Update on Incretin-Based Therapy

Jennifer Green, MD
Professor of Medicine
Division of Endocrinology, Metabolism, and Nutrition
Duke University Medical Center
Duke Clinical Research Institute
Durham, NC

CONTINUING EDUCATION COMPANY

1

Disclosure

Consultant: Anji; Astra Zeneca; Bayer; Boehringer Ingelheim; Lilly; Novo Nordisk; Valo; Vertex

Grant Recipient: Bluedrop; Boehringer Ingelheim; Lilly

Research Grant: Merck; Roche

CONTINUING EDUCATION COMPANY

2

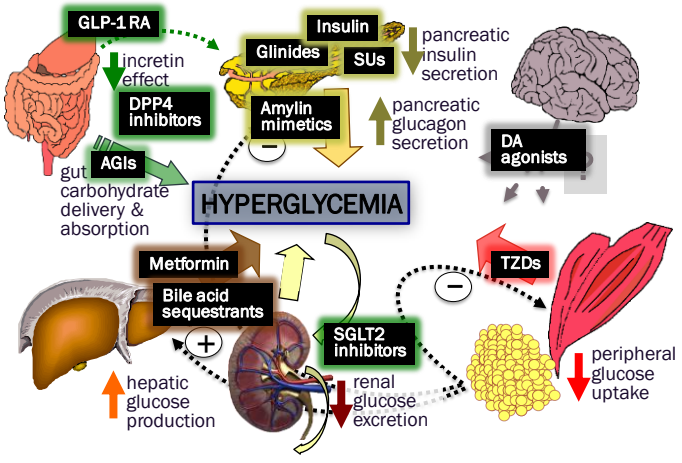
Overview

- Incretin physiology
- Incretin-based therapy in type 2 diabetes
  - Metabolic control
  - Cardiorenal risk reduction
- GLP-1RA therapy in obesity
- Dual agonist therapy (tirzepatide)
- On the horizon

3

Complex Pathophysiology of Hyperglycemia in T2DM

GLP-1 RAs, DPP4 inhibitors work through the incretin system to improve glycemia but do not restore the incretin effect

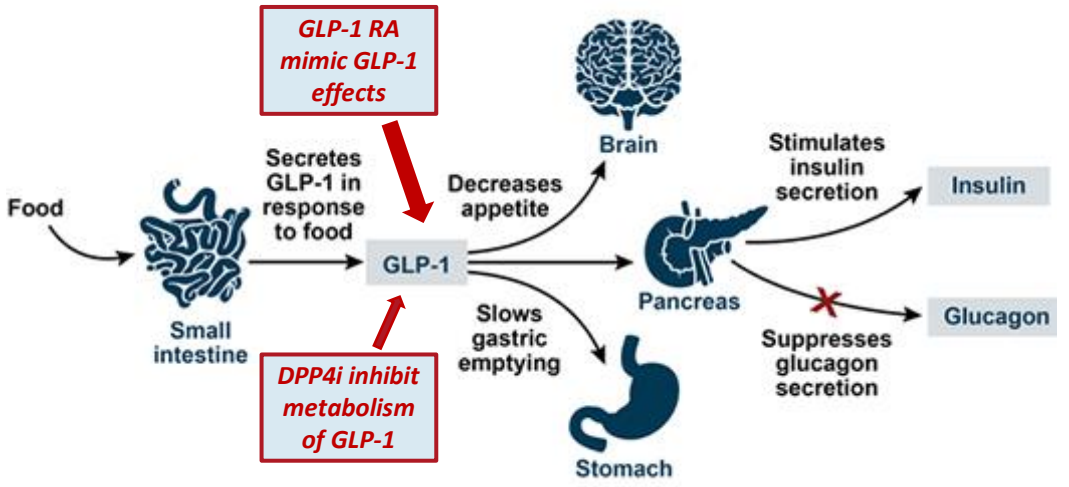


T2DM = type 2 diabetes mellitus; GLP-1 RA = glucagon-like peptide 1 receptor agonist; DPP2 = dipeptidyl-peptidase 4; AGI = alpha-glucosidase inhibitors; SU = sulfonylurea; DA = dopamine; TZD = thiazolidinediones; SGLT2 = sodium-glucose cotransporter-2

Adapted from: Inzucchi SE, Sherwin RS in: *Cecil Medicine*. Saunders; 2011. Nauck MA. *Lancet Diabetes Endocrinol.* 2016;4:525-536.

