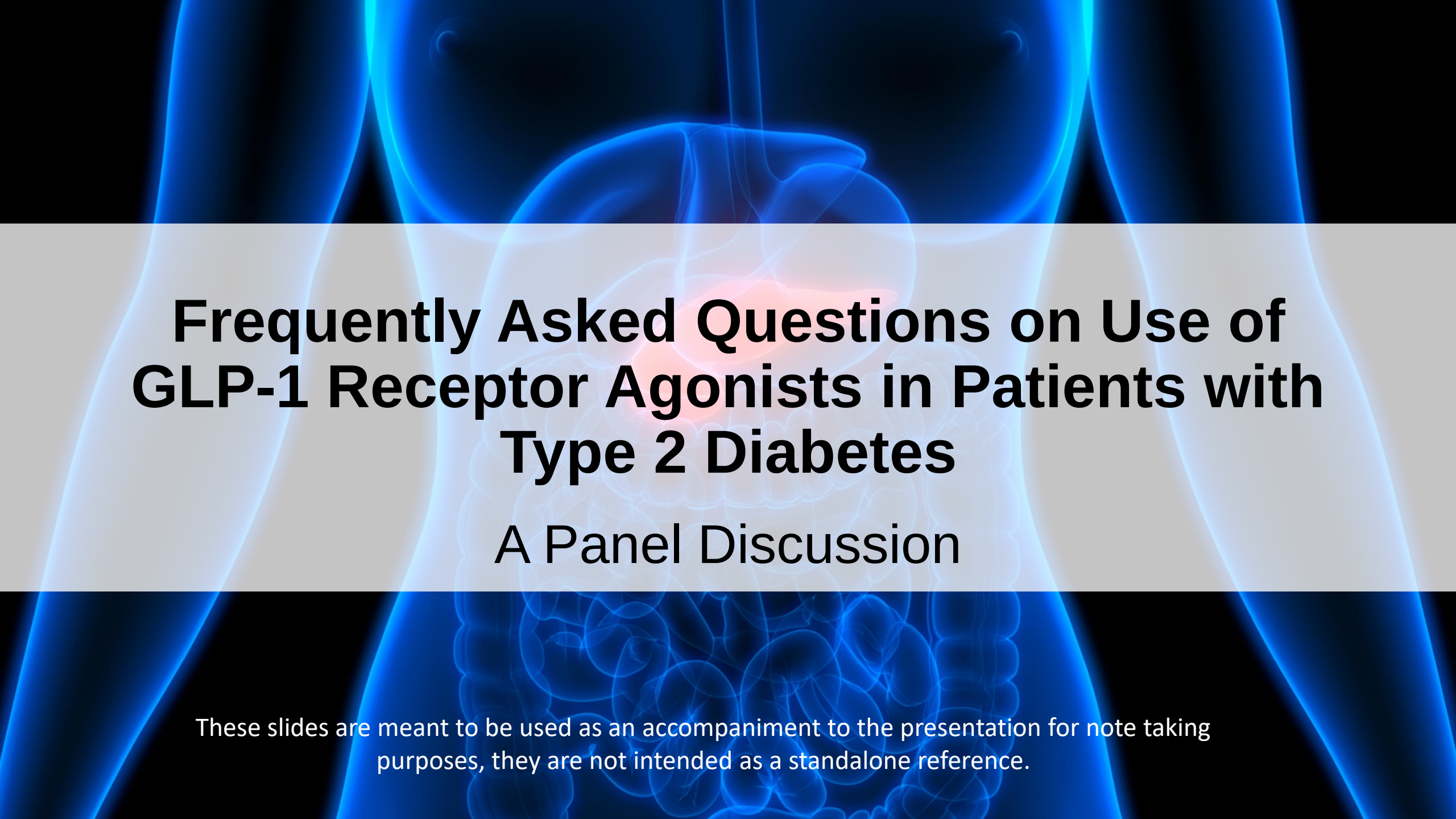
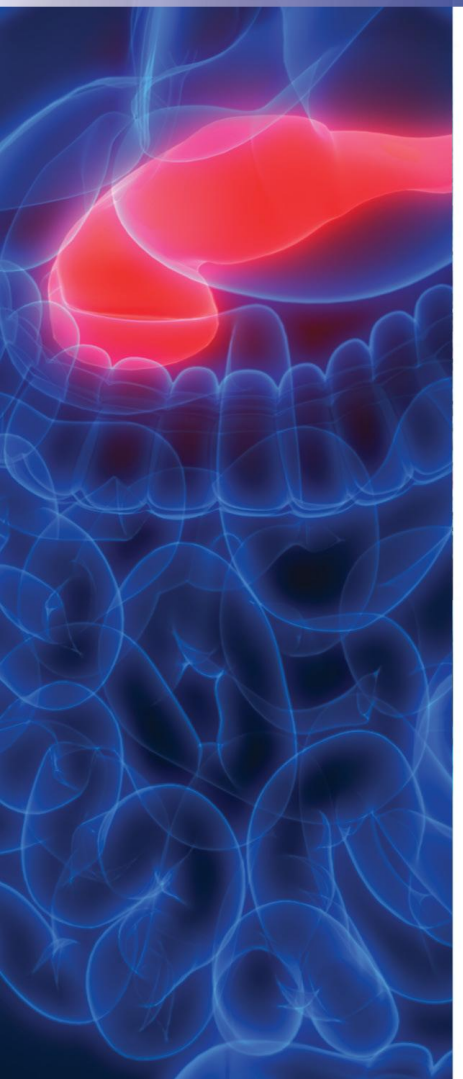


Frequently Asked Questions on Use of GLP-1 Receptor Agonists in Patients with Type 2 Diabetes

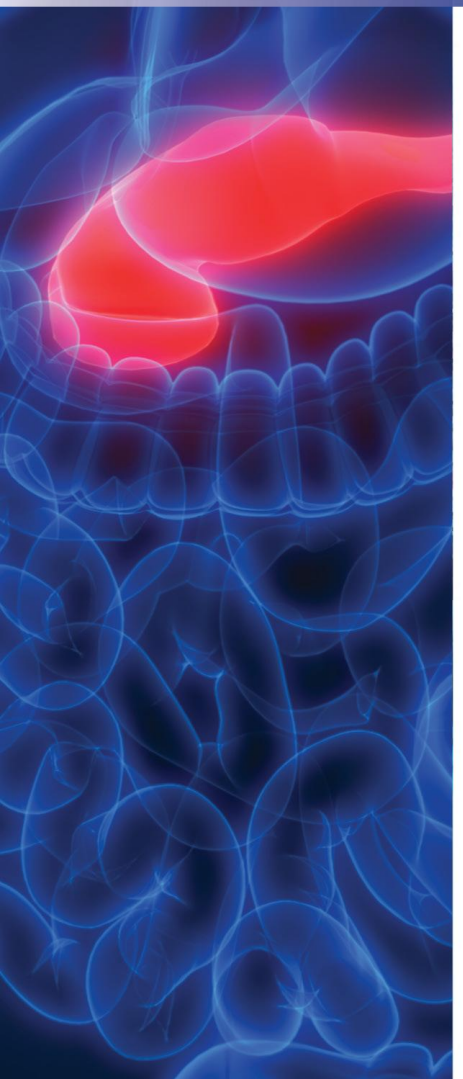
A Panel Discussion

These slides are meant to be used as an accompaniment to the presentation for note taking purposes, they are not intended as a standalone reference.



This educational activity is sponsored by Postgraduate Healthcare Education, LLC and is supported by an educational grant from Novo Nordisk Inc.

Faculty

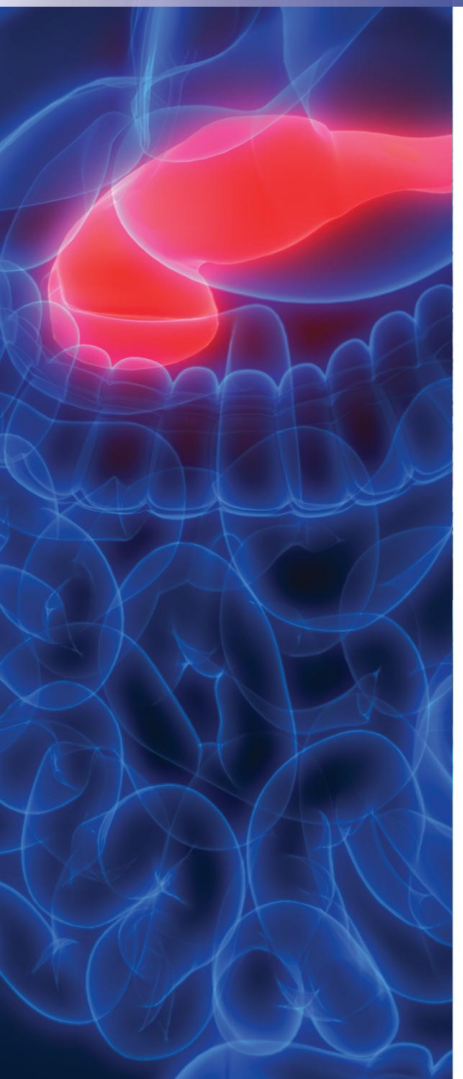


Joshua J. Neumiller, PharmD, CDCES, FASCP, FADCES

Vice Chair & Allen I. White Distinguished Associate Professor, Pharmacotherapy
Washington State University
Spokane, WA

Dr. Neumiller is Vice-Chair and the Allen I. White Distinguished Associate Professor in the Department of Pharmacotherapy at Washington State University. He is a Certified Diabetes Care and Education Specialist (CDCES), a Fellow of the Association for Diabetes Care and Education Specialists (ADCES), a Fellow of the American Society of Consultant Pharmacists, and a member of the WSU Geriatrics Team. Josh is a contributing author for the ADA books *Medications for the Treatment of Diabetes* and *Practical Insulin*. Josh recently served as Chairman of the ADA's Professional Practice Committee whose primary responsibility is revising the ADA Standards of Medical Care in Diabetes each year. Josh was awarded with the 2016 Albert B. Prescott Pharmacy Leadership Award and was named the 2021 ADCES Diabetes Educator of the Year for his work in diabetes care.

Faculty

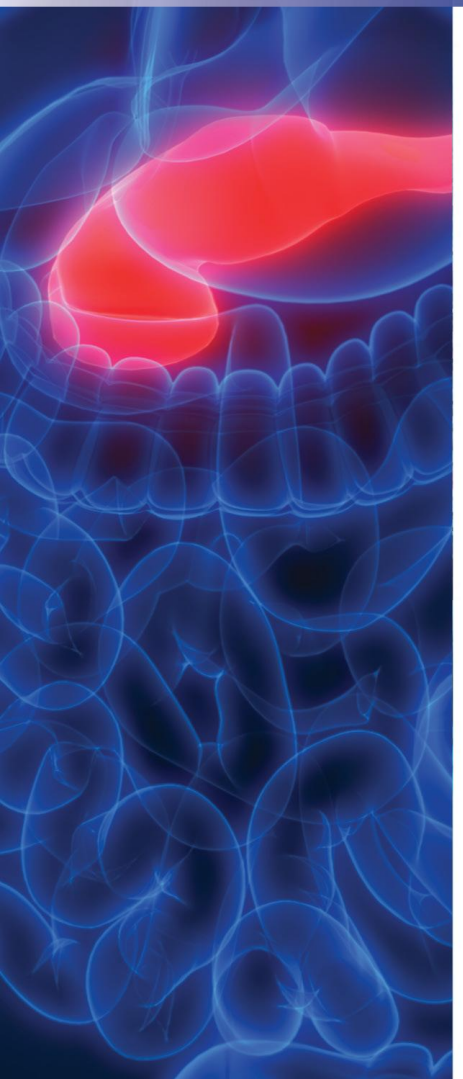


Jennifer Trujillo, PharmD, FCCP, BCPS, CDCES, BC-ADM

Professor, Department of Clinical Pharmacy
Skaggs School of Pharmacy and Pharmaceutical Sciences
University of Colorado Anschutz Medical Campus
Aurora, CO

Dr. Trujillo is a professor at the University of Colorado Skaggs School of Pharmacy and Pharmaceutical Sciences in Aurora, Colorado. She received her Doctor of Pharmacy at the University of Arizona and completed her pharmacy practice residency at Boston Medical Center. Dr. Trujillo currently practices as a clinical pharmacist and Certified Diabetes Care and Education Specialist at the UCHealth Diabetes and Endocrinology Clinic on the University of Colorado Anschutz Medical Campus. She is an active member of the American Diabetes Association's Primary Care Advisory Group and "Diabetes Is Primary" program planning committee. She has published several book chapters and has authored more than 50 peer-reviewed journal articles in the field of diabetes.

Faculty

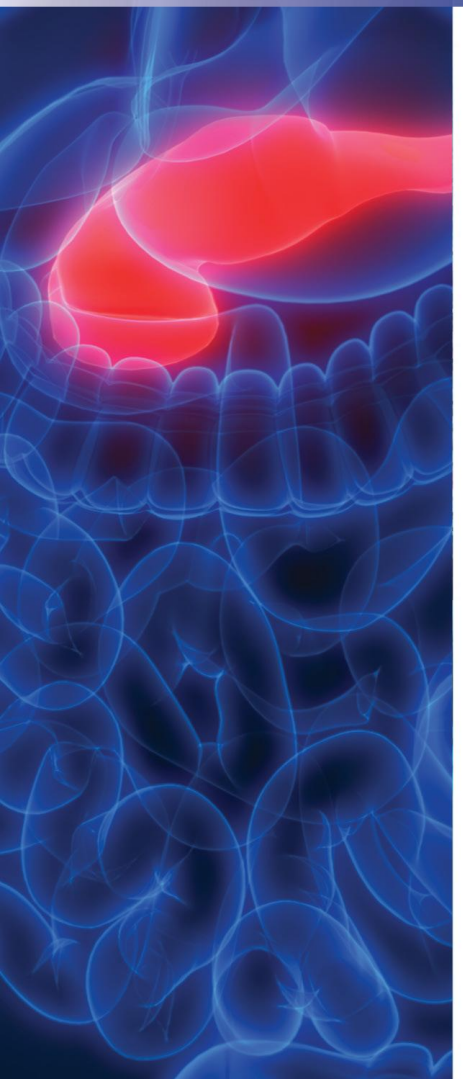


Heather P. Whitley, PharmD, BCPS, CDCES

Clinical Professor, Pharmacy Practice
Auburn University Harrison School of Pharmacy
Auburn, AL

Dr. Whitley is a Clinical Professor of Pharmacy Practice at Auburn University Harrison School of Pharmacy. She completed her Doctor of Pharmacy degree from the Medical University of South Carolina, and ASHP-accredited residency programs in Pharmacy Practice and Primary Care. She is also a Board Certified Pharmacotherapy Specialist (BCPS) and a Certified Diabetes Care and Education Specialist (CDCES). She has practiced in multiple locations in Alabama as a Clinical Pharmacy Diabetes Specialist, including family medicine practices in the rural Black Belt, FQHC facilities, and, since 2014, a family medicine residency program in Montgomery, Alabama. She has published nearly 40 manuscripts and presented at the national and international arena predominantly on her diabetes-related research.

Disclosures



Dr. Neumiller has disclosed that he has served as a consultant for Novo Nordisk.

Dr. Trujillo has disclosed that she has served as a consultant for Sanofi.

Dr. Whitley has disclosed that she has no actual or potential conflict of interest in relation to this program.

The clinical reviewer, **Cynthia Moreau, PharmD, BCACP** has disclosed that she has no actual or potential conflict of interest in relation to this program.

Susanne Batesko, RN, BSN, Robin Soboti, RPh, and Susan R. Grady, MSN, RN-BC, as well as the planners, managers, and other individuals, not previously disclosed, who are in a position to control the content of Postgraduate Healthcare Education (PHE) continuing education (CE) activities hereby state that they have no relevant conflicts of interest and no financial relationships or relationships to products or devices during the past 12 months to disclose in relation to this activity. PHE is committed to providing participants with a quality learning experience and to improve clinical outcomes without promoting the financial interests of a proprietary business.

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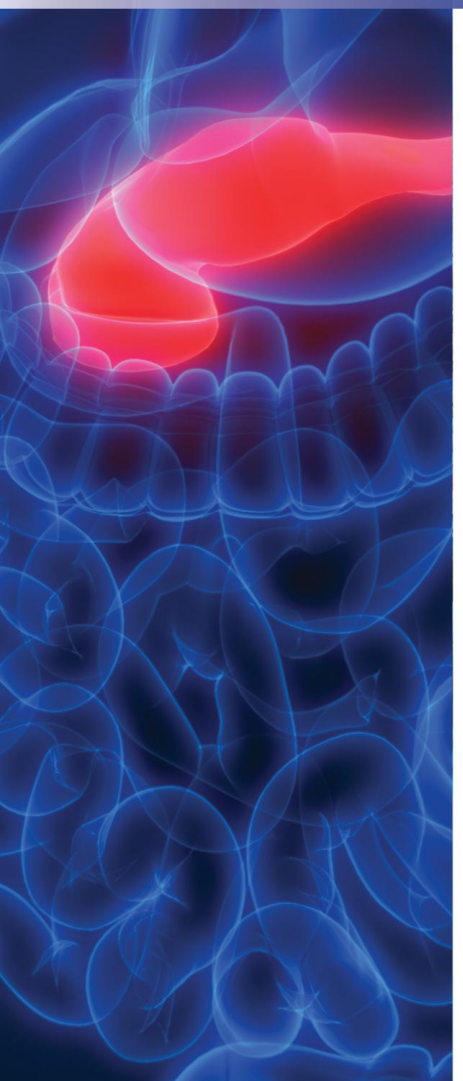

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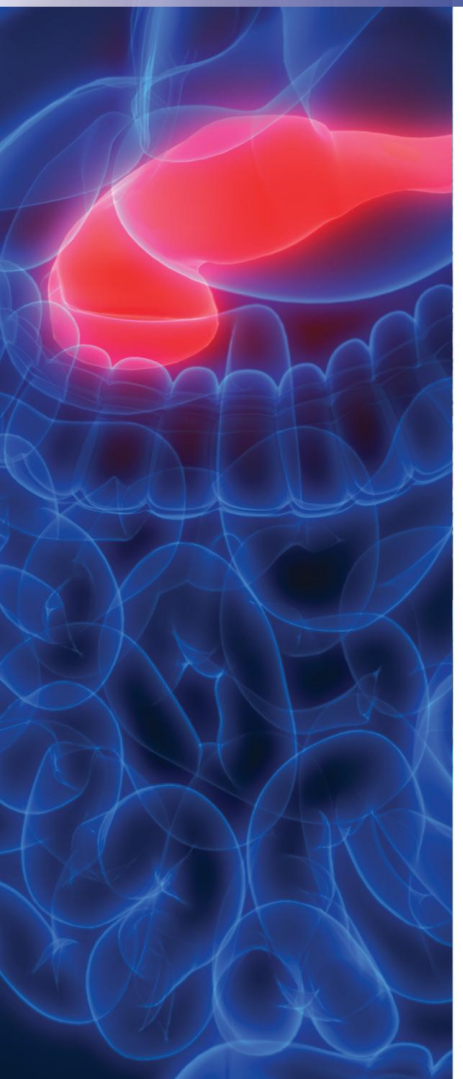
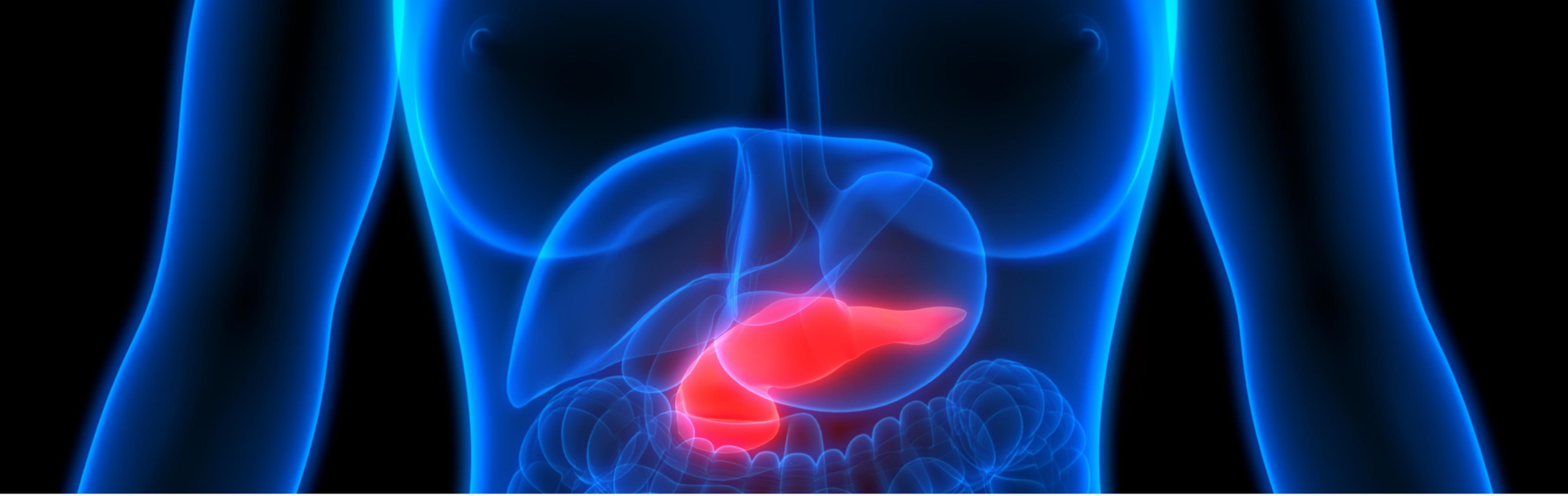
UAN: 0430-0000-20-124-H01-P
Credits: 1.25 hour (0.125 CEU)
Type of Activity: Application

