2023 Medication Update

Caressa Trueman, PharmD, BCACP, BC-ADM
Ambulatory Care Pharmacist
Diabetes and Endocrinology Clinic

Nebraska Medicine

1

Conflict of Interest

Dr. Trueman has no conflicts of interest to disclose

2

2

Objectives

1. Summarize and apply the 2023 American Diabetes Association and 2023 American Association of Clinical Endocrinologists guideline updates
2. Discuss hot topic issues related to diabetes management
3. Identify novel therapies in phase II and III clinical trials

3

3

Abbreviations

- **AACE**: American Association of Clinical Endocrinology
- **ACE**: angiotensin-converting enzyme
- **ADA**: American Diabetes Association
- **ALT**: alanine transaminase
- **ARB**: angiotensin II receptor blocker
- **ASCVD**: atherosclerotic cardiovascular disease
- **BID**: twice daily
- **BMI**: body mass index
- **CGM**: continuous glucose monitor
- **CKD**: chronic kidney disease
- **CVD**: cardiovascular disease
- **CVOT**: cardiovascular outcomes trial
- **DPP-4i**: dipeptidyl peptidase 4 inhibitor
- **eGFR**: estimated glomerular filtration rate
- **ESRD**: end-stage renal disease
- **FDA**: Food & Drug Administration
- **GI**: gastrointestinal
- **GIP**: glucose-dependent insulinotropic polypeptide
- **GLP-1 RA**: glucagon-like peptide-1 receptor agonist
- **HF**: heart failure
- **HFpEF**: heart failure with preserved ejection fraction
- **HR**: hazard ratio
- **KCCQ**: Kansas City Cardiomyopathy Questionnaire
- **KCCQ – CSS**: Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score
- **LVEF**: left ventricle ejection fraction

4

4

Abbreviations, cont.

- **MACE**: major adverse cardiovascular events
- **MI**: myocardial infarct
- **NAFLD**: nonalcoholic fatty liver disease
- **NASH**: nonalcoholic steatohepatitis
- **NSAID**: nonsteroidal anti-inflammatory drug
- **OGTT**: oral glucose tolerance test
- **OSA**: obstructive sleep apnea
- **SGLT-2i**: sodium-glucose cotransporter-2 inhibitor
- **SQ**: subcutaneous
- **T1D**: type 1 diabetes mellitus
- **T2D**: type 2 diabetes mellitus
- **TIA**: transient ischemic attack
- **UACR**: urinary albumin creatinine ratio

5

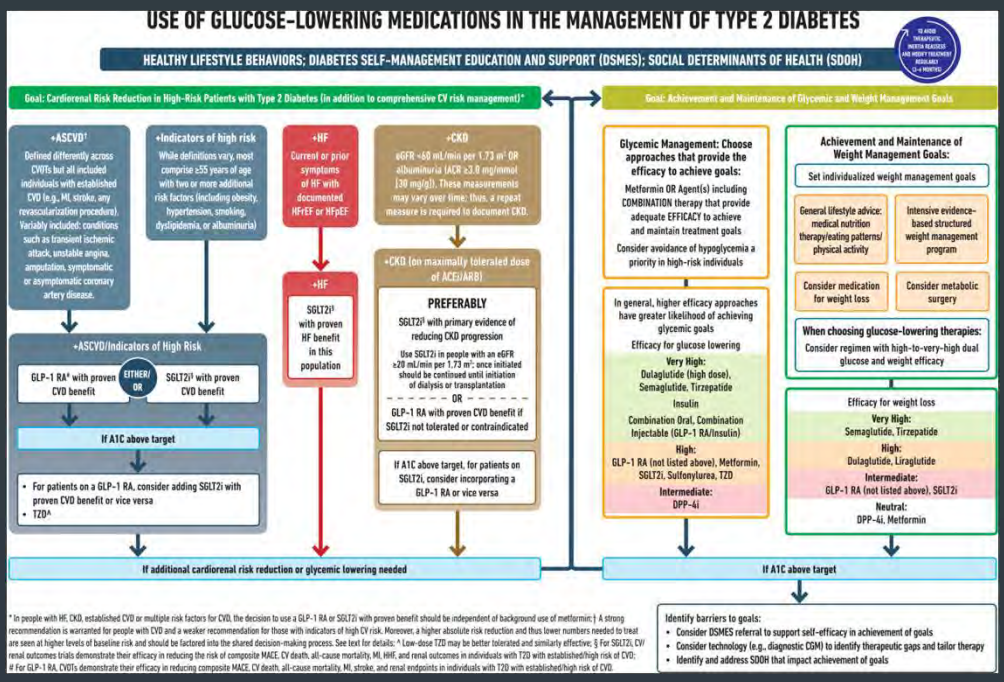
5

Guideline Review

2023 ADA T2D Guidelines
2023 AACE T2D Guidelines
2022 AACE NASH/NAFLD Guidelines

Nebraska Medicine

6



American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

7

7

2023 ADA Guideline Recommendations

Major Changes

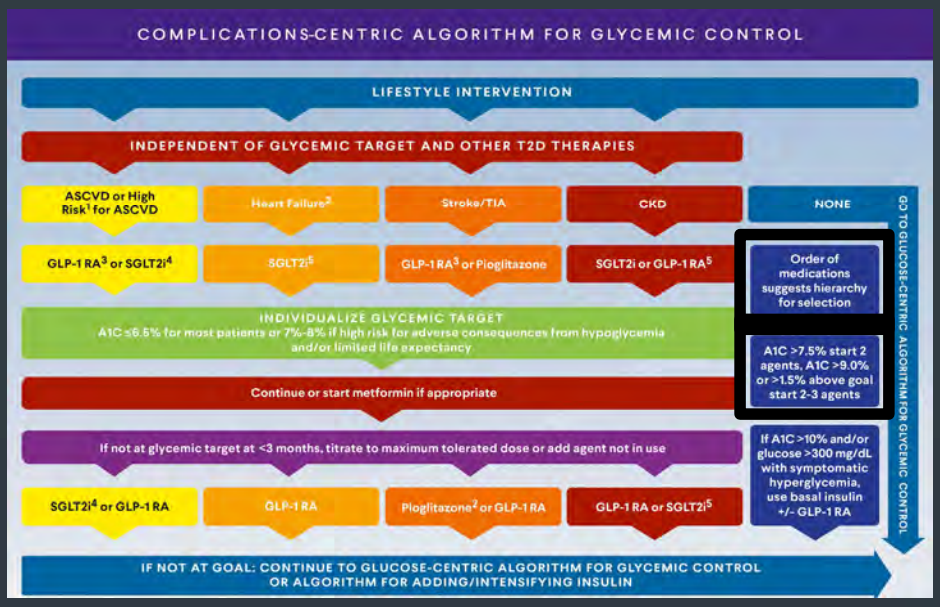
- Metformin is no longer uniform first line recommendation
- Pharmacotherapy selection is goal driven

