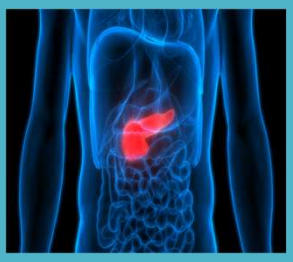
A New Era in the Management of Type 2 Diabetes



Marile L. Santamarina, MS, PharmD, CDCES, CPT

Sr Medical Science Liaison – Fresenius-Kabi- Biosimilars

August 24th, 2024

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Speaker Bio

- Clinical pharmacists with 17 years of experience in ambulatory care with an emphasis in endocrinology, cardiometabolic disorders and autoimmune inflammatory diseases
- PGY-1 – West Palm Beach VA Hospital
- PharmD – Nova Southeastern University
- Masters' degree in Immunology – University of Florida
- Bachelors' degree in Chemistry – University of Miami
- For 13 years – Dual academic appointment, clinical pharmacist and Assistant Professor of Pharmacy Practice
- Clinical pharmacist for University Miami Internal Medicine Residency Program
- Clinical pharmacist in Department Cardiology at Cleveland Clinic Florida
- Board certified Diabetes Care and Education Specialist, insulin pump and continuous glucose monitor trainer
- Passionate about patient care and healthcare education

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CPE Information

_____ is accredited by the Accreditation Council for Pharmacy Education (ACPE) as a provider for continuing pharmacy education. **This activity offers 1.5 contact hours (0.15 CEU).**

- Target Audience: Pharmacy Technicians, Consultant Pharmacists, Pharmacists
- ACPE #: Place Here
- **Place Here**
- Activity Type: Application-based

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Speaker Disclosures

Nothing to disclose.

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Learning Objectives (Pharmacists)

- Overview of Complex Pathophysiology of Type 2 Diabetes (T2D)
- Review of the progression in American Diabetes Association Clinical Practice Guidelines from 2018 through 2024
- Discuss the clinical positioning of newer drug classes in the management of type 2 diabetes
- Discuss and make clinical recommendations using Patient Practice Cases

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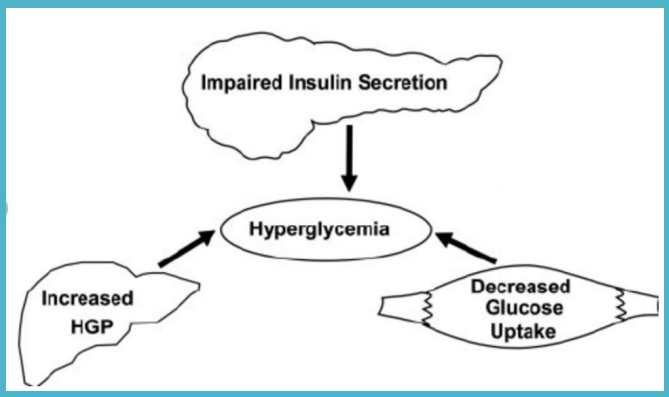
Learning Objectives (Technicians)

- Overview of Complex Pathophysiology of Type 2 Diabetes (T2D)
- Review of the progression in American Diabetes Association Clinical Practice Guidelines from 2018 through 2024
- Discuss the clinical positioning of newer drug classes in the management of type 2 diabetes

6

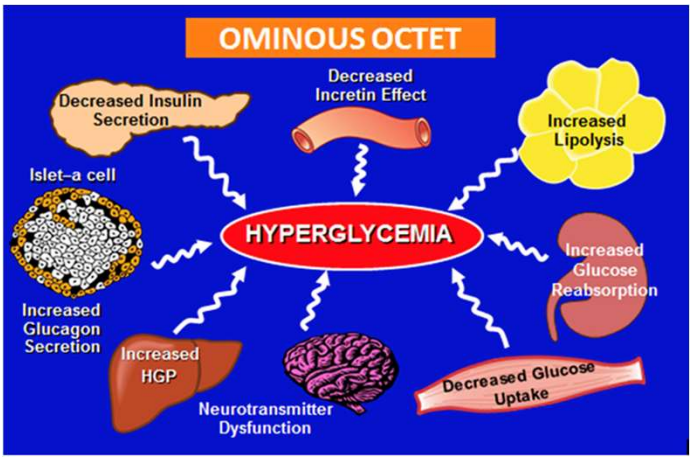
Triumvirate Pathophysiology of T2D



Jallut D, Golay A, Munger R et al. Impaired glucose tolerance and diabetes in obesity: a 6-year follow-up study of glucose metabolism. Metabolism 1990; 39:1068-75

7

Recent Pathophysiology of T2D



DeFronzo RA. From the Triumvirate to the Ominous Octet: A new paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes Care 2009;58(4):773-795.

