summary – T2DM with ASCVD or High Risk for ASCVD



PreDiabetes
Overweight or Obese with ASCVD or high risk?

"…Pharmacotherapy for weight loss should be considered when lifestyle measures alone are inadequate to achieve goal weight loss in those with ABCD (Adipose Based Chronic Disease)…"

AACE CONSENSUS STATEMENT|_MAY 2023

PreDiabetes
Overweight or Obese with ASCVD or high risk?

GLP1-RA

semaglutide 2.4 mg (Wegovy)
liraglutide 3 mg (Saxenda)

Why not Ozempic, Victoza, or Trulicity?

Who Qualifies?

For both Saxenda or Wegovy

- BMI - 30 or greater (obese)
- BMI - 27 or greater (overweight) with at least one weight-related comorbidity

Contraindications

Contraindications
Thyroid

All GLP1 drugs currently on the market are contraindicated in patients with a certain type of thyroid cancer or disorder.

All GLP1 drugs are contraindicated in patients with

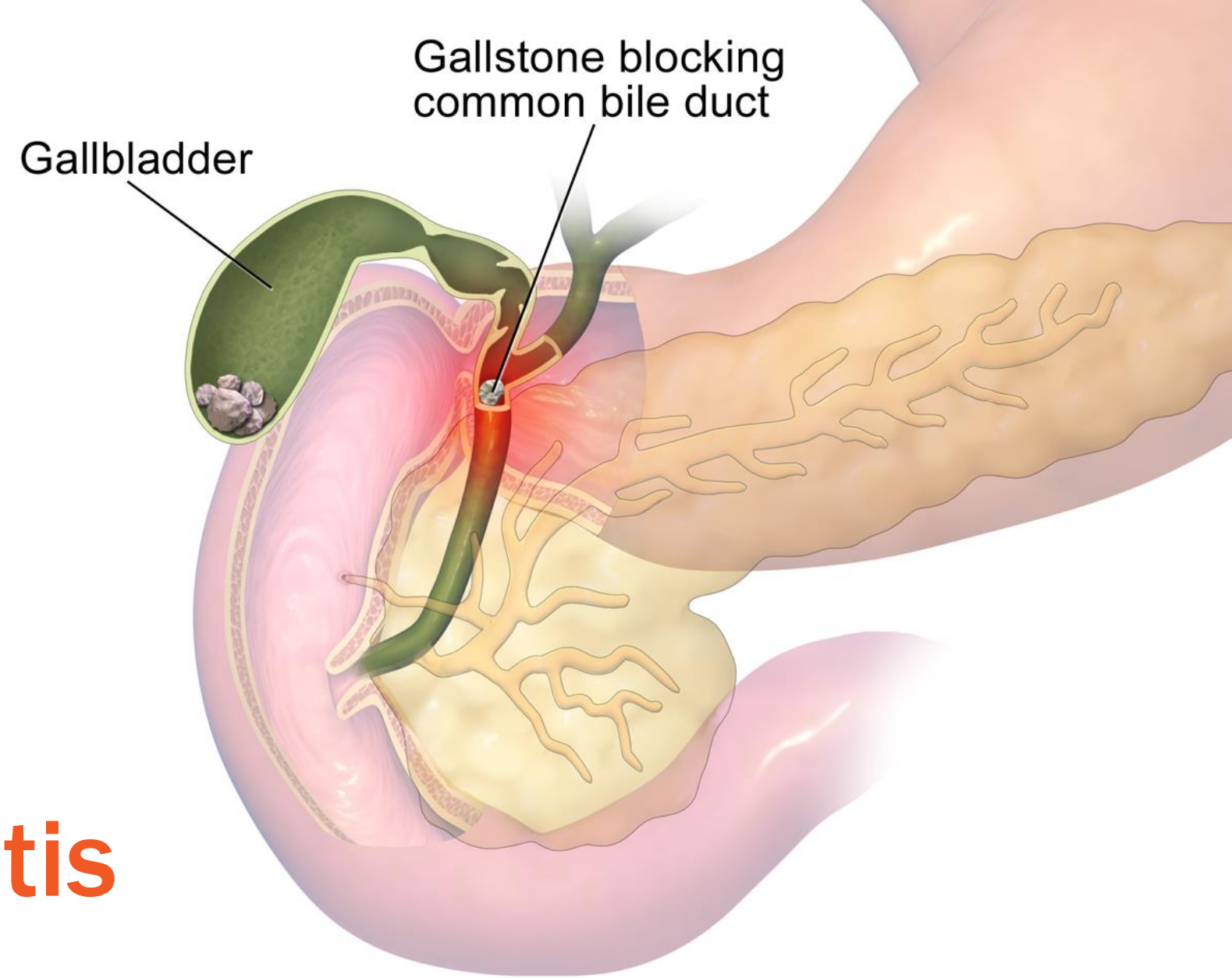
A personal or family history of medullary thyroid carcinoma (MTC)