Learning Objectives

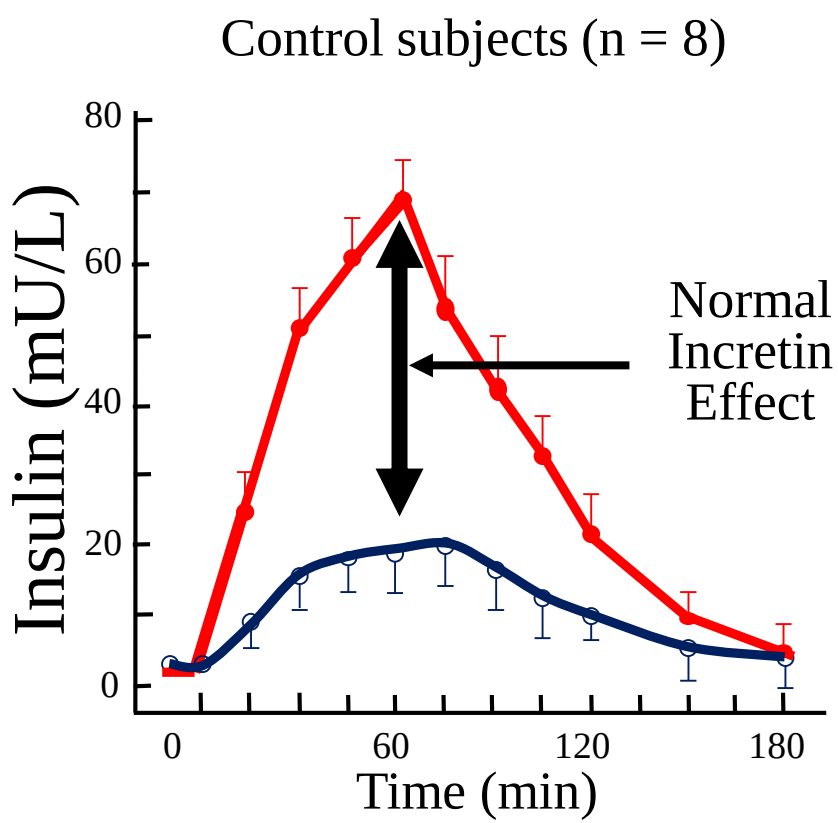


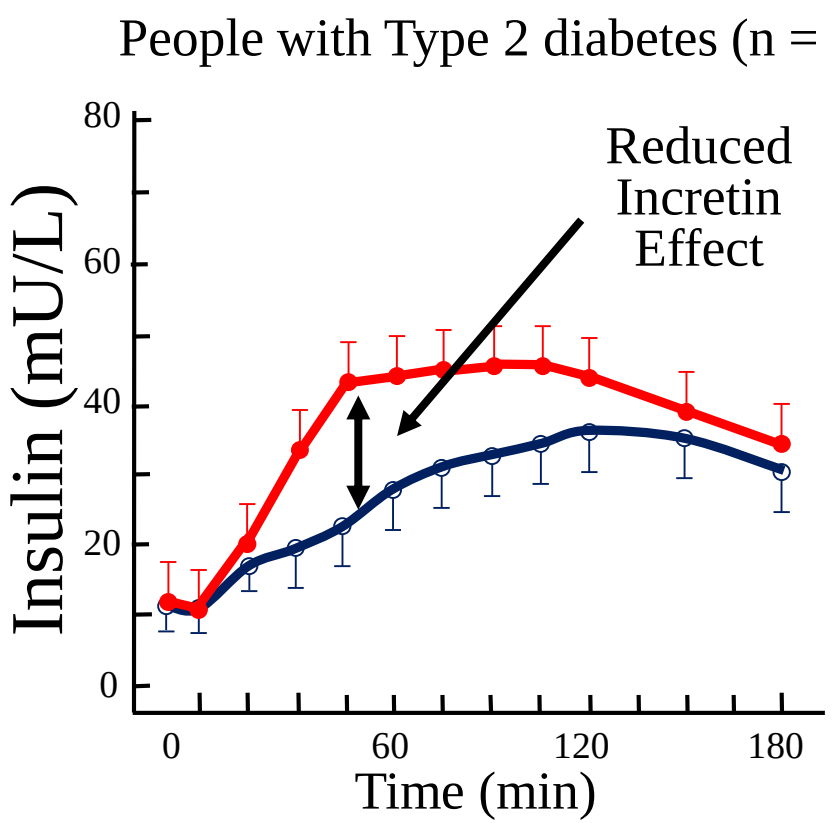
- **Describe** practical considerations for use of GLP-1 RAs in combination with other glucose-lowering agents
- **Discuss** selection of GLP-1 RA based on clinical needs, administration and device implications
- **Explain** practical strategies and considerations for GLP-1 RA product substitutions
- **Recognize** key safety and tolerability considerations with use of specific GLP-1 RA products



Should GLP-1 RAs be used in Combination with DPP-4 Inhibitors?

The Incretin Effect

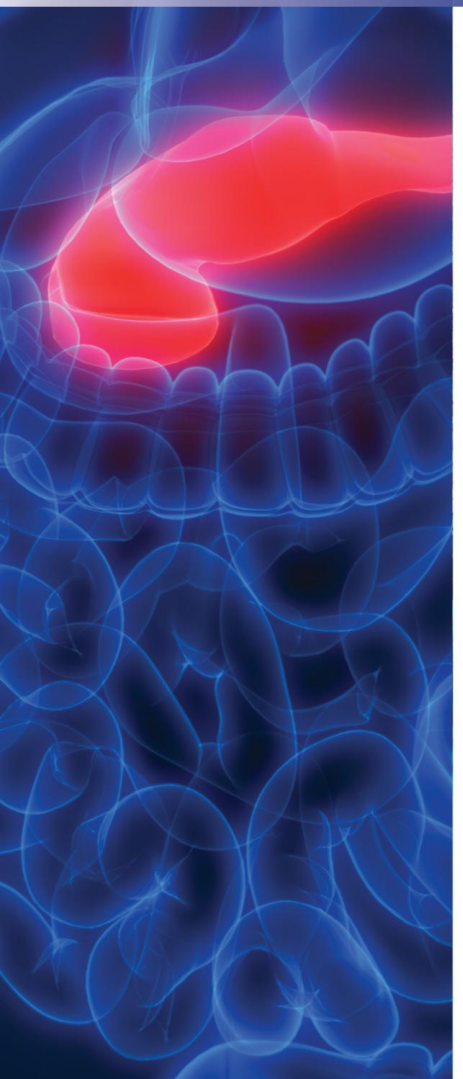




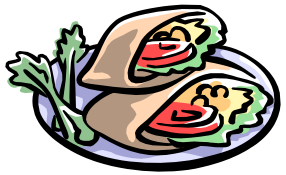
Oral glucose load
Intravenous glucose infusion

Nauck M, et al. *Diabetologia.* 1986;29:46-52.

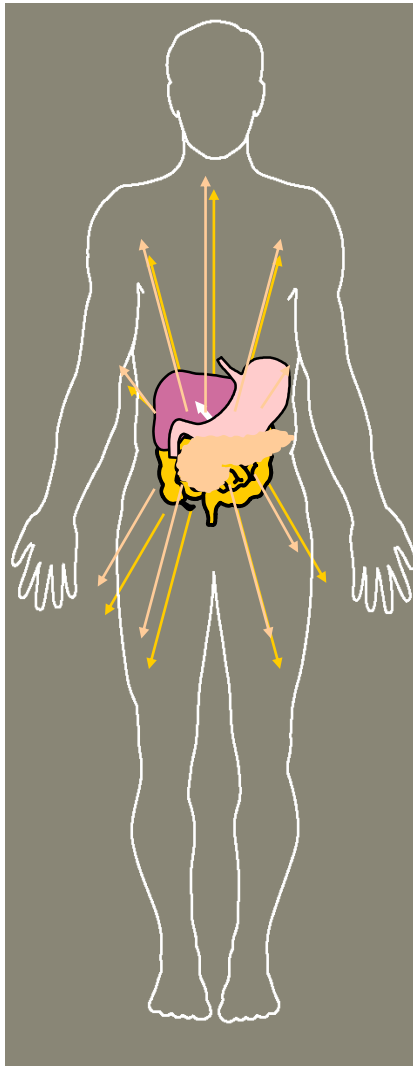
GLP-1: Effects in Humans



After food ingestion…



GLP-1 is secreted from L-cells of the jejunum and ileum

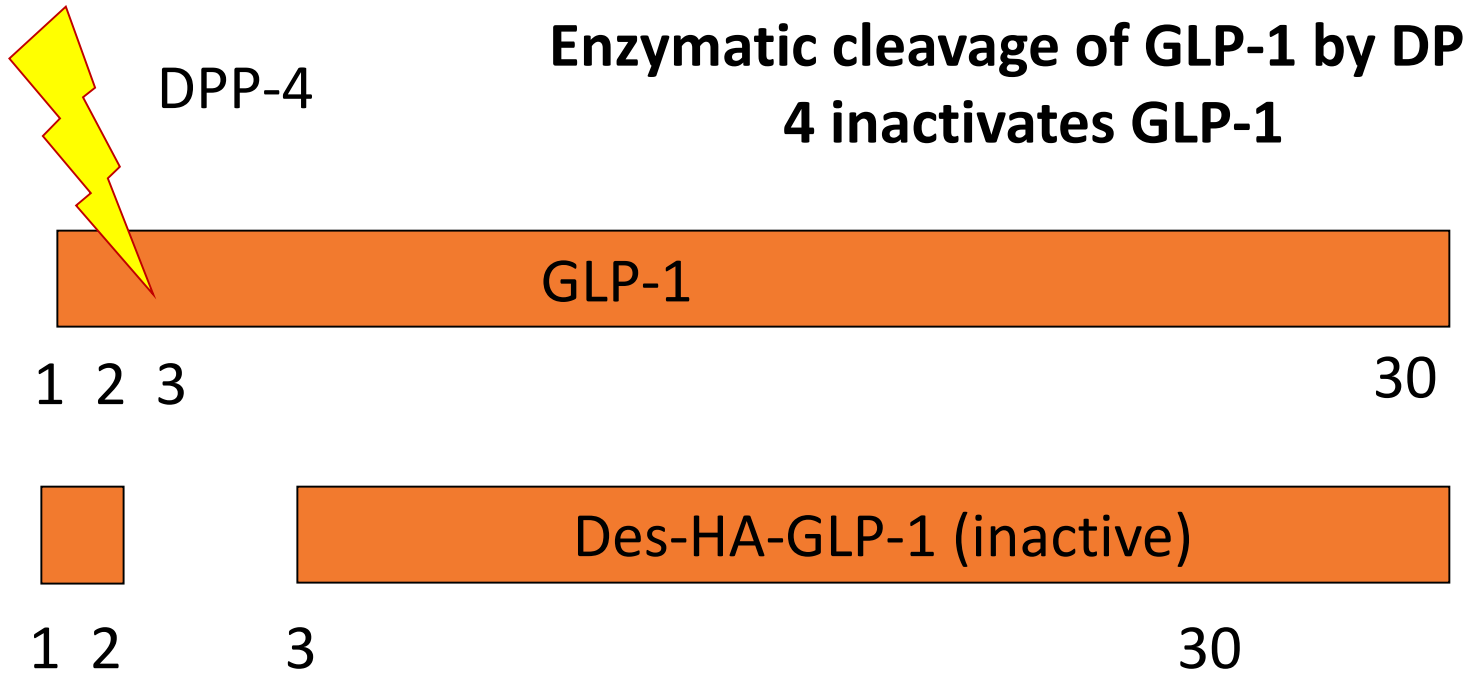


That in turn…

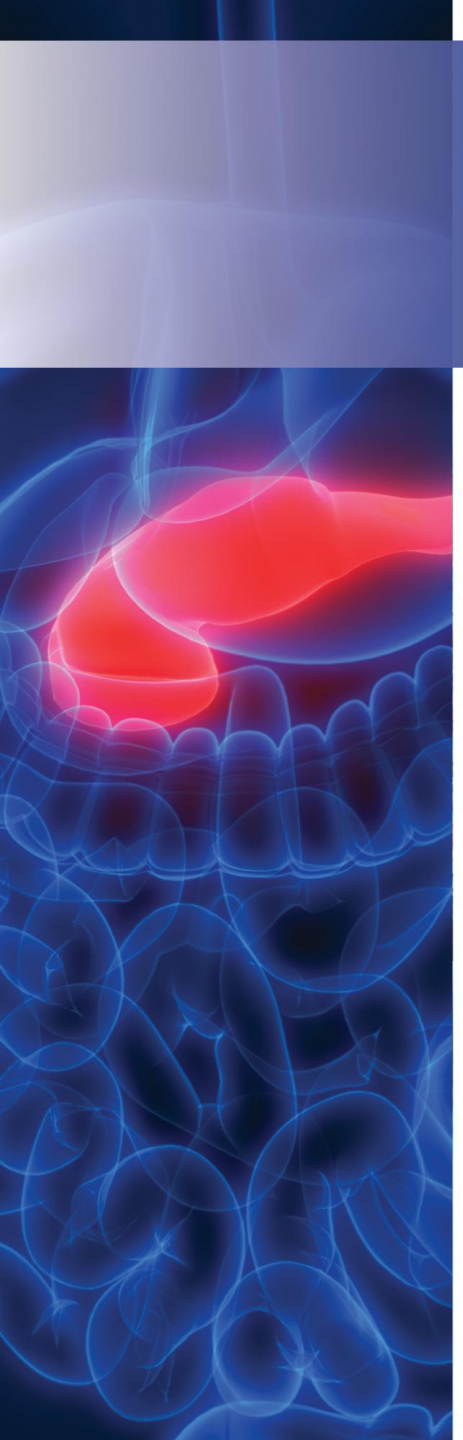
- Stimulates glucose-dependent insulin secretion
- Suppresses glucagon secretion
- Slows gastric emptying
- Leads to a reduction of food intake

Drucker DJ. *Curr Pharm Des.* 2001;7:1399-1412.
Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.
Drucker DJ. *Cell Metab.* 2006;3:153-165.

Degradation of Endogenous GLP-1



Mentlein R, et al. *Eur J Biochem*. 1993;214:829-835.



Pharmacologic Approaches to Enhancing the Incretin Effect

The incretin effect is blunted in people with type 2 diabetes and endogenous GLP-1 has an extremely short half-life

Block DPP-4 to slow the enzymatic degradation of endogenous GLP-1:

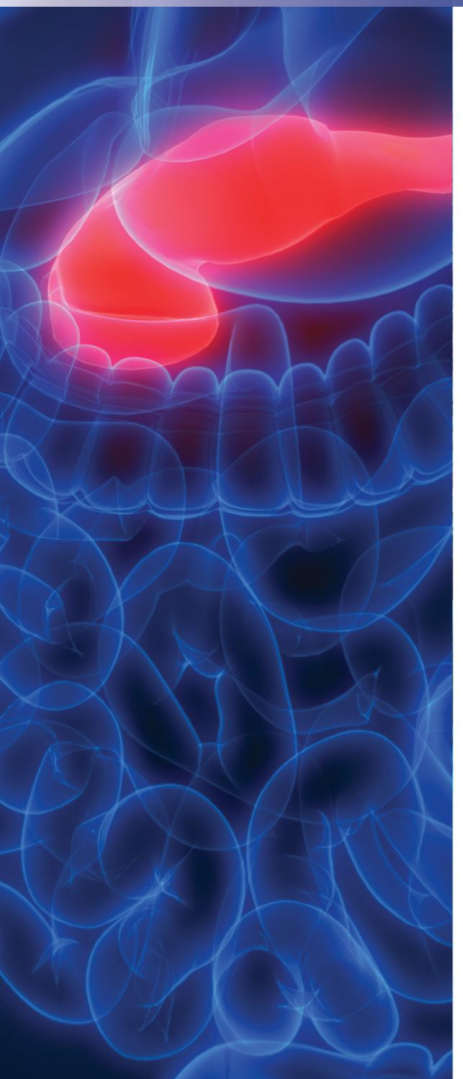
- Alogliptin
- Linagliptin
- Saxagliptin
- Sitagliptin

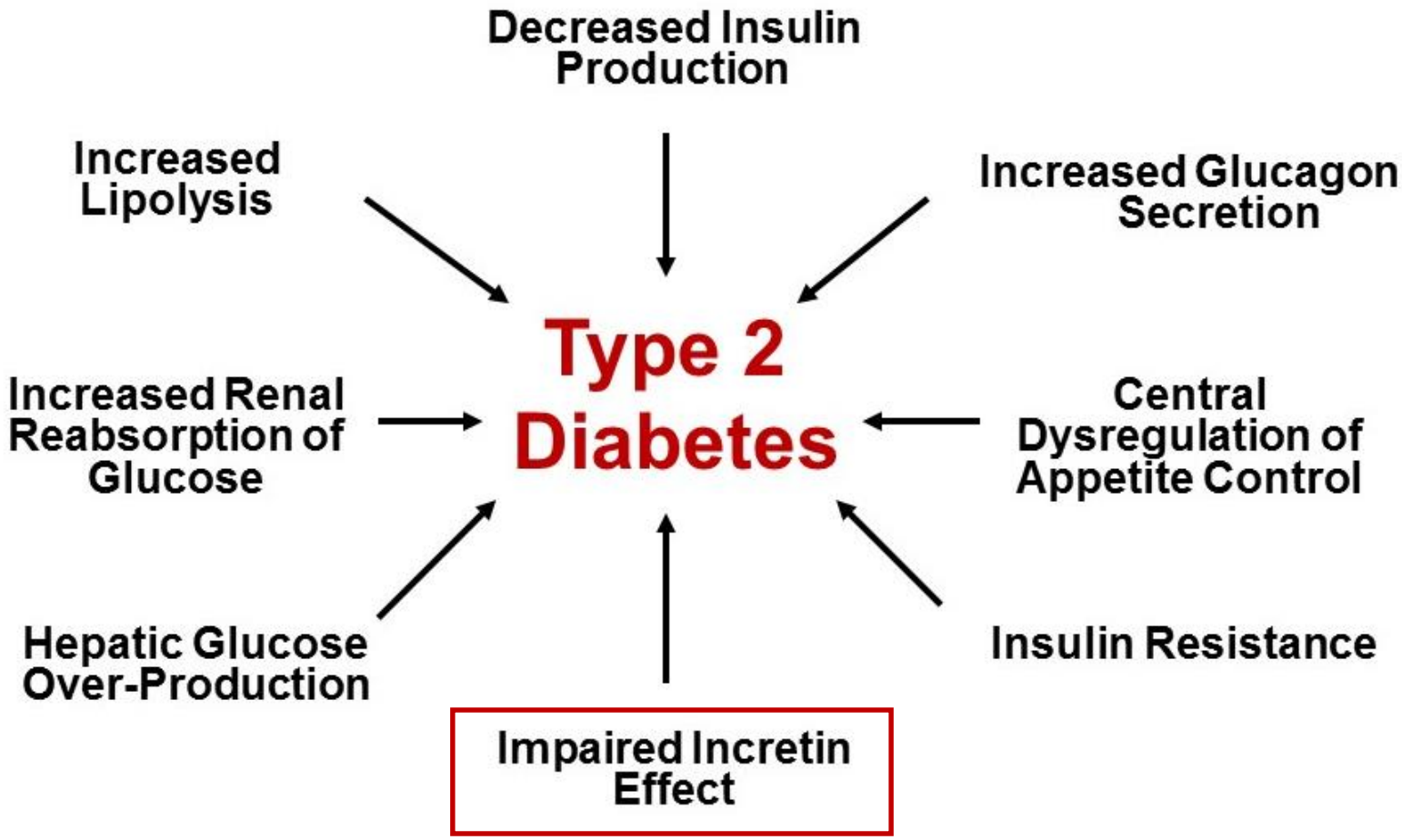
Use GLP-1 analogs with longer half-lives:

- Exenatide
- Lixisenatide
- Liraglutide
- Exenatide XR
- Dulaglutide
- Semaglutide (Injectable & Oral)

Drucker DJ. *Curr Pharm Des.* 2001;7:1399-1412.
Drucker DJ. *Mol Endocrinol.* 2003;17:161-171.
Drucker DJ. *Cell Metab.* 2006;3:153-165.

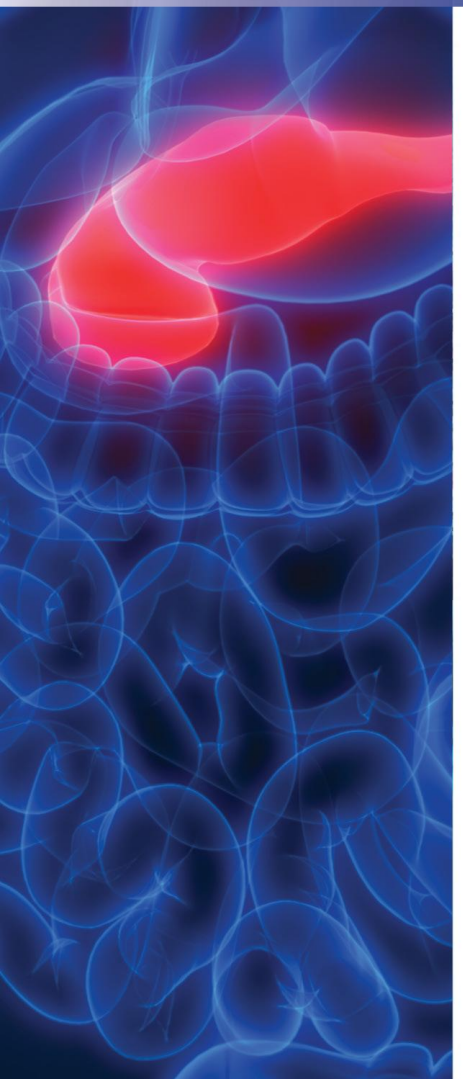
Pathophysiologic Defects in Type 2 Diabetes Mellitus

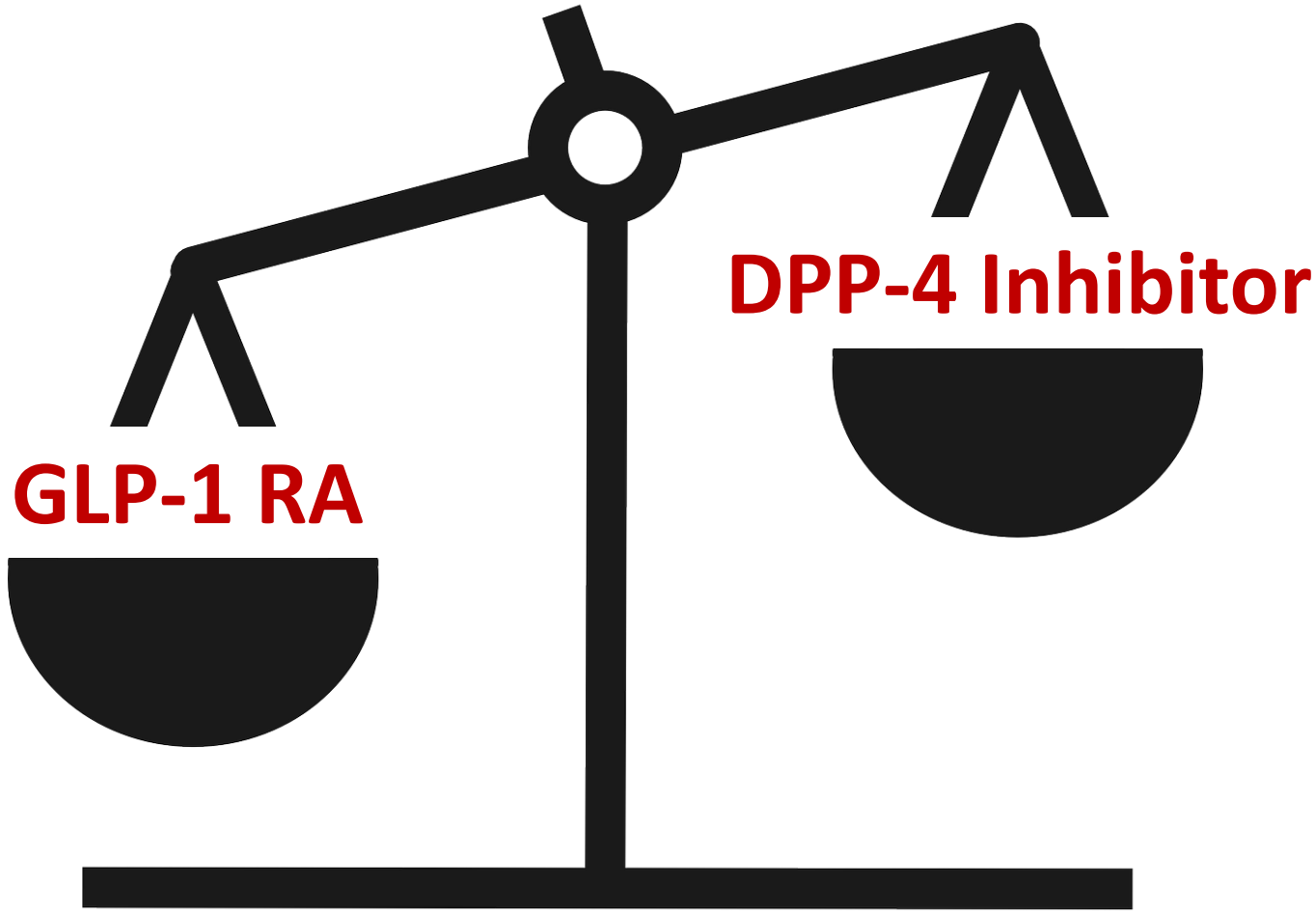




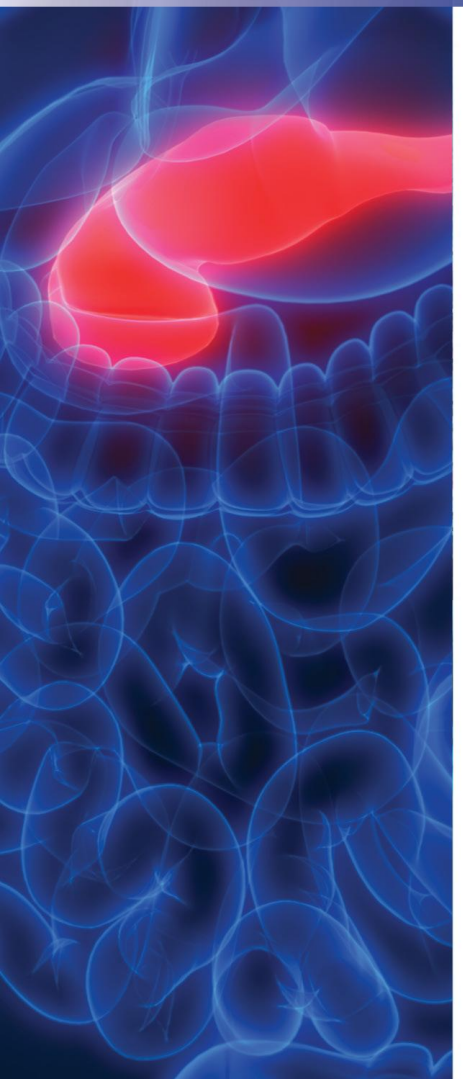
DeFronzo RA. *Diabetes*. 2009;58(4):773-795.