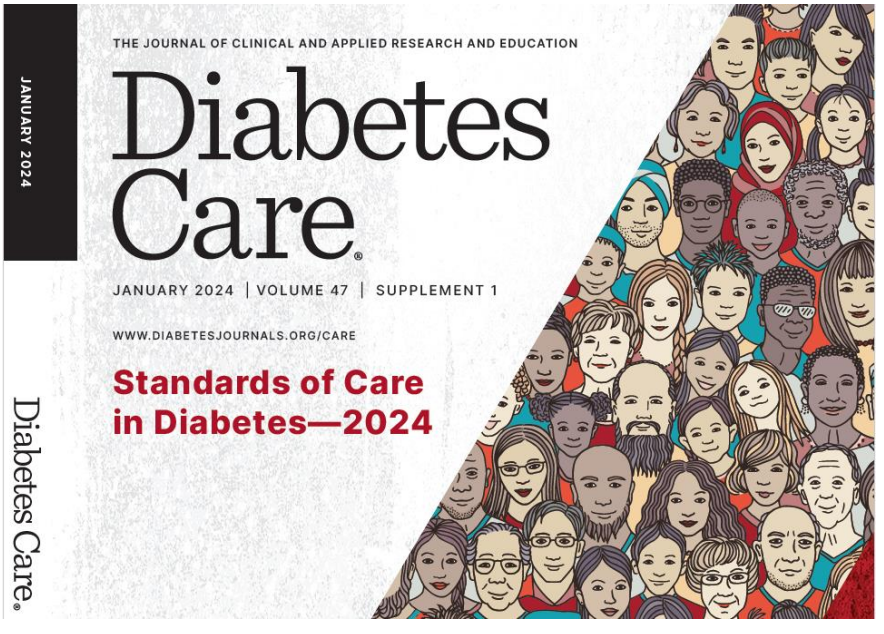
4

Effects of Incretin-Based Therapy



Meier JJ et al. Nat Rev Endocrinol. 2012

5



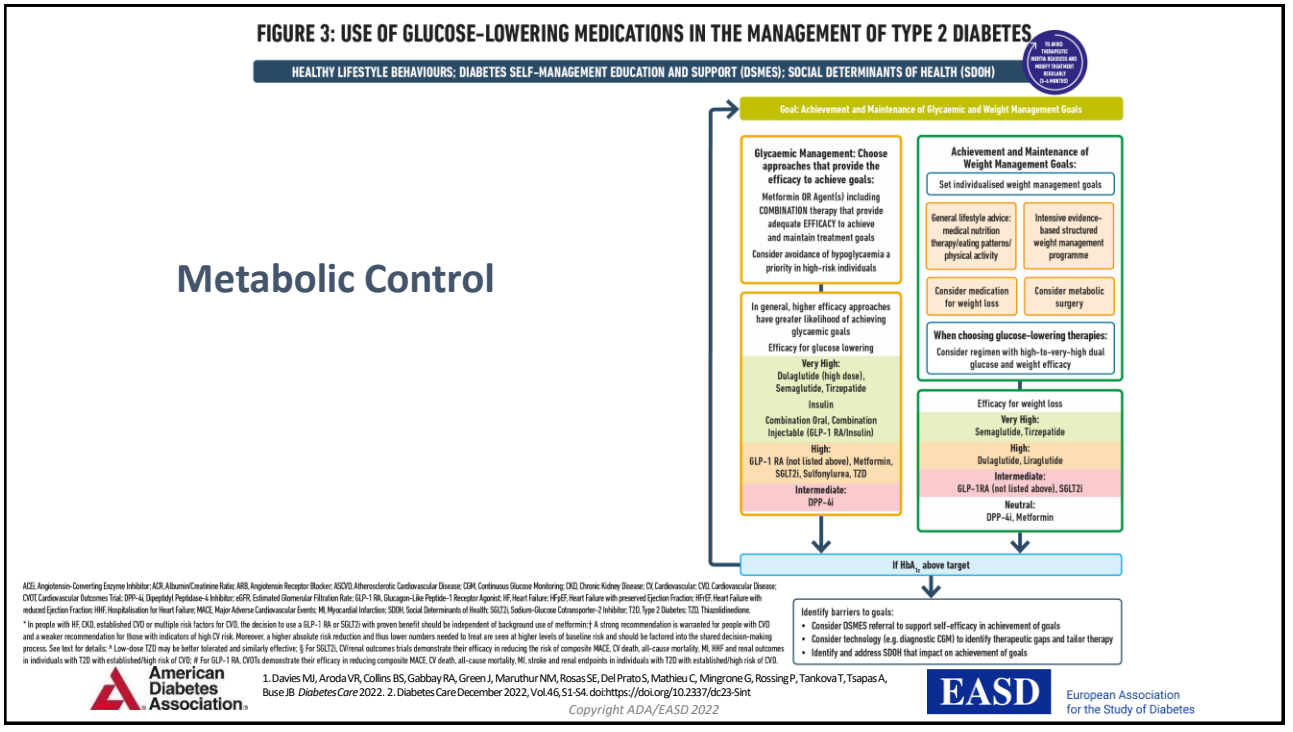
6


FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES
HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CVrenal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.
American Diabetes Association
1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint
Copyright ADA/EASD 2022
EASD
European Association for the Study of Diabetes

7


FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES
HEALTHY LIFESTYLE BEHAVIOURS; DIABETES SELF-MANAGEMENT EDUCATION AND SUPPORT (DSMES); SOCIAL DETERMINANTS OF HEALTH (SDOH)
Goal: Cardiorenal Risk Reduction in High-Risk Patients with Type 2 Diabetes (In addition to comprehensive CV risk management)*
Goal: Achievement and Maintenance of Glycaemic and Weight Management Goals
ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CVrenal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.
American Diabetes Association
1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint
Copyright ADA/EASD 2022
EASD
European Association for the Study of Diabetes

8



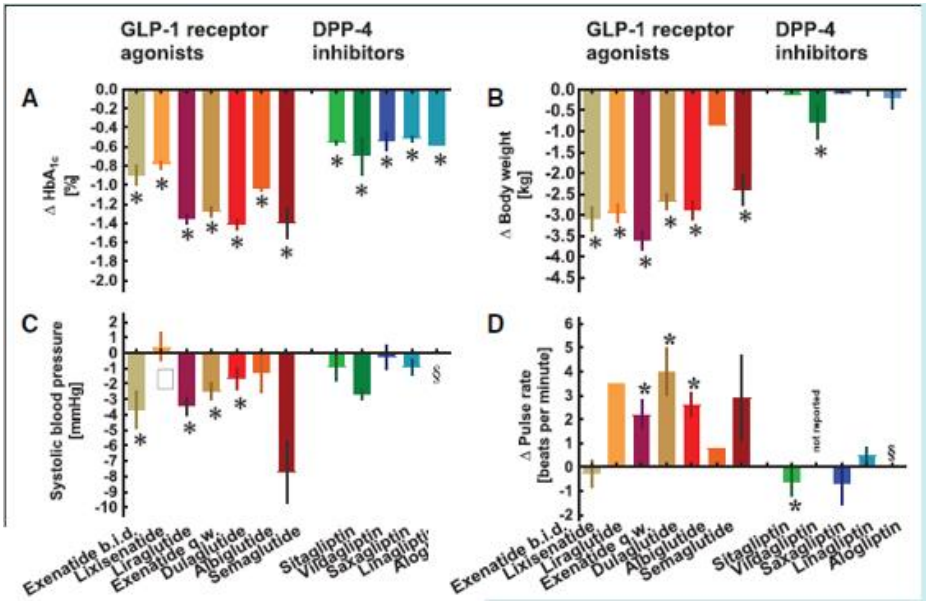
1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

9

Effects of Treatment with GLP-1 RA and DPP-4 Inhibitors

HbA1c

SBP



Weight

HR

Nauck MA, et al. Circulation. 2017 Aug 29;136(9):849-870. doi: 10.1161/CIRCULATIONAHA.117.028136. PMID: 28847797.

10

Pharmacologic Approaches to Glycemic Treatment – ADA SOC

Pharmacologic Therapy for Adults With Type 2 Diabetes

- In adults with type 2 diabetes, **a GLP-1RA, including a dual GIP and GLP-1RA, is preferred to insulin**. **A**
- **If insulin is used, combination therapy with a GLP-1RA or dual GIP and GLP-1RA is recommended** for greater glycemic effectiveness, and weight and hypoglycemia benefit. **A**

https://diabetesjournals.org/care/issue/47/Supplement_1

11

Available Long-acting GLP-1 and Dual Receptor Agonists for T2DM

	Once daily		Once weekly			
	Liraglutide (Victoza)	**Semaglutide (Rybelsus)**	**Exenatide ER (Bydureon and Bydureon BCise)**	**Dulaglutide (Trulicity)**	**Semaglutide (Ozempic)**	**Tirzepatide (Mounjaro)** Dual agonist
Admin.	Injectable	Oral	Injectable	Injectable	Injectable	Injectable
Receptor Agonist	GLP-1	GLP-1	GLP-1	GLP-1	GLP-1	GLP-1/GIP
Common Adverse Reactions	**Nausea, diarrhea, vomiting,** decreased appetite, constipation	**Nausea, diarrhea, vomiting,** abdominal pain, decreased appetite, constipation	Bydureon: **nausea, diarrhea, vomiting,** headache, constipation, injection-site pruritus or nodule, dyspepsia Bydureon BCise: injection site nodules, **nausea**	**Nausea, diarrhea, vomiting,** abdominal pain, decreased appetite	**Nausea, diarrhea, vomiting,** abdominal pain, constipation	**Nausea, vomiting, diarrhea**, decreased appetite

GIP, gastric inhibitory peptide. Table adapted from Chun JH, Butts A. *JAAPA*. 2020;33(S8 Suppl 1):3-18.