or

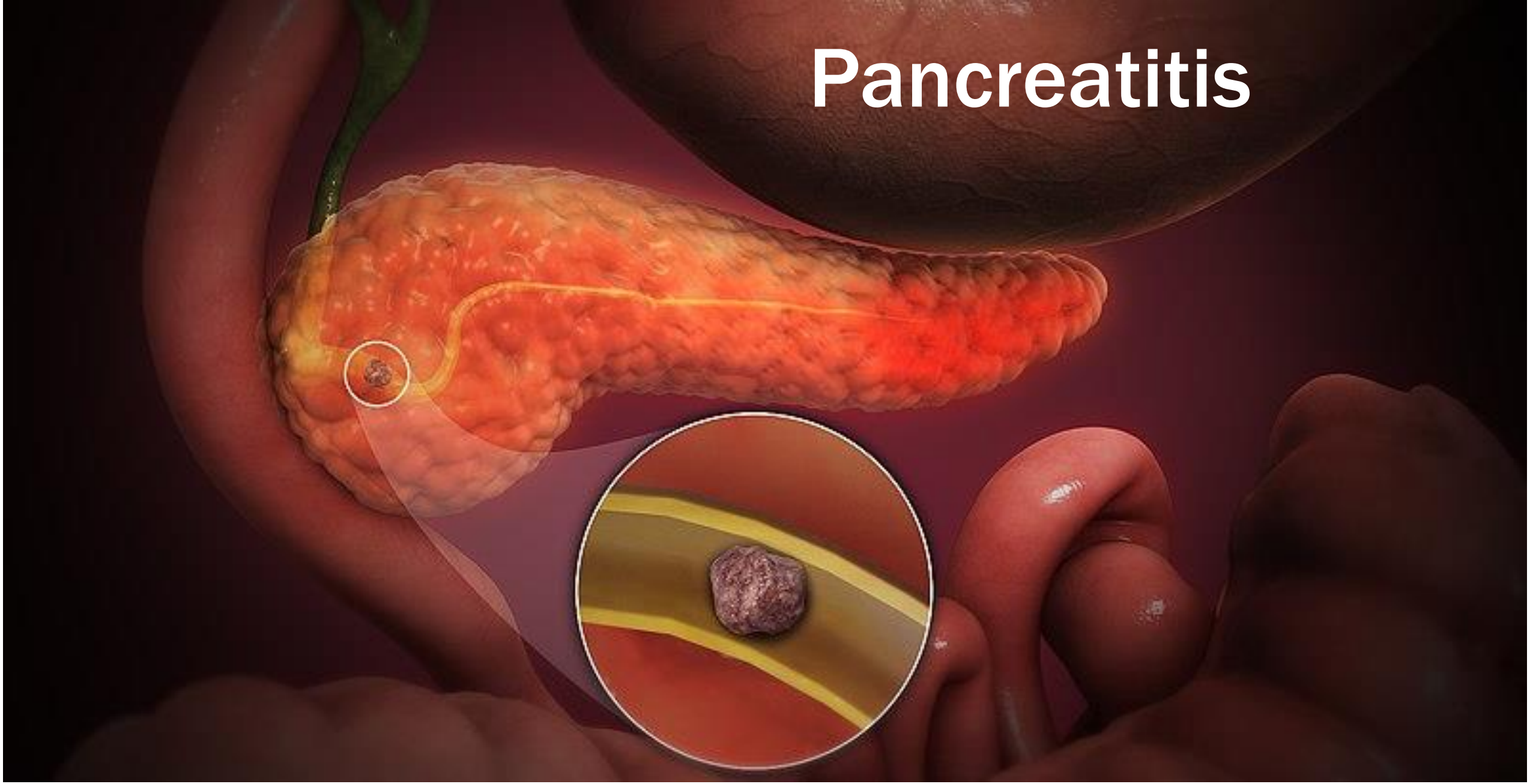
Multiple Endocrine Neoplasia syndrome type 2 (MEN2)