8

Drug Classes available in the Management of T2D

1) Sulphonylureas
2) α – Glucosidase Inhibitor
3) Meglitinides
4) Biguanide (Metformin)
5) Thiazolidinedione (TZD)
6) Dipeptidyl Peptide-4 Inhibitors (DPP4i)
7) Glucagon-like Peptide-1 receptor agonists (GLP-1 RA)
8) Sodium-glucose Cotransporter-2 Inhibitor (SGLT2i)
9) Gastric Inhibitory Polypeptide/ GLP-1 RA (GIP-GLP-1 RA)
10) Amylin
11) Insulins
12) Cholestyramine
13) Bromocriptine

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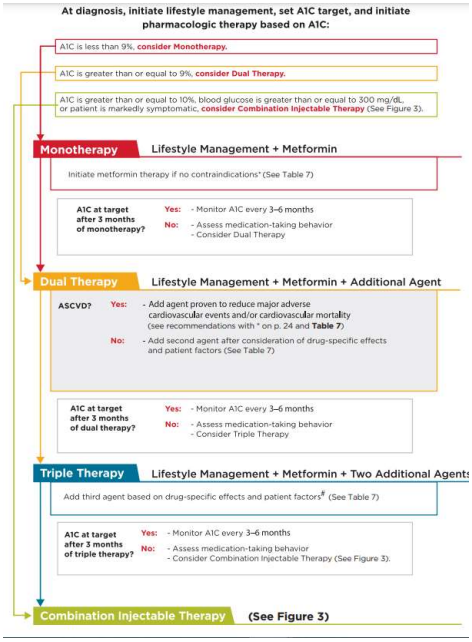

American Diabetes Association - Standards of Medical Care in Diabetes-2018. Diabetes Care 2018 ;41(S1):S1-S159.

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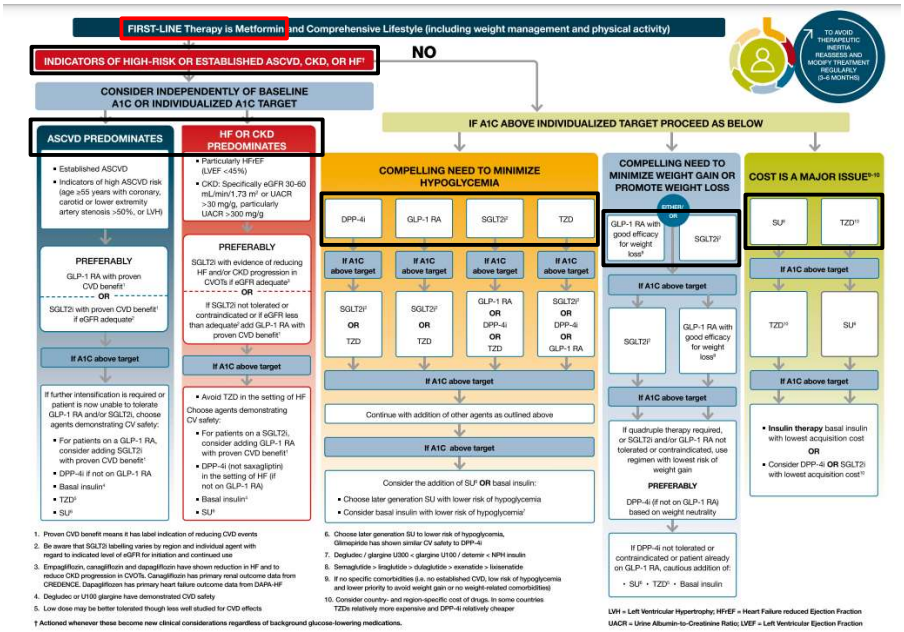

American Diabetes Association Standards of Medical Care in Diabetes -2020 Diabetes Care 2020 ;43(S1):S1-S225.

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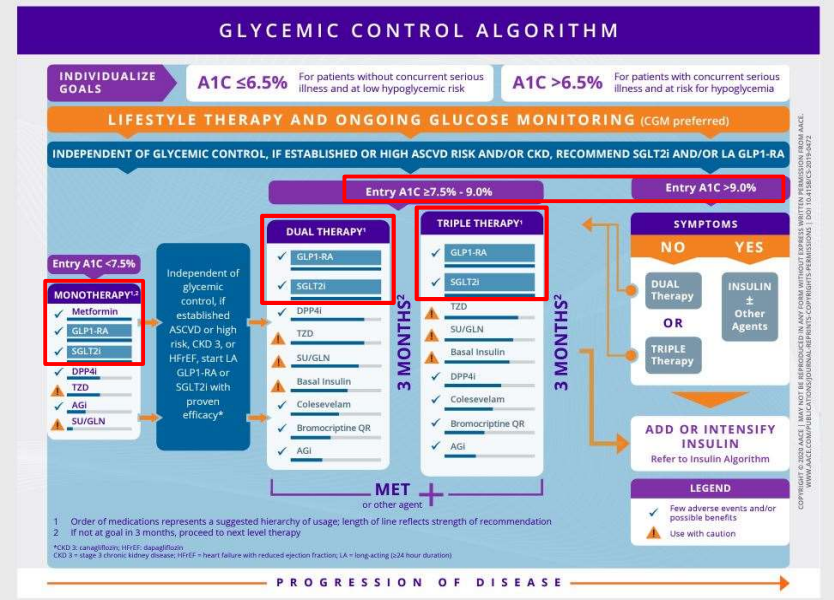

Consensus Statement by AACE /ACE on the Comprehensive Type 2 Diabetes Management Algorithm 2020. Endocr Pract 2020;26(1):107-139

