

Type 2 Diabetes Mellitus
New Medications to Treat
Co-Morbidities
2024

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Disclosure

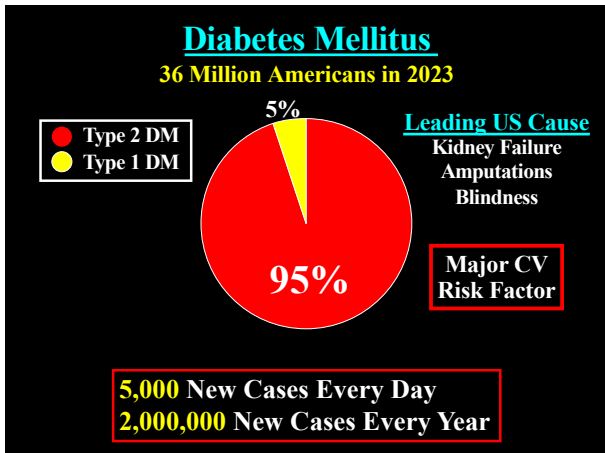
Michael McDermott has no conflict of interest or relationships to disclose in relation to this educational activity.

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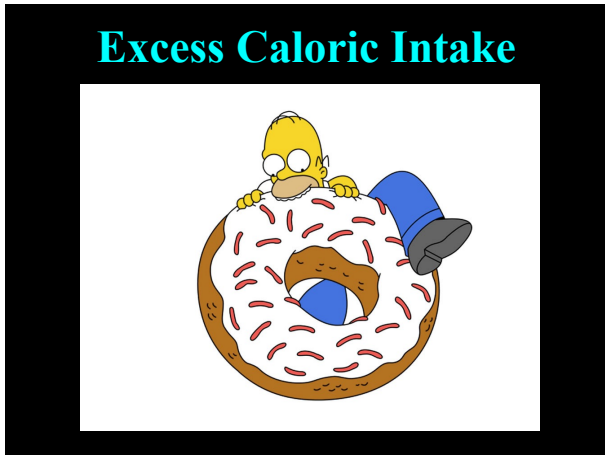
Learning Objectives

- Review mechanism of action of Glucagon-like Peptide Receptor Agonists (GLP-1 RA) and Sodium Glucose Transporter Inhibitors (SGLT2-I).
- Discuss effects of GLP-1 RA and SGLT2-I on Co-morbidities associated with Type 2 Diabetes Mellitus.
- Develop strategies for optimal use of GLP-1 RA and SGLT2-I in people with Type 2 Diabetes Mellitus.

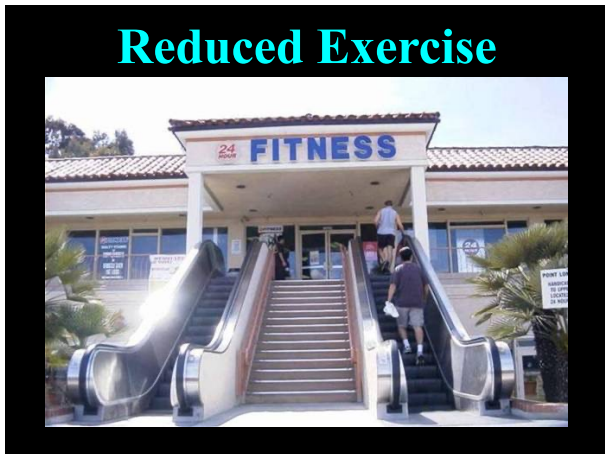
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No Exercise