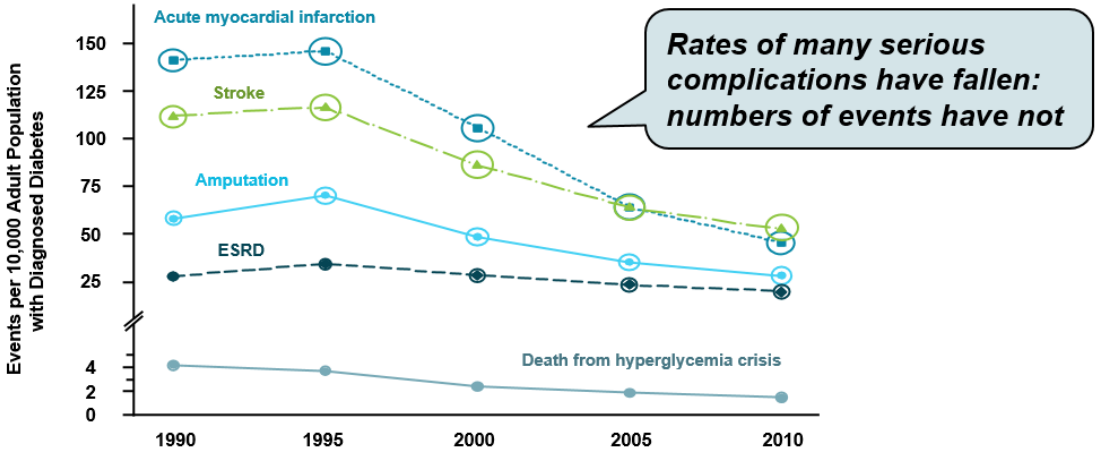
12

Incretin-Based Therapy and Cardiorenal Risk Reduction in Type 2 Diabetes

13

Impact of Traditional Risk Reduction Strategies in Diabetes

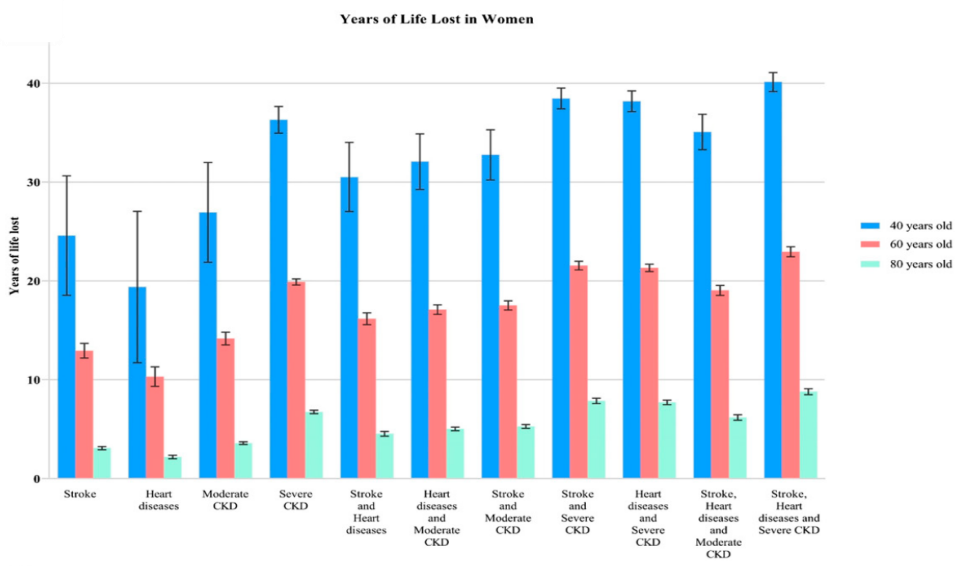
Focus on control of BP, lipids, glucose



Gregg EW, Li Y, et al. NEJM 370(16) pp 1514-1523. April, 2014

14

Years of Life Lost by Diabetes Comorbidity



Wan EYF et al. The Impact of Cardiovascular Disease and Chronic Kidney Disease on Life Expectancy and Direct Medical Cost in a 10-year Diabetes Cohort Study Diabetes Care Publish Ahead of Print, published online May 26, 2020

15

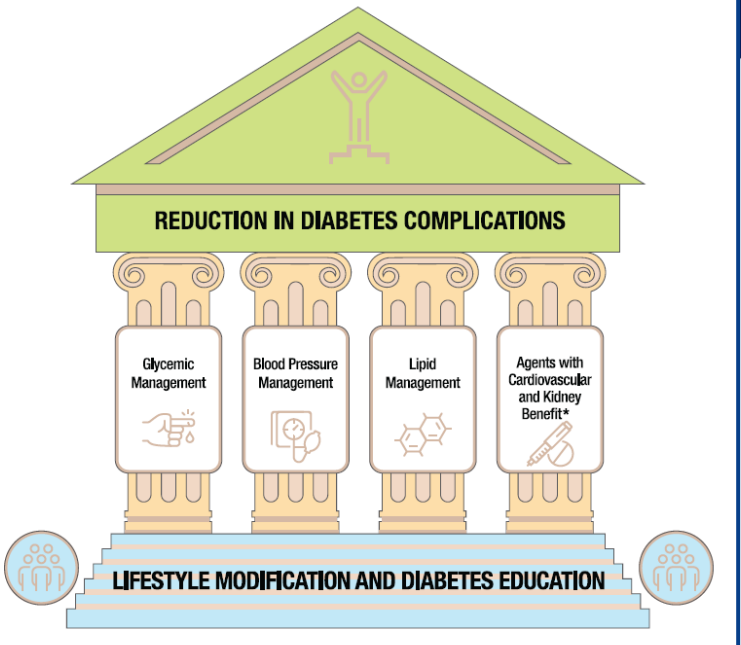


Figure 10.1—Multifactorial approach to reduction in risk of diabetes complications. *Risk reduction interventions to be applied as individually appropriate.