American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

8

8

2023 AACE Guidelines

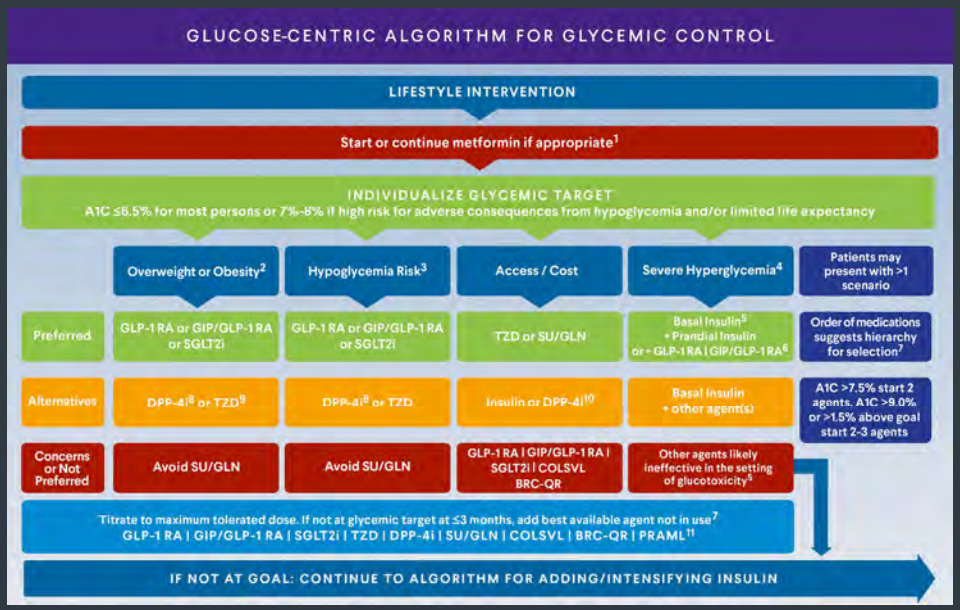


Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.

9

9

2023 AACE Guidelines



Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.