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Type 2 Diabetes Mellitus

Pathophysiology

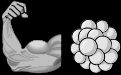
↑ Glucose Production



↓ Insulin Secretion



Hyperglycemia



↑ Insulin Resistance



↓ Incretin Effect

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Type 2 Diabetes Mellitus

Pathophysiology Based Therapy

↓ Glucose Production



Metformin

↑ Insulin Secretion



Sulfonylurea
Meglitinide

Euglycemia



↓ Insulin Resistance

Thiazolidinedione

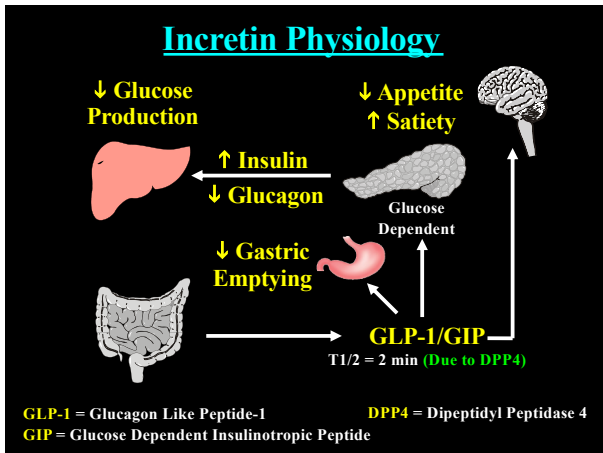


↑ Glycosuria

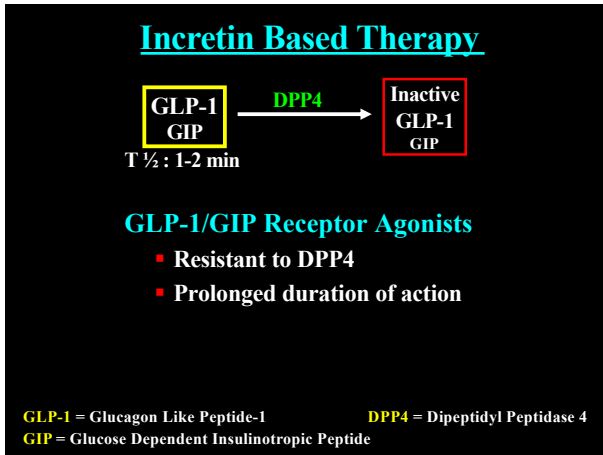


↑ Incretin Effect
GLP-1 RA
GLP-1/GIP RA
DPP4 Inhibitor

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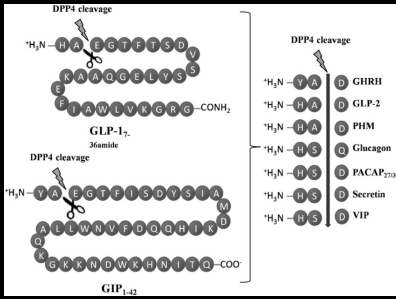


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- ### Incretin Based Therapy
- #### GLP-1 Receptor Agonists
- Exenatide (Byetta) SQ BID
 Liraglutide (Victoza) SQ Daily
 Lixisenatide (Adlyxin) SQ Daily
 Exenatide QW (Bydureon) SQ Weekly
 Dulaglutide (Trulicity) SQ Weekly
 Semaglutide (Ozempic) SQ Weekly
 Semaglutide (Rybelsus) PO Daily
- #### GLP-1 / GIP Receptor Agonist
- Tirzepatide (Mounjaro) SQ Weekly

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GLP-1 and GIP

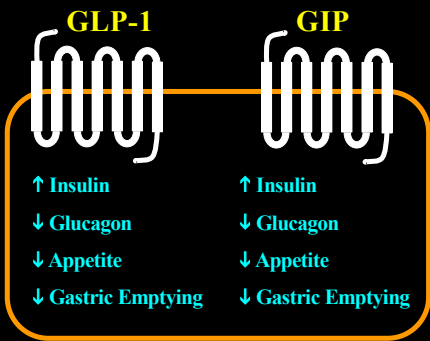


GLP-1: Glucagon Like Peptide 1

GIP: Glucose Dependent Insulinotropic Peptide

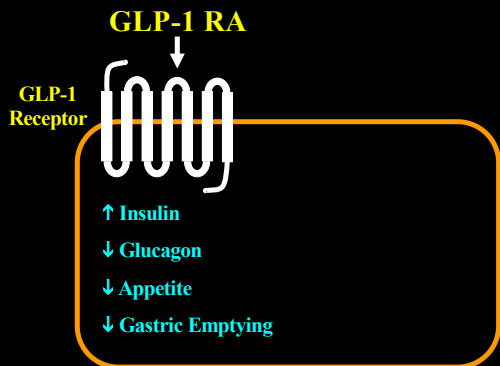
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GLP-1 and GIP Receptors