Warnings and Precautions

Cholelithiasis and Cholecystitis

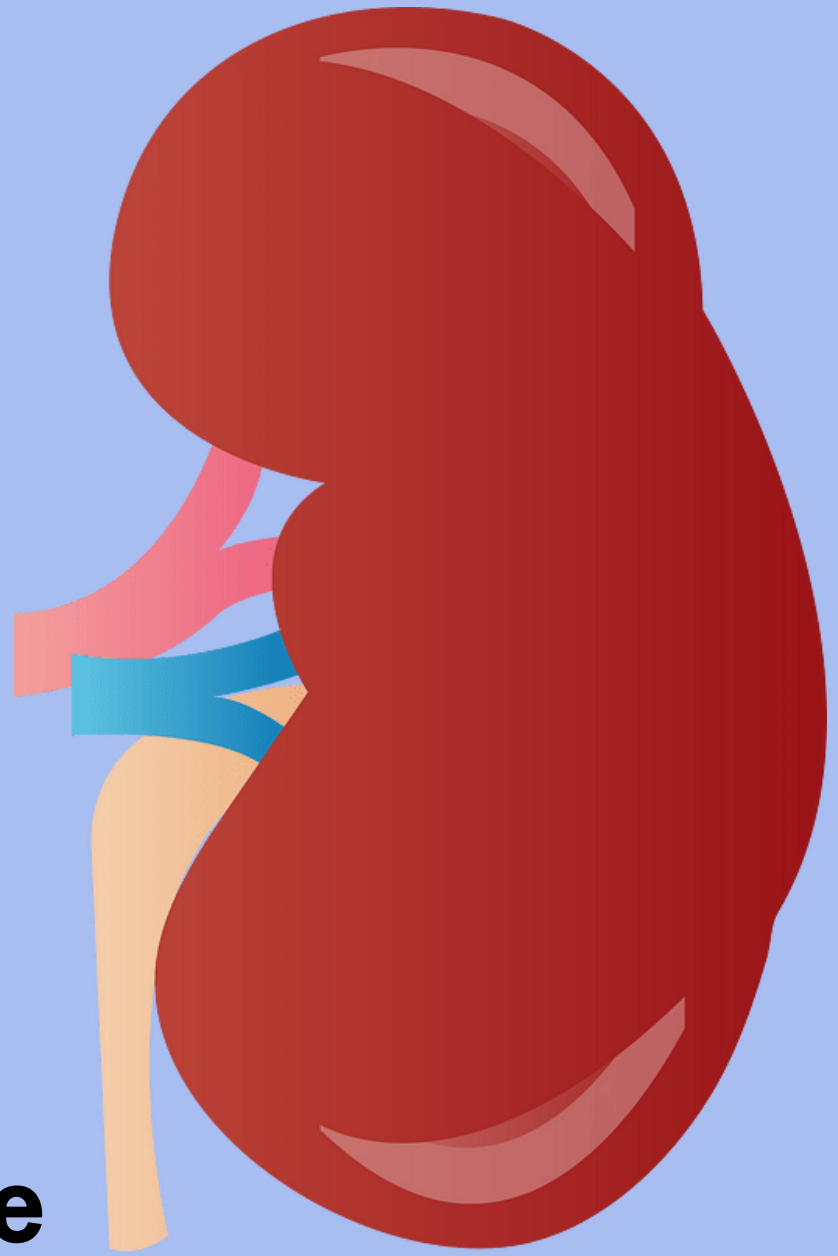


Pancreatitis



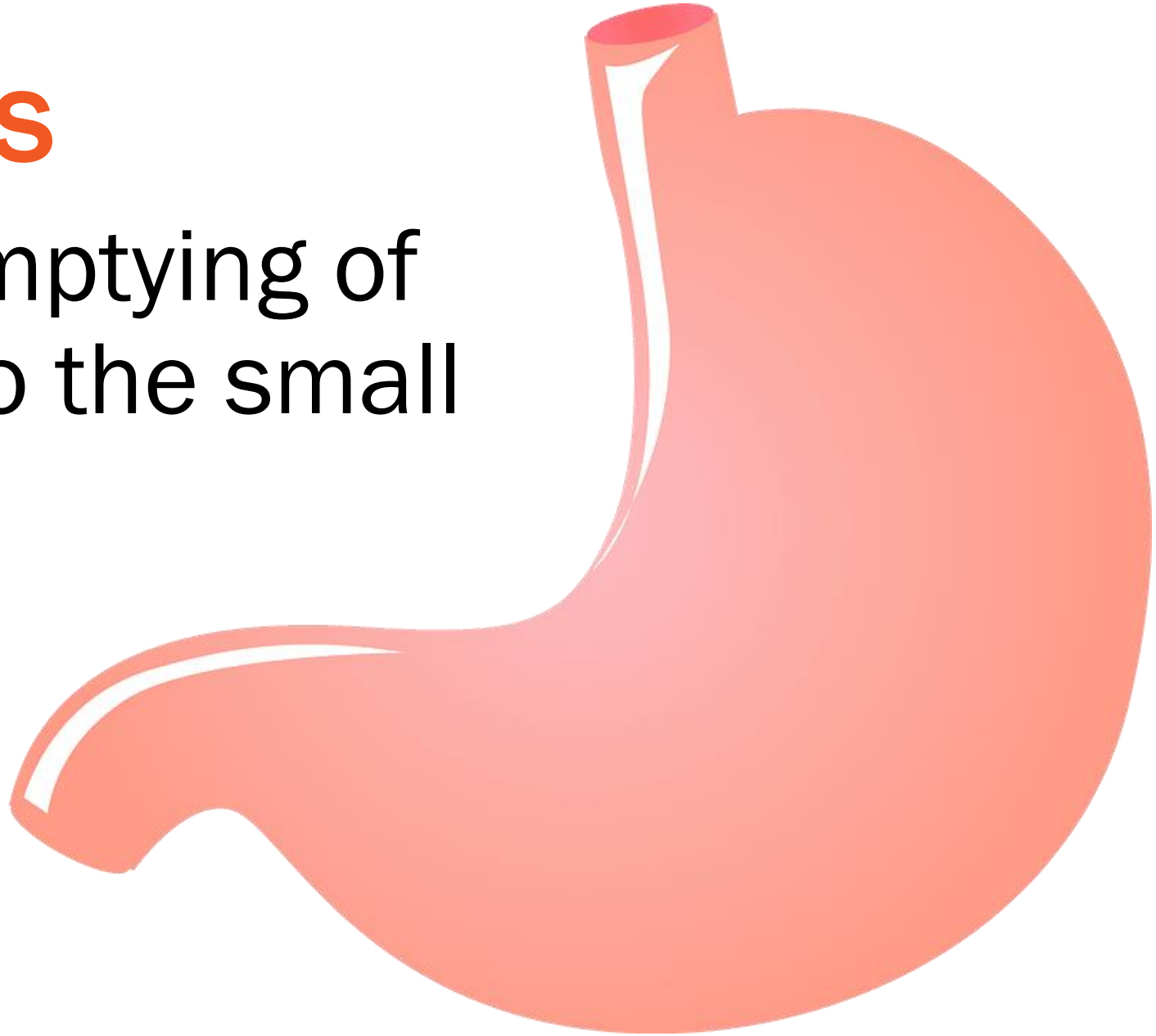
Retinopathy

Renal Disease



Gastroparesis

A delay in the emptying of the stomach into the small intestine.