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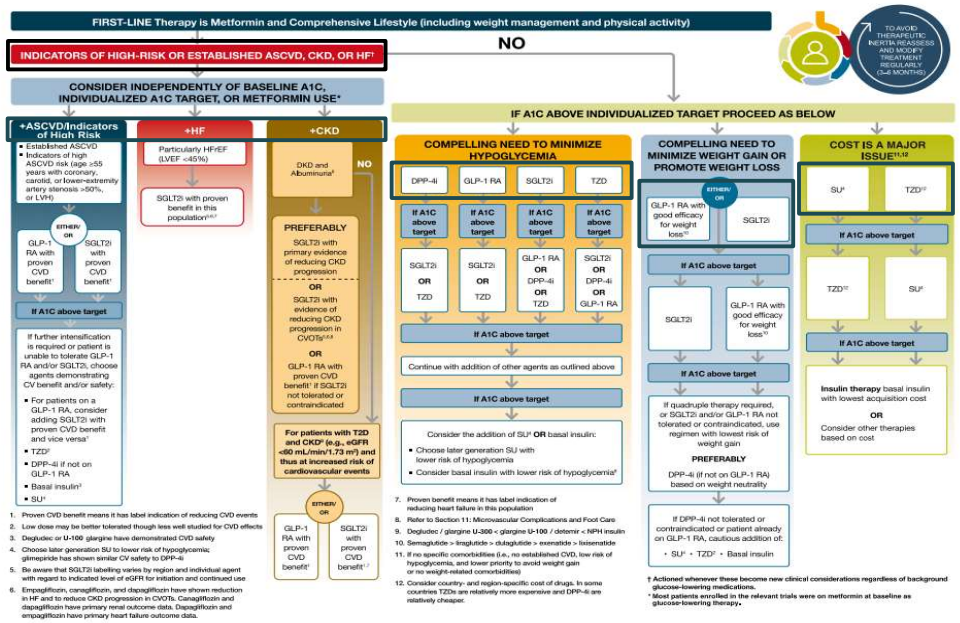

American Diabetes Association – Standards of Medical Care 2021. Diabetes Care 2021;44(S1):S1-S225.

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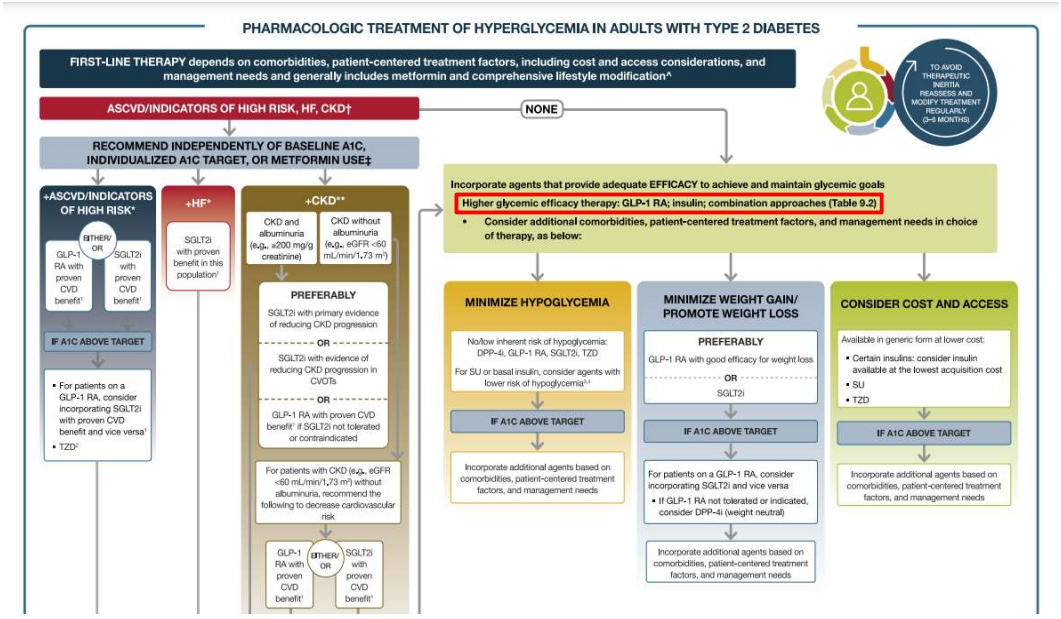

American Diabetes Association – Standards of Medical Care 2022 Diabetes Care 2022;45(S1):S1-S253.

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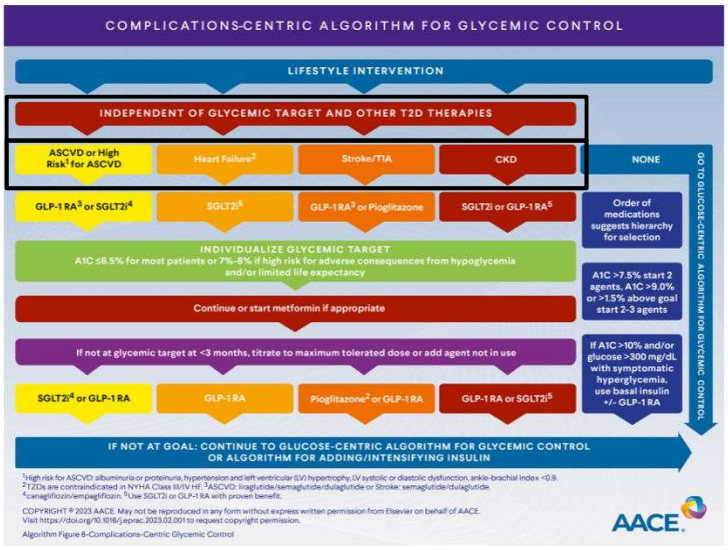

Algorithm Fig. 6. Complications-Centric Algorithm for Glycemic Control.