10

10

2023 Guideline Recommendations

ADA

Cardiorenal protection

Weight or glycemic management

- ASCVD diagnosis or at risk for ASCVD
- Heart failure
- Chronic Kidney Disease

AACE

Complications-Centric Algorithm

- ASCVD or high risk for ASCVD
- Heart Failure
- Stroke/TIA
- CKD
- None

Glucose-Centric Algorithm

- Overweight or Obesity
- Hypoglycemia Risk
- Access/Cost
- Severe Hypoglycemia

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

11

11

2023 Guidelines - Cardiorenal

Established ASCVD and at increased risk for ASCVD

- GLP-1 RA or SGLT-2i with proven cardiovascular benefit

A1c above goal

- Add agent not in use
- Thiazolidinedione

Established ASCVD and at increased risk for ASCVD

- 1st: Dulaglutide, liraglutide, semaglutide
- 2nd: Canagliflozin, empagliflozin

Stroke/TIA

- Dulaglutide, liraglutide, semaglutide
- Pioglitazone

A1c above goal

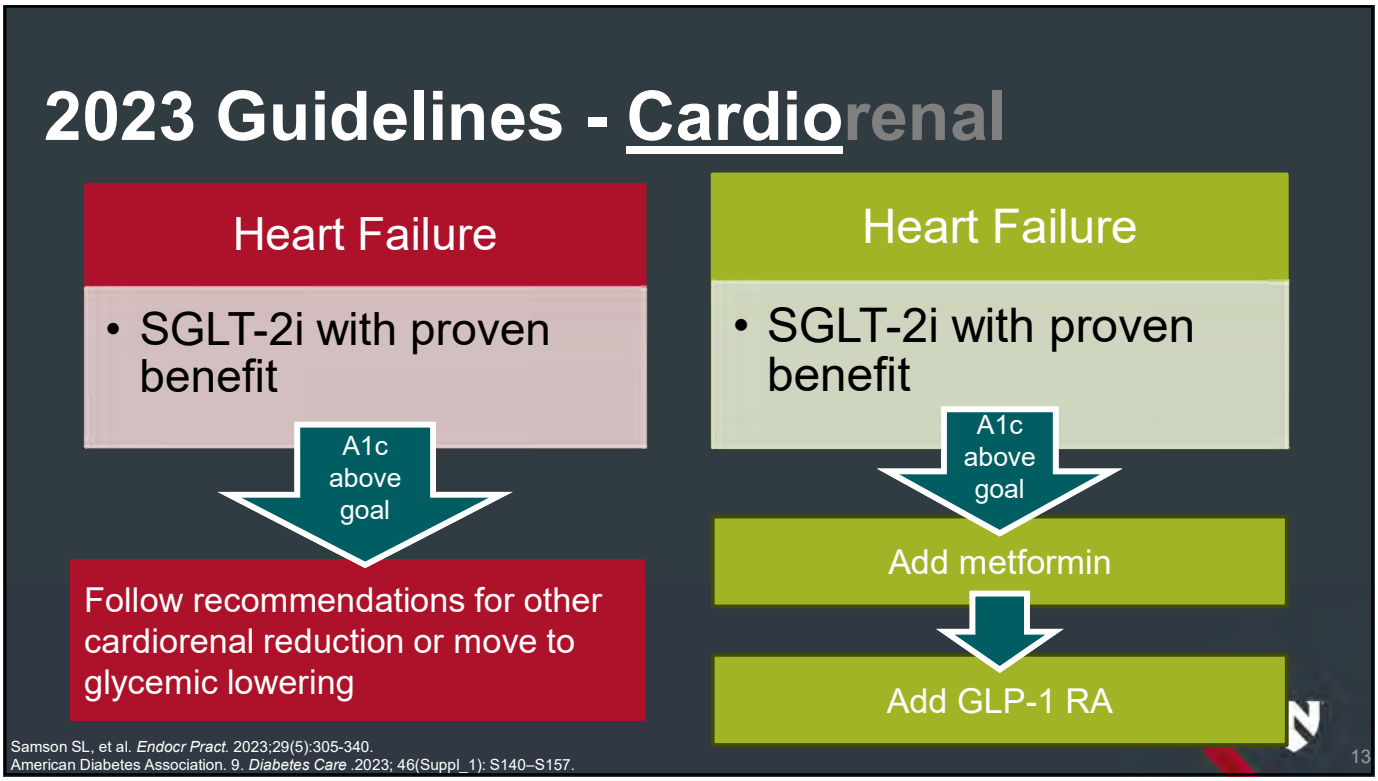
Add metformin

Add agent not in use

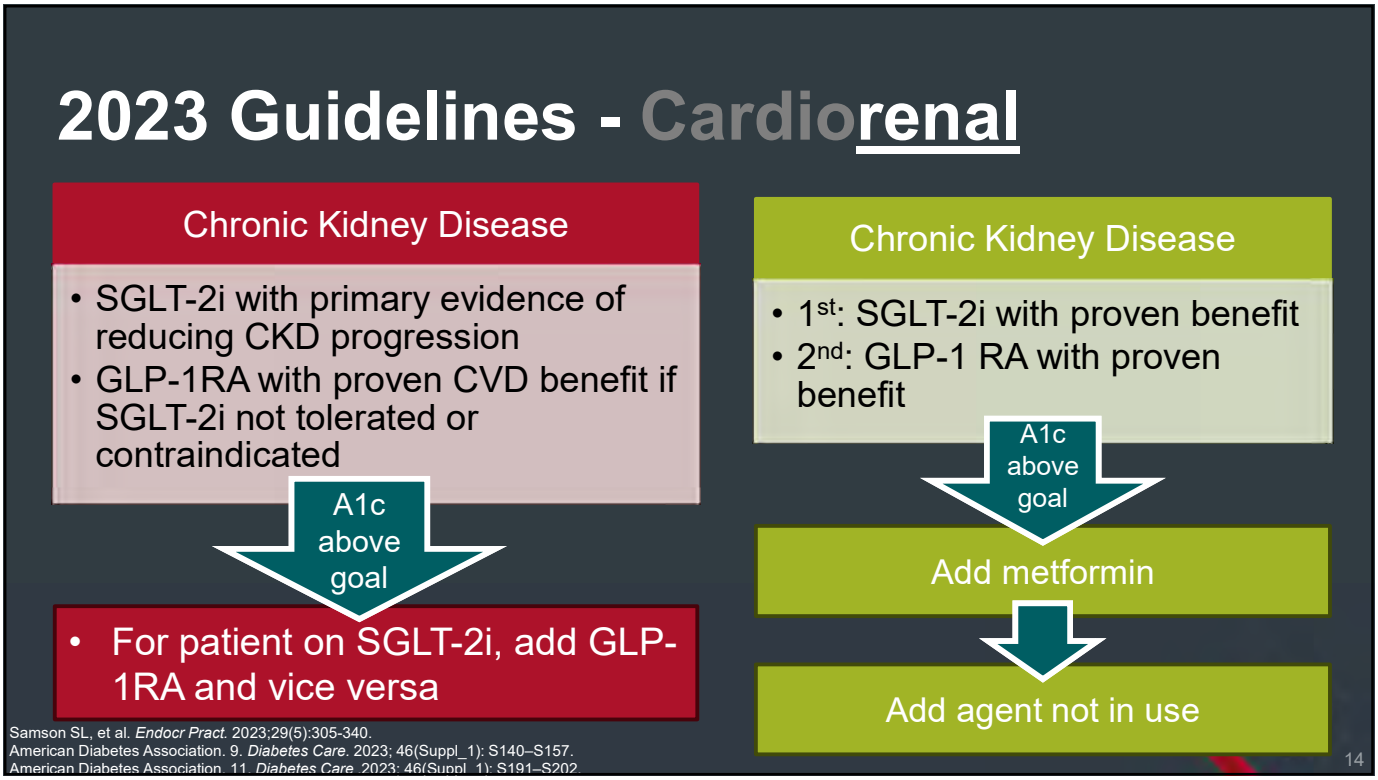
Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

12

12


2023 Guidelines - Cardiorenal
Heart Failure
• SGLT-2i with proven benefit
A1c above goal
Follow recommendations for other cardiorenal reduction or move to glycemic lowering
Heart Failure
• SGLT-2i with proven benefit
A1c above goal
Add metformin
Add GLP-1 RA
Samson SL, et al. Endocr Pract. 2023;29(5):305-340.
American Diabetes Association. 9. Diabetes Care .2023; 46(Suppl_1): S140–S157.
13

13


2023 Guidelines - Cardiorenal
Chronic Kidney Disease
• SGLT-2i with primary evidence of reducing CKD progression
• GLP-1RA with proven CVD benefit if SGLT-2i not tolerated or contraindicated
A1c above goal
• For patient on SGLT-2i, add GLP-1RA and vice versa
Chronic Kidney Disease
• 1st: SGLT-2i with proven benefit
• 2nd: GLP-1 RA with proven benefit
A1c above goal
Add metformin
Add agent not in use
Samson SL, et al. Endocr Pract. 2023;29(5):305-340.
American Diabetes Association. 9. Diabetes Care. 2023; 46(Suppl_1): S140–S157.
American Diabetes Association. 11. Diabetes Care. 2023; 46(Suppl_1): S191–S202.
14

14

2023 Guidelines - Cardiorenal

Use SGLT-2i in patients with eGFR ≥ 20 mL/min*

Once initiated, should be continued until initiation of dialysis or transplantation

Baseline UACR ≥ 300: reduction of ≥ 30% in mg/g recommended to slow CKD progression

Medications should be titrated to achieve this goal

Finerenone

- Reduction of cardiovascular events
- Reduction of kidney disease progression in patients with CKD + albuminuria

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care.* 2023; 46(Suppl_1): S140–S157.
American Diabetes Association. 11. *Diabetes Care* .2023; 46(Suppl_1): S191–S202.

15

2023 Guidelines – Weight Management

Weight Management

- Lifestyle advice
- Intensive evidence-based structured weight-loss program
- Medication for weight loss
- Metabolic surgery

Weight Management

- Entire complications-centric flowchart
  - Incorporates nutrition, activity, counseling, medications
  - Stratified by BMI
- No priority for medication selection
  - Includes non-diabetes medications

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

16

2023 Guidelines – Weight Management

Very high:
Semaglutide, tirzepatide

High:
Dulaglutide, liraglutide

Intermediate:
GLP-1 RA *(not listed above)*, SGLT-2i

Neutral:
DPP-4i, metformin

Preferred: GLP-1 RA or GIP/GLP-1 RA or SGLT-2i

Alternatives: DPP-4i or TZD

Not preferred: sulfonylurea, glinides

Education to patient on need to continue medication to maintain weight loss

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl 1): S140–S157.

17

17

2023 ADA Guidelines – Glycemic Management

Glycemic Management

- Metformin OR agents(s) with adequate efficacy to achieve and maintain goals

Very high:
Dulaglutide (high dose), semaglutide, tirzepatide
Insulin
Combination oral, combination injectable (GLP-1RA/Insulin)

High:
GLP-1 RA (not listed above), metformin, SGLT-2i, sulfonylurea, thiazolidinedione

Intermediate:
DPP-4i

American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl_1): S140–S157.

18

18

2023 AACE Guidelines

	Hypoglycemia Risk	Access/Cost	Severe Hyperglycemia
Preferred	GLP-1 RA or GLP-1 RA/GIP or SGLT-2i	Thiazolidinedione or sulfonylurea	Basal insulin + prandial or GLP-1 RA or GLP-1 RA/GIP
Alternative	DPP-4i or thiazolidinedione	Insulin or DPP-4i	Basal insulin + other agent(s)
Not preferred	Avoid sulfonylurea or glinides	Anything brand name only	Agents ineffective in setting of glucotoxicity

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.

19

19

GLP-1 RA & SGLT-2i Indications

ASCVD	HF	CKD
GLP-1 RA: dulaglutide, liraglutide, semaglutide (*Ozempic*) **SGLT-2i**: canagliflozin, empagliflozin	**GLP-1 RA**: N/A **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	**GLP-1 RA**: dulaglutide, liraglutide, semaglutide (*Ozempic*) • Renal benefit from CVOTs *(driven by albuminuria)* **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin
GLP-1 RA: dulaglutide, liraglutide, semaglutide *(Ozempic)* **SGLT-2i**: canagliflozin, empagliflozin	**GLP-1 RA**: N/A **SGLT-2i**: None specified, although reduced risk noted	**GLP-1 RA**: dulaglutide, semaglutide (*Ozempic*) **SGLT-2i**: canagliflozin, dapagliflozin, empagliflozin

Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl 1): S140–S157.