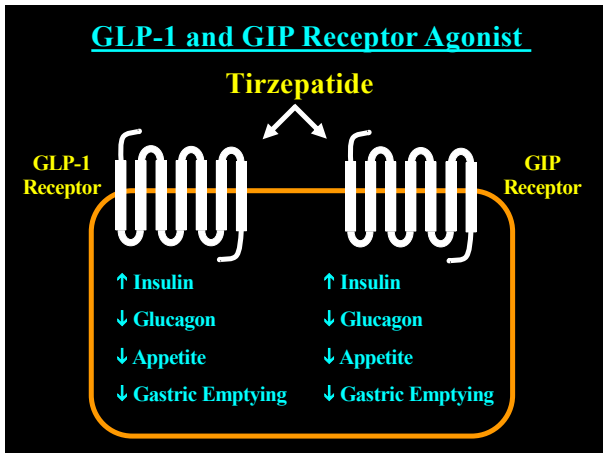


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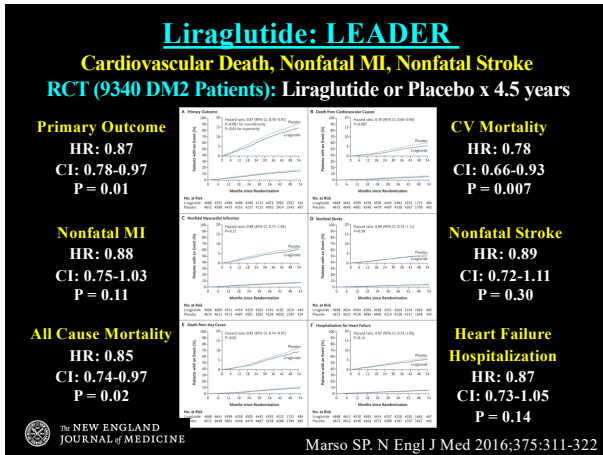
GLP-1 Receptor Agonist



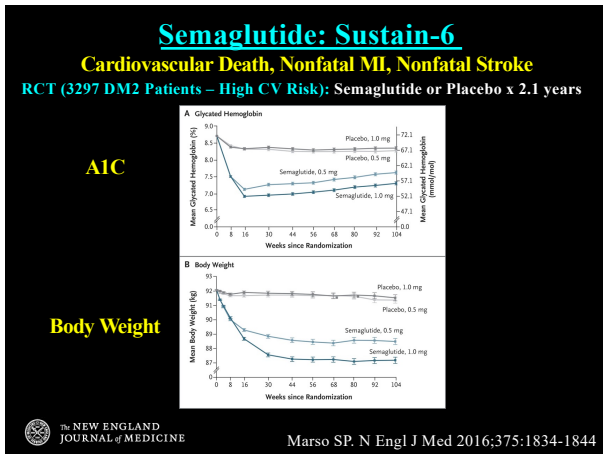
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Semaglutide: Sustain-6

Cardiovascular Death, Nonfatal MI, Nonfatal Stroke

RCT (3297 DM2 Patients – High CV Risk): Semaglutide or Placebo x 2.1 years

Primary Outcome
HR 0.74
P = 0.02

Nonfatal Stroke
HR 0.61
P = 0.04

Nonfatal MI
HR 0.74
P = 0.12

CV Death
HR 0.98
P = 0.92

The NEW ENGLAND JOURNAL of MEDICINE Marso SP. N Engl J Med 2016;375:1834-1844

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GLP-1/GIP Receptor Agonist

2539 Obese Adults (BMI > 30 or > 27 + Co-morbidity)

Tirzepatide vs Placebo x 72 weeks

Body Weight % ↓ c/w Baseline

Body Weight % ↓ by Week

Surmount-1. Jastreboff AM. N Engl J Med 2022;387:205-16.