Samson SL, Vellanki P, Blonde L et al. American Association of Clinical Endocrinology Consensus Statement: Comprehensive Type 2 Diabetes Management Algorithm – 2023 Update. Endocr Pract 2023;29:305-340.

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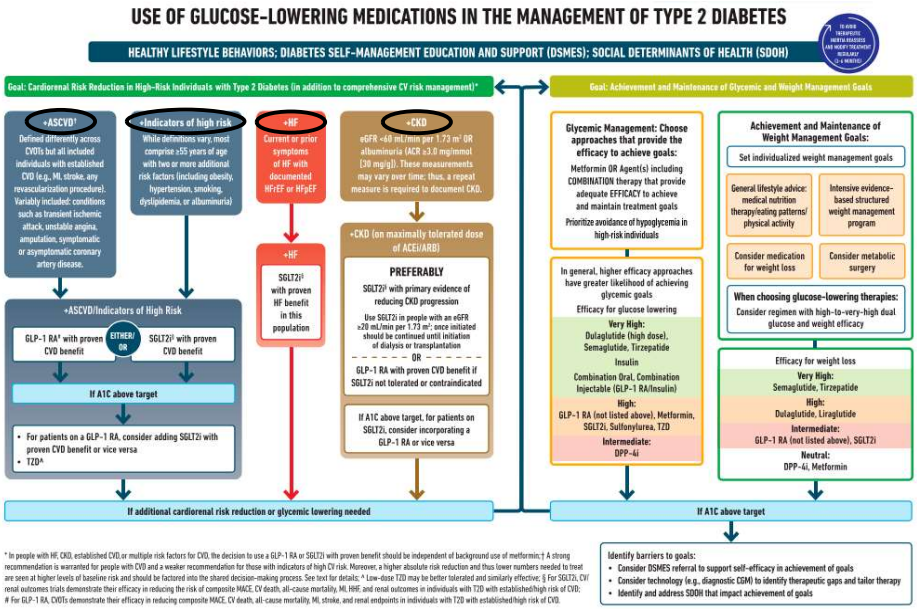

American Diabetes Association – Standards Medical Care 2024 – Diabetes Care 2024;47:S1-S321.

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Drug Classes available in the Management of T2D

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2) α – Glucosidase Inhibitor
3) Meglitinides
4) Biguanide (Metformin)
5) Thiazolidinedione (TZD)
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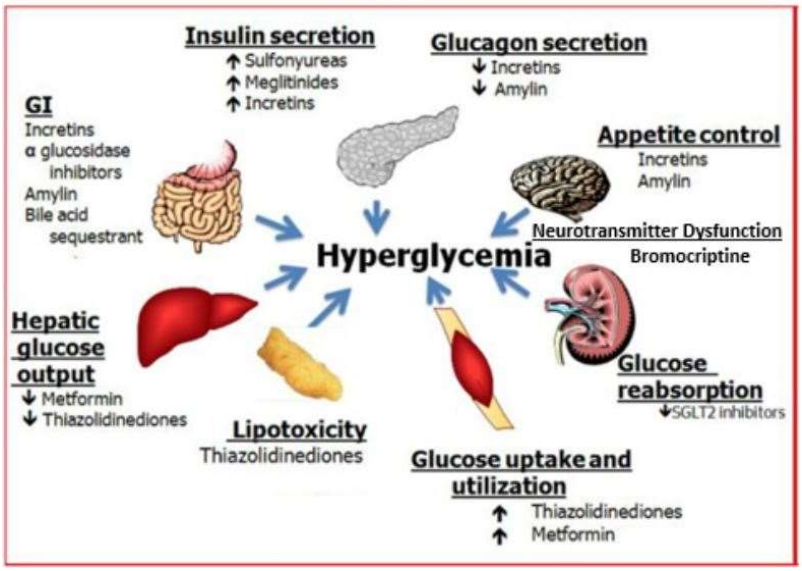

Feingold KP. Oral and injectable (non-insulin) pharmacological agents for the treatment of type 2 diabetes. J Diab Melli. 2021; (11) 1-78.

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Antiglycemic Efficacy of Various Drug Classes

	Fasting Glucose	Post-meal glucose
Metformin	↓↓	↓
GLP-1 RA	↓ To ↓↓	↓↓ To ↓↓↓
SGLT-2I	↓↓	↓
DPP-4I	↓	↓↓
TZD	↓↓	↓
AGI	-	↓↓
Colesevalem	↓	↓
BCR-QR	-	↓
SFU	↓↓	↓↓
Glinide	↓	↓↓
Basal Insulin	↓↓ To ↓↓↓	-
Prandial Insulin	-	↓↓ To ↓↓↓
Pramlintide	↓	↓↓ To ↓↓↓

Cavaiola TS and Pettus JH. Management of Type 2 Diabetes: Selecting amongst available pharmacological agents. https://www.ncbi.nlm.nih.gov/books/NBK425702. [Accessed Jun 2,2024].