20

20

Other Hot Topics in Guidelines

- Therapeutic Inertia
- Treatment at diagnosis
- Nonalcoholic fatty liver disease

American Diabetes Association. 9. *Diabetes Care* .2023; 46(Suppl 1): S140–S157.

21

21

T2D and Liver Disease

Significant link between patients with T2D & development of NAFLD

→ 2022 AACE NAFLD, 2023 AACE & ADA T2D guidelines highly recommend screening for liver disease

Treatment for liver disease:

- GLP-1 RA
- Pioglitazone

Cusi K, et al. *Endocr Pract.* 2022;28(5):528-562.
Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.
Addendum. 4. Diabetes Care 2023;46(Suppl. 1):S49–S67.

22

22

Medication Changes and Updates

New/Updated Approvals
Tirzepatide & Semaglutide *(Wegovy)* Trials

Nebraska Medicine

23

FDA Label Updates – Semaglutide *(Ozempic)*

Hypoglycemia

- *"Patients receiving (semaglutide) Ozempic in combination with an insulin secretagogue (e.g. sulfonylurea) or insulin may have an increased risk of hypoglycemia, including severe hypoglycemia"*

Adverse Effect: gastrointestinal ileus

- Voluntarily reported
- Unable to determine frequency or causality to drug exposure

FDA Gives Ozempic Two Drug Safety–Related Label Changes - *Medscape* - Sep 28, 2023. Accessed October 3, 2023.

24

24

FDA Approval Updates

Empagliflozin & empagliflozin/metformin
- T2D indication expanded to patients 10 years and older

Empagliflozin
- Reduction in CKD progression in patients WITHOUT T2D

Bexagliflozin *(Brenzavvy)*
- New SGLT-2i
- Treatment of T2D

Sotagliflozin *(Inpefa)*
- Heart Failure – May

Finerenone*
- Reduction in risk of composite death from cardiovascular causes, nonfatal MI, nonfatal stroke, hospitalization for heart failure

Teplizumab *(Tzield)*
- Delay onset of stage 3 type 1 diabetes

25

25

Teplizumab *(Tzield)*

Indication: Delay onset of stage 3 T1D

Delayed progression by 25 months
- *Time to stage 3 diagnosis 50 months in active vs 25 months in placebo*

HR: 0.41
- *95% CI: 0.22 – 0.78, p=0.0066*

Use: patients 8 years and older with stage 2 T1D

Generally, children or siblings of someone with T1D

Must confirm Stage 2 T1D by:
- 2+ positive pancreatic islet cell autoantibodies
- Dysglycemia without overt hyperglycemia using OGTT
- Clinical history does not suggest T2D

Teplizumab. Package insert. Provention Bio, Inc; 2022.

26

26

Teplizumab *(Tzield)*

Warnings/Precautions:	• Cytokine release syndrome – requires pre-medication • Serious infections • Lymphopenia • Hypersensitivity
Side effects	• Rash, leukopenia, headache, neutropenia, gastrointestinal upset, increase in ALT, nasophyngitis

Teplizumab. Package insert. Provention Bio, Inc; 2022.

27

27

Teplizumab *(Tzield)*

IV infusion, minimum 30 minutes

Pre-medicate for at least first 5 doses:
- NSAID or acetaminophen
- Antihistamine and/or antiemetic

Body surface area-based dosing over 14 consecutive days:
- Day 1: 65 mcg/m^2
- Day 2: 125 mcg/m^2
- Day 3: 250 mcg/m^2
- Day 4: 500 mcg/m^2
- Day 5 - 14: 1,030 mcg/m^2

Cost of Infusion:
- 1 vial = $15,794

14-year-old, 60kg, 65in boy = $221,116

Teplizumab. Package insert. Provention Bio, Inc; 2022.

28

28

Clinical Trial Updates

Tirzepatide	Semaglutide *(Wegovy)*
SURPASS – T2D	STEP-HFpEF – Heart failure
SURMOUNT – Obesity	STEP HFpEF DM – Heart failure + T2D
SYNERGY - NASH	SELECT - Cardiovascular disease

Reminder: FDA-approved for chronic weight management, not treatment of T2D

29

29

Tirzepatide – Diabetes Trials

SURPASS – 6	SURPASS – CVOT	SURPASS – PEDS
Trial Population Adults with T2D taking insulin ± metformin	**Trial Population** Adults with T2D, confirmed ASCVD, and BMI ≥ 25	**Trial Population** Children aged 10-17 years with T2D, BMI > 85th percentile, taking metformin ± insulin
Intervention Tirzepatide 5, 10, 15mg + glargine	**Intervention** Tirzepatide @ max tolerated dose	**Intervention** Tirzepatide
Comparator Lispro	**Comparator** Dulaglutide 1.5mg	**Comparator** Placebo
Primary Outcome Change in A1c *(52 weeks)*	**Primary Outcome** Time to 3-pt MACE	**Primary Outcome** Change in A1c *(30 weeks)*
Expected Completion Completed, no data available	**Estimated Completion** October 2024	**Estimated Completion** July 2025

SURPASS-CVOT. Clinical Trials.gov. Updated July 13, 2023. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT04255433.
SURPASS-PEDS. Clinical Trials.gov. Updated August 1, 2023. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT05260021.
SURPASS-6. Clinical Trials.gov. Updated November 23, 2022. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT04537923.

30

30

Tirzepatide – Diabetes Trials

SURPASS – EARLY	SURPASS – SWITCH	SURPASS – SWITCH-2
Trial Population Adults with T2D diagnosed within the last 4 years taking metformin	**Trial Population** Adults with T2D, taking a stable dose of dulaglutide (0.75mg or 1.5mg) for ≥ 6 months	**Trial Population** Adults with T2D, taking a stable dose of listed GLP-1 RA for ≥ 3 months
Intervention Tirzepatide @ max tolerated dose	**Intervention** Tirzepatide	**Intervention** Tirzepatide
Comparator Intensified conventional care dose	**Comparator** Dulaglutide 3 & 4.5mg	**Comparator** Placebo
Primary Outcome Change in A1c *(104 weeks)*	**Primary Outcome** Change in A1c *(40 weeks)*	**Primary Outcome** Change in A1c *(12 weeks)*
Expected Completion November 2027	**Estimated Completion** August 2024	**Estimated Completion** November 2023

SURPASS-EARLY. Clinical Trials.gov. Updated September 14, 2023. Accessed September 19, 2023. https://clinicaltrials.gov/study/NCT05433584.
SURPASS-SWITCH. Clinical Trials.gov. Updated September 15, 2023. Accessed September 20, 2023. https://clinicaltrials.gov/study/NCT05564039.
SURPASS-SWITCH-2. Clinical Trials.gov. Updated September 15, 2023. Accessed September 20, 2023. https://clinicaltrials.gov/study/NCT05706506.