Degree of GLP-1 Receptor Activation with Treatment





Considering Oral Therapies in Combination with Injectable Therapies



METFORMIN

Continue treatment with metformin

SGLT2i

If on SGLT2i, continue treatment

Consider adding SGLT2i if

- Established CVD
- If HbA_{1c} above target or as weight reduction aid

Beware

- DKA (euglycemic)
- Instruct on sick-day rules
- Do not down-titrate insulin over-aggressively

SULFONYLUREA

If on SU, stop or reduce dose by 50% when basal insulin initiated

Consider stopping SU if prandial insulin initiated or on a premix regimen

DPP-4i

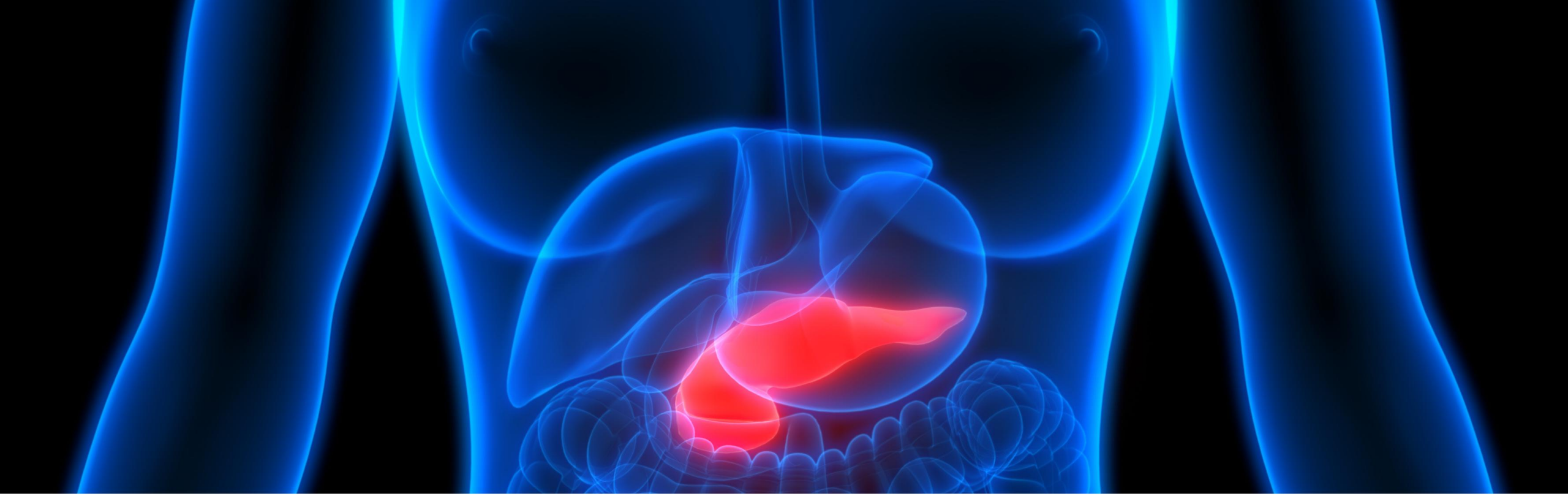
Stop DPP-4i if GLP-1 RA initiated

TZD[1]

Stop TZD when commencing insulin OR reduce dose

DKA, diabetic ketoacidosis; DPP-4i, dipeptidyl peptidase 4 inhibitor; SU, sulfonylurea.

Davies MJ, et al. *Diabetes Care.* 2018;41(12):2669-2701.



What are the Different Effects of GLP-1 RAs on Glucose?

Impact on the Glucose Profile

	Short-acting		Long-acting				
Agent	Exenatide (Byetta)	Lixisenatide (Adlyxin)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)	Oral Semaglutide (Rybelsus)
Glucose profile target	PPG	PPG	FPG/PPG	FPG/PPG	FPG/PPG	FPG/PPG	FPG/PPG
Dosing duration	Twice daily	Once daily	Once daily	Once weekly	Once weekly	Once weekly	Once daily

- Short-acting agents predominantly lower post-prandial glucose (PPG), likely due to their effect on gastric emptying.
- Long-acting agents demonstrate larger effects on fasting plasma glucose (FPG) levels compared to short-acting agents.

Trujillo JM. Glucagon-like peptide-1 receptor agonists. In: White JR, ed. *2019 Guide to Medications for the Treatment of Diabetes Mellitus*. Arlington, VA: American Diabetes Association; 2019:190-210.

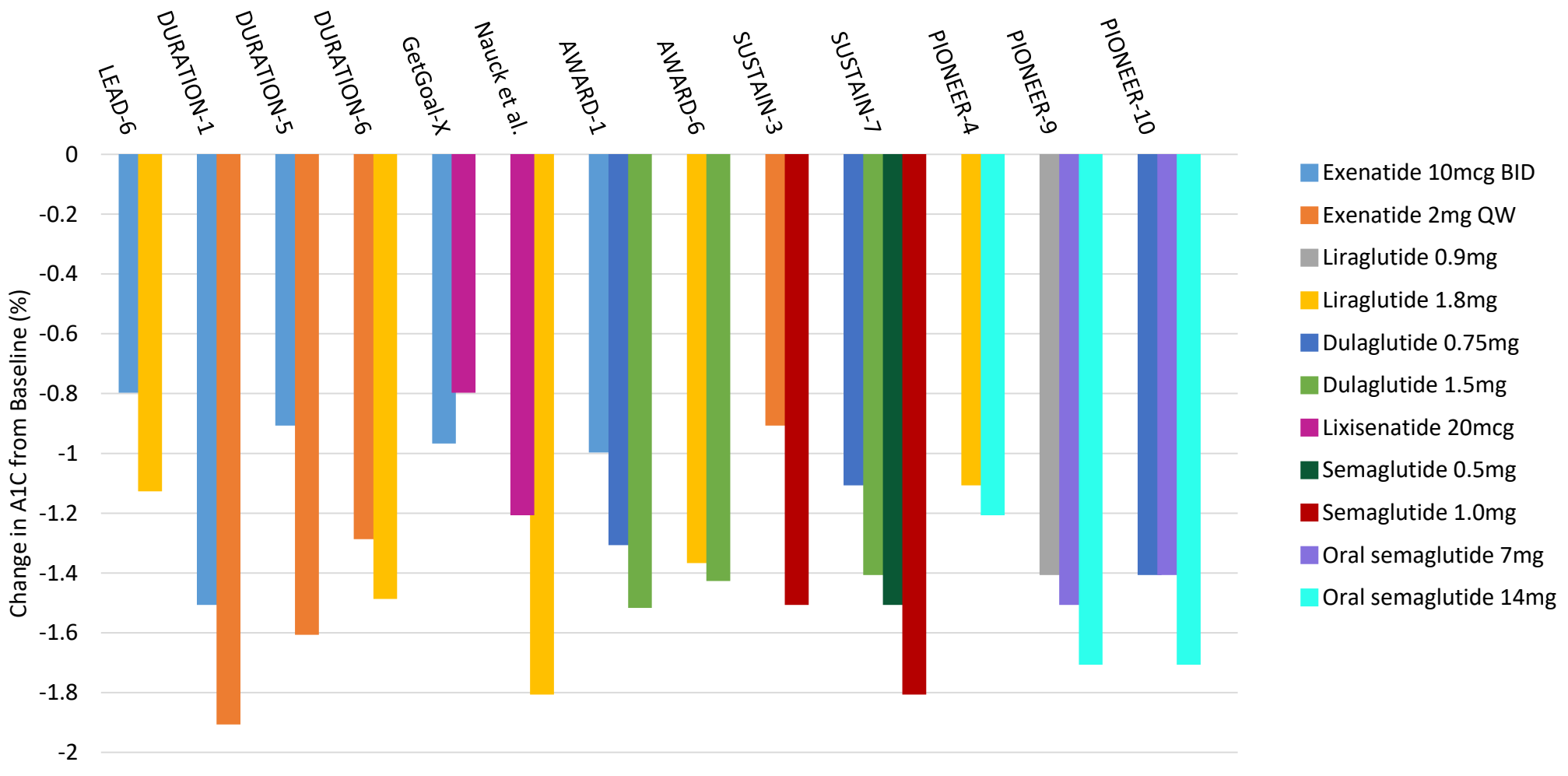
Comparison of Phase 3 Studies of GLP-1 RAs

	Exenatide (Byetta)	Lixisenatide (Lyxumia)	Liraglutide (Victoza)	Exenatide XR (Bydureon)	Dulaglutide (Trulicity)	Semaglutide (Ozempic)	Oral semaglutide (Rybelsus)
Phase 3 clinical trial	AMIGO	GetGoal	LEAD	DURATION	AWARD	SUSTAIN	PIONEER
Background therapy	Drug-naïve, metformin, SU	Drug-naïve, metformin, SU, TZD, basal insulin	Drug-naïve, metformin, SU, TZD	Drug-naïve, metformin, SU, TZD	Drug-naïve metformin, SU, TZD, SGLT2i; basal, bolus insulin	Drug-naïve, metformin, SU, TZD; basal, bolus, premixed insulin	Drug-naïve, metformin, SU, TZD, SGLT2i; basal, bolus, pre-mixed insulin
A1C lowering (%)*	-0.4 to -1.1	-0.46 to -0.99	-0.84 to -1.5	-1.48 to -1.9	-0.71 to -1.9	-1.1 to -2.2	-0.6 to -1.4
Weight lowering (kg)	-0.3 to -2.8	+0.3 to -2.96	+0.3 to -3.24	-2.0 to -4.0	+0.2 to -4.7	-1.4 to -6.5	-1.2 to -4.4

* Includes all doses studied

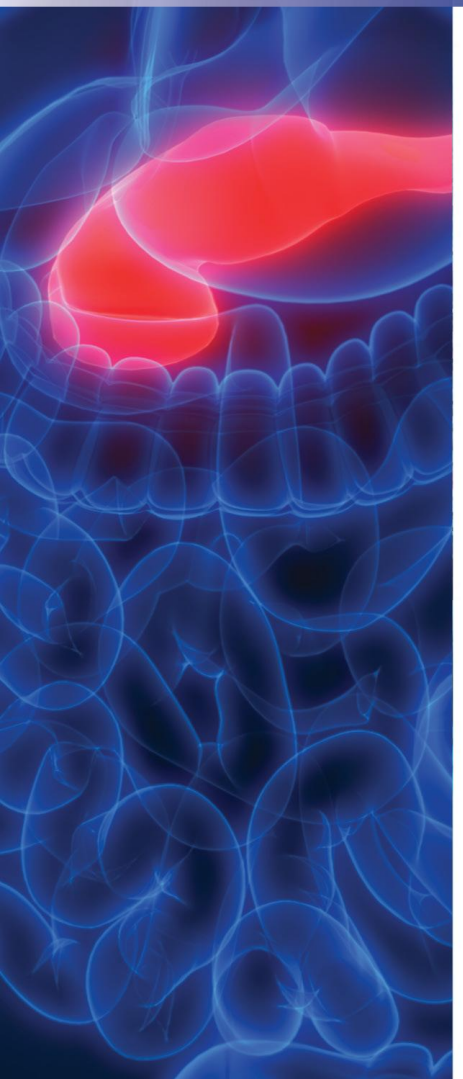
SGLT2i, sodium-glucose transport protein 2 inhibitor.

Head-to-Head Trials: A1C



GLP-1 receptor agonists: an updated review of head-to-head clinical studies
Available at: https://journals.sagepub.com/doi/full/10.1177/2042018821997320

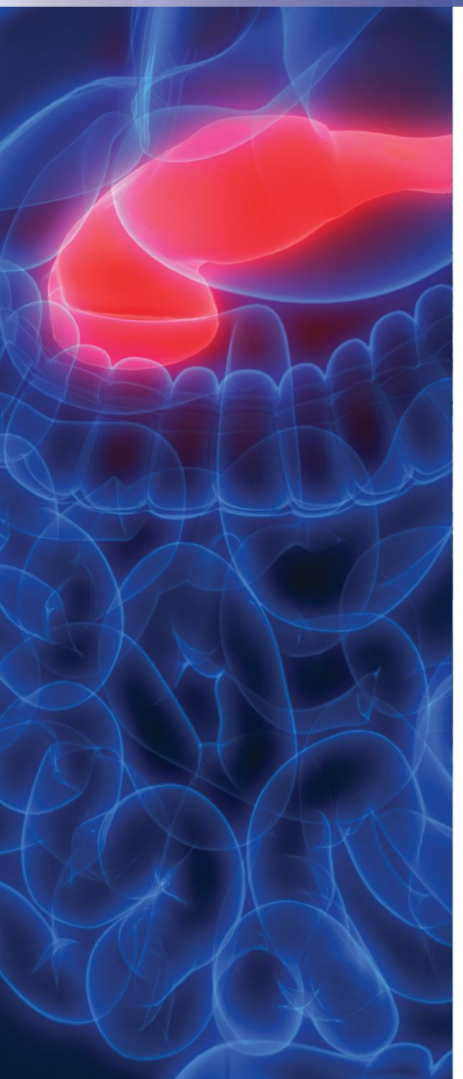
Short-Acting vs Long-Acting GLP-1 RAs in Combination with Basal Insulin



- Meta-analysis of 14 studies in combination with basal insulin
- Change in A1C
  - Short-acting GLP-1 RA + basal insulin = -0.5%
  - Long-acting GLP-1 RA + basal insulin = -1.0%
- Proportion of patients achieving target A1C
  - Short-acting GLP-1 RA + basal insulin = 18.6% risk difference
  - Long-acting GLP-1 RA + basal insulin = 37.2% risk difference

Huthmacher JA, et al. *Diabetes Care*. 2020;43(9):2303-2312.

Semaglutide: Differences Between Subcutaneous and Oral Formulations

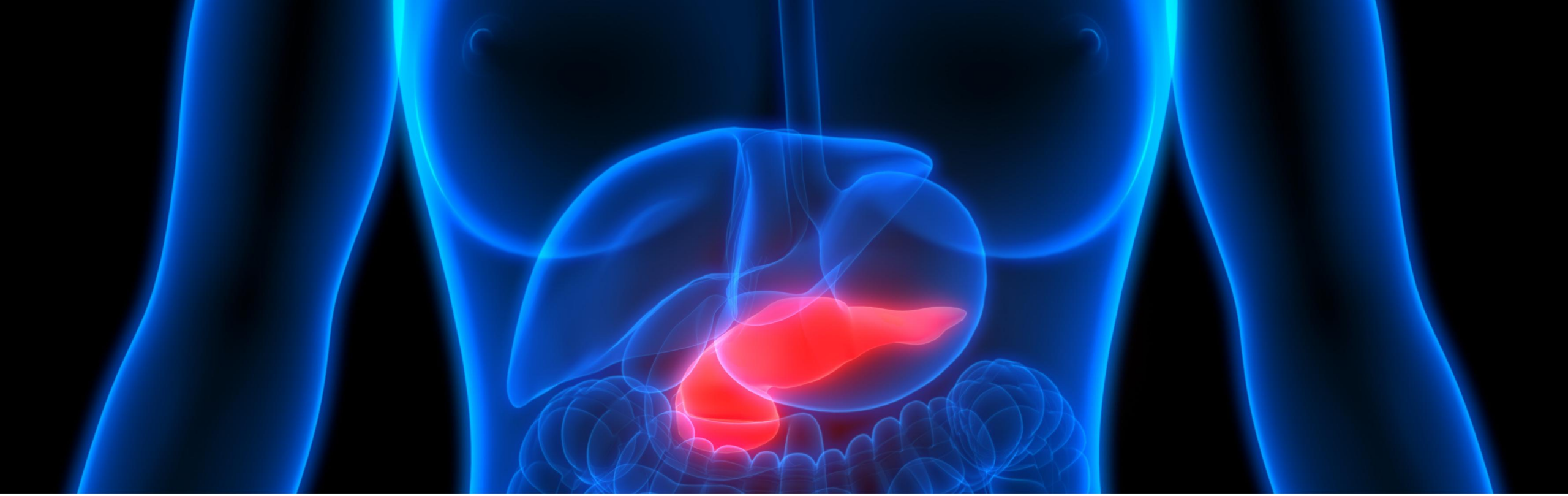


- No direct head-to-head studies
- SUSTAIN 10: SC semaglutide 1 mg achieved greater A1C reduction compared to liraglutide 1.2 mg
- PIONEER 4: Oral semaglutide achieved similar A1C reduction compared to liraglutide at 26 weeks (primary outcome); but greater A1C reduction at 52 weeks

Capehorn MS, et al. *Diabetes Metab*. 2020;46(2):100-109.
Pratley R, et al. *Lancet*. 2019;394(10192):39-50.