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What Pathophysiology defects do GLP1RA and SGLT2i address?

DeFronzo RA. From the Triumvirate to the Ominous Octet: A new paradigm for the Treatment of Type 2 Diabetes Mellitus. Diabetes Care 2009;58(4):773-795.

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Managing T2D with Newer Drug Classes: GLP-1 RA and SGLT2i

- Efficacy and long-term safety <u>important</u> since T2D is a progressive chronic disease
- Provide weight loss, drop in BP, and improvement of lipid profile
- Reduced adverse Cardiovascular and Renal events

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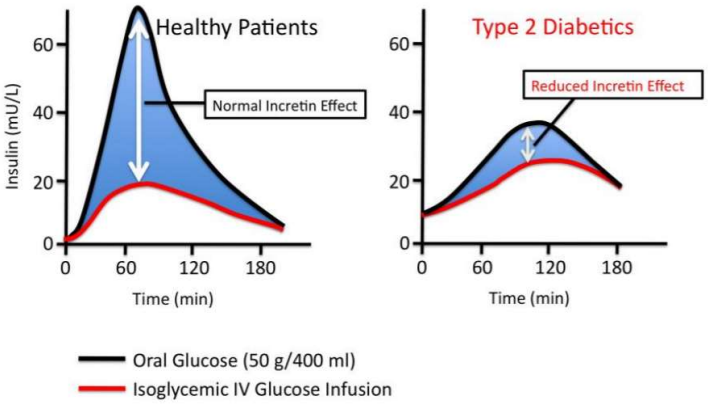
'Incretin Effect' discovery led to development of GLP1RA and GIP



Nauck M, Stockmann F, Ebert R et al. Reduced Incretin effect in Type 2 (non-insulin-dependent) diabetes.Diabetologia 1986;29:46-52.

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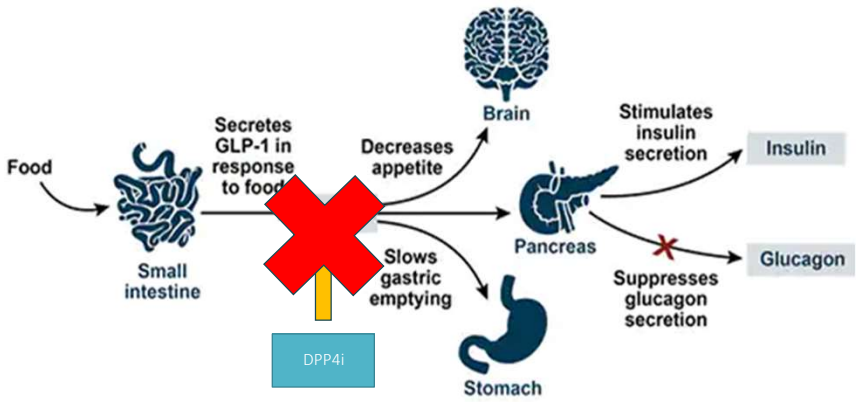
GLP-1 RA Mechanism of Action



Meier JJ. GLP-1 receptor agonist for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012;8(12):728-742.

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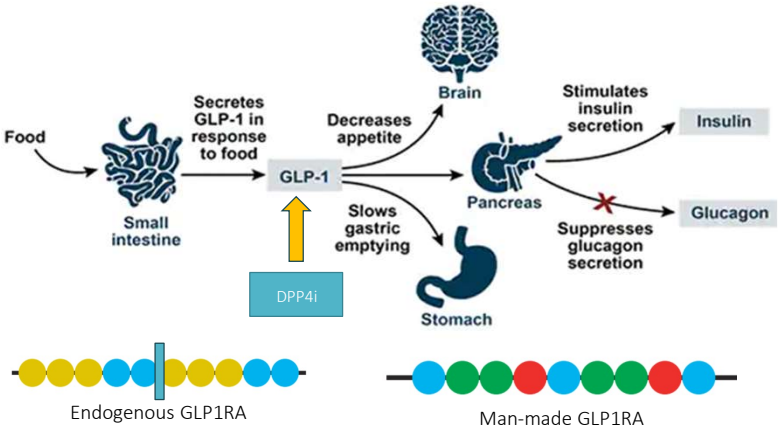
GLP-1 RA Mechanism of Action



Does DPP4i have a clinical role if a GLP1RA is part of the medication regimen?

Meier JJ. GLP-1 receptor agonist for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 2012;8(12):728-742.

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FDA Approved GLP-1 RA

Byetta® - exenatide
Victoza® - liraglutide
Bydureon® - exenatide XR
Trulicity® - dulaglutide
Adlyxin® - lixisenatide
Ozempic® / Rybelsus® - semaglutide (subq) and (oral)
Rybelsus® - oral semaglutide
Tanzeum® - albiglutide ***
Mounjaro® - tirzepatide

RYBELSUS® semaglutide tablets

NOW APPROVED once weekly mounjaro™ (tirzepatide) injection 0.5 mL 2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

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GLP-1 RA – FDA indication

- Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- To reduce the risk of major adverse cardiovascular events in adults with type 2 diabetes mellitus and established cardiovascular disease
- FLOW Trial →semaglutide reduced the risk of adverse renal events and death in patients with T2D and chronic kidney disease – NEJM online

Perkovic V, Tuttle KR, Rossing P et al. Effects of semaglutide on chronic kidney disease in patients with type 2 diabetes. FLOW Trial. NEJM – online May 24,2024.