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GLP-1/GIP Receptor Agonist

938 DM2 Adults (BMI > 27): Tirzepatide vs Placebo x 72 weeks

Body Weight % ↓ c/w Baseline

Body Weight % ↓ by Week

Surmount-2. Garvey WT. Lancet 2023; 402: 613-26.

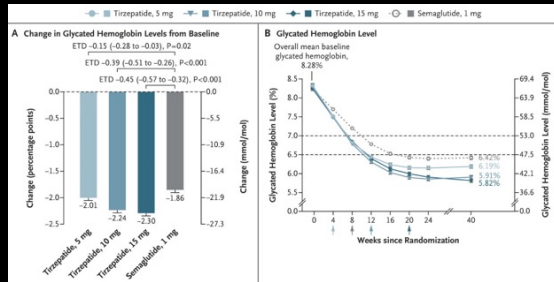
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GLP-1/GIP Receptor Agonist

1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks

A1C % ↓ c/w Baseline

A1C % ↓ by Week



Surpass-2. Frias JP. N Engl J Med 2021; 385:503-15.

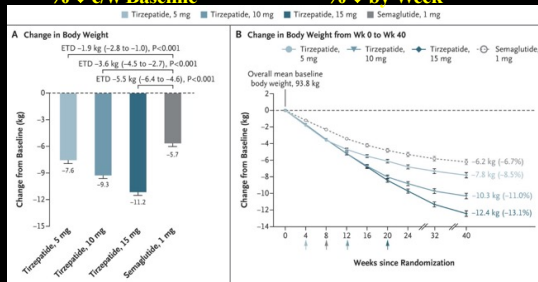
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GLP-1/GIP Receptor Agonist

1879 DM2 Adults: Tirzepatide vs Semaglutide x 40 weeks

Body Weight % ↓ c/w Baseline

Body Weight % ↓ by Week



Surpass-2. Frias JP. N Engl J Med 2021; 385:503-15.

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GLP-1 Receptor Agonist Benefits

- Glucose Lowering (1.0-1.5% ↓ A1C)
- Cardiovascular Benefit
- Stroke Benefit
- Renal Benefit
- NAFL Benefit
- Weight Loss (10-15 lb)

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GLP-1/GIP Receptor Agonist
Benefits

- Glucose Lowering (2.0-2.8% ↓ A1C)
- Weight Loss (20-50 lb)
- Under Investigation
 - Cardiovascular Benefit
 - Stroke Benefit
 - Renal Benefit
 - NAFL Benefit

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GLP-1/GIP Receptor Agonist
Risks

- Medullary Thyroid Cancer
- Retinopathy Worsening
- Acute Pancreatitis
- Gall Bladder / Biliary Disease
- Gastroparesis

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GLP-1/GIP Receptor Agonist
Medullary Thyroid Cancer

- Medullary Thyroid Cancer Risk (Black Box*)
- Differentiated Thyroid Cancer - Uncertain

* Contraindicated in people with personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)

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GLP-1/GIP Receptor Agonist
Acute Pancreatitis

- Post-marketing case reports: potential link
- Retrospective and observational studies: inconsistent
- Systematic reviews and meta-analyses: no association
- FDA: causal relationship could not be established
- Use with caution in people with prior history of pancreatitis, particularly when cause is unknown or persists

Egan AG. New Engl J Med 2014;370:794-797
Monami M. Diabetes Obes Metab 2017;19:1233-1241
Storgaard H. Diabetes Obes Metab 2017;19:906-908