- Hold GLP-1 agonists on the day of the procedure/surgery for patients who take the medication daily.

- Hold GLP-1 agonists a week prior to the procedure/surgery for patients who take the medication weekly.

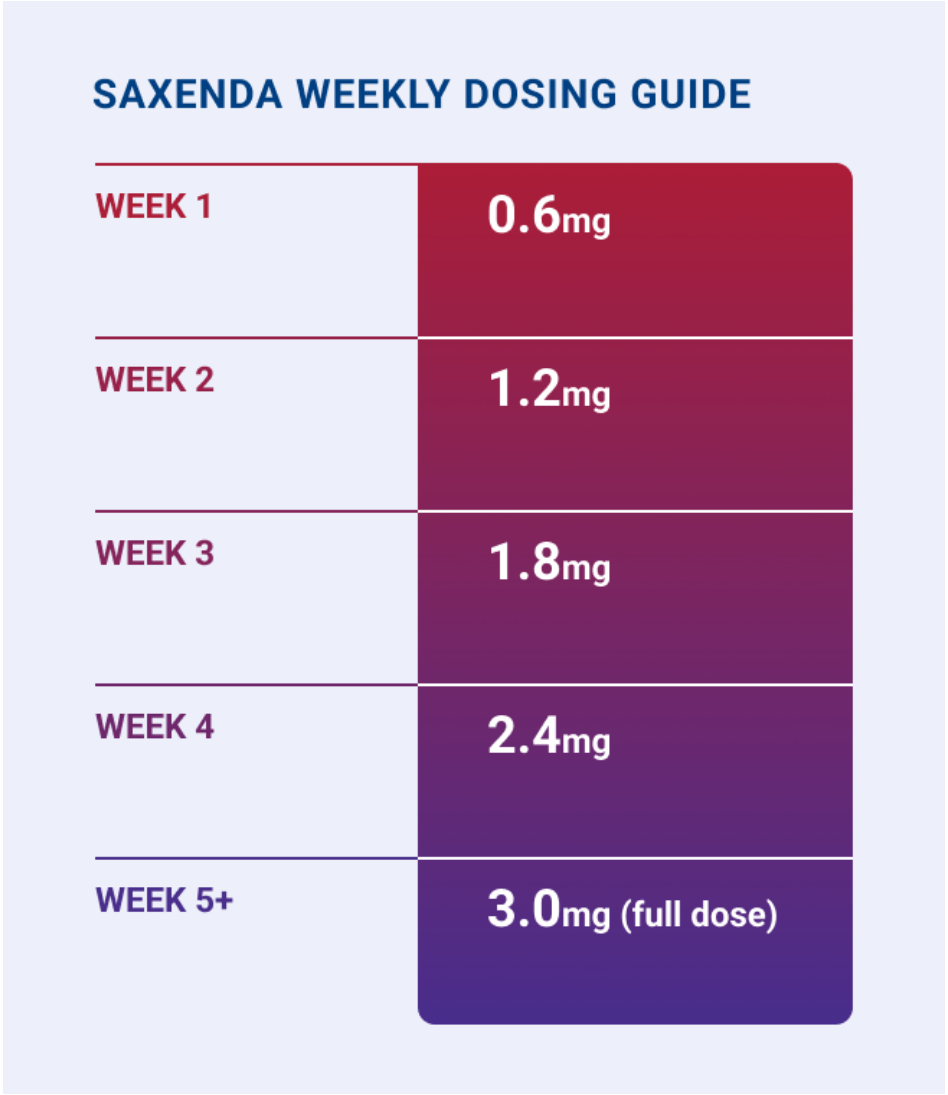
Side Effects


DIARRHEA


DIARRHEA

Titration is Important

Titration is Important



Titration is Important

Titration is Important

Titration is Important

Titrate to Minimize GI Symptoms

How bad is it?

For all GLP1 drugs except one….

~4-8% discontinued due to GI symptoms

Once-weekly

BYDUREON® BCise™

- Only 2% D/C due to GI symptoms
- Not as strong for weight loss
- Still 1.4% A1C reduction

EASY
Proven A1C reductions with no titration[1]

Heart Rate Increase

~2-3 bpm

General Guidelines - FAQs

Can They Be Left Out of The Refrigerator?

Yes! – up to 86°F for at least 2 weeks

Bydureon BCise	28 days
Victoza	30 days
Saxenda	30 days
Trulicity	14 days
Ozempic	56 days
Wegovy	28 days
Mounjaro	21 days

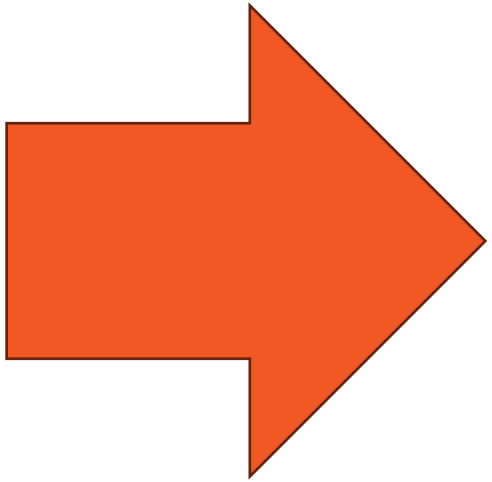
What if I Missed a dose?