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GLP-1 RA Efficacy

- Lowers A1C
- Decreases fasting and post-prandial blood glucose
- Weight loss ≈ average 6.4 kg
- Does not increase hypoglycemia
- Reduces the risk of cardiovascular, and renal events
- Reduction of undesirable habits (smoking, drinking, nail biting) – anecdotal**
- Clinical trials are being conducted to assess effect of GLP1RA in NASH and Alzheimer disease

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GLP-1 RA Formulations / Dosing

- Dosing available: Daily (injectable and oral) and weekly (injectable)
- Vast majority are to be administered via subcutaneous injection
- Only ONE Oral GLP1 RA → Rybelsus®

RYBELSUS®
semaglutide tablets

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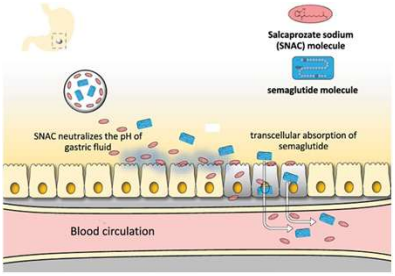
Rybelsus® Oral Formulation

- Protein molecule administered orally instead of injected subcutaneously formulated uses Sodium N-(8-(2-hydroxybenzoyl)amino) caprylate (SNAC)
- SNAC safeguard and transport semaglutide intact across the gastric epithelium
- Low bioavailability of semaglutide requires daily oral administration – special patient counseling for administration



Bucheit JD, Pamulapati LG, Carter N et al. Oral semaglutide: A review of the first oral Glucagon-like peptide 1 receptor agonist. Diab Technol & Ther2020 ; 22 (1): 10-18.

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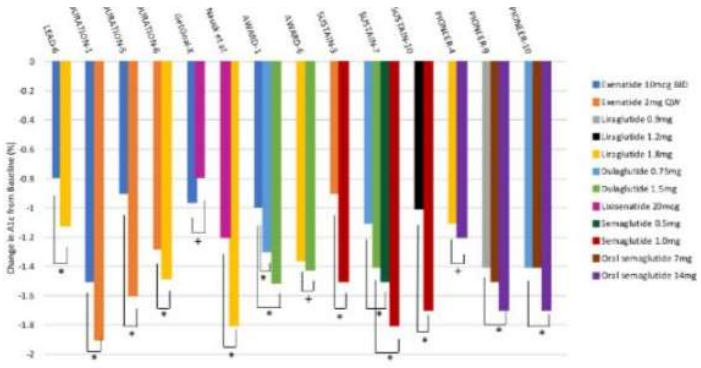
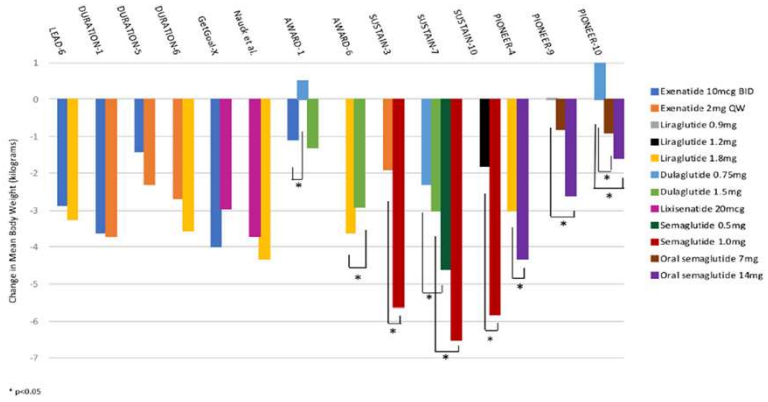
GLP-1RA Antiglycemic Properties



Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an update review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2021;12:1-15.

30

GLP-1RA Weight Loss Properties



Trujillo JM, Nuffer W, Smith BA. GLP-1 receptor agonists: an update review of head-to-head clinical studies. Ther Adv Endocrinol Metab 2021;12:1-15.

31

In vitro Benefits of GLP-1 RA

Glucagon-like Peptide-1: islet β cell augmentation and cell proliferation and inhibition of apoptosis

Drucker DJ. Glucagon-like peptide -1 and the islet β-cell: Augmentation of cell proliferation and inhibition of apoptosis. Endocrinology 2003 ; 144 (12):5145-5148.

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Safety concerns with GLP-1 RA use

- **Contraindications**
  - In individuals with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2
  - Serious hypersensitivity to active drug or any of the excipients

- **Warnings**
  - Pancreatitis
  - Patients with history of diabetic retinopathy should be monitored
  - Warning some increase cases of cholelithiasis or cholecystitis
  - In mice and rats, GLP-1 RA caused a dose-dependent and treatment-duration-dependent increase in the incidence of thyroid C-cell tumors (adenomas and carcinomas) after lifetime exposure at clinically relevant plasma exposure
  - Increase in incidence of retinopathy → associated with large drops in A1C – not caused by the medication

Packet Insert- Ozempic. chrome-extension://efaidnbmnnnibpcajpcglclefindmkaj/https://www.novo-pi.com/ozempic.pdf [Accessed Jun 2, 2024].