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GLP-1/GIP Receptor Agonist
Retinopathy Worsening

Meta-Analyses

- Bethel: GLP-1 RA use not associated with worsening retinopathy (OR 1.10; 95% CI 0.93-1.30)
 - Positive association with magnitude of A1C reduction
- Yoshida: GLP-1 RA use associated with worsening retinopathy (OR 1.23; 95% CI 1.05-1.44)

Bethel MA. Diabetes Care 2021; 44:290-96.
Yoshida Y. J Diab Complications 2022; 36(8):108255

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GLP-1/GIP Receptor Agonist
Anesthesia

Prior to Procedure:
Daily GLP-1 RA: consider holding GLP-1 RA the day of the procedure.
Weekly GLP-1 RA: consider holding GLP-1 RA a week prior to procedure.

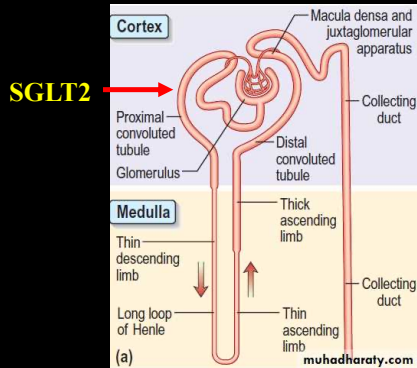
If GLP-1 RA are held for longer than the dosing schedule, consider consulting an endocrinologist for bridging the antidiabetic therapy to avoid hyperglycemia.

Day of Procedure:
GI symptoms present (severe nausea/vomiting/retching/bloating/pain): consider delaying elective procedure and discuss concerns of potential risk of regurgitation and pulmonary aspiration of gastric contents with the proceduralist and patient.
GI symptoms absent, but GLP-1 RA was not held as advised: proceed with 'full stomach' precautions or consider evaluating gastric volume by ultrasound. If the stomach is empty, proceed. If the stomach is full or if gastric US inconclusive, consider delaying the procedure or treat the patient as 'full stomach'.

Joshi GP. American Society of Anesthesiologists Consensus Based Guidance on Preoperative Management of Patients on Glucagon-Like Peptide-1 Receptor Agonists

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Sodium Glucose Transporter 2 Inhibitors



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Sodium Glucose Transporter 2 Inhibitors

Kidneys Filter + Reabsorb Glucose: 180 g/day
 SGLT2 (proximal tubules): 90%

Normal



Glycosuria
 BG > 180 mg/dl

SGLT2 Inhibitor



Glycosuria
 BG > 80 mg/dl

Glucose Loss
 80-100 g/day
 320-400 kcal/day

Blood Glucose ↓
Weight Loss

No Renal Damage

GU Infections / UTI

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Sodium Glucose Transporter 2 Inhibitors

Generic	Trade Name	Doses
Canagliflozin	Invokana	100, 300 mg
Dapagliflozin	Farxiga	5, 10 mg
Empagliflozin	Jardiance	10, 25 mg
Ertugliflozin	Steglatro	5, 15 mg
Bexagliflozin	Brenzavvy	20 mg

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Sodium Glucose Transporter 2 Inhibitors

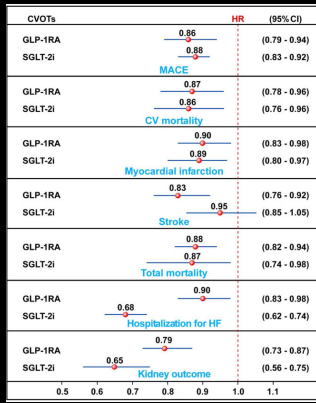
Risks

- Genitourinary Mycotic Infections
- Urinary Tract Infections
- Euglycemic DKA*
- Dehydration
- Fournier's Gangrene – Perineum
- Lower Limb Amputations (Canagliflozin)

* Euglycemic DKA (BG < 200): Occasionally Develops
Common Precipitants: Fasting, NPO, Low Carb Diets