Multifactorial Approach to Risk Reduction

https://diabetesjournals.org/care/issue/47/Supplement_1

16

Known Effects of Incretin Therapies on MACE

DPP-4 inhibitor	SAVOR TIMI-53 saxagliptin	EXAMINE alogliptin	TECOS sitagliptin	CARMELINA linagliptin		
	Neutral	Neutral	Neutral	Neutral		
GLP-1 agonist	LEADER liraglutide	ELIXA lixisenatide	SUSTAIN-6 semaglutide **injection**	EXSCEL exenatide once weekly	REWIND dulaglutide	AMPLITUDE-O Efpeglenatide*
	Beneficial	Neutral	Beneficial	Neutral	Beneficial	Beneficial

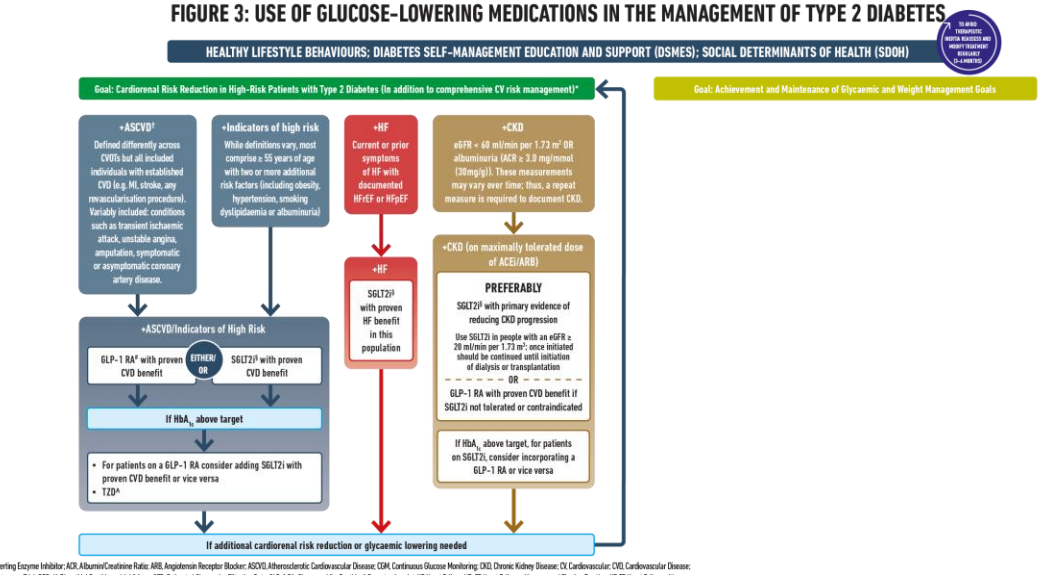
DPP4i: no significant effects on major adverse CV events (MACE)
GLP-1RA: several available agents significantly reduce risk of MACE

*Efpeglenatide not presently available for clinical use

All trials listed enrolled patients with T2DM and established atherosclerotic CV disease, or multiple risk factors for the same. REWIND enrolled many patients with multiple risk factors rather than established ASCVD. Harmony trial of the GLP-1 RA albiglutide also showed benefit, but not shown because no longer marketed.

17

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ACEi, Angiotensin-Converting Enzyme Inhibitor; ACR, Albumin/Creatinine Ratio; ARB, Angiotensin Receptor Blocker; ASCVD, Atherosclerotic Cardiovascular Disease; CGM, Continuous Glucose Monitoring; CKD, Chronic Kidney Disease; CV, Cardiovascular; CVD, Cardiovascular Disease; CVOT, Cardiovascular Outcomes Trial; DPP-4i, Dipeptidyl Peptidase-4 Inhibitor; eGFR, Estimated Glomerular Filtration Rate; GLP-1 RA, Glucagon-Like Peptide-1 Receptor Agonist; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HFrEF, Heart Failure with reduced Ejection Fraction; HHF, Hospitalisation for Heart Failure; MACE, Major Adverse Cardiovascular Events; MI, Myocardial Infarction; SDOH, Social Determinants of Health; SGLT2i, Sodium-Glucose Cotransporter-2 Inhibitor; T2D, Type 2 Diabetes; TZD, Thiazolidinedione.

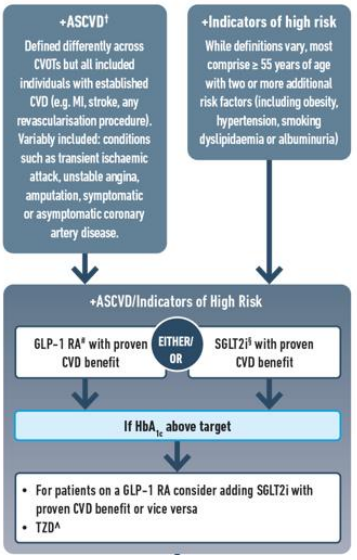
* In people with HF, CKD, established CVD or multiple risk factors for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin; † A strong recommendation is warranted for people with CVD and a weaker recommendation for those with indicators of high CV risk. Moreover, a higher absolute risk reduction and thus lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. See text for details; ^ Low-dose TZD may be better tolerated and similarly effective; § For SGLT2i, CVrenal outcomes trials demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, HHF and renal outcomes in individuals with T2D with established/high risk of CVD; # For GLP-1 RA, CVOTs demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and renal endpoints in individuals with T2D with established/high risk of CVD.

1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

American Diabetes Association. EASD European Association for the Study of Diabetes

18

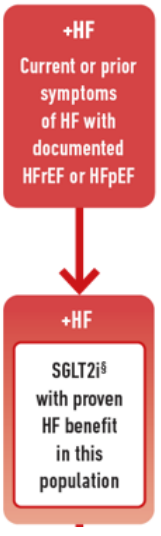
Choosing Glucose-lowering Medication in People with High ASCVD Risk



1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

19

Choosing Glucose-lowering Medication in People with Heart Failure



1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

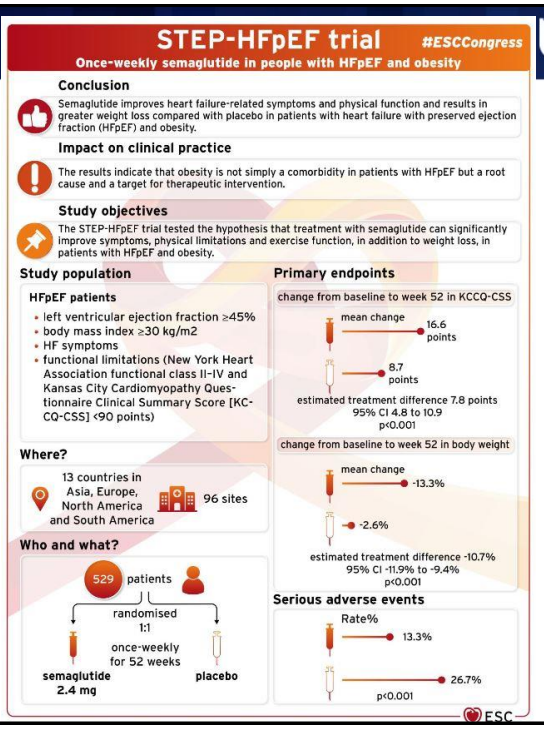
20

STEP-HFpEF Trial

Effects of GLP-1RA therapy on symptoms and physical function in HFpEF

- Semaglutide treatment of HFpEF patients
  - + obesity, +HF symptoms
- Results
  - Semaglutide increased KCCQ-CSS by 16.6 points (ETD 7.8 pts vs. PBO)
  - Semaglutide decreased body weight by 13.3% (ETD -10.7% vs. PBO)
  - No increase in SAEs vs. PBO