Depends on how many days since this missed dose

	If up to this many days since missed dose – take missed dose. If more take next schedule dose.
Bydureon BCise	4 days
Trulicity	4 days
Ozempic	5 days
Wegovy	5 days
Mounjaro	4 days

Missed a DAILY dose?

Victoza
Saxenda
Rybelsus



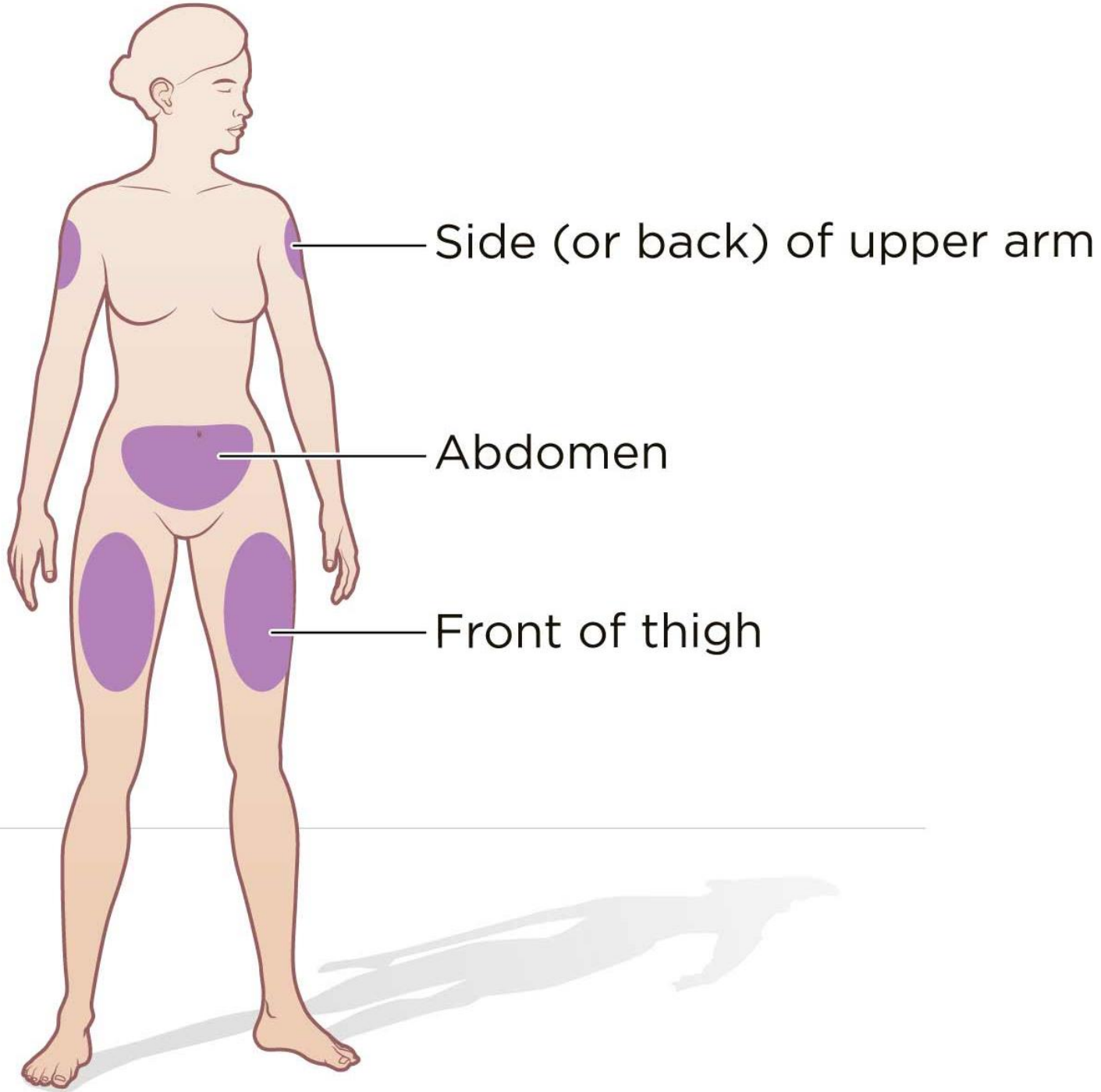
Skip and take next daily dose.

Can I Switch the Day I Take it?

Yes – as long as the time between doses is at least….