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GLP-1 RA vs SGLT2 Inhibitors



Giugliano D. Cardiovasc Diabetol 2021; 20: 205

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GLP-1 RA vs SGLT2 Inhibitors

	SGLT2-I	GLP-1 RA	GLP-1/GIP RA
A1C Reduction	0.5-1.0%	1.0-1.5%	2.5-2.8%
Weight Loss	5-10 lb	10-15 lb	20-50 lb
Hypoglycemia	Low Risk	Low Risk	Low Risk
CKD Protection	Benefit	Benefit	Probable
CVD Protection	Benefit	Benefit	Probable
HF Protection	Benefit	Benefit	
Stroke Protection		Benefit	
NAFL/NASH	Benefit	Benefit	

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Personalized Diabetes Care

Choose Agent with Adequate Potency to Achieve Goal

↓ A1C > 2%	↓ A1C > 1-2%	↓ A1C > 0.5-1%
Insulins GLP-1 RA GLP-1/GIP RA	Metformin Pioglitazone Sulfonylureas GLP-1 RA GLP-1/GIP RA Insulins	SGLT-2 Inhibitors DPP4 Inhibitors
Usually With Metformin		

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

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Personalized Diabetes Care

Choose Agent with Proven Benefits for Co-Morbidities

CKD	CVD	HF
GLP-1 RA SGLT-2 Inhibitors	GLP-1 RA SGLT-2 Inhibitors	SGLT-2 Inhibitors GLP-1 RA?
	NAFL/NASH Pioglitazone GLP-1 RA	

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

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Personalized Diabetes Care

Promote Weight Loss or Minimize Weight Gain

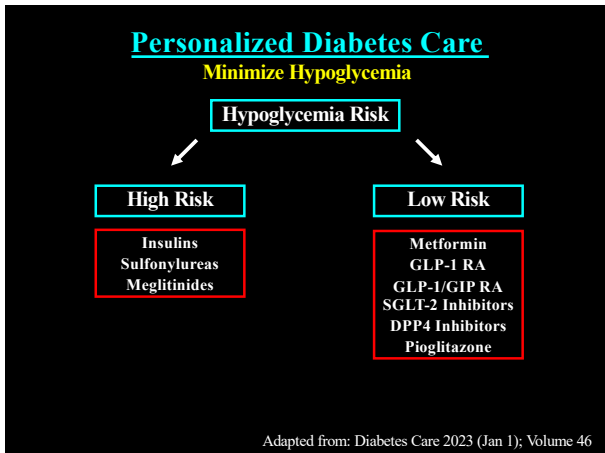
Weight Effects

↙ ↓ ↘

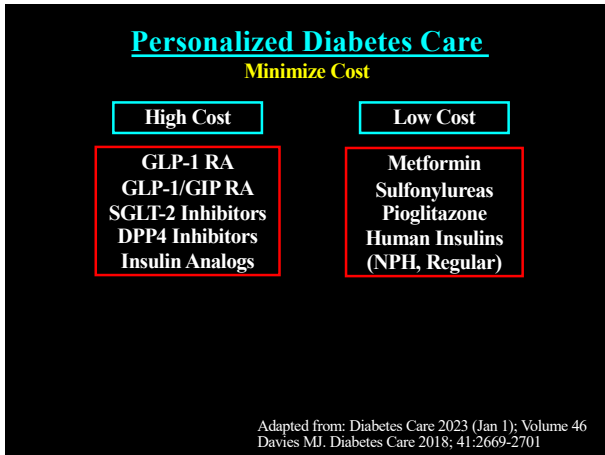
Weight Loss	Weight Neutral	Weight Gain
GLP-1 RA GLP-1/GIP RA SGLT-2 Inhibitors	Metformin DPP4 Inhibitors	Insulins Sulfonylureas Pioglitazone Meglitinides

Adapted from: Diabetes Care 2023 (Jan 1); Volume 46

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