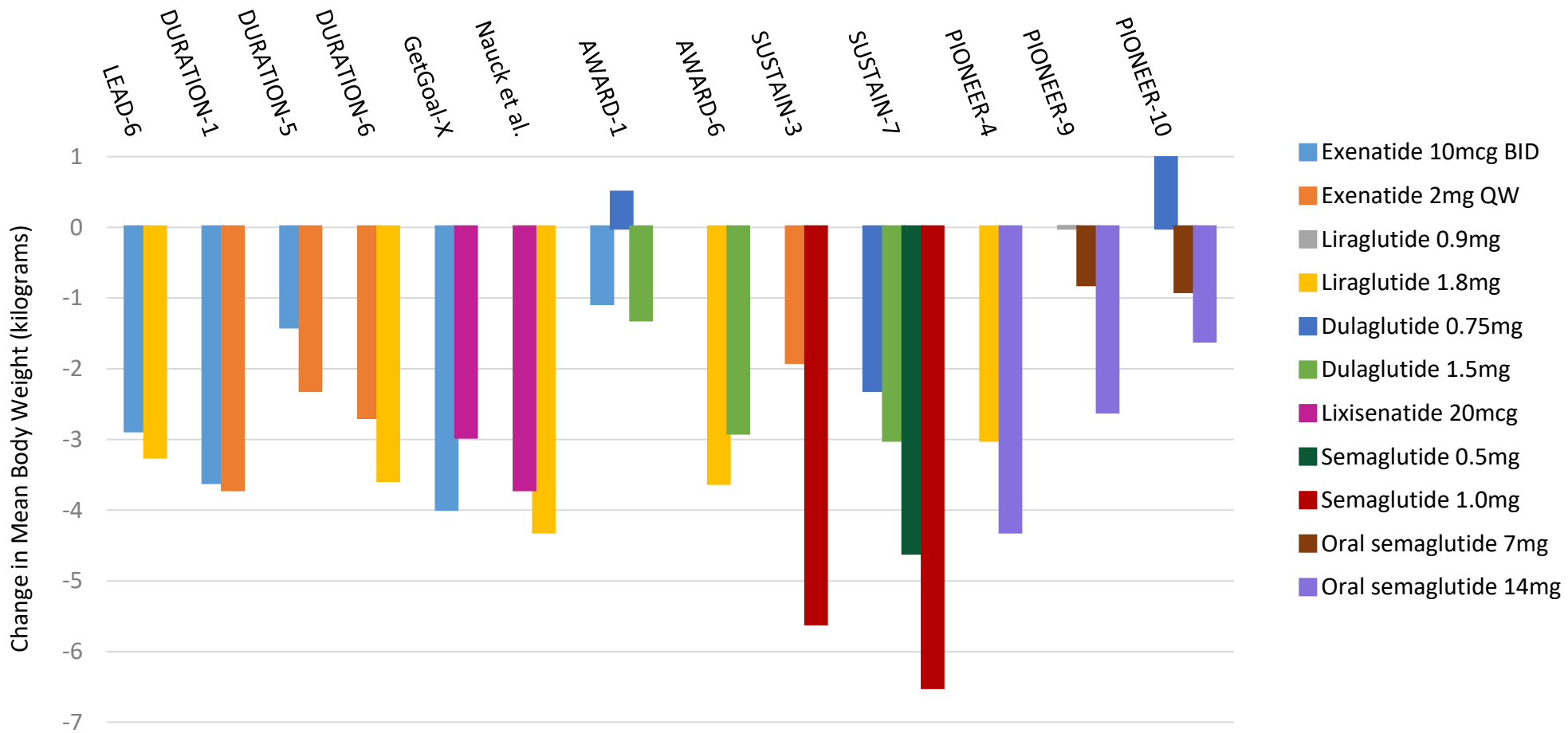
Summary of GLP-1 RA Effects

	A1C	Weight	CV Effects	GI Adverse Effects
Exenatide (Byetta)	Low	Low	No data	Highest
Lixisenatide (Adlyxin)	Low	Low	Safety	Intermediate
Liraglutide (Victoza)	High	High	Benefit	Intermediate
Exenatide XR (Bydureon)	Intermediate	Low	Safety	Low
Dulaglutide (Trulicity)	High	Intermediate	Benefit	Intermediate/High
Semaglutide (Ozempic)	Highest	Highest	Benefit	High
Oral Semaglutide (Rybelsus)	High/Highest	Highest	Safety	Intermediate/High



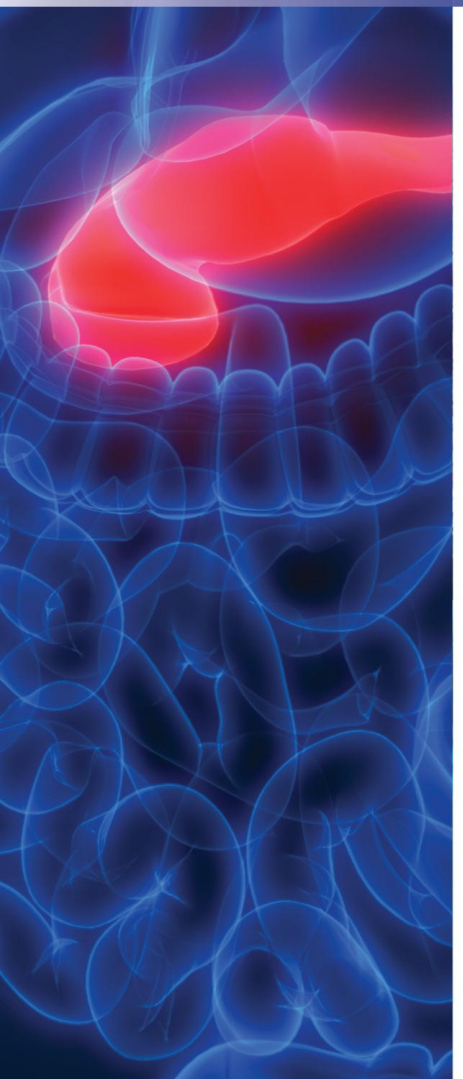
Which GLP-1 RA Should be Considered when Weight Loss is the Highest Priority?

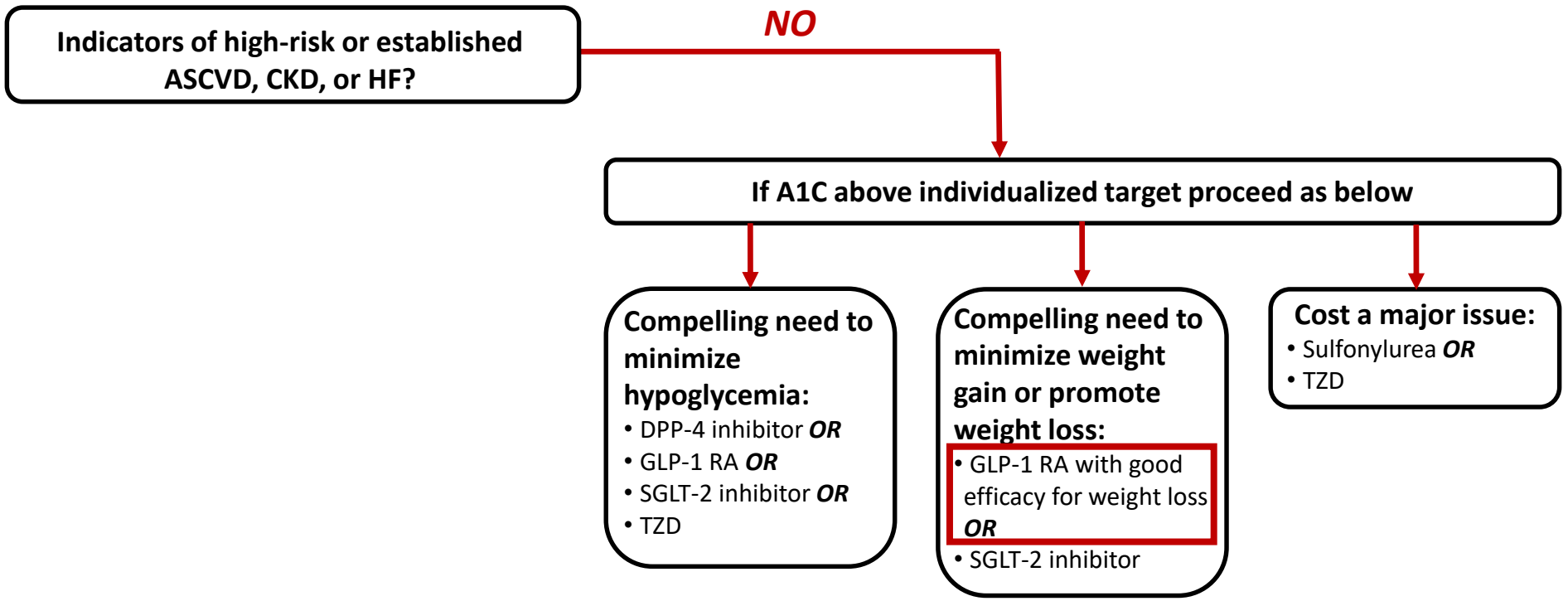
Head-to-Head Trials: Weight



GLP-1 receptor agonists: an updated review of head-to-head clinical studies
Available at: https://journals.sagepub.com/doi/full/10.1177/2042018821997320

ADA Treatment Algorithm: Compelling Need to Minimize Weight

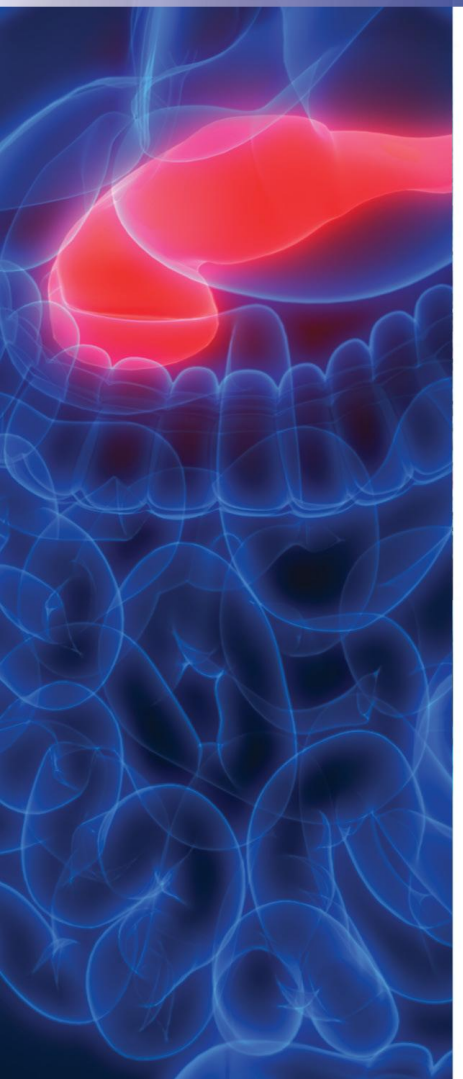




Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide

American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S98-110.

Higher Doses of GLP-1 RAs for Weight



- Liraglutide 3 mg (Saxenda)
  - Approved for weight loss
- AWARD-11
  - Dulaglutide once weekly 1.5 mg, 3.0 mg, 4.5 mg
  - 1.5 mg (A1C: -1.5%; weight: -6.8 lb)
  - 3.0 mg (A1C: -1.7%; weight: -8.8 lb)
  - 4.5 mg (A1C: -1.9%; weight: -10.4 lb)
- STEP Trials 1-5
  - Phase 3 trials of 5000 participants
  - Semaglutide 2.4 mg once weekly

Frias JP, et al. *Diabetes*. 2020;69(suppl 1). https://doi.org/10.2337/db20-357-OR.
Kushner RF, et al. *Obesity*. 2020;28(6):1050-1061.

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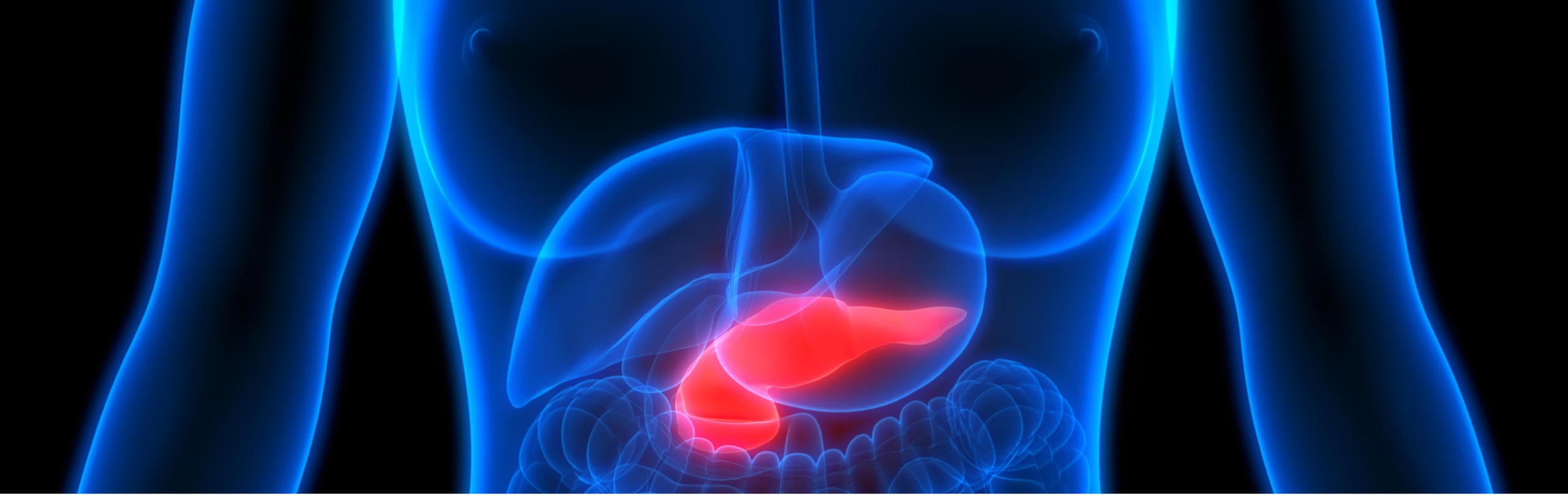
Exenatide XR (Bydureon)	Intermediate	Low	Safety	Low
Dulaglutide (Trulicity)	High	Intermediate	Benefit	Intermediate/High
Semaglutide (Ozempic)	Highest	Highest	Benefit	High
Oral Semaglutide (Rybelsus)	High/Highest	Highest	Safety	Intermediate/High



Which GLP-1 RAs have Shown CV Benefit and Carry CV Indications?

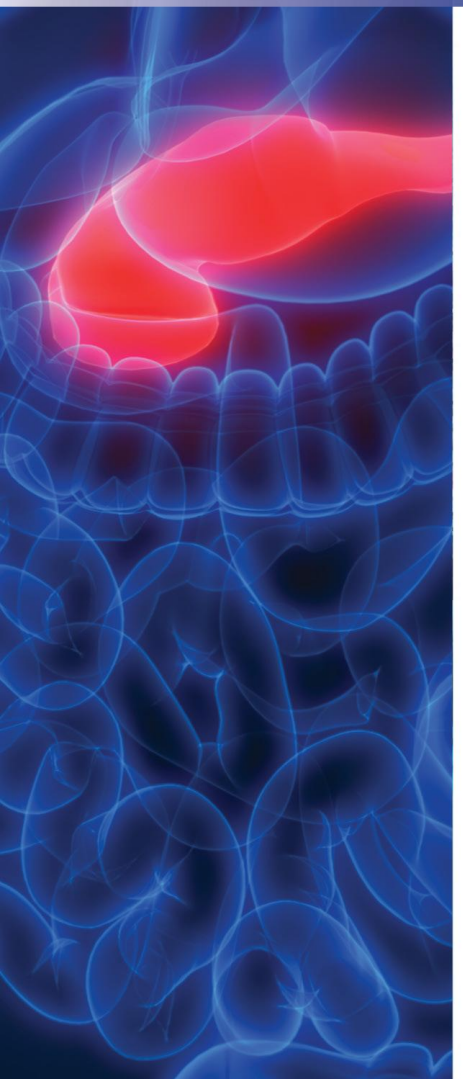
Overview of GLP-1 RA CVOTs

Study identifier	No. of patients	Follow-up Time	Study design	Primary endpoint	Results HR (95% CI)
ELIXA[1] ACS < 180 days; A1C 5.5%-11%	6068	2.1 y	Lixisenatide Placebo	4-pt MACE	**1.02 (0.89-1.17)** *P* < 0.001 (non-inferiority) p = 0.81 (superiority)
LEADER[2] CV risk/CVD; A1C ≥ 7.0%	9340	3.8 y	Liraglutide Placebo	3-pt MACE	**0.87 (0.78-0.97)** p =0.01 (superiority)
SUSTAIN 6[3] CVD; A1C ≥ 7.0%	3297	2.1 y	Semaglutide (SC) Placebo	3-pt MACE	**0.74 (0.58-0.95)** p = 0.02 (superiority)
PIONEER 6[4] CVD or CKD	3183	1.3 y	Semaglutide (PO) Placebo	3-pt MACE	**0.79 (0.57-1.11)** *P* < 0.001 (non-inferiority) P = 0.17 (superiority)
EXSCEL[5] High CV risk/CVD; A1C 6.5%-10.0%	14,752	3.2 y	Exenatide ER Placebo	3-pt MACE	**0.91 (0.83-1.00)** *P* < 0.001 (non-inferiority) p = 0.06 (superiority)
REWIND[6] High CV risk; A1C ≤ 9.5%	9901	5.4 y	Dulaglutide Placebo	3-pt MACE	**0.88 (0.79-0.99)** p = 0.026 (superiority)

CKD, chronic kidney disease; HR, hazard ratio.

1. Pfeffer MA, et al. *N Engl J Med.* 2015;373(23):2247-2257. 2. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-322.3. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-1844. 4. Husain M, et al. *N Engl J Med.* 2019;381(9):841-851. 5. Holman RR, et al. *N Engl J Med.* 2017;377(13):1228-1239. 6. Gerstein HC, et al. *Lancet.* 2019;394(10193):121-130.

GLP-1 RA Expanded FDA-Approved Cardiovascular Indications



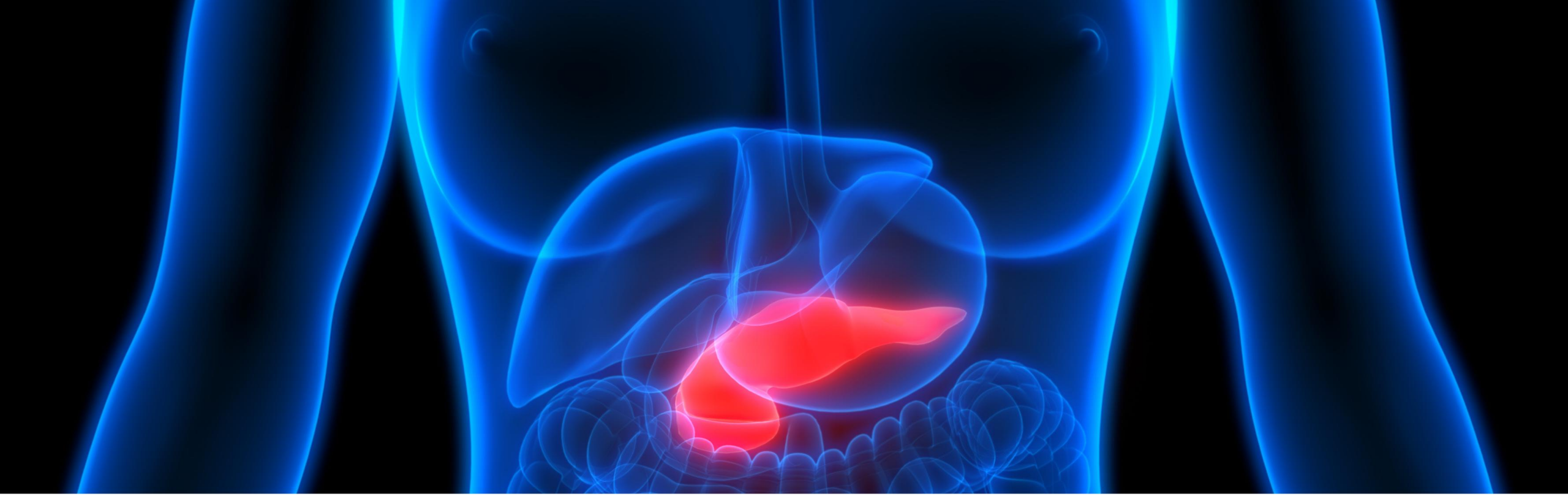
Medication	Expanded CV FDA Indication
Liraglutide (Victoza)	"…reduce the risk of major adverse CV events in adults with T2D and established CVD"
Semaglutide (Ozempic)	"…to reduce the risk of major adverse CV events in adults with T2D and established CVD"
Semaglutide (Rybelsus)	None
Exenatide XR (Bydureon, Bydureon BCise)	None
Dulaglutide (Trulicity)	"…to reduce the risk of major adverse CV events in adults with T2D who have established CVD or multiple CV risk factors."

ASCVD, atherosclerotic cardiovascular disease.

Bydureon BCise [package insert]. AstraZenica; 2020; Ozempic [package insert]. Novo Norsdisk; 2020; Rybelsus [package insert]. Novo Nordisk; 2020; Trulicity [package insert]. Lilly; 2020; Victoza [package insert]. Novo Nordisk; 2020.

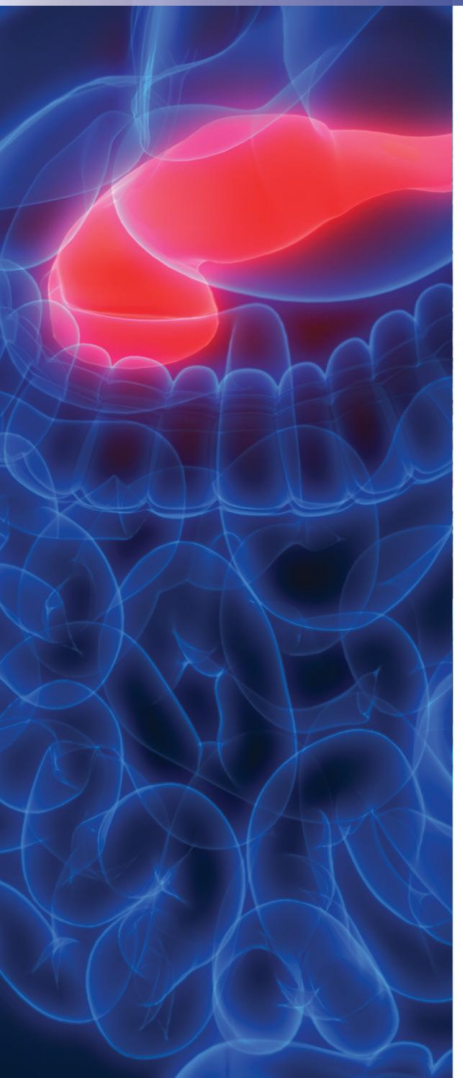
Summary of GLP-1 RA Effects

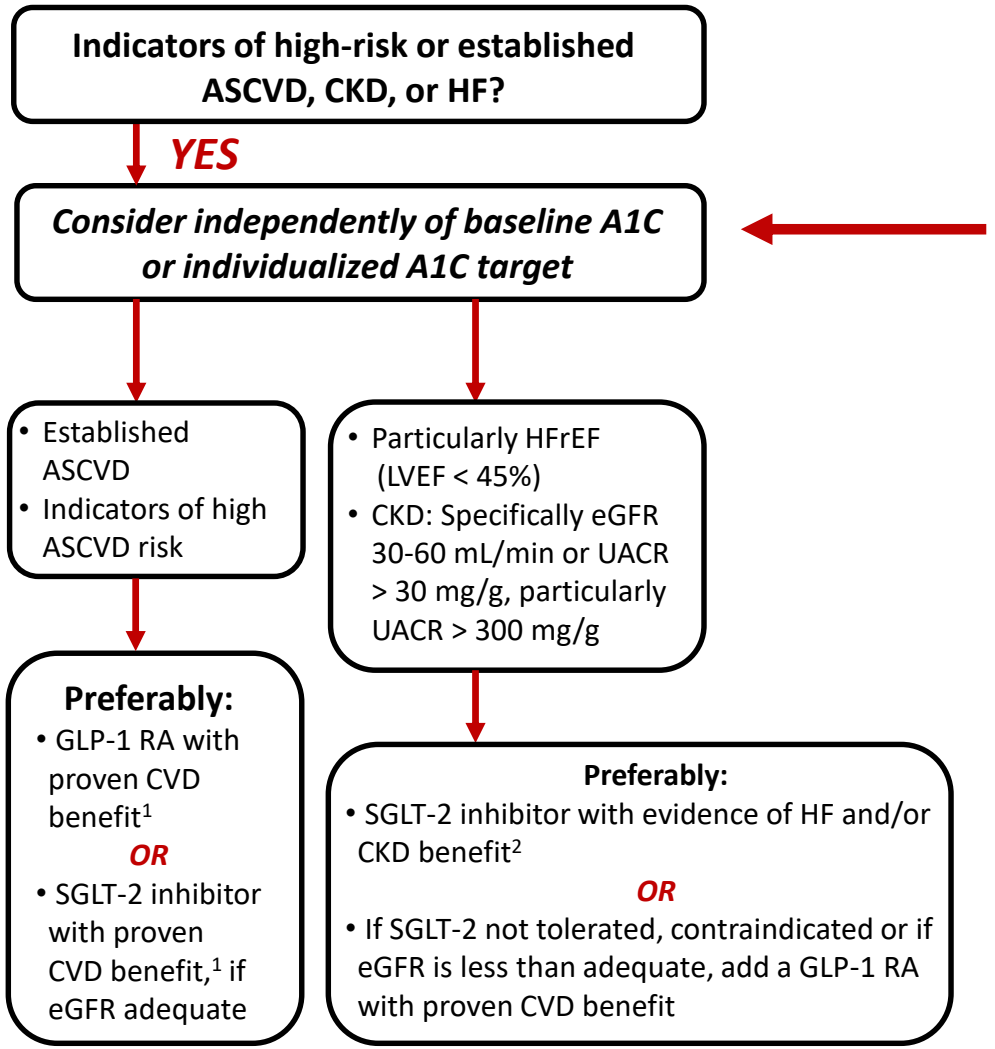
	A1C	Weight	CV Effects	GI Adverse Effects
Exenatide (Byetta)	Low	Low	No data	Highest
Lixisenatide (Adlyxin)	Low	Low	Safety	Intermediate
Liraglutide (Victoza)	High	High	Benefit	Intermediate
Exenatide XR (Bydureon)	Intermediate	Low	Safety	Low
Dulaglutide (Trulicity)	High	Intermediate	Benefit	Intermediate/High
Semaglutide (Ozempic)	Highest	Highest	Benefit	High
Oral Semaglutide (Rybelsus)	High/Highest	Highest	Safety	Intermediate/High



Does Using a GLP-1 RA in Combination with a SGLT2 Inhibitor Further Improve Cardiovascular Outcomes?