Kosiborod et al. NEJM online first August 25, 2023.
DOI: 10.1056/NEJMoa2306963



21

STEP-HFpEF Diabetes Trial

Effects of GLP-1RA therapy on symptoms and physical function in HFpEF + T2D

- Semaglutide treatment of HFpEF patients
  - + obesity, +HF symptoms, +T2D
- Results
  - Semaglutide increased KCCQ-CSS by 13.7 points (ETD 7.3 pts vs. PBO)
  - Semaglutide decreased body weight by 9.8% (ETD -6.4% vs. PBO)
  - No increase in SAEs vs. PBO

N Engl J Med. 2024 Apr 18;390(15):1394-1407. doi: 10.1056/NEJMoa2313917. Epub 2024 Apr 6. PMID: 38587233

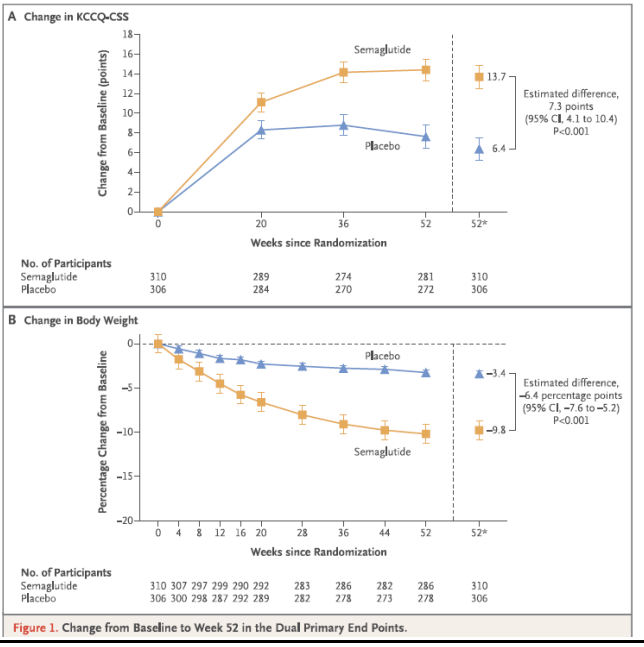
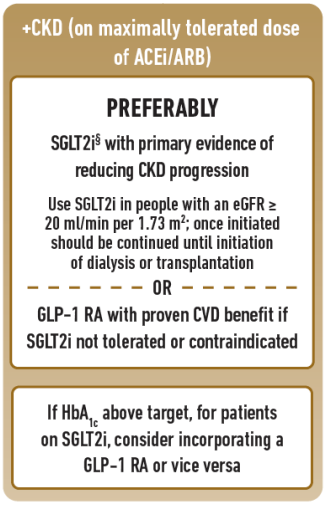


Figure 1. Change from Baseline to Week 52 in the Dual Primary End Points.

22

Choosing Glucose-lowering Medication in People with Chronic Kidney Disease



American Diabetes Association.

1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

EASD European Association for the Study of Diabetes

23

FLOW Study of Semaglutide in T2D with CKD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes

Vlado Perkovic, M.B., B.S., Ph.D., Katherine R. Tuttle, M.D., Peter Rossing, M.D., D.M.Sc., Kenneth W. Mahaffey, M.D., Johannes F.E. Mann, M.D., George Bakris, M.D., Florian M.M. Baeres, M.D., Thomas Idorn, M.D., Ph.D., Heidrun Bosch-Traberg, M.D., Nanna Leonora Lausvig, M.Sc., and Richard Pratley, M.D., for the FLOW Trial Committees and Investigators*

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

24

FLOW Study of Semaglutide in T2D with CKD

Methods

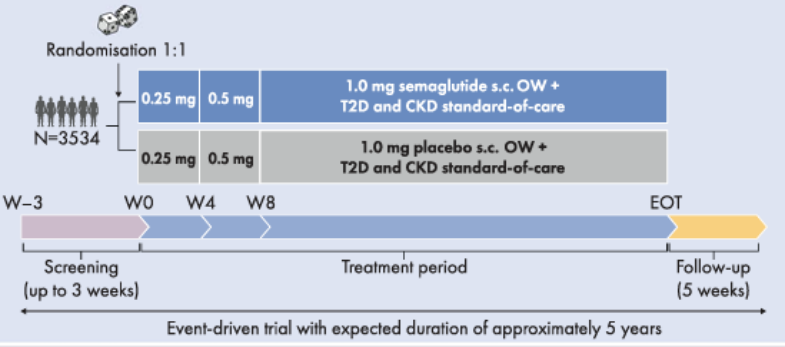
Participants:

- Adults with T2D
- eGFR ≥50 to ≤75 ml/min/1.73 m² and UACR >300 to <5000 mg/g OR
- eGFR ≥25 to <50 ml/min/1.73 m² and UACR >100 to <5000 mg/g

Composite primary endpoint:

Time to first occurrence of:

- Kidney failure (persistent eGFR <15 ml/min/1.73 m² or initiation of CKRT);
- Persistent ≥50% reduction in eGFR; or
- Death from kidney or CV causes



Baseline characteristics

68.2% at very high risk for CKD progression according to KDIGO categorisation, eGFR of 47.0 (15) ml/min/1.73 m²; median UACR of 568 (range: 2–11 852) mg/g

Advanced type 2 diabetes:
Mean age 66.6 years
Mean diabetes duration 17.4 years
Mean HbA_{1c} 7.8%

15.5% receiving SGLT-2is

CKD, chronic kidney disease; CKRT, chronic kidney replacement therapy; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EOT, end of treatment; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycosylated haemoglobin; KDIGO, Kidney Disease: Improving Global Outcomes; OW, once weekly; s.c., subcutaneous; SGLT-2i, sodium-glucose cotransporter-2 inhibitor; T2D, type 2 diabetes; UACR, urine albumin-to-creatinine ratio; W, week.

Nephrol Dial Transplant. 2023 Aug 31;38(9):2041-2051. doi: 10.1093/ndt/gfad009. PMID: 36651820; PMCID: PMC10469096.