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Most common Side Effects of GLP-1 RA

- Gastrointestinal symptoms → nausea, vomiting, diarrhea or constipation
  - IMPORTANT → Start low and titrate up to therapeutic dose
  - Counsel patients on serving smaller portions than usual
- Weight Loss → Range 4.8 – 7.2 kg
- Increased incidence of hypoglycemia when use concomitantly with secretagogues or insulin
- Headache
- Nasopharyngitis

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GLP-1 RA Initiation/Titration

- To mitigate GI side effects → Start and Titrate "SLOW"
- Some agents have more detailed starting dose and titration schedule
- Rybelsus® the only oral GLP-1 RA -- Start Rybelsus® 3 mg daily x 30 days. Titrate to 7 mg daily after at least 30 days, may titrate to 14 mg daily

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Switching between Ozempic® and Rybelsus®

- Patients on Ozempic® 0.5 mg subq once weekly → Can convert to Rybelsus® 7 mg or 14 mg oral once daily – Start Rybelsus® 7 days after last injection of Ozempic®
- Patients on Ozempic® 1 mg weekly → NO equivalent dose for Rybelsus®
- Patients on Rybelsus® 14 mg daily → Can convert to Ozempic® subq 0.5 mg once weekly. Ozempic® can be started the day after the last dose of Rybelsus®

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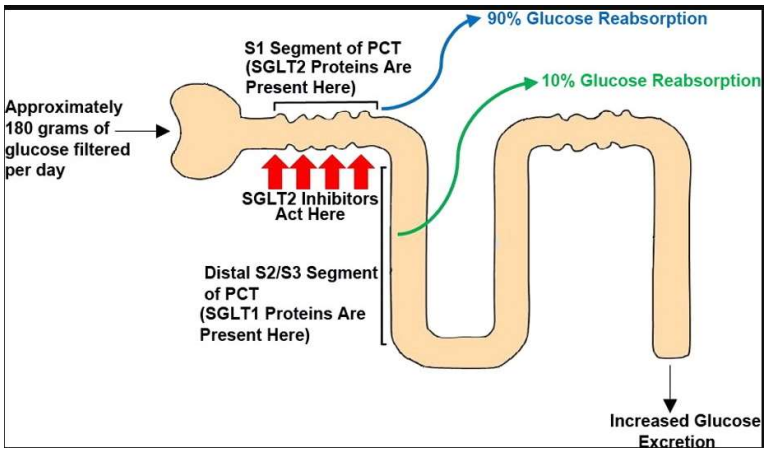
Mechanism of Action of SGLT2i



Madaan T, Akhtar m and Najmi AK. Sodium-glucose Co-trasnporter 2 inhibitors: Current Status and future perspectives. Eur J Pharmaceu Sci 2016;93(10):244-252.

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FDA Approved SGLT2i

Invokana® - canagliflozin
Farxiga® - dapagliflozin
Jardiance® - empagliflozin
Steglatro® - ertugliflozin
Inpefa® - sotagliflozin

- All agents are once daily oral agents

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FDA Indication of SGLT2i

- As an adjunct to diet and exercise to improve the management of T2D
- To reduce the risk of cardiovascular death in adults with T2D and establish cardiovascular disease
- To reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure
- Prevents the progression to end-stage kidney disease

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SGLT2i Efficacy

- Lowers A1C
- Decreases fasting and post-prandial blood glucose
- Reduces body weight → 2 - 3 kg
- Reduces blood pressure → SBP and DBP 2 - 4 mm Hg
- Do not increase hypoglycemia (under most circumstances)
- Reduces the risk of cardiovascular and renal events

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Safety concerns with SGLT2i use

- **Contraindications**
  - Hypersensitivity to active ingredient or excipients
  - Patients on dialysis

- **Warnings/Precautions**
  - Euglycemic Ketoacidosis
  - Volume depletion
  - Warning some increase cases of cholelithiasis or cholecystitis
  - Necrotizing soft tissue infection of the perineum, external genitalia and perianal regions – Fournier's gangrene – incidence is rare

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Most Common Side Effects associated with the use of SGLT2i

- Genital Mycotic Infections
- Dehydration
- Urosepsis and pyelonephritis
- Fournier's gangrene
- Hypoglycemia increases when used concomitantly with secretagogue or insulin

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Assessing Knowledge #1

Which of the following is a defect in the pathophysiology of T2D which is ONLY addressed by using an GLP-1 RA?

a) Increase secretion of insulin
b) Decreased insulin resistance
c) Increased secretion of glucose via urine
d) Decreased secretion of glucagon

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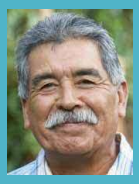
Practice Case 1



TR is 59 yo HM at Clinic for a follow up visit. During TR's last visit his T2D was Uncontrolled; HCP suggested adding a new medication. TR wanted to try to lose weight On his own without a new med. TR owns a landscaping business.