Tirzepatide – Quick Update!

Poster 5: Tirzepatide compared to sq semaglutide for T2D: a meta-analysis

Meta-analysis of semaglutide and tirzepatide using common comparators

A1c results:
- Tirzepatide 15mg: -2.0%
- Tirzepatide 12.5mg: -1.86%
- Semaglutide 2mg: -1.62%

Tirzepatide – weight loss without adverse effects on muscle composition

Tirzepatide – reduces muscle fat infiltration relative to deludec

Tirzepatide – reduction in albuminuria pooled analysis of SURPASS 1-5

Tirzepatide – health-related quality of life compared to lispro

EASD European Association for the Study of Diabetes

Tirzepatide Superior to Semaglutide for A1c Control, Weight Loss - *Medscape* - Sep 22, 2023. Accessed October 3, 2023.

Tirzepatide – Obesity Trials

SURMOUNT – 2	SURMOUNT – 3	SURMOUNT – 4
Trial Population Adults with T2D and BMI ≥ 27	**Trial Population** Adults with obesity or a BMI ≥ 27 with related comorbidity	**Trial Population** Adults with obesity or a BMI ≥ 27 with related comorbidity
Intervention Tirzepatide 10, 15mg	**Intervention** Tirzepatide following intensive lifestyle intervention	**Intervention** Tirzepatide 10, 15mg following 36-week lead-in period
Comparator Placebo	**Comparator** Placebo following intensive lifestyle intervention	**Comparator** Placebo
Primary Outcome -12.8% body weight with 10mg, -14.7% with 15mg dose	**Primary Outcome** - 21.1% body weight at 72 weeks vs +3.3% in placebo	**Primary Outcome** Additional -6.7% body weight change vs +14.8% in placebo

Garvey WT, et al. *Lancet.* 2023;402(10402):613-626.
Tirzepatide demonstrated significant and superior weight loss compared to placebo in two pivotal studies. 2023. Accessed September 11, 2023.

33

Tirzepatide – Obesity Trials

SURMOUNT – 5	SURMOUNT – MMO	SURMOUNT – OSA
Trial Population Adults with BMI ≥ 30 OR BMI ≥ 27 with related comorbidity	**Trial Population** Adults with BMI ≥ 27 with related ASCVD comorbidity or ASCVD risk factors	**Trial Population** Adults with BMI ≥ 30 and OSA ± CPAP usage
Intervention Tirzepatide	**Intervention** Tirzepatide	**Intervention** 2 doses of tirzepatide
Comparator Semaglutide 2.4mg	**Comparator** Placebo	**Comparator** Placebo
Primary Outcome % change in body weight *No. with ≥ 5% body weight reduction*	**Primary Outcome** Time to *(modified)* MACE+	**Primary Outcome** Change in baseline Apnea-Hypopnea Index
Expected Completion December 2024	**Estimated Completion** October 2027	**Estimated Completion** March 2024

SURMOUNT-OSA. Clinical Trials.gov. Updated July 12, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT05412004.
SURMOUNT-5. Clinical Trials.gov. Updated September 5, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT05822830.
SURMOUNT-MMO. Clinical Trials.gov. Updated September 5, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT05556512.

34

Tirzepatide – Other Comorbidities

SYNERGY - NASH	SUMMIT
Trial Population Adults with BMI between 27 and 50 with NASH stage 2 or 3	**Trial Population** Adults with BMI ≥ 30, stable HF with LVEF ≥ 50%
Intervention Tirzepatide 5, 10, 15mg	**Intervention** Tirzepatide
Comparator Placebo	**Comparator** Placebo
Primary Outcome % of patients without NASH + no worsening of liver fibrosis	**Primary Outcome** Hierarchical composite of mortality, HF events, symptoms
Expected Completion February 2024	**Estimated Completion** July 2024

SUMMIT. Clinical Trials.gov. Updated July 25, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04847557.
SYNERGY-NASH. Clinical Trials.gov. Updated September 7, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04166773.

Semaglutide *(Wegovy)* Updates

STEP HFpEF	STEP HFpEF DM	SELECT
Trial Population Adults with symptomatic HFpEF and BMI ≥ 30 without diabetes	**Trial Population** Adults with symptomatic HFpEF and BMI ≥ 30 **AND** diabetes	**Trial Population** Adults 45+ years old with established ASCVD and BMI ≥ 27 without diabetes
Intervention Semaglutide 2.4mg	**Intervention** Semaglutide 2.4mg	**Intervention** Semaglutide 2.4mg
Comparator Placebo	**Comparator** Placebo	**Comparator** Placebo
Primary Outcome* Change in KCCQ-CSS score: 16.6 points vs 8.7 with placebo	**Primary Outcome** Change in KCCQ score Change in body weight	**Primary Outcome** Superior to placebo for 20% reduction in 3-point MACE events
	Estimated Completion* October 2023	

Kosiborod MN, et al. *NEJM*. 2023. Online ahead of print.
STEP HFpEF DM. Clinical Trials.gov. Updated September 13, 2023. Accessed September 21, 2023. https://clinicaltrials.gov/study/NCT04916470.
Semaglutide 2.4mg reduces risk of major adverse cardiovascular events by 20% in adults with overweight/obesity in SELECT trial. 2023. Accessed August 28,2023

Upcoming FDA Approvals?

Tirzepatide

- Obesity
  - Granted fast-track designation in fall 2022
  - Anticipated approval before end of 2023
- ASCVD risk reduction, OSA, HF
  - Await trial results

Semaglutide *(Wegovy)*

- ASCVD risk reduction
  - Anticipated FDA submission before end of 2023
- HFpEF
  - Anticipate results of STEP-HFpEF DM

Novo, with new data, builds care for using Wegovy to protect heart health. 2023. Accessed September 21, 2023.
Diabetes drug Mounjaro shown to have extraordinary weight loss for people without diabetes. 2023. Accessed September 21,2023.

37

Hot Topics

Insulin Price Caps & the Inflation Reduction Act
GLP-1 Shortages
GLP-1 RA & Diabetic Retinopathy
GLP-1 RA & Suicidal Ideation
GLP-1 RA & Preprocedural Management

Nebraska Medicine

38

Insulin Price Caps

Inflation Reduction Act

- Enacted January 2023
- Caps insulin costs for Medicare patients at $35/month or 25% of negotiated price
- Basal/GLP-1 RA combos included in price cap

Lily insulin price cuts – March 2023

- 4/1/23: Rezvoglar *(Lantus biosimilar)* launched at $92/5 pack of pens
- 5/1/23: $25/vial lispro *(non-branded)*
- Q4 2023: cut list price by 70% for Humalog *(lispro)* U-100, Humulin
- Lily Insulin Value Program: $35/month with $16,000 annual benefit for commercial or uninsured

Lily cuts insulin prices by 70% and caps patient insulin out-of-pocket costs at $35 per month. 2023. Accessed August 15, 2023.