25

FLOW Study of Semaglutide in T2D with CKD

Outcome	Semaglutide (N=1767)	Placebo (N=1766)	Hazard Ratio (95% CI)	Estimated Difference (95% CI)	P Value
Primary outcome: major kidney disease events — no. (%)†	331 (18.7)	410 (23.2)	0.76 (0.66 to 0.88)	—	0.0003
Components of primary outcome — no. (%)					
Persistent ≥50% reduction from baseline in eGFR	165 (9.3)	213 (12.1)	0.73 (0.59 to 0.89)	—	—
Persistent eGFR <15 ml/min/1.73 m²	92 (5.2)	110 (6.2)	0.80 (0.61 to 1.06)	—	—
Initiation of kidney-replacement therapy	87 (4.9)	100 (5.7)	0.84 (0.63 to 1.12)	—	—
Death from kidney-related causes	5 (0.3)	5 (0.3)	0.97 (0.27 to 3.49)	—	—
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Composite of kidney-specific components of the primary outcome	218 (12.3)	260 (14.7)	0.79 (0.66 to 0.94)	—	—
Confirmatory secondary outcomes					
Mean annual rate of change in eGFR — ml/min/1.73 m²	−2.19	−3.36	—	1.16 (0.86 to 1.47)	<0.001
Major cardiovascular events — no. (%)	212 (12.0)	254 (14.4)	0.82 (0.68 to 0.98)	—	0.029
Death from cardiovascular causes	123 (7.0)	169 (9.6)	0.71 (0.56 to 0.89)	—	—
Nonfatal myocardial infarction	52 (2.9)	64 (3.6)	0.80 (0.55 to 1.15)	—	—
Nonfatal stroke	63 (3.6)	51 (2.9)	1.22 (0.84 to 1.77)	—	—
Death from any cause — no. (%)	227 (12.8)	279 (15.8)	0.80 (0.67 to 0.95)	—	0.01

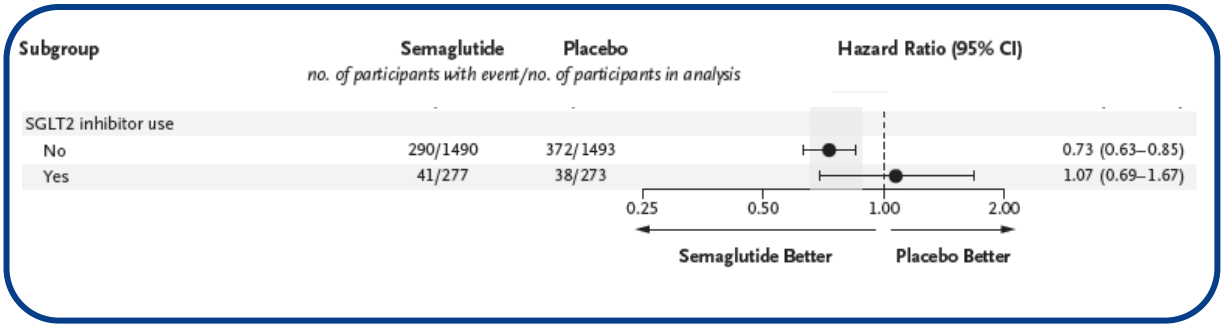
median participant follow-up was 3.4 years

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

26

FLOW Study of Semaglutide in T2D with CKD

What about the effects of combination therapy (semaglutide +/- SGLT2i)?
550 (15.6%) of participants were on an SGLT2i at baseline

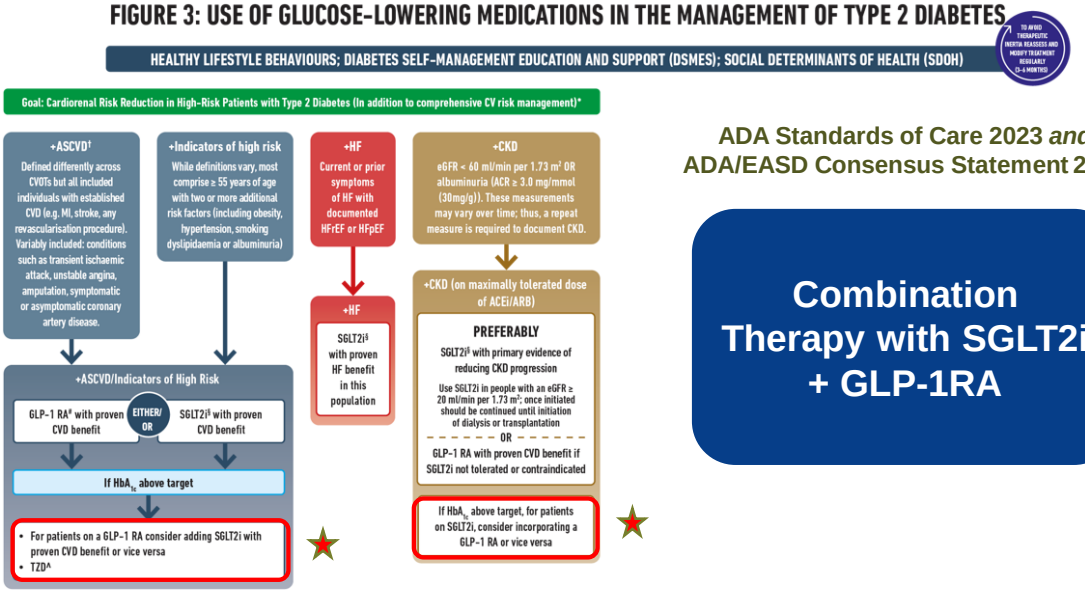


Additional analyses are pending

N Engl J Med. 2024 May 24. doi: 10.1056/NEJMoa2403347. Online ahead of print. PMID: 38785209

27

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES



ADA Standards of Care 2023 *and* ADA/EASD Consensus Statement 2022

Combination Therapy with SGLT2i + GLP-1RA

1. Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB *Diabetes Care* 2022. 2. Diabetes Care December 2022, Vol.46, S1-S4. doi:https://doi.org/10.2337/dc23-Sint

28

GLP-1RA Therapy and Weight Management

29

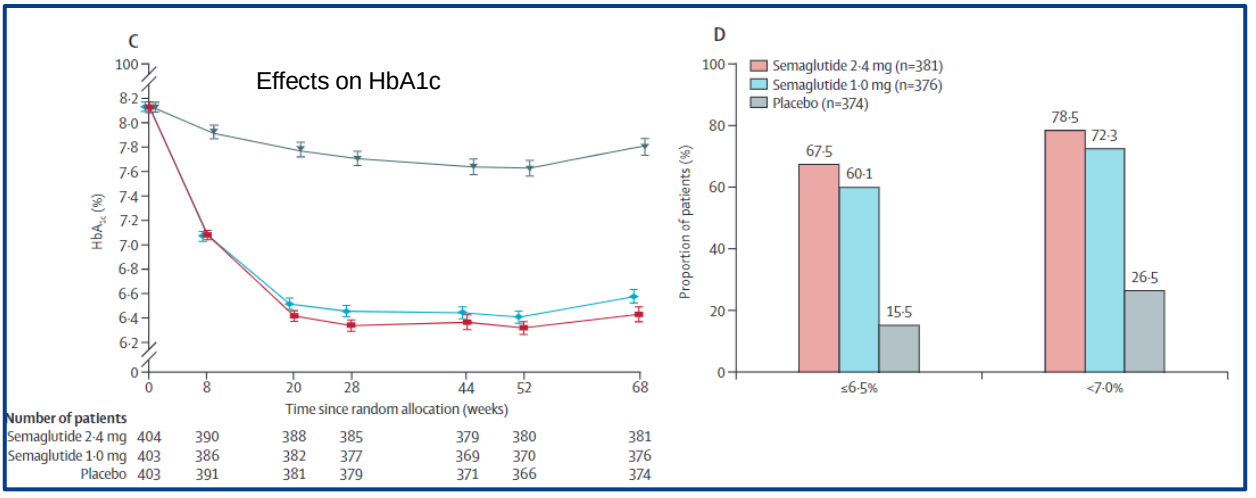
Which One of the Following Patients Has an Indication for Use of an Anti-obesity Medication?