Glucose-Lowering Medication Use in T2D



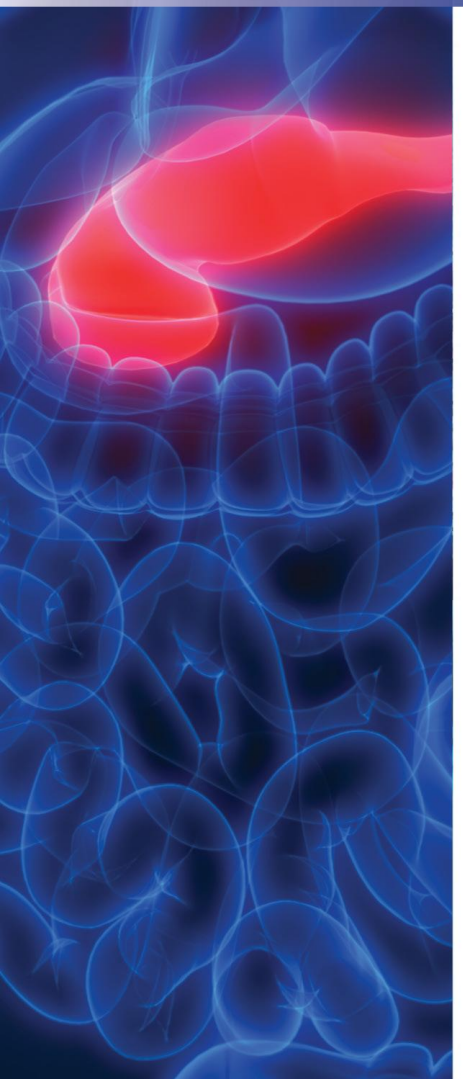


Key Change in 2020:

- For patients with indicators of high-risk or established ASCVD, CKD, or HF – use of agents with established evidence for risk reduction should be considered ***independently*** of current A1C and/or A1C target

American Diabetes Association. *Diabetes Care.* 2020;43(suppl 1):S98-110.

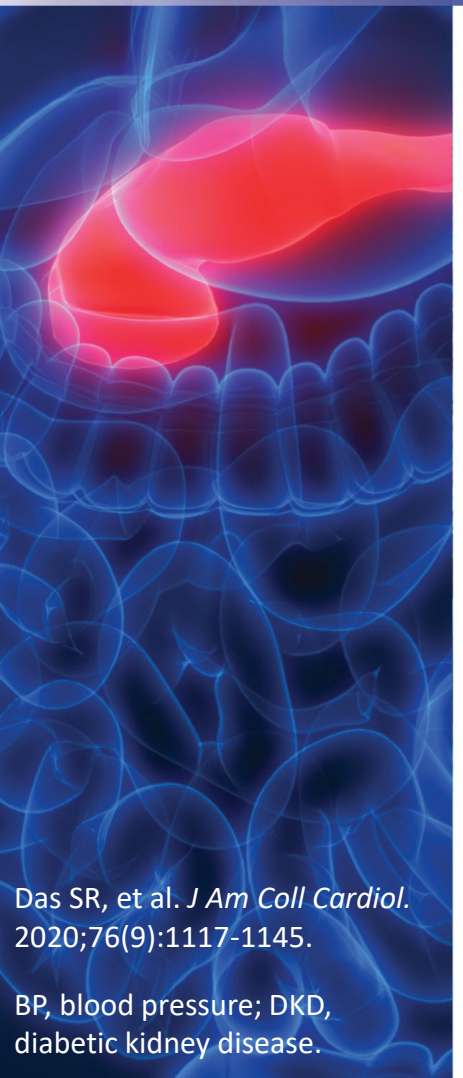
GLP-1 RA + SGLT2 Inhibitor Combination Therapy: Evidence to Date

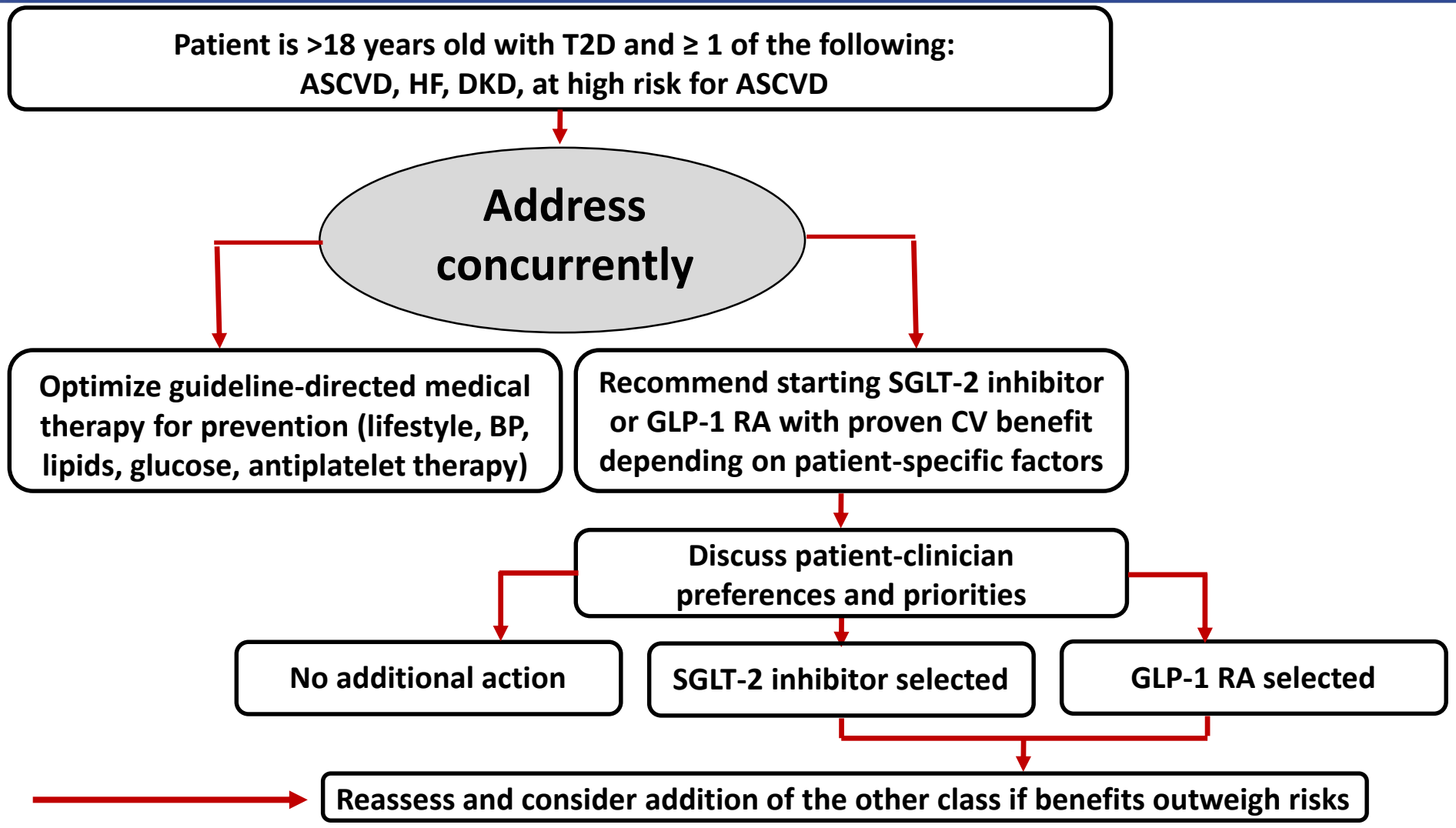


- No trials to date examining GLP-1 RA + SGLT2 inhibitor to assess the effects of the combination on cardiovascular outcomes
- Phase III trials have shown greater blood pressure and weight lowering with the combination when compared to each class used alone
- GLP-1 RA + SGLT2 inhibitors for glucose lowering is appropriate per current treatment guidelines
- Cost is a likely barrier for some patients

Das SR, et al. *J Am Coll Cardiol.* 2020;76(9):1117-1145.

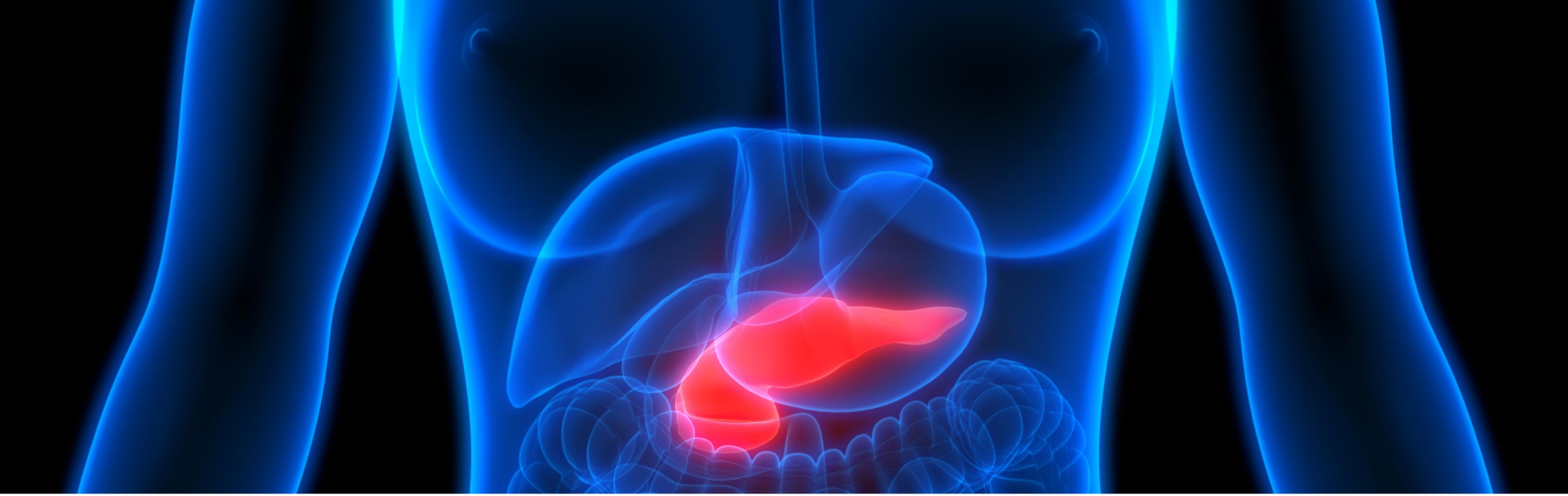
2020 American College of Cardiology (ACC) Expert Consensus Decision Pathway





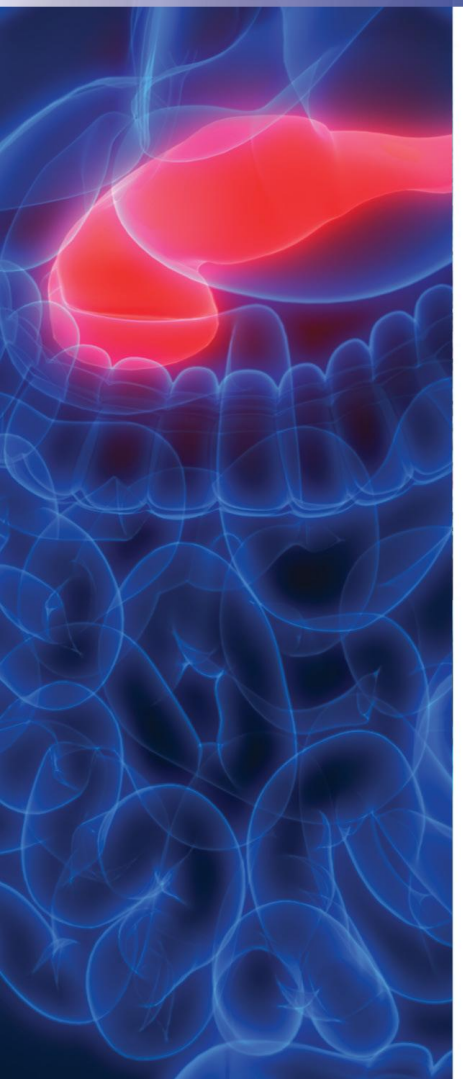
Das SR, et al. *J Am Coll Cardiol.* 2020;76(9):1117-1145.

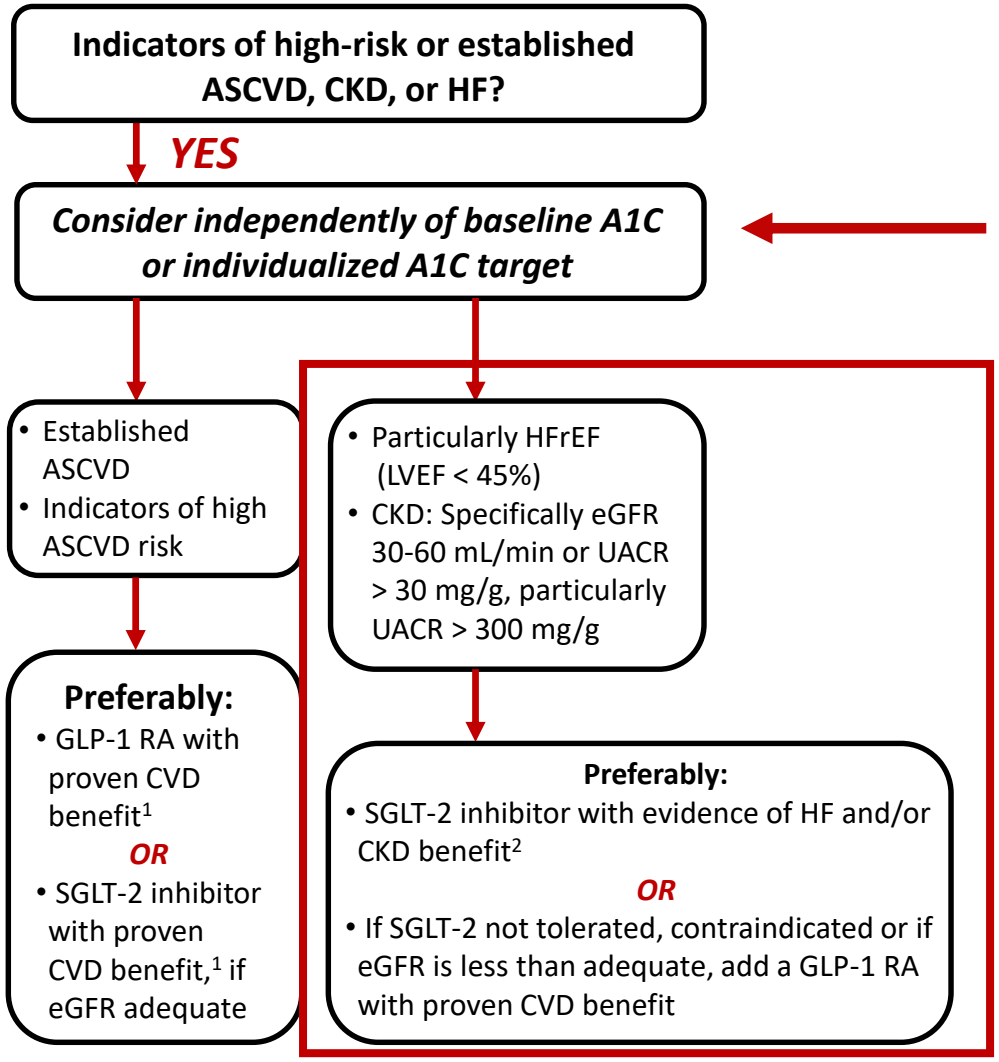
BP, blood pressure; DKD, diabetic kidney disease.



Do GLP-1 RAs Improve Kidney Outcomes in People with Type 2 Diabetes?

Glucose-Lowering Medication Use in T2D



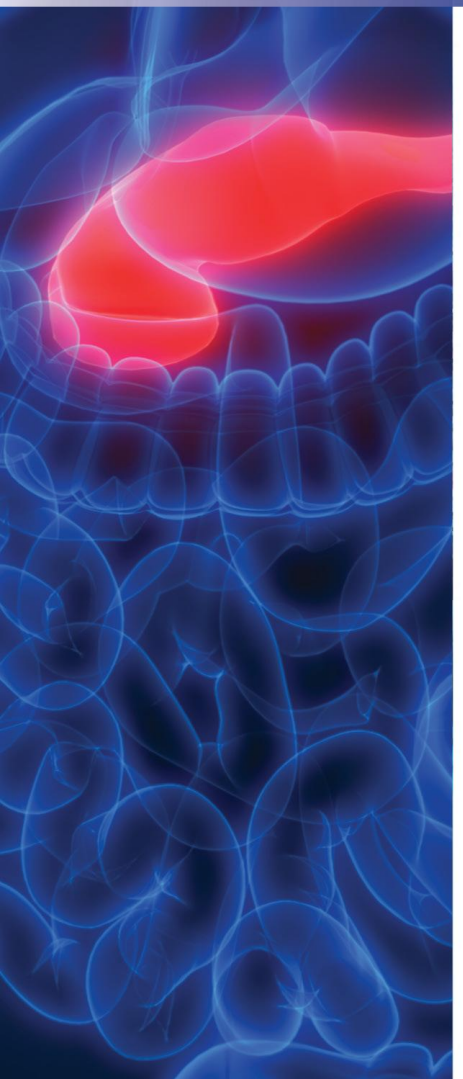


Key Change in 2020:

- For patients with indicators of high-risk or established ASCVD, CKD, or HF – use of agents with established evidence for risk reduction should be considered ***independently*** of current A1C and/or A1C target

American Diabetes Association. *Diabetes Care.* 2020;43(Suppl. 1):S98-110.

Primary Kidney Outcomes with SGLT2 Inhibitors

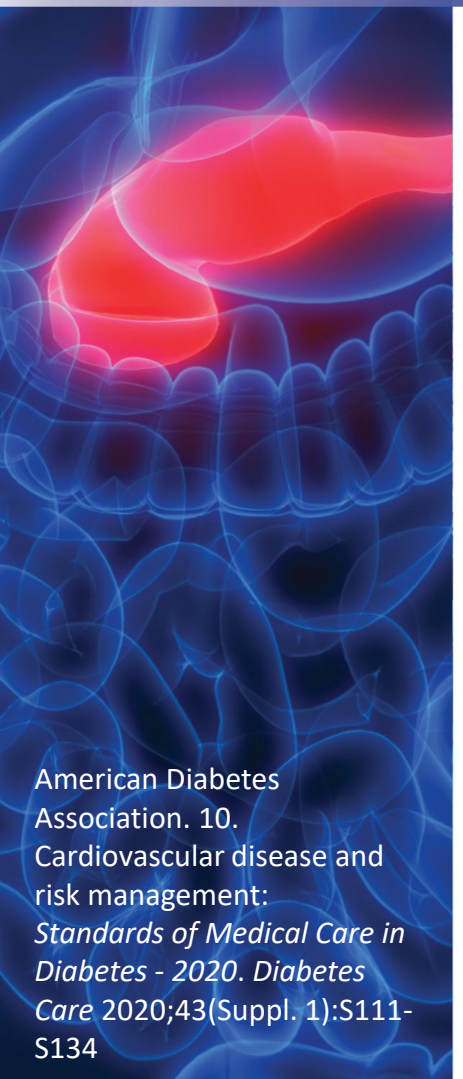


Agent	Canagliflozin	Dapagliflozin
Study	CREDENCE (N = 4401)	DAPA-CKD (N = 4304)
Median follow-up (years)	2.6	2.4
Kidney-related enrollment criteria[†]	• eGFR 30 to < 90 • UACR: > 300 to 5000 mg/g	• eGFR 25 to 75 • UACR: 200 to 5000 mg/g
Mean baseline eGFR	56 mL/min/1.73m^2	43 mL/min/1.73m^2
Median Baseline UACR	927 mg/g	949 mg/g
Kidney outcome(s)	**Primary Outcome** • ESKD (dialysis, transplantation, or sustained eGFR < 15 mL/min/1.73m^2), doubling of SCr, or death from renal causes **HR: 0.70 (0.59-0.82)**	**Primary Outcome** • ≥ 50% decrease in eGFR, ESKD, or death from renal or cardiovascular causes **HR: 0.61 (0.51-0.72)**

eGFR, estimated glomerular filtration rate; ESKD, end-stage kidney disease; HR, hazard ratio; SCr, serum creatinine; UACR, urinary albumin-to-creatinine ratio.

Heerspink HJL, et al. *N Engl J Med*. 2020;383:1436-1446.
Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306.