39

39

Insulin Price Caps

Novo Nordisk – January 2024

- Novolog *(aspart)* reduced 75%
- Novolin *(NPH)* and Levemir *(detemir)* reduced 65%

Sanofi – January 2024

- Lantus *(glargine)* reduced by 78%
- $35 out of pocket cap for Lantus *(glargine)* for commercial insurance patients
- Apidra *(glulisine)* reduced by 70%

Wingrove P, et al. *Reuters*. March 14, 2023. Accessed August 15, 2023
Sanofi cuts U.S list price of Lantus, it's most prescribed insulin, by 78% and caps out-of-pocket. 2023. Accessed August 15, 2023.

40

40

Inflation Reduction Act

First round of price negotiations:
Negotiations end in Aug 2024 → Maximum fair prices published in Sept 2024 → prices take effect in 2026

Apixaban	Empagliflozin	Rivaroxaban	Sitagliptin	Dapagliflozin
Sacubitril-valsartan	Etanercept	Ibrutinib	Ustekinumab	Aspart *(Fiasp)* & Detemir

Cubanski J, et al. *KFF*. Published January 24, 2023. Accessed September 22, 2023.

41

41

Inflation Reduction Act - Nebraska

	No. of Patients	Mean Out of Pocket Cost
Empagliflozin	7,000 patients	$325
Sitaglipitin	3,000 patients	$502
Dapagliflozin	3,000 patients	$443
Aspart *(Fiasp)* & Detemir	5,000 patients	$202

Inflation reduction act research series: Medicare use & OOP expenditures for drugs selected for negotiation under drug price negotiation program. (Fact sheet no. HP-2023-21). August 2023.

42

42

GLP-1 RA Shortages

Medication	Dosage													
*Tirzepatide			2.5	2.5	2.5	2.5	2.5	5	5	5	7.5	10	12.5	15
Semaglutide *(SQ)*			0.25	0.5			1	1.7	2	2.4				
Semaglutide *(PO)*		3	7	14										
Dulaglutide			0.75	1.5		3	4.5							
Liraglutide		0.6	1.2	1.8	2.4	3								
Exenatide *(weekly)*			2											
Exenatide *(BID)*	5	10												

*Insufficient data to suggest dose equivalency between tirzepatide 2.5mg and available GLP-1RAs

Davis C, et al. *WJPR*. 2023;12(12):140-166.

43

43

GLP-1 RAs & Diabetic Retinopathy

Package Labeling

- Noted increased risk: dulaglutide, semaglutide
- Current warning: rapid improvement in glucose control associated with temporary worsening of diabetic retinopathy

Current Evidence

- Evidence is varied
- Yoshida et al: meta-analysis showed slight increase in risk
- Douros et al: cohort study showed decreased risk

Recommendation

- Close monitoring in patients with history of diabetic retinopathy
- Await results of FOCUS trial (2026)
  - Semaglutide vs placebo with pre-existing T2D up to 5 years and evaluating evidence of retinopathy progression

Davis C, et al. *WJPR*. 2023;12(12):140-166.
Douros A, et al. *Diabetes Care*. 2018;41(11):2330-2338.
Yoshida Y, et al. *J Diabetes Complications*. 2022:36(8):108255.

44

44

GLP-1 RAs & Suicidal Ideation

Historically…

Liraglutide *(Saxenda)* & Semaglutide *(Wegovy)*

Not seen in Liraglutide *(Victoza)* or Semaglutide *(Ozempic)* trials*

"Patients treated with *** should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior. Discontinue *** in patients who experience suicidal thoughts or behaviors. Avoid *** in patients with a history of suicidal attempts or active suicidal ideation.

EU labeling does not include this risk

Victoza. Package insert. Novo Nordisk A/S; 2010.
Wegovy. Package insert. Novo Nordisk A/S; 2021.
Saxenda. Package insert. Novo Nordisk A/S; 2014.
EMA statement on ongoing review of GLP-1 receptor agonists. European Medicines Agency. Published July 11, 2023. Accessed October 3, 2023.

45

45

GLP-1 RAs & Suicidal Ideation

Now…

	Europe	US
July 2023	European Medicines Agency launches investigation for multiple GLP-1 drugs • Dulaglutide, exenatide, liraglutide*, lixisenatide, semaglutide*	FDA: no investigation at this time
		9/28/23: received 265 reports since 2010 **potential for duplicates*
		113 detailed narratives
		36 deaths by suicide or suspected suicide 30 include h/o mental health condition
Nov 2023	Expected to be completed • Analyzing 150 reports	

EMA statement on ongoing review of GLP-1 receptor agonists. European Medicines Agency. Published July 11, 2023. Accessed October 3, 2023.
Respaut R, et al. Wegovy, other weight-loss drugs scrutinized over reports of suicidal thoughts. *Reuters*. Published September 28, 2023. Accessed October 3, 2023.

46

46

GLP-1 RAs & Suicidal Ideation

REMEMBER:

- Correlation does not equal causation
- Diabetes & obesity are complex conditions that impact mental health

Recommendations:

- Stop[illegible]ibing[illegible]?
- Take[illegible]ts off [illegible]s?
- Closely monitor patients with a history of mental health disorders
- Consider prioritizing other agents in patients with history of suicidal thoughts or attempts
- **EDUCATE PATIENTS!**

EMA statement on ongoing review of GLP-1 receptor agonists. European Medicines Agency. Published July 11, 2023. Accessed October 3, 2023.
Respaut R, et al. Wegovy, other weight-loss drugs scrutinized over reports of suicidal thoughts. *Reuters*. Published September 28, 2023. Accessed October 3, 2023.

47

47

GLP-1 RAs & Surgeries

American Society of Anesthesiologists

GLP-1 RAs cause delays in gastric emptying + Lack of gastric emptying increases risk of regurgitation and pulmonary aspiration of gastric contents while under general anesthesia = Theoretically, GLP-1 RA use increases risk of regurgitation and aspiration while under general anesthesia

- Guideline recommendation based on limited data
- 2023 ADA Guidelines: no data on use or influence of GLP-1 RA on glycemia in perioperative care
- Medication will likely not be cleared from system with 1 held dose
- Role of hyperglycemia in peri- and post-operative

ASA consensus-based guidance on preoperative management of patients on GLP-1 RA. 2023. Accessed September 12, 2023.

48

48

GLP-1 RAs & Surgeries

American Society of Anesthesiologists

Preoperative

- **Weekly GLP-1 RA**: hold for 1 week prior to procedure
- **Daily GLP-1 RA**: hold day of procedure

Perioperative

Severe GI symptoms	Held and no symptoms	Not held and no GI symptoms
Consider delaying elective procedures Discuss risks if nonelective	Proceed as usual	Proceed with "full stomach" precautions or US of gastric volume
	Empty: Proceed as usual	Full or inconclusive: Consider delaying Treat as "full stomach" and manage accordingly

ASA consensus-based guidance on preoperative management of patients on GLP-1 RA. 2023. Accessed September 12, 2023.