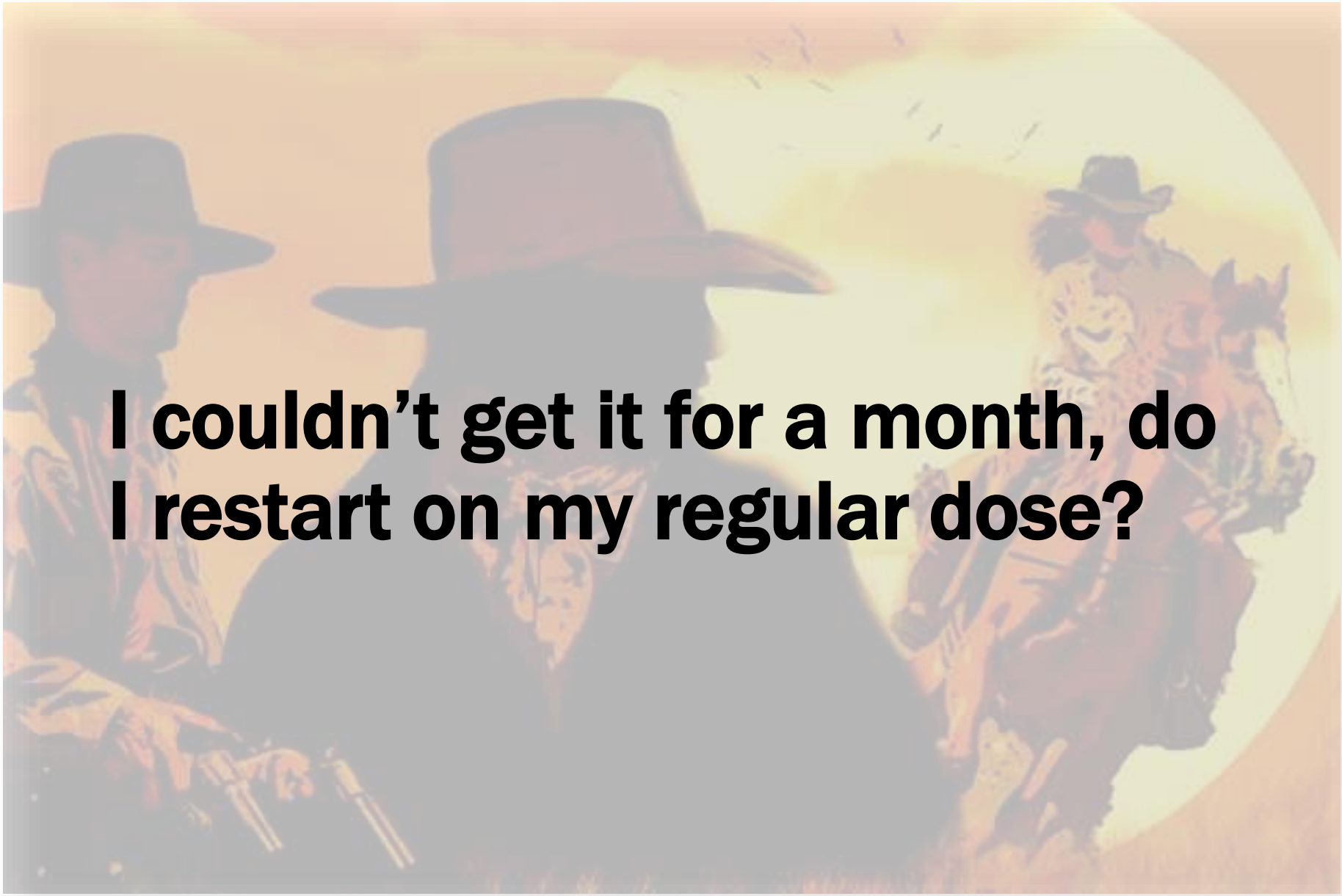
Bydureon BCise	3 days
Trulicity	3 days
Ozempic	3 days
Wegovy	2 days
Mounjaro	3 days

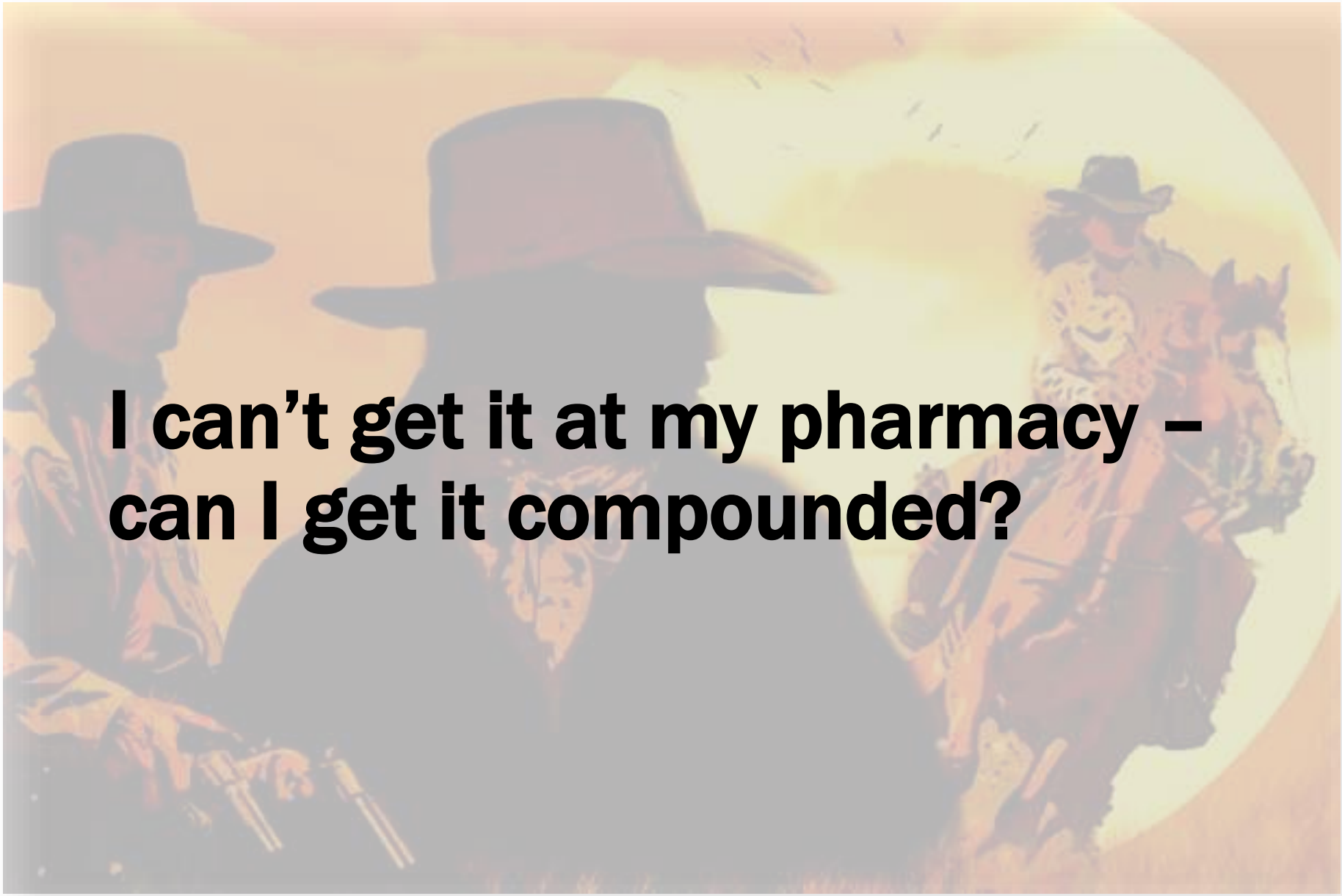
Where do I give my shot?