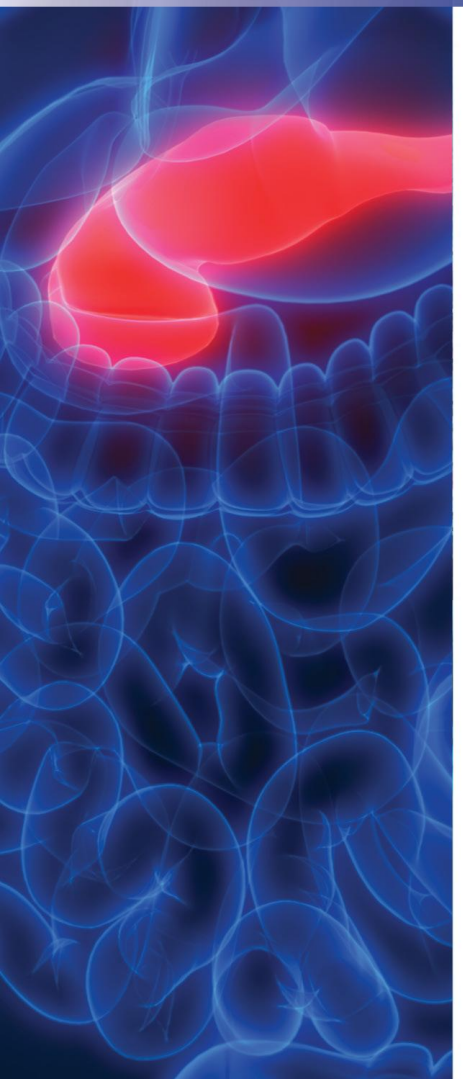
CVOT Summary of Trials with Injectable GLP-1 RAs



	ELIXA (n = 6068)	LEADER (n = 9340)	SUSTAIN-6 (n = 3297)	EXSCEL (n = 14,752)	REWIND (n=9901)
Agent	Lixisenatide	Liraglutide	Semaglutide	Exenatide XR	Dulaglutide
Median follow-up (years)	2.1	3.8	2.1	3.2	5.4
Metformin use (%)	66	76	73	77	81
Prior CVD (%)	100	81	60	73.1	32
Mean baseline A1C (%)	7.7	8.7	8.7	8.0	7.4
Primary outcome	4-point MACE 1.02 (0.89–1.17)	**3-point MACE 0.87 (0.78–0.97)**	**3-point MACE 0.74 (0.58–0.95)**	3-point MACE 0.91 (0.83–1.00)	**3-point MACE 0.88 (0.79-0.99)**
Cardiovascular death	0.98 (0.78–1.22)	**0.78 (0.66–0.93)**	0.98 (0.65–1.48)	0.88 (0.76–1.02)	0.91 (0.78-1.06)
MI	1.03 (0.87–1.22)	0.86 (0.73–1.00)	0.74 (0.51–1.08)	0.97 (0.85–1.10)	0.96 (0.79-1.15)
Stroke	1.12 (0.79–1.58)	0.86 (0.71–1.06)	**0.61 (0.38–0.99)**	0.85 (0.70–1.03)	**0.76 (0.61–0.95)**
All-cause mortality	0.94 (0.78–1.13)	**0.85 (0.74–0.97)**	1.05 (0.74–1.50)	**0.86 (0.77–0.97)**	0.90 (0.80-1.01)
Worsening nephropathy	-	**0.78 (0.67–0.92)**	**0.64 (0.46–0.88)**	-	**0.85 (0.77-0.93)**

American Diabetes Association. 10. Cardiovascular disease and risk management: *Standards of Medical Care in Diabetes - 2020. Diabetes Care* 2020;43(Suppl. 1):S111-S134

Select Ongoing GLP-1 RA Trials Examining Kidney Outcomes

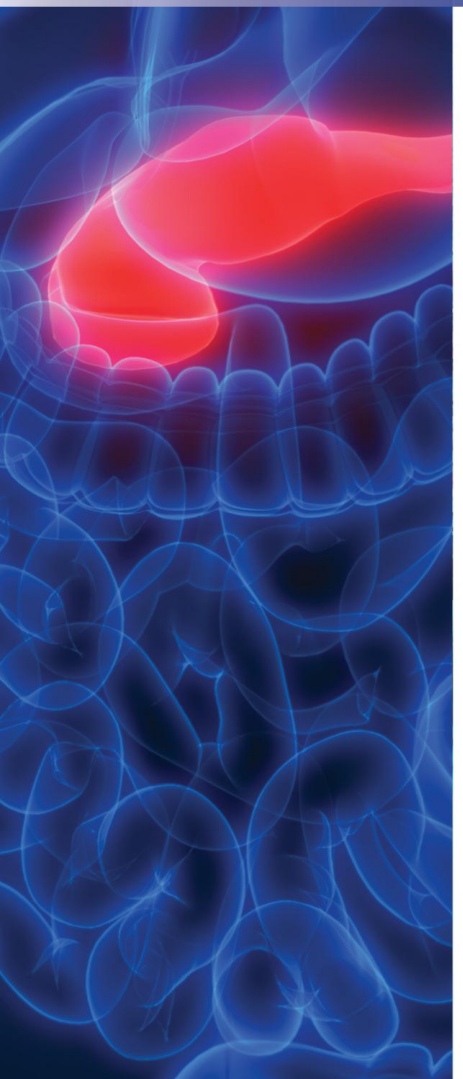


Drug Under Study	Trial	Key kidney-related outcomes
Semaglutide	FLOW	○ Primary Outcome: ▪ Time to first occurrence of a composite of: eGFR decline of ≥ 50% from baseline, ESRD, or death from kidney or cardiovascular disease ○ Secondary Outcome Measures: ▪ Annual rate of change in eGFR ▪ Time to occurrence of all-cause death ▪ Time to occurrence of each individual component of the primary composite outcome ▪ Relative change in UACR
Semaglutide (in combination with empagliflozin)	EmpaSema	○ Primary Outcome: ▪ Change in albuminuria (from randomization to week 52) ○ Secondary Outcome Measures: ▪ Change in GFR (from randomization to week 52) ▪ Change in inflammatory and endothelial biomarkers

eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; UACR, urinary albumin-to-creatinine ratio.

www.clinicaltrials.gov. Accessed October 26, 2020.

KDIGO 2020 Recommendations for Use of Antihyperglycemic Therapies in Patients with Type 2 Diabetes and Chronic Kidney Disease



First-Line Therapy

Metformin
- Reduce dose if eGFR < 45
- Discontinue if eGFR < 30 or dialysis

+

SGLT2 Inhibitor
- Don't initiate if eGFR < 30
- Discontinue with dialysis

Additional Drug Therapy As Needed for Glycemic Control

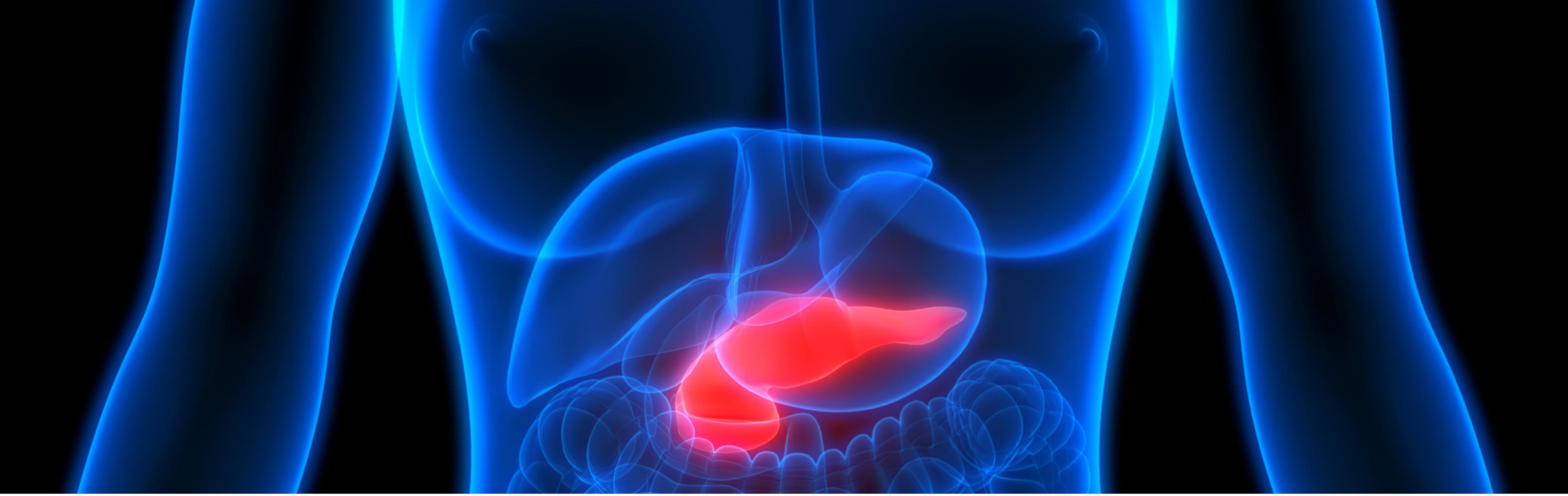
GLP-1 Receptor Agonist
Preferred Next Agent

DPP-4 Inhibitor | **Insulin**

Sulfonylurea | **TZD**

Alpha-glucosidase inhibitor

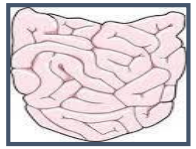
Boer IH, et al. *Kidney Int.* 2020;98(4):839-848.



What is the Mechanism of Nausea and Vomiting and What are Strategies for Minimization?

GLP-1 RAs: Actions on Target Tissues

Food



Gut

GLP-1

$t_{1/2}$ = 1-2 min

DPP-4

Inactive GLP-1

Pancreas

- ↑Glucose-dependent insulin secretion
- ↓Glucose-dependent glucagon secretion

Stomach

- ↓Gastric emptying

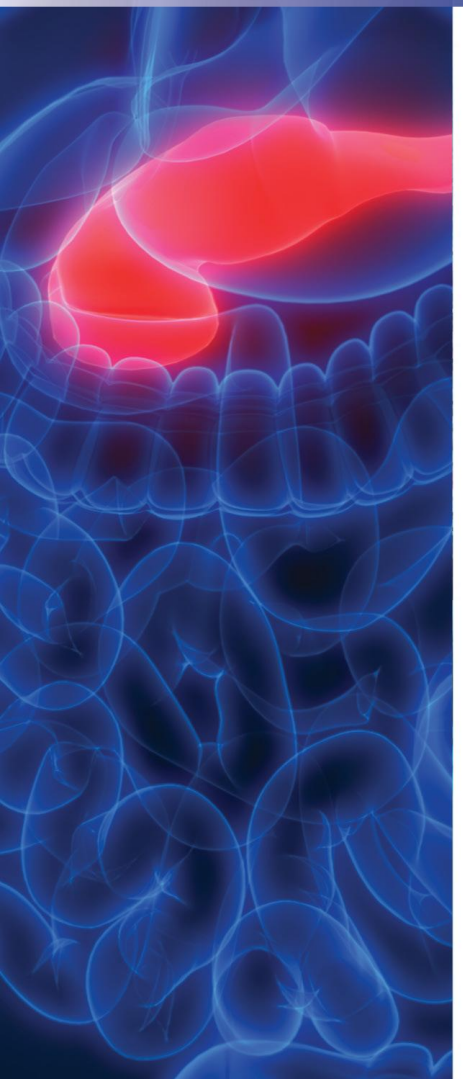
Brain

- ↑Satiety

↓Glucose
↓Weight

DPP-4, dipeptidyl peptidase 4.

GI Adverse Effects with GLP-1 RAs



	Drug	Glucose profile target	Phase 3 clinical program	Nausea (%)^	Vomiting (%)^	Diarrhea (%)^
Short-acting	Exenatide	PPG	AMIGO	8-44*	4-18*	6-18*
	Lixisenatide	PPG	GetGoal	25	10	8
Long-acting	Liraglutide	FPG > PPG	LEAD	18-20	6-9	10-12
	Exenatide XR	FPG > PPG	DURATION	8.2	3.4	4
	Dulaglutide	FPG > PPG	AWARD	12.4-21.1	6-12.7	8.9-12.6
	Semaglutide	FPG > PPG	SUSTAIN	15.8-20.3	5-9.2	8.8-8.9
	Oral semaglutide	FPG > PPG	PIONEER	11-20	6-8	9-10

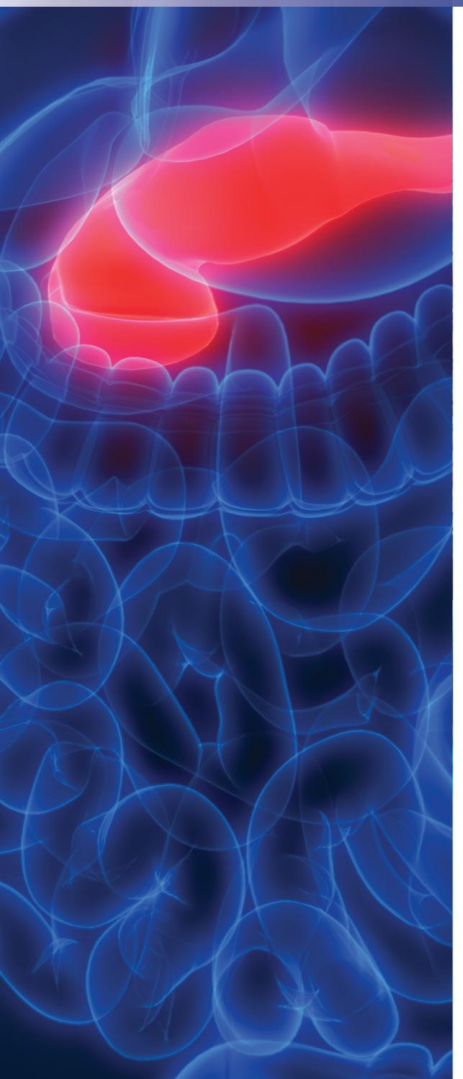
^ averages from phase 3 trials taken from prescribing information; ranges based on different doses, except for exenatide
* ranges based on reported data from separate studies based on background therapy

Trujillo JM. Glucagon-Like Peptide-1 Receptor Agonists. In: White JR, ed. *2019 Guide to Medications for the Treatment of Diabetes Mellitus*. Arlington, VA: American Diabetes Association; 2019:190-210.

Summary of GLP-1 RA effects

	A1C	Weight	CV Effects	GI Adverse Effects
Exenatide (Byetta)	Low	Low	No data	Highest
Lixisenatide (Adlyxin)	Low	Low	Safety	Intermediate
Liraglutide (Victoza)	High	High	Benefit	Intermediate
Exenatide XR (Bydureon)	Intermediate	Low	Safety	Low
Dulaglutide (Trulicity)	High	Intermediate	Benefit	Intermediate/High
Semaglutide (Ozempic)	Highest	Highest	Benefit	High
Oral Semaglutide (Rybelsus)	High/Highest	Highest	Safety	Intermediate/High

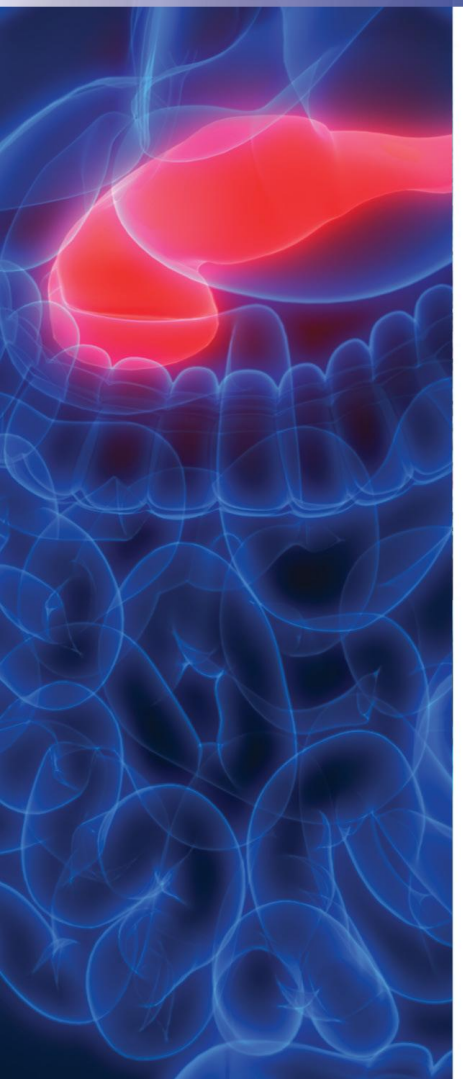
Mitigation of GI Adverse Effects

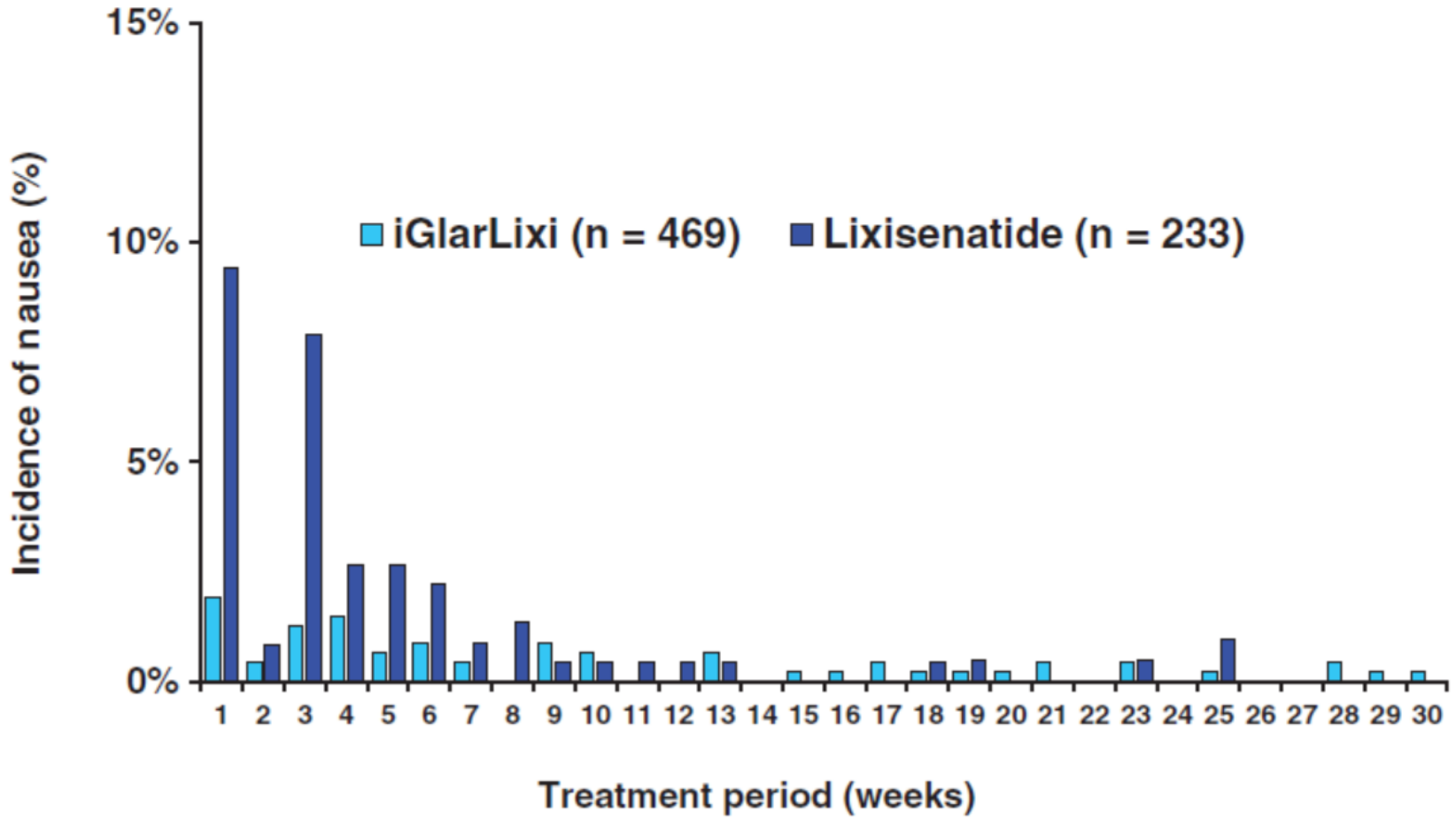


- Educate the patient that it is usually mild and usually transient
- Resolves in ~ 90% of cases
- Educate patients to decrease portions and eat slowly
- Start at low dose
- Consider agent with lower rates of GI adverse effects
- Consider slower titration if possible
- Consider fixed-ratio combination

Cefalu WT, et al. *Diabetes Care.* 2014;37(9):2647-2659.;
Nauck M. *Diabetes Care.* 2013;36(7):2126-2132.;
Shomali M. *Clin Diabetes.* 2014;32(1):32-43.