49

49

Investigational Drugs

Insulin Icodec – Follow-Up
High dose oral semaglutide
Orforglipron
Retatrutide
Survodutide

Nebraska Medicine

50

Insulin Icodec

ONWARDS 1	ONWARDS 2	ONWARDS 3
78 week randomized, open-label trial	26 week randomized, open-label, active control trial	26 week randomized, double-masked, double-dummy trial
Insulin naïve	Previously uncontrolled on basal insulin	Insulin naïve
Noninferior A1c reduction compared to daily glargine	Superior A1c reduction compared to daily degludec	Superior A1c reduction compared to daily degludec
Numerically greater incidence of Level 2 or 3 hypoglycemia	Showed numerically high rates of hypoglycemia	Statistically higher rates of Level 2 or 3 hypoglycemia*

Lingvay I, et al. *JAMA*. 2023;330(3):228-237
Philis-Tsimikas A, et al. *Lancet*. 2023;11(6):414-425.
Rosenstock J, et al. *N Engl J Med*. 2023;389:297-308.

51

51

Insulin Icodec

ONWARDS 4	ONWARDS 5	ONWARDS 6
26 week randomized, open-label trial	52 week randomized, open-label, active control trial	52 week randomized, open-label, parallel group trial
Previously on basal + bolus insulin	Insulin naïve	T1D
Noninferior A1c reduction compared to daily glargine (+ bolus)	Superior A1c reduction compared to daily glargine *(U100 or U300)*	Noninferior A1c reduction compared to degludec
Similar rates of hypoglycemia	No difference in rates of Level 2 or 3 hypoglycemia	Higher rates of severe hypoglycemia (<54mg/dL)

Wingrove P, et al. *Reuters*. March 14, 2023. Accessed August 15, 2023
Once-weekly insulin icodec demonstrates superior reduction in A1c with dosing guide app vs basal insulin T2D in ONWARDS 5 trial. 2023. Accessed September 1, 2023.
Novo Nordisk achieve primary objectives of ONWARDS 1 and 6 with once-weekly insulin icodec demonstrating superior reduction in HbA1c. Accessed September 1, 2023.

52

52

Insulin Icodec – Upcoming

ONWARDS 9

- 26 week open-label, single arm trial for insulin naïve patients
- A1c reduction using CGM-based dose titration
- April 2024

Phase 1 trial: children and teenagers

COMBINE 1

- 52 week randomized, open-label, active control trial for patients not controlled on basal insulin
- A1c reduction comparing IcoSema vs icodec
- April 2024

COMBINE 2

- 52 week randomized, open-label, parallel group trial for insulin naïve on stable dose of GLP-1 RA
- A1c reduction comparing IcoSema to semaglutide
- January 2024

Single arm study evaluating semaglutide added on to icodec if A1c goal not reached at 26 weeks

ONWARDS 9. Clinical Trials.gov. Updated April 28, 2023. Accessed September 21, 2023. https://clinicaltrials.gov/study/NCT05823948.
COMBINE 1. Clinical Trials.gov. Updated September 21, 2023. Accessed September 21, 2023. https://clinicaltrials.gov/study/NCT05352815.
COMBINE 2. Clinical Trials.gov. Updated September 21, 2023. Accessed September 21, 2023. https://clinicaltrials.gov/study/NCT05259033.

New Investigational Drugs

novo nordisk®

Lilly

Boehringer Ingelheim

Semaglutide, oral
- Higher doses than previously studied
- Obesity

Orforglipron
- Daily oral non-peptide GLP-1 receptor agonist
- Obesity & T2D

Retatrutide
- Triple agonist: GLP-1, GIP, glucagon receptors
- Obesity & T2D

Survodutide
- Glucagon/GLP-1 receptor agonist
- Obesity & NASH

Mechanisms of Action

Brain	Whole Body	Pancreas	Stomach	New Agents
GIP ↓ food intake	GIP ↑ insulin sensitivity	GIP ↑ insulin ↑ glucagon		Orforglipron GLP-1
GLP-1 ↓ food intake ↑ satiety		GLP-1 ↑ insulin ↓ glucagon	GLP-1 ↓ gastric emptying	Retatrutide GIP / GLP-1 / Glucagon
	Glucagon ↑ energy expenditure			Survodutide GLP-1 / Glucagon

Nauck MA, et al. *Diabetes Metab J.* 2021;23(S3):5-29.

55

55

Semaglutide, oral

	OASIS – 1	OASIS – 4
Trial Population	Adults with BMI ≥ 30 or a BMI ≥ 27 with related comorbidity *Excluded if 5kg weight change in 90 days prior to study period*	
Intervention	Oral semaglutide **50mg**	Oral semaglutide **25mg**
Comparator	Placebo	Placebo
Primary Outcome	Change in body weight at 68 weeks: -15.1% vs -2.4% with placebo	Change in body weight at 72 weeks
Anticipated Completion		May 2024

Knop FK, et al. *Lancet.* 2023;23:01185-6.
OASIS-4. Clinicaltrials.gov. Updated January 5, 2023. Accessed September 11, 2023. https://clinicaltrials.gov/study/NCT05564117.

56

56

Orforglipron

Daily oral **nonpeptide** GLP-1 receptor agonist

Type 2 Diabetes	Obesity
Phase 2: 5 doses vs placebo vs dulaglutide	Phase 2: 4 doses vs placebo
Primary outcome: A1c at 26 weeks 2.1% vs 0.43% with placebo vs 1.1% with dulaglutide	Primary outcome: body weight at 36 weeks 9.4 – 14.7% reduction vs 2.3% with placebo 10% body weight reduction: 46 – 75% vs 9% placebo
Safety profile consistent with other GLP-1 RA GI issues: 44.1 – 70.4% with drug, 18.2% with placebo, 34% with dulaglutide	Safety profile consistent with other GLP-1 RA
Phase 3 trials: ACHIEVE	Phase 3 trials: ATTAIN

Frias JP, et al. *Lancet.* 2023;402(10400):472-483.
Wharton S, et al. *N Engl J Med.* 2023;online ahead of print.

57

57

Retatrutide

GLP-1, GIP & glucagon receptor agonist (triple agonist)

Type 2 Diabetes	Obesity
Phase 2: 6 doses vs placebo vs dulaglutide	Phase 2: 6 doses/regimens vs placebo
Primary outcome: A1c at 24 weeks 0.43 – 2.02% vs 0.12% with placebo vs 1.41% with dulaglutide	Primary outcome: body weight at 24 weeks 7.2 – 17.5% reduction vs 1.6% with placebo >5% body weight reduction in 100% of active participants *(except lower dose – 92% achieved)*
Dose-dependent decrease in body weight GI issues: 13 – 50% with drug, 13% with placebo, 35% with dulaglutide	Mild to moderate GI issues; dose-dependent increase in HR; peaks at 24 weeks and declines
Phase 3 trials: TRIUMPH 3	Phase 3 trials: TRIUMPH

Jastreboff AM, et al. *N Engl J Med.* 2023;389:514-526.
Rosenstock J, et al. *Lancet.* 2023;402(10401):529-544.