A. Patient with a BMI of 25 kg/m2 and hyperlipidemia
B. Patient with a BMI of 26 kg/m2 and sleep apnea
C. Patient with a BMI of 27 kg/m2 and hypertension
D. Patient with a BMI of 28 kg/m2 and no weight-related comorbidities

Apovian CM, Aronne LJ, Bessesen DH et al. Pharmacological Management of Obesity: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2015;100(2):342-362. https://academic.oup.com/jcem/article/100/2/342/2813109

30

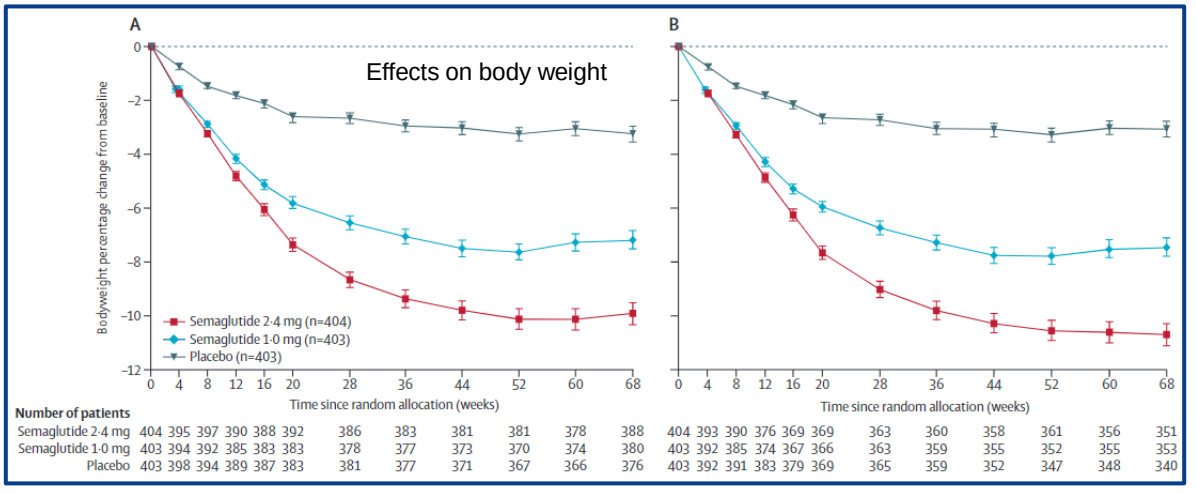
STEP 2: Patients with Overweight or Obesity and T2DM



www.thelancet.com Vol 397 March 13, 2021

31

STEP 2: Patients with Overweight or Obesity and T2DM

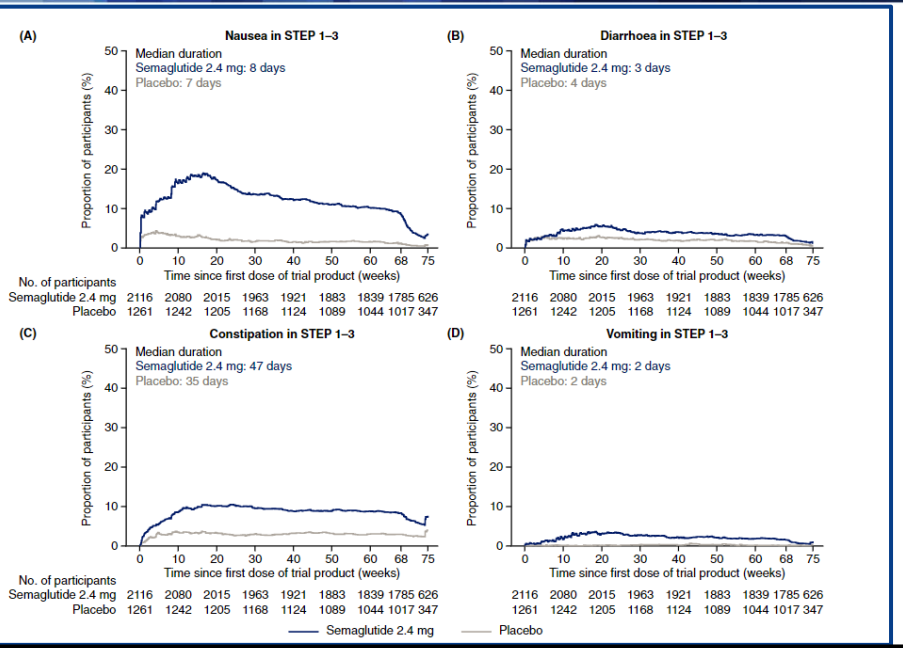


A = full analysis set; B = on-treatment analysis set

www.thelancet.com Vol 397 March 13, 2021

32

Tolerability of High Dose Semaglutide



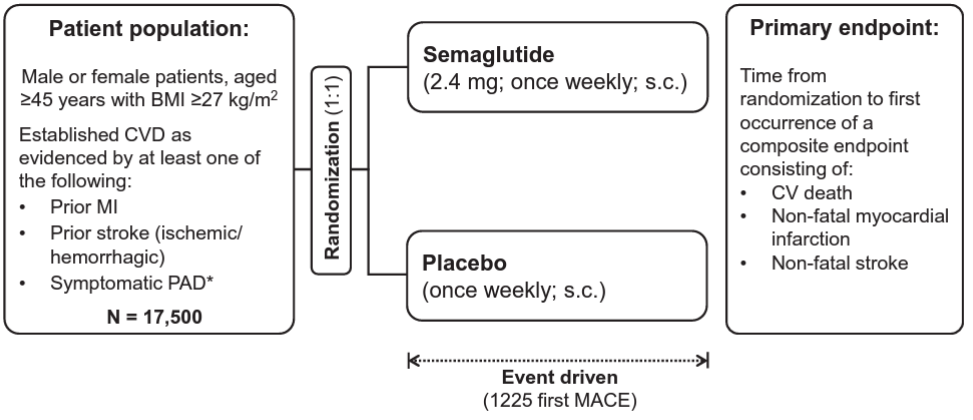
Prevalence of adverse events (nausea, diarrhea, constipation and vomiting) over time in the (A-D) STEP 1-3 trials

The prevalence of nausea, diarrhea and vomiting in the semaglutide 2.4 mg arm peaked at about week 20 and decreased thereafter. Individual nausea, diarrhea and vomiting events were relatively short-lived