GI Adverse Effects Over Time with Fixed-Ratio Combination vs GLP-1 RA

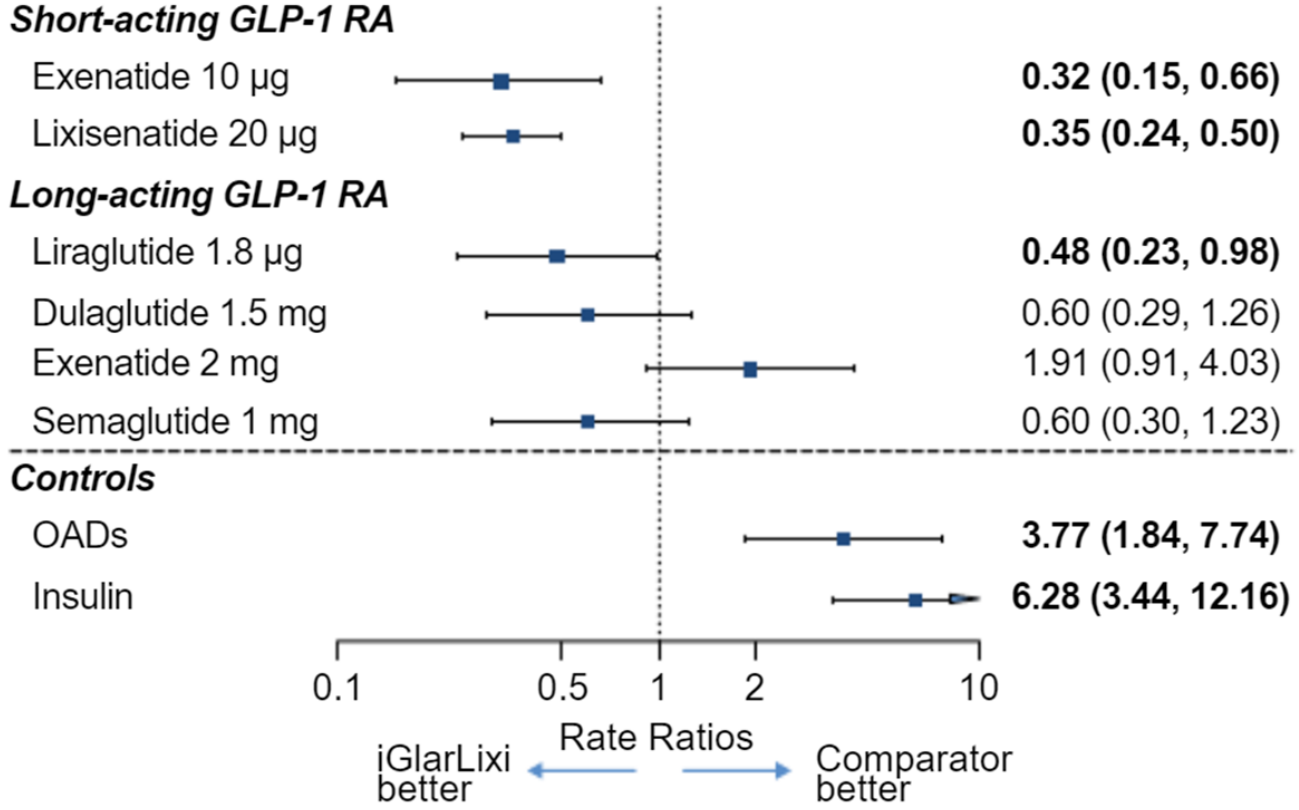




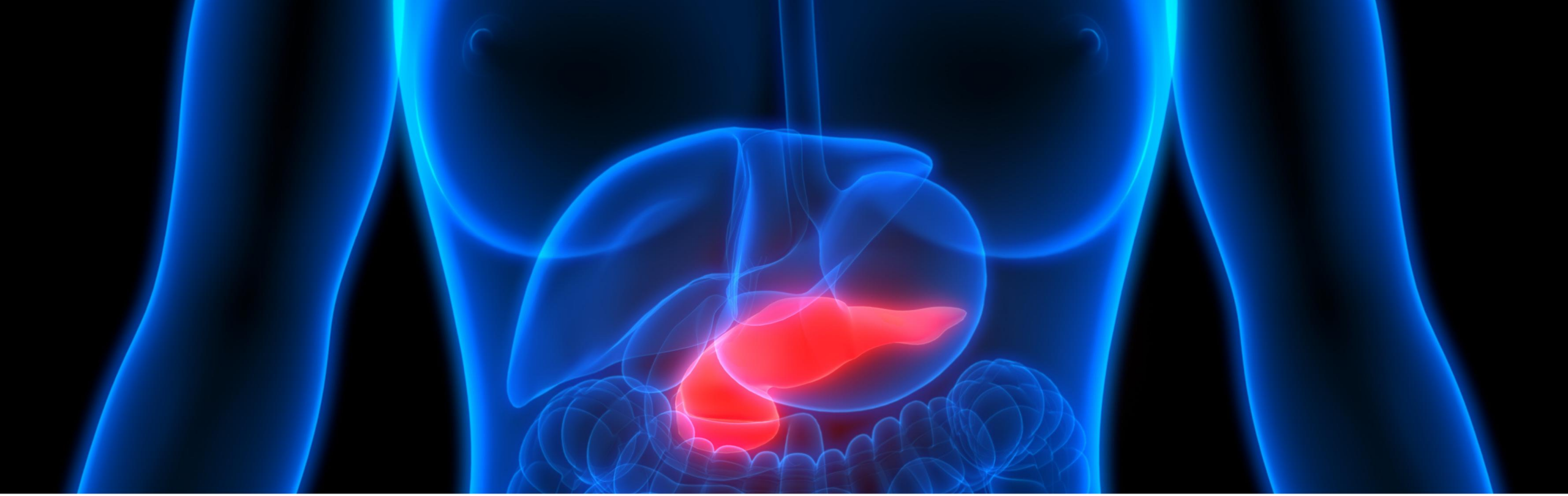
Trujillo JM, et al. *Diabetes Obes Metab*. 2018;20:2690-2694.

GI Adverse Effects with Fixed-Ratio Combination vs GLP-1 RA

A network meta-analysis of 17 trials (9030 patients with 3665 event weeks)

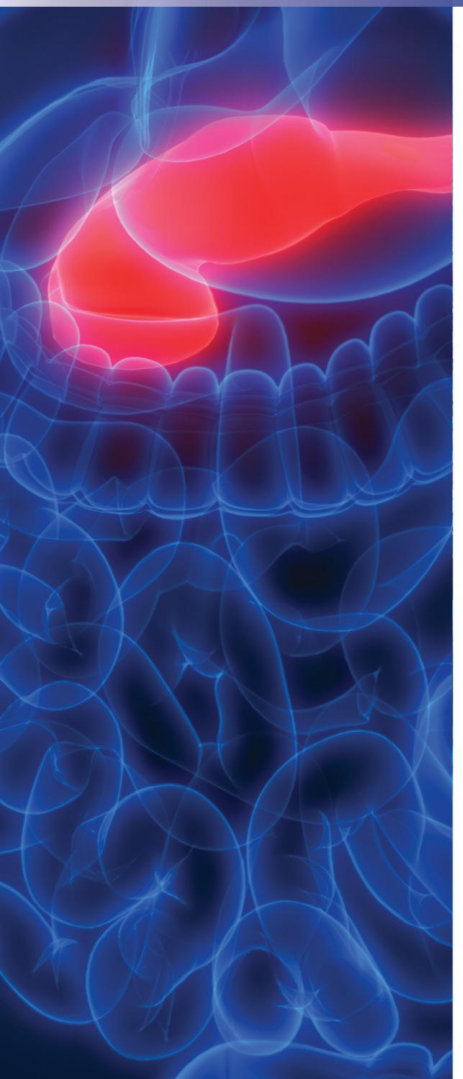


Rayner CK, et al. [published online ahead of print September 29, 2020]. *Diabetes Obes Metab*. https://doi.org/10.1111/dom.14202.



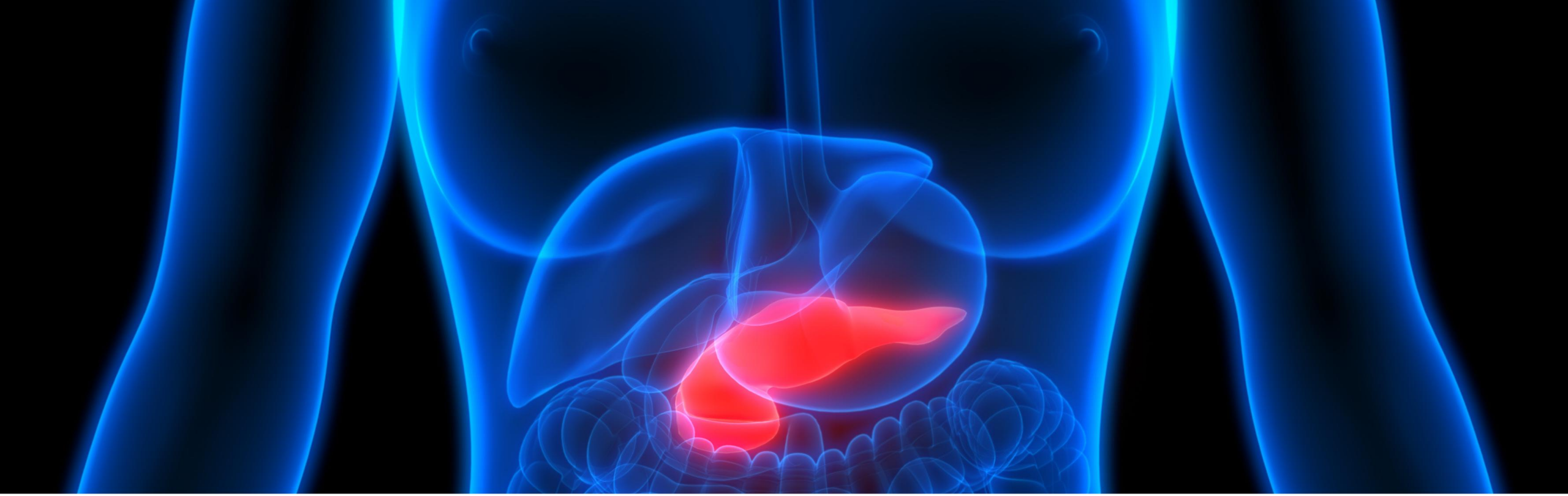
What Should we Know about Injection Site Nodules with Exenatide XR?

Exenatide XR Injection Site Nodules



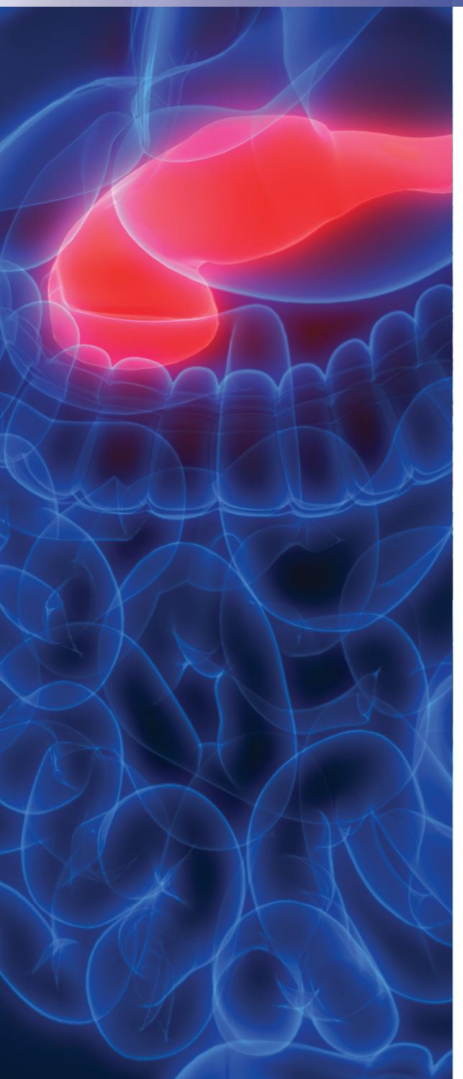
- Formulated to encapsulate exenatide in poly-(D,L-lactide-co-glycolide (PLG) microspheres, which releases drug over a sustained period
- 2 pen devices: Bydureon and Bydureon BCise
- Injection site nodule rates in clinical trials:
  - 17.1% Bydureon
  - 10.5% Bydureon BCise
- Described as small, asymptomatic, non-serious
- Some case reports of more serious nodules or granulomas

Jones SC, et al. *Diabetes Spectr*. 2015;28(4):283-288.
Bydureon Bcise [package insert]. Bydureon [package insert]. AstraZenica; 2020.



What is the Relationship of GLP-1 RA Therapy and Retinopathy?

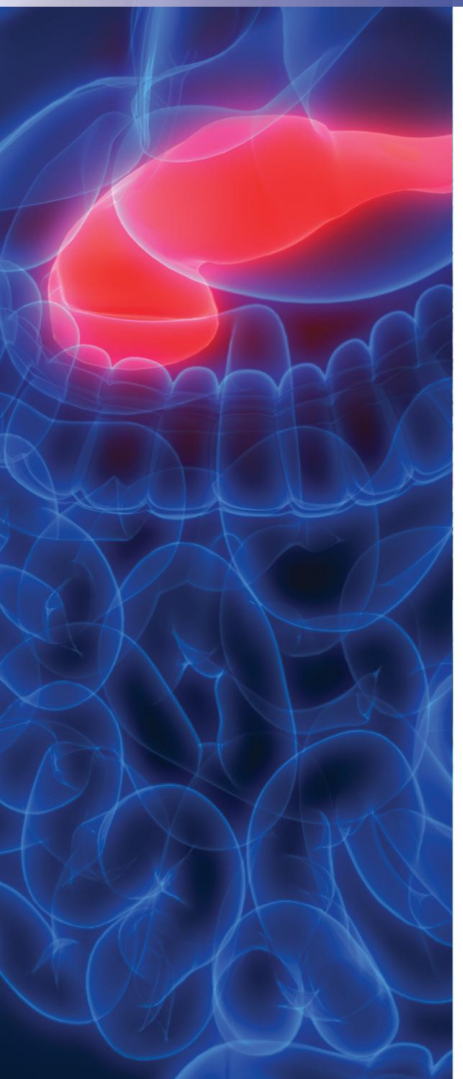
Incidence of Retinopathy in GLP-1 RA CVOTs



CVOT (GLP-1 RA)	**Retinopathy** HR (95% CI); p-value
LEADER [1] (liraglutide)	1.15 (0.87-1.52); 0.33
SUSTAIN 6 [2] (SC semaglutide)	1.76 (1.11-2.78); 0.02
PIONEER 6 [3] (PO semaglutide)	7.1 vs 6.3%
REWIND [4] (dulaglutide)	1.24 (0.92-1.68); 0.16

1. Marso SP, et al. *N Engl J Med.* 2016;375(4):311-322. 2. Marso SP, et al. *N Engl J Med.* 2016;375(19):1834-1844. 3. Husain M, et al. *N Engl J Med.* 2019;381(9):841-851. 4. Gerstein HC, et al. *Lancet*. 2019;394(10193):121-130.

Reported Rates of Retinopathy in SUSTAIN Clinical Trial Program



Rates of retinopathy based on study and dose:

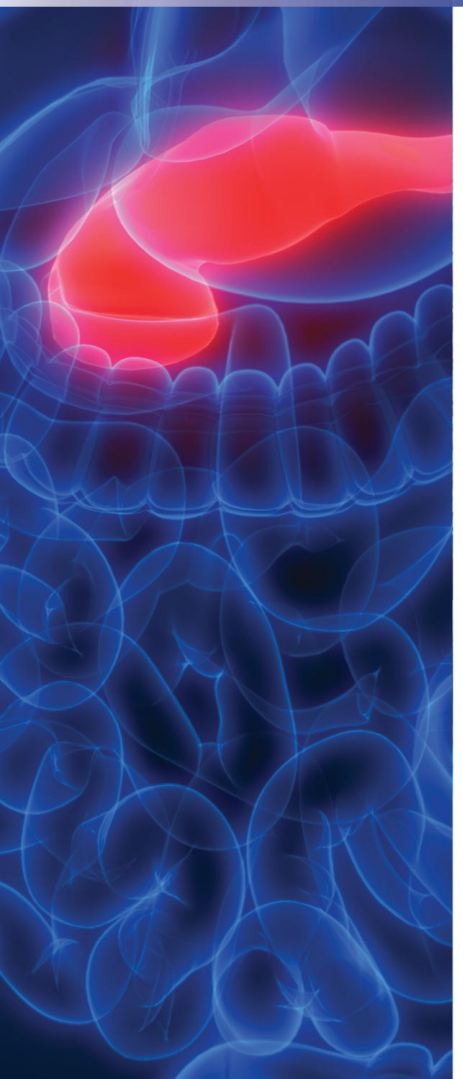
Trials	0.5 mg	1 mg	Comparator
SUSTAIN 1-5	2.1%	1.5%	2%
SUSTAIN 6	9%	10%	7.6%

Difference in study populations baseline demographics:

Trials	Age	A1C	Duration T2D	Hx Retinopathy
SUSTAIN 1-5	53.7-58.8 years	8.1-8.4%	4.2-13.3 years	3.9-13.9%
SUSTAIN 6	64.6 years	8.7%	13.9 years	29.4%

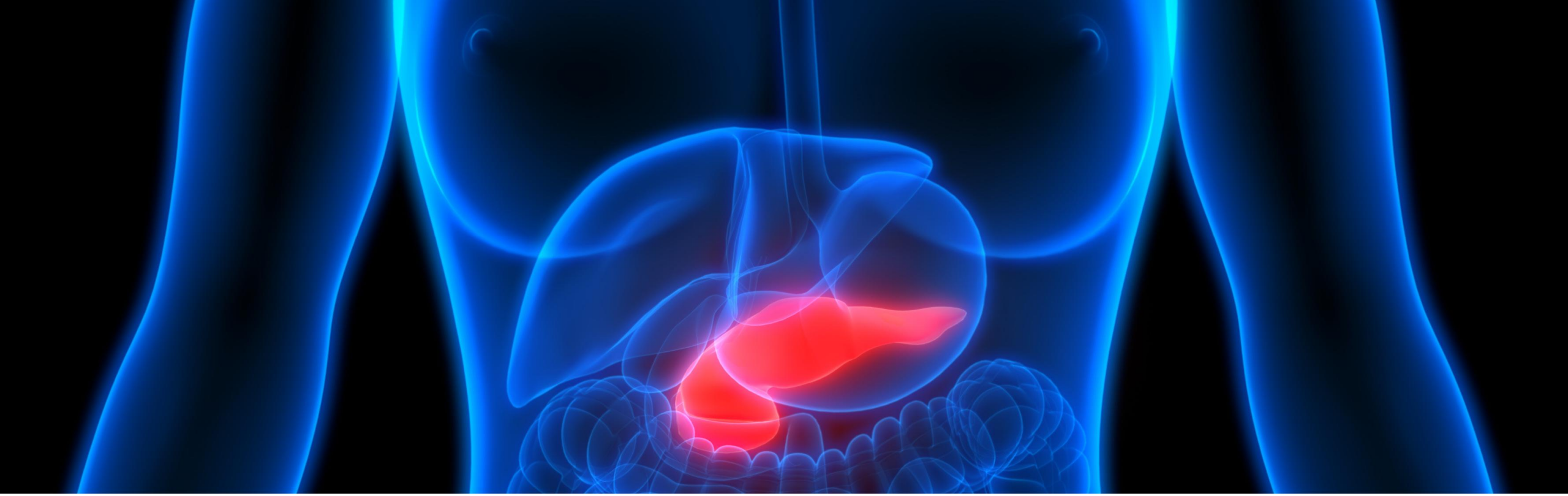
VilsbØll T, et al. *Diabetes Obes Metab*. 2018;20:889-897.

Subanalysis of SUSTAIN 6 and Retinopathy



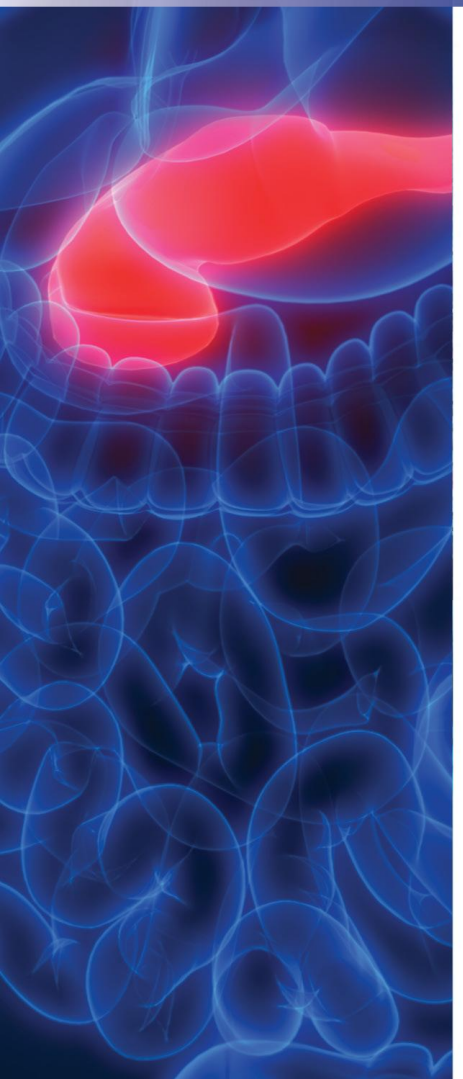
- Those at highest risk of retinopathy:
  - PMH of retinopathy
  - Longer duration of diabetes
  - High baseline A1C
  - Correlated with insulin use
  - Associated with a large and rapid A1C decline during first 16 weeks
- Implications:
  - Consider risk benefit in patients with a PMH of retinopathy
  - Titrate GLP-1 RA slowly to lower A1C over time
- FOCUS trial: currently recruiting to evaluate long term effects of SC semaglutide on diabetic eye disease

Vilsbøll T, et al. *Diabetes Obes Metab*. 2018;20:889-897; https://clinicaltrials.gov/ct2/show/NCT03811561.



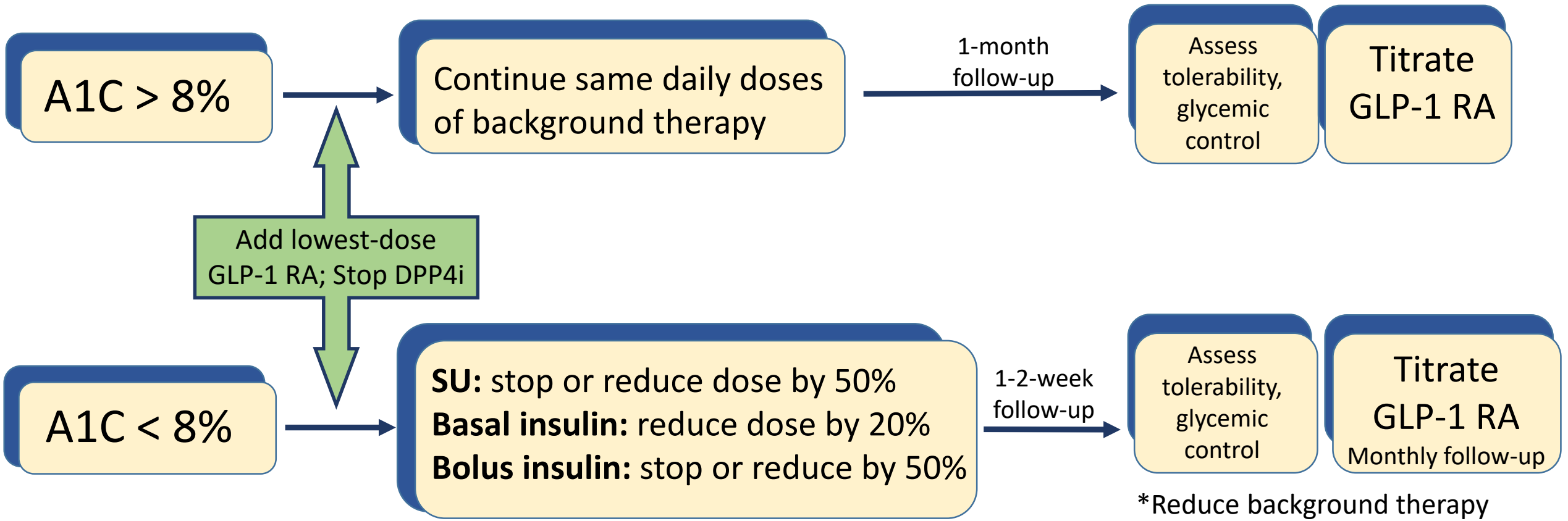
How Should GLP-1 RAs be Safely Initiated and Interchanged?