58

58

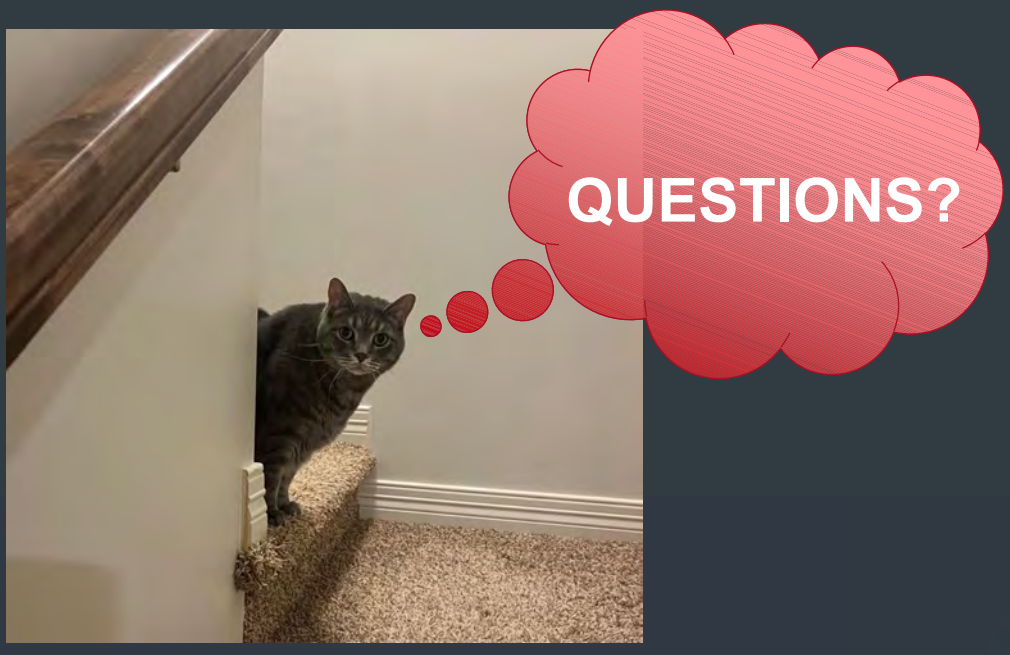
Survodutide

GLP-1 & glucagon receptor agonist

Obesity	NASH & Fibrosis
Phase 2: 4 doses vs placebo	Phase 2: 3 doses vs placebo
Primary outcome: % weight change @ 46 weeks 6.2 - 14.9% vs 2.8% with placebo	Primary outcome: % of patients with histological improvement of NASH @ 48 weeks
AE: 90.9% with drug vs 75.8% with placebo Primarily GI issues	Anticipated completion: December 2023 Given fast-track status by FDA in 2021
Phase 3 trials: 3 trials to be conducted	Phase 3 trials: Unclear

Novel weight loss drug, survodutide, shows significant weight loss of nearly 19% at 46 weeks. 2023. Accessed September 12, 2023.
BI456906 with NASH. Clinical Trials.gov. Updated September 9, 2023. Accessed September 12, 2023. https://clinicaltrials.gov/study/NCT04771273.

59



60

61

“Extra” Details

Slide 15: Finerenone
Slide 18: AACE Obesity Management Algorithm
Slide 41: Inflation Reduction Act – Price negotiations

62

62

Finerenone

Nonsteroidal mineralocorticoid receptor antagonist

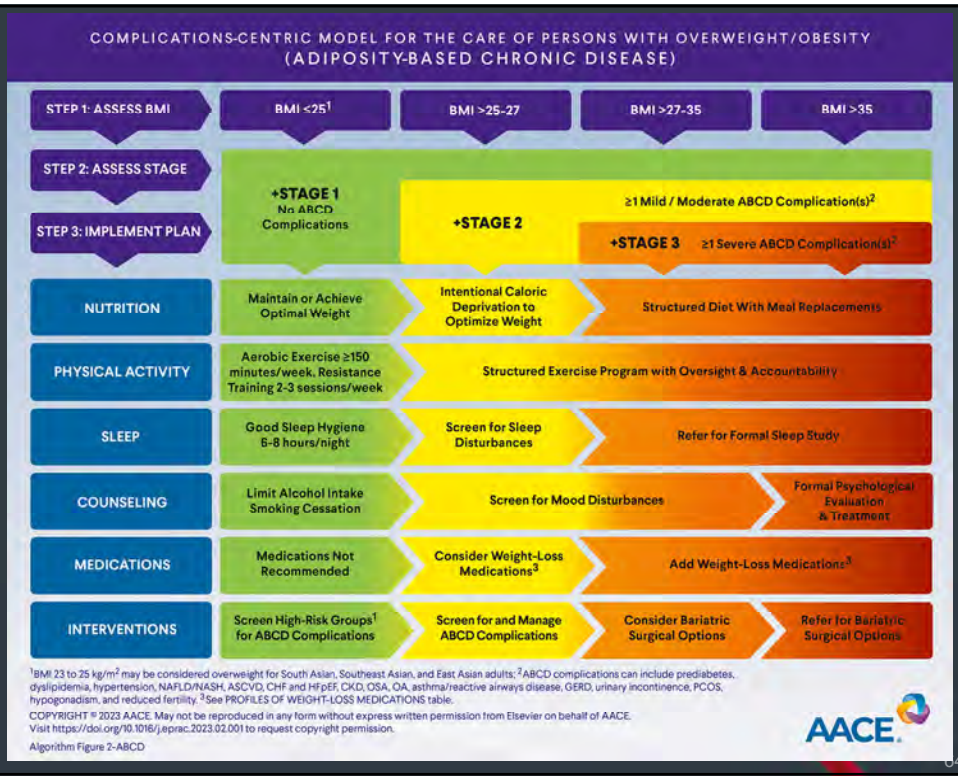
Patient Population	Reduce risk of:	Dosing
Adults with T2D and chronic kidney disease associated with T2D	Sustained eGFR decline, ESRD, renal death	10mg – 20mg based on baseline eGFR
Generally focused on albuminuria	HR: 0.82 *(0.73-0.93; p = 0.001)*	Adjustments based on K levels after 4 weeks and periodically thereafter
Studied in patients on max tolerated ACE/ARB	Cardiovascular death, non-fatal MI & hospitalization for HF	
	HR: 0.87 *(0.76-0.98; p = 0.026)*	

Finerenone. Package labeling. Bayer Healthcare Pharmaceuticals, Inc; 2022.

63

63

AACE Obesity Management



Samson SL, et al. *Endocr Pract.* 2023;29(5):305-340.

64

64

Inflation Reduction Act – Pricing

Over the next 4 years, Medicare will negotiate prices for up to 60 medications covered under Medicare Part D and Part B, and up to an additional 15-20 medications every year after that.

Medications will be selected each year from the 50 drugs with the highest total Medicare Part D and Part B spending

Exclusions:

- "Small biotech drugs"
- All plasma-derived products
- Drugs with Medicare spending < $200 million in 2021 *(increased each year)*
- Drugs < 9 years *(small-molecule)* or < 13 years *(biologic)* from FDA-approval date
- Drugs with generic or biosimilar
- Drugs with orphan designation

Cubanski J, et al. *KFF*. Published January 24, 2023. Accessed September 22, 2023.

65

65