Trying to get Rx filled


Trying to get Rx filled


I couldn’t get it for a month, do I restart on my regular dose?


I can’t get it at my pharmacy –
can I get it compounded?

“Patients should be aware that some products sold as ‘semaglutide’ may not contain the same active ingredient as FDA-approved semaglutide products and may be the salt formulations, products containing these salts, such as semaglutide sodium and semaglutide acetate, have not been shown to be safe and effective.”

Compounded “semaglutide” may not be the same and may not be safe or effective.

Controversies

But –
These drugs are really for diabetes –
not weight loss

If you start taking them, you'll have to take them for the rest of your life!

Obesity is a chronic, progressive, relapsing disease.

Ozempic face!

Media buzzword

When people lose weight, their faces lose weight.

They make you lose too much muscle!

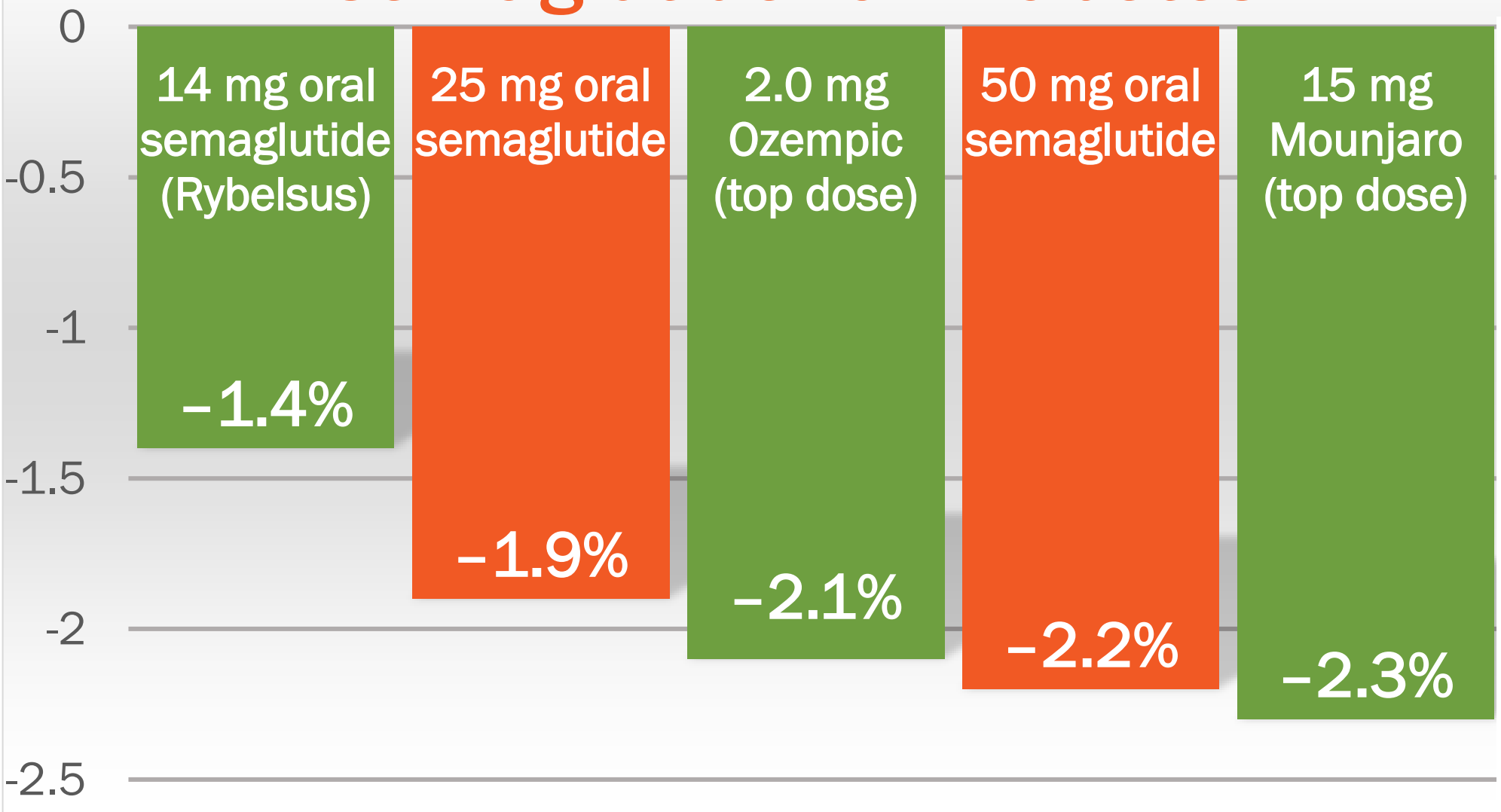
What’s Coming!