Considerations when Initiating GLP-1 RAs



- Background therapy
  - Continue, reduce, or discontinue
  - Redundant incretin therapies
- Current glycemic control
  - Risk of hypoglycemia
- Rationale for GLP1-RA addition
  - Efficacy: glucose control, weight reduction, cardioprotection

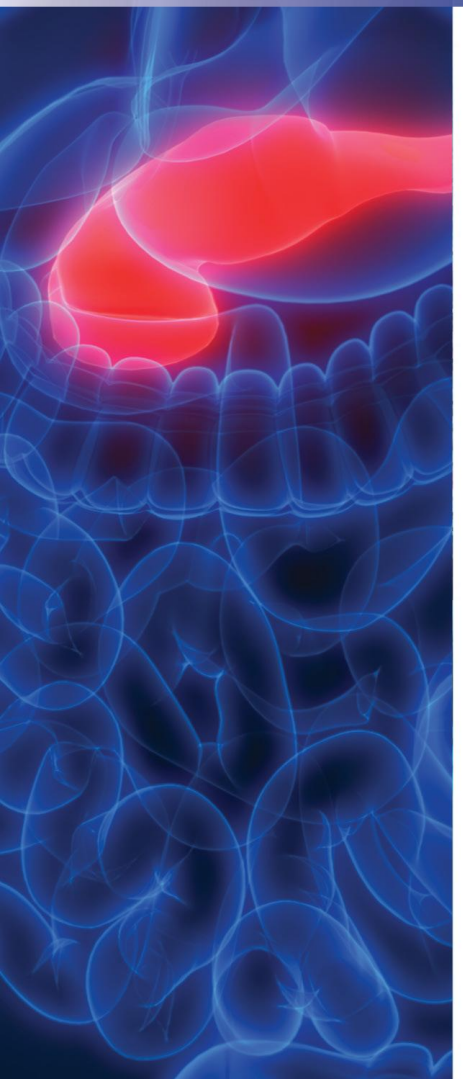
Adjusting Background Antihyperglycemic Therapy



*Reduce background therapy per SMBG to prevent hypoglycemia:
bolus insulin/SU > basal insulin > TZD >MET

SU, sulfonylurea; TZD, thiazolidinedione; MET, metformin.

Rationale for Switching GLP-1 RA



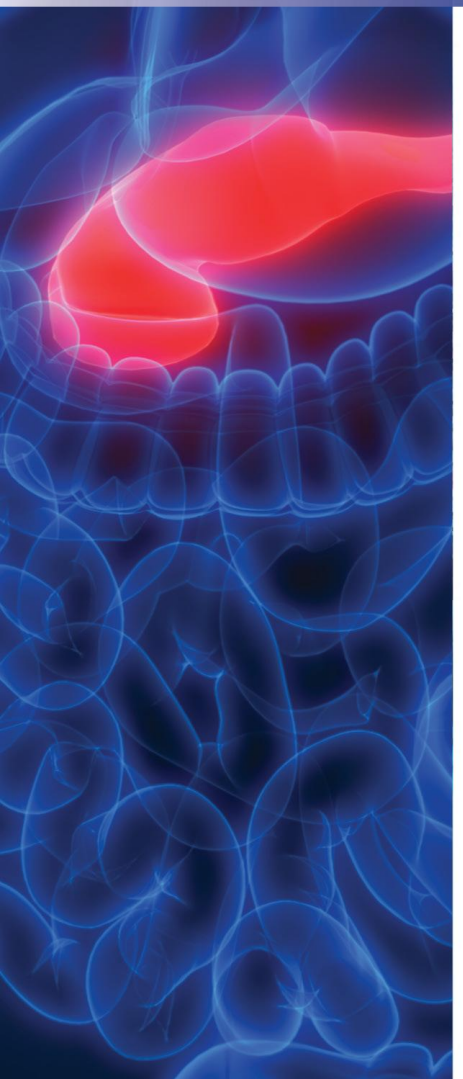
- Enhanced efficacy
  - Glycemic control
  - Weight reduction
  - Added cardioprotection
- Improved safety or tolerability
  - Gastrointestinal
  - Injection site reactions
- Dosing & convenience
  - Alternative dosing frequency
  - Patient preferred delivery device
  - Alternative route of administration
  - Replace more cumbersome therapies

Almandoz JP, et al. *Clin Diabetes*. 2020;38(4):390-402.

Summary of GLP-1 RA Effects

	A1C	Weight	CV Effects	GI Adverse Effects
Exenatide (Byetta)	Low	Low	No data	Highest
Lixisenatide (Adlyxin)	Low	Low	Safety	Intermediate
Liraglutide (Victoza)	High	High	Benefit	Intermediate
Exenatide XR (Bydureon)	Intermediate	Low	Safety	Low
Dulaglutide (Trulicity)	High	Intermediate	Benefit	Intermediate/High
Semaglutide (Ozempic)	Highest	Highest	Benefit	High
Oral Semaglutide (Rybelsus)	High/Highest	Highest	Safety	Intermediate/High

Rationale for Switching GLP-1 RAs



Prompted by GI Side Effects

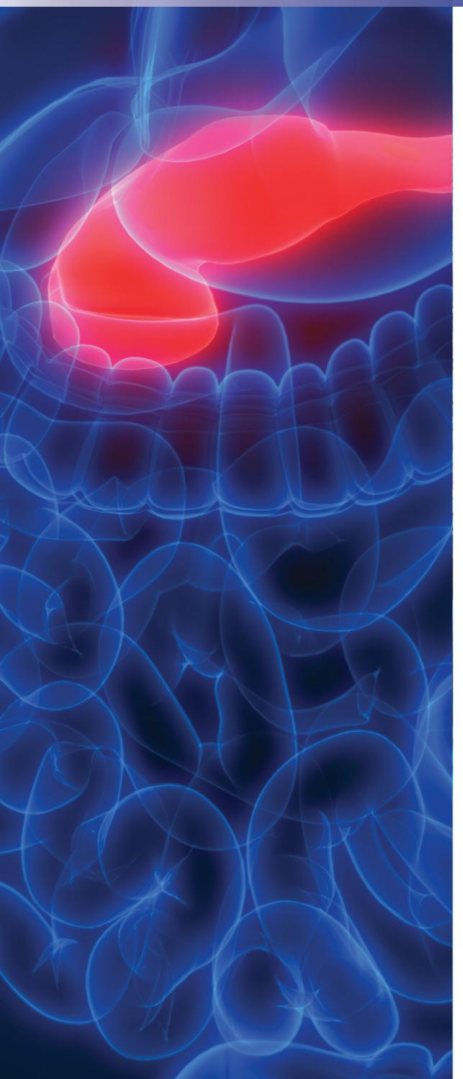
- Discontinue first GLP-1 RA
- Wait for symptoms to resolve
- Select GLP-1 RA with lower GI ADE
- Initiate new GLP-1 RA at lowest dose
- Consider slower dose titration

Prompted for Other Reasons

- Discontinue first GLP-1 RA
- Select GLP-1 RA with desired aspect
- Start with equivalent (or lower) dose
- Titrate accordingly

Almandoz JP, et al. *Clin Diabetes*. 2020;38(4):390-402.

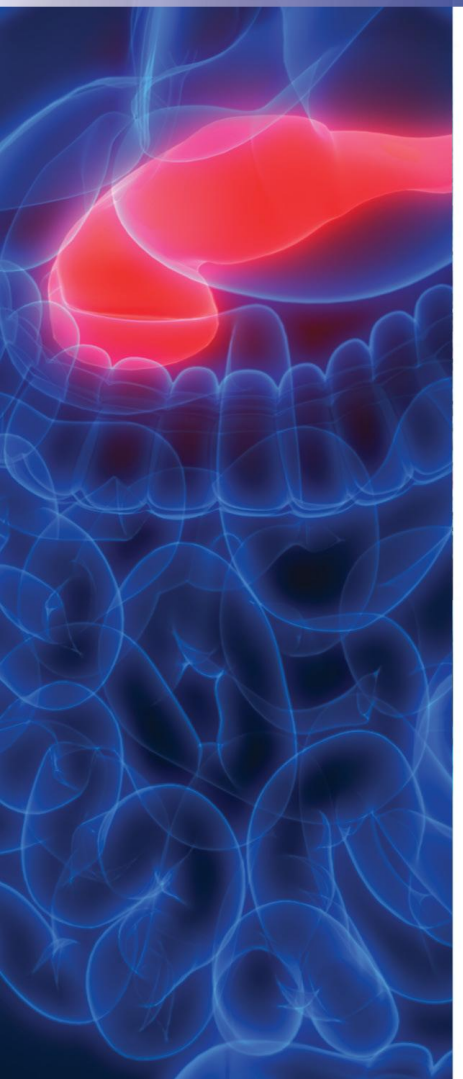
Equivalent GLP-1 RA Doses



GLP-1 RA	Dosing route & frequency	Equivalent dose			
Exenatide	SC BID	5 ug	10 ug		
Lixisenatide	SC daily	10 ug	20 ug		
Liraglutide	SC daily	0.6 mg	1.2 mg	1.8 mg	
Exenatide XR	SC weekly			2 mg	
Dulaglutide	SC weekly		0.75 mg	1.5 mg	4.5 mg*
Semaglutide	SC weekly		0.25 mg	0.5 mg	1 mg
Semaglutide	PO daily	3 mg	7 mg	14 mg	

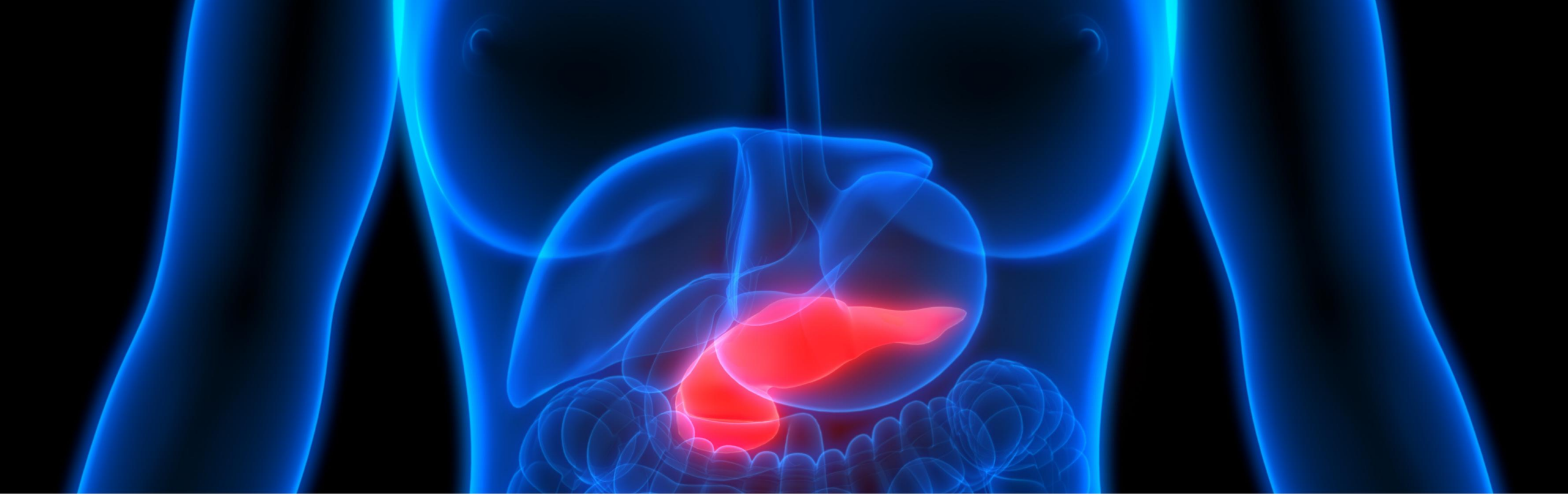
Almandoz JP, et al. *Clin Diabetes*. 2020;38(4):390-402.
*Frias JP, et al. *Diabetes*. 2020;69(suppl 1). doi.org/10.2337/db20-357-OR.

Practical Steps for Switching GLP-1 RAs



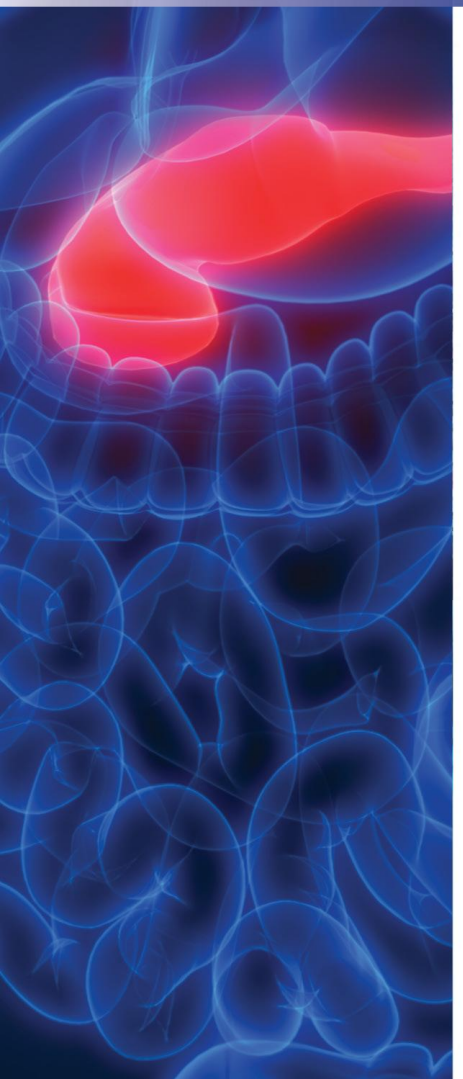
Switch From Old GLP-1 RA	Switch To New GLP-1 RA	Administration Timing
BID/Daily (SQ or PO) GLP-1 RA	Any GLP-1 RA	Give first dose the following day after discontinuation
Weekly GLP-1 RA	Any GLP-1 RA	Give first dose 7 days after discontinuation

Almandoz JP, et al. *Clin Diabetes*. 2020;38(4):390-402.



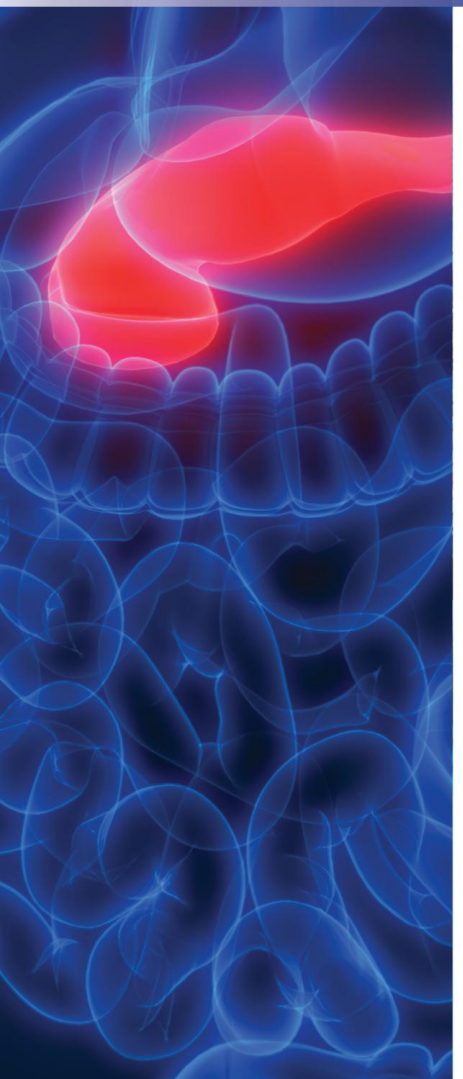
What Should we Know about Administration Differences Between Agents?

Comparing Injection Devices



- Dosing
- Single-use vs multi-use
- Needles
- Preparation
- Accuracy
- Ease of use
- Patient Preference
- Time required for training

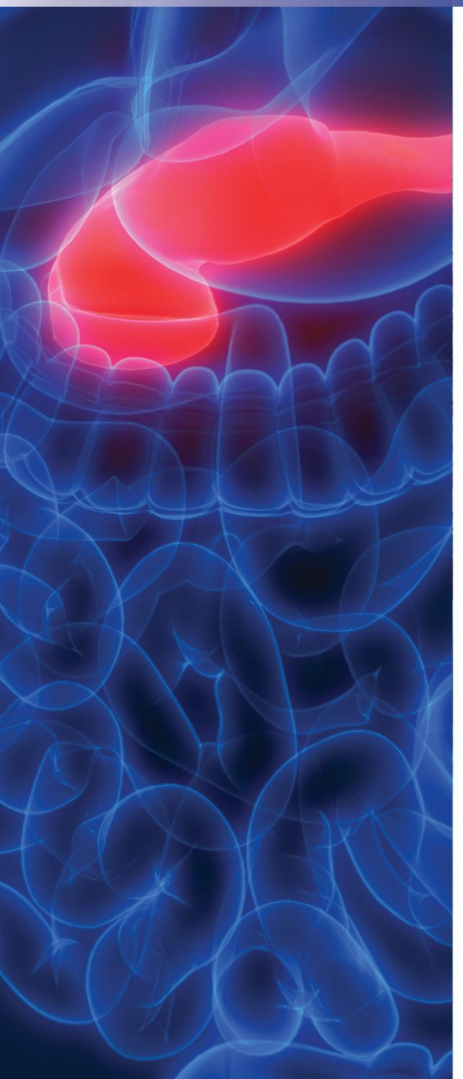
Accuracy and Patient Preference



- PREFER Study
  - 310 patients – semaglutide SC vs dulaglutide
  - More participants preferred the dulaglutide device (84.2% vs 12.3%; $p < 0.0001$).
  - More participants perceived the dulaglutide device as easier to use (86.8% vs 6.8%; $p < 0.0001$).
  - Training participants to use the dulaglutide device took less time (3.38 vs 8.14 minutes; $p < 0.0001$).
- Wettergreen Study
  - 60 patients – semaglutide SC vs dulaglutide vs exenatide XR BCise
  - More participants preferred the dulaglutide device compared to exenatide XR BCise or semaglutide (75% vs 12% vs 13%)
  - Dulaglutide took the least amount of time to demonstrate; but accuracy was lower with dulaglutide compared to exenatide XR BCise or semaglutide (62.7% vs 74.4% vs 73.1%)

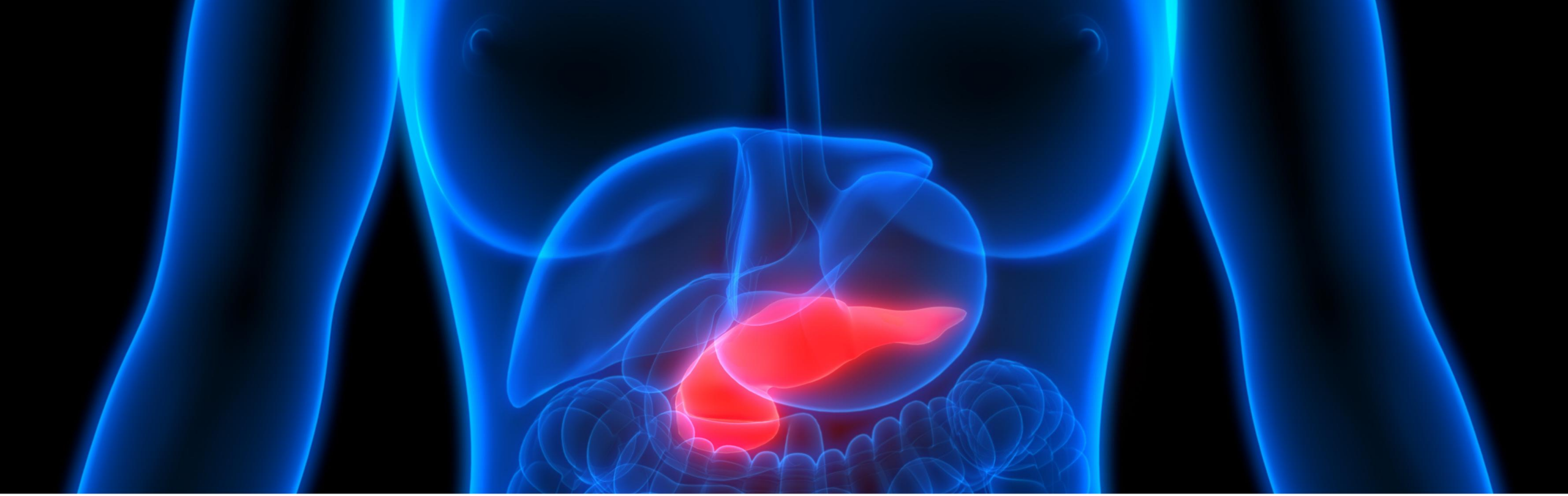
Matza LS, et al. *Diabetes Obes Metab*. 2020;22(3):355-364.
Wettergreen, et al. ACCP Virtual Poster Symposium. Annual Meeting, Oct 19-30, 2020.

Oral Semaglutide: Administration Requirements

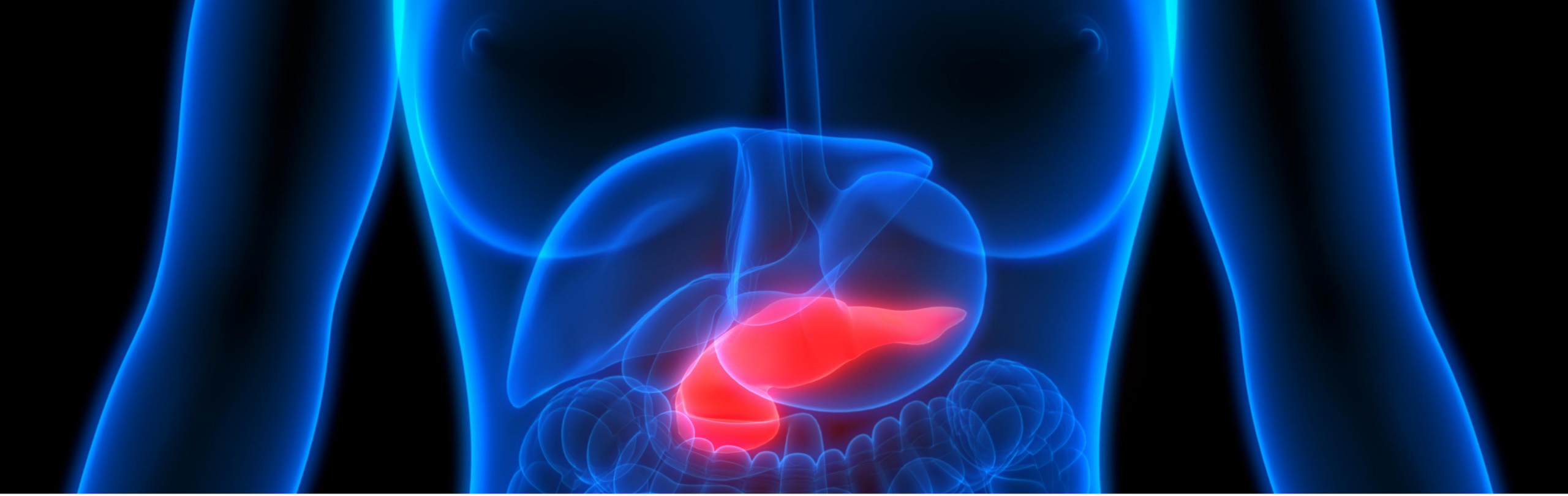


- Take at least 30 minutes before the first food, beverage, or other oral medication of the day
- Take with no more than 4 oz of plain water only
- Swallow tablets whole: do not crush or chew
- Start with 3 mg once daily for 30 days; increase to 7 mg once daily for 30 days; increase to 14 mg once daily if needed
- Drug interactions
  - Levothyroxine
  - Oral bisphosphonates

Rybelsus (semaglutide) tablets [package insert]. Novo Nordisk; 2019.



Questions & Answers



Thank You!