PMH: T2DM (11 yrs), HTN (11 yrs), TIA (2 yrs ago) hyperlipidemia (10 yrs), allergies(seasonal)
Meds: Metformin 1000 mg po BID, Januvia 100 mg daily, Lisinopril 20 mg daily,
Pravastatin 40 mg daily, Claritin prn – allergies

Clinic visit = 3/6/2024 Ht 5' 9" Wt 196 lbs (BMI 29.8) A1C 8.4%
TC 206, LDL 115, HDL 29 , TG 308 BP 131/ 82
FBG = 195, 201, 163, 215 2 hrs after lunch = 192, 173, 248, 197
Today's visit = 6/14/2024 Wt 198 lbs (BMI 30.1) A1C 8.6%
TC 209 , LDL 114, HDL 32, TG 315 BP 141/ 93

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Case 1 continuation

1) What are your thoughts about TR's general health. Discuss his: A1C, Lipids and BP for (3/6/2024) visit.

2) Any questions you would like to ask TR?

3) Do you want to make any recommendation(s) for TR during today's visit?

4) If TR accepts your recommendations, how would you counsel TR before the end of his visit?

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Cardiovascular Outcomes Trials (CVOT)

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Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

This guidance provides recommendations for the development of drugs and therapeutic biologics regulated within the Center for Drug Evaluation and Research at the Food and Drug Administration (FDA) for the treatment of diabetes mellitus.[2] Specifically, this guidance makes recommendations about how to demonstrate that a new antidiabetic therapy to treat type 2 diabetes is not associated with an unacceptable increase in cardiovascular risk.

https://www.fda.gov/media/71297/download

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Characteristics of CVOT

- All industry funded trials included as part FDA approval process
- All studies: multi-center, double-blind, randomized, placebo-controlled studies
- Randomized patients received GLP-1 RA studied, or matched control (placebo) treated with standard of care + HCP were allowed to add antiglycemic medications different from incretin therapies
- Primary endpoint (most common) were first occurrence of:
  - 3-point MACE → CV death, non-fatal MI, non-fatal stroke
  - 4-point MACE → CV death, non-fatal MI, non-fatal stroke or hospitalization due to unstable angina

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GLP1 RA CVOTs

- ELIXA → lixisenatide
- LEADER → liraglutide
- EXSCEL → exenatide
- HARMONY → albiglutide
- REWIND → dulaglutide
- SUSTAIN 1-6 and PIONEER 1-6 → semaglutide (injectable and oral)
- REWIND → dulaglutide
- SURPASS → tirzepatide → on-going

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GLP1 RA CVOTs (cont.)

- DECLARE-TIMI 58 & DAPA-CKD → dapagliflozin
- CANVAS & CREDENCE → canagliflozin
- EMPA-REG, EMPEROR-REDUCED, EMPEROR-Preserved → empagliflozin
- VERTIS-CV → ertugliflozin
- SOLOIST-WHF and SCORED → sotagliflozin

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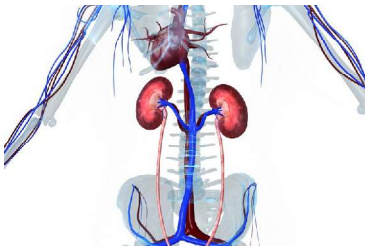
CVOT Designs / Comparisons and Results

- Multiple differences among CVOTs:
  - Different trial designs
  - Different patient populations
  - Different patient inclusion criteria
  - Follow-up for different time
  - Difficult to compare with one another



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Assessing Knowledge #2

Which of the following medication(s) have clinical trial data that demonstrated its use was associated with decreased CV events?

a) Glipizide
b) Metformin
c) Ozempic®
d) Jardiance®

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Summary: GLP-1 RA and SGLT2i

- Are newer antiglycemic agents which provide healthy benefits beyond lowering blood glucose
- Associated with Cardio–Renal benefits → stronger evidence for SGLT2i than for GLP-1 RA
- Associated with weight loss (greater weight loss for users of GLP-1 RA than for users of SGLT2 inhibitors)

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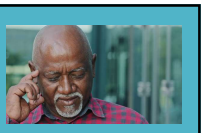
Practice Case 3



CT is 69 yo AAF army retiree who presents to Clinic for 3 month follow up appointment. CT says he was hospitalized 1 month ago with SOB, and swollen feet. He saw the cardiologist after being discharged and was diagnosed with heart failure.

PMH: T2DM (17 yrs), HTN (18 yrs), hyperlipidemia (20 yrs), DES (x2 – LAD & RCA) – 2 years ago, HF (2 months ago)

FMH: Both parents deceased - Mother – T2DM, HTN, MI and PCI

Father CKD – Stage 4 – died of an MI

Meds: Amaryl 5 mg daily, Metformin 1000 mg BID, Januvia 100 mg daily, Crestor 10 mg daily,

Furosemide 25 mg daily, Losartan 25 mg daily

Exercise Regimen: Walks daily 1 hr, weights (2x/week), swims 20 min (2X week).

Labs (5/9/24) = A1C 8.7% , TC 171, LDL 62, HDL 71, TG 201, LFT – wnl

Today in Clinic - Random BG (2:30 pm) 201, BP 131/72 , Ht 5'11"

Wt 183 BMI=25.5

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Case 3 Continuation

1) What are just thoughts on CT's T2D glycemic control?
2) Any recommendations for CT?

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Thank you for your kind attention!

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