New Oral GLP1-RA

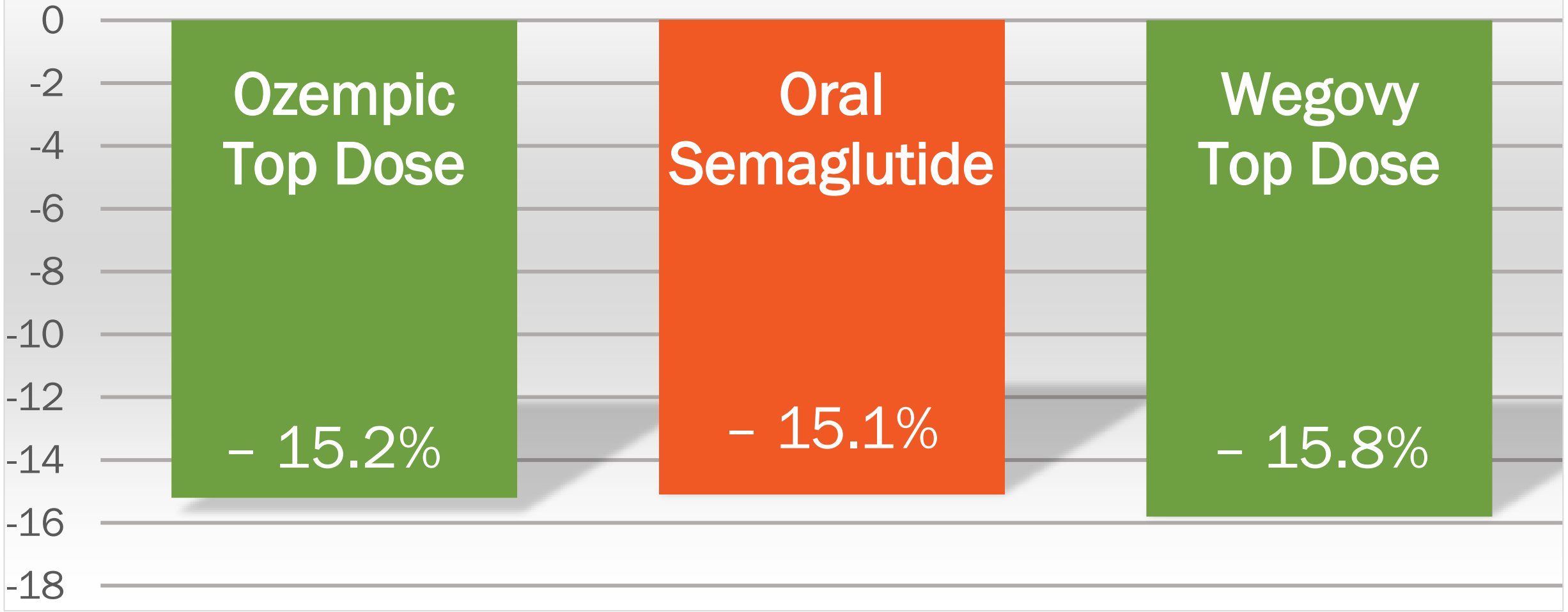
Danuglipron - twice daily pill with no special dosing instructions

Higher Dose Semaglutide in a Pill

A1C Reductions on Higher Doses of semaglutide for Diabetes



High Dose Oral Semaglutide vs Top Dose Injectable Semaglutide (Ozempic and Wegovy) for weight loss



2 New Drugs Enter the Fray

Amylin

Glucagon Receptor Agonists

Both combined with existing treatment and enhance glycemic benefit and weight loss.

Combo Drugs in the Pipeline For Both Diabetes and Weight Loss

Drug	Drug Info
Mazdutide	Weekly injectable GLP1 & Glucagon RA
Survodutide	Weekly injectable GLP1 & Glucagon RA
CagriSema	Weekly injectable - Amylin & semaglutide
Retatrutide	Weekly injectable GLP1, GIP, & Glucagon RA

Let’s Wrap It Up!

Incretin Drugs are Game Changers

Unparalleled glycemic benefit

Unparalleled weight loss

Some are cardioprotective

Incretin Drugs are Game Changers

Make note of contraindications and risks

Most side effects are GI related and do subside over time

Recommended as first line therapy for diabetes patients with ASCVD or high risk

Recommended for Pre-DM patients when diet and lifestyle aren’t enough

Incretin Drugs are Game Changers

The tide is turning!

Thanks for joining us!

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