Diabetes Obes Metab.2022;24:94–105.wileyonlinelibrary.com/journal/dom

33

SELECT CV Outcomes Trial

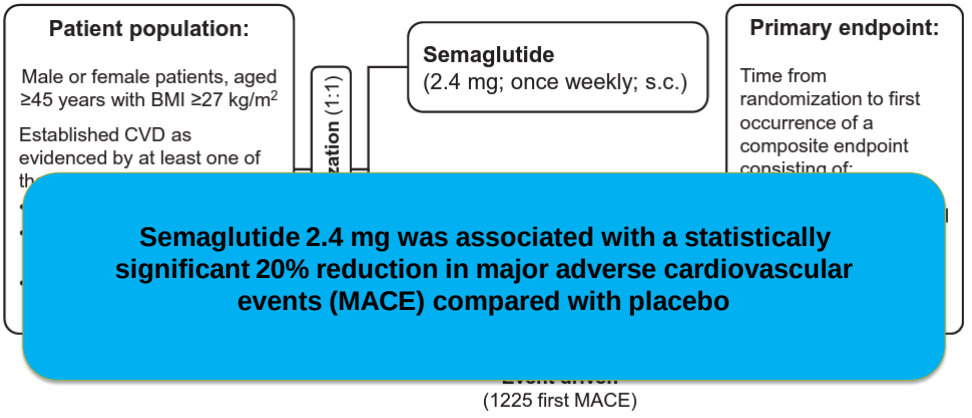


SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design.*Symptomatic PAD defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

AmHeartJ2020;229:61-9

34

SELECT CV Outcomes Trial



Semaglutide 2.4 mg was associated with a statistically significant 20% reduction in major adverse cardiovascular events (MACE) compared with placebo

SELECT: trial design, population, and primary end point. The figure provides a snapshot of key components of SELECT trial design.*Symptomatic PAD defined as intermittent claudication with ankle-brachial index <0.85 (at rest) **OR** peripheral arterial revascularization procedure **OR** amputation due to atherosclerotic disease.

AmHeartJ2020;229:61-9

35

Dual Agonist Therapy (Tirzepatide)

36

Tirzepatide

Novel dual GLP-1/GIP receptor agonist

- Approved for glycemic control in adults with T2DM as an adjunct to diet and exercise, and for treatment of excess weight
- Not approved for type 1 diabetes mellitus
- 39 amino acid linear and multifunctional peptide based on the native GIP peptide sequence[1]
  - Modified to bind to both GIP and GLP-1 receptors[1] but has higher affinity for GIP receptors than GLP-1 receptors
- Mean half-life: ~5 days, enabling once-weekly dosing[1]

No difference in plasma concentrations between people with renal and hepatic impairment and healthy people[2]

1. Coskun T et al. *Mol Metab*. 2018;18:3-14. 2. Urva S et al. *Diabetes*. 2020;69(suppl 1):Abstract 971-P.

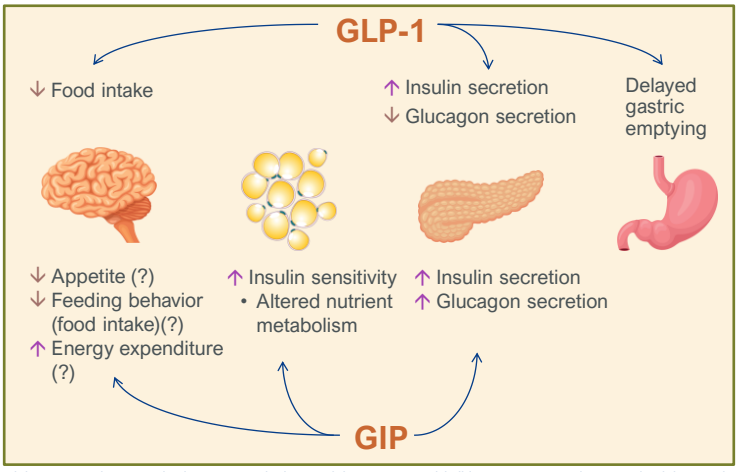
37

GLP-1 & GIP Dual Agonism

Potential synergistic effect

- GLP-1 has suggested direct actions in CNS, islets, and stomach[1,2]
- GIP has shown potential actions in CNS, adipose, and islets[2,3,4]
- A single molecule GIP/GIP-1 receptor dual agonist may enable improved physiology over the sum of its individual agonist components[5,6]

CNS = central nervous system



1. Müller TD et al. *Mol Metab.* 2019;30:72-130. 2. Seino Y et al. *J Diabetes Investig*. 2010;1(1-2):8-23. 3. Fukuda M. *Diabetes*. 2021;70(8):dbi210001. 4. Nauck MA et al. *Diabetes Obes Metab*. 2021 (ahead of print). doi:10.1111/dom.14496. 5. Samms RJ et al. *Trends Endocrinol Metab.* 2020;31(6):410-421. 6. Bastin M et al. *Diabetes Metab Syndro Obes.* 2019;12:1973-1985.

38

Tirzepatide (TZP): SURPASS Trials in T2DM

Monotherapy	**SURPASS-1:** TZP vs placebo[1] Drug-naïve or washout from any OAM
2-drug combination	**SURPASS-2:** TZP vs semaglutide[2] Add-on to metformin
2-3–drug combination	**SURPASS-3:** TZP vs insulin degludec[3] Add-on to metformin with or without SGLT2 inhibitor
2-4–drug combination	**SURPASS-4:** TZP vs insulin glargine[4] Add-on to ≥1 and ≤3 OAMs (metformin, SGLT2 inhibitor, or SU)
Combination with insulin	**SURPASS-5:** TZP vs placebo[5] Both with insulin glargine with or without metformin **SURPASS-6:** TZP vs insulin lispro[6] (TID) Both with insulin glargine with or without metformin (ongoing)

SURPASS-CVOT[7]

Head-to-head trial comparing tirzepatide vs dulaglutide

>12,000 participants (ongoing)

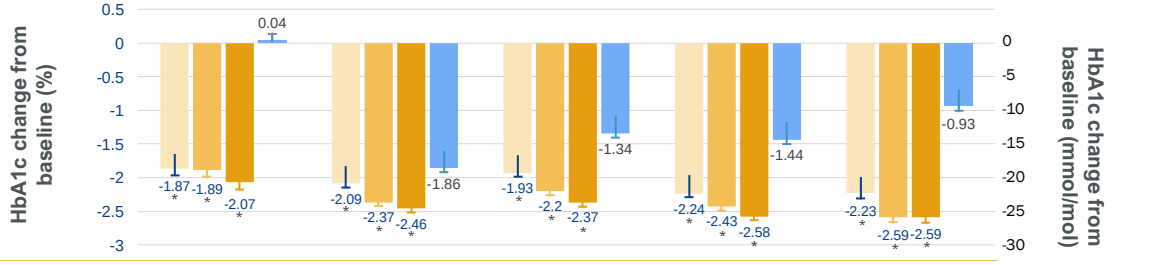
OAM, oral antihyperglycemic medication; sodium-glucose cotransporter 2 inhibitor, SGLT2 inhibitor; SU, sulfonylurea; TID, 3 times daily

1. Rosenstock J et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato et al. *Lancet*. 2021;(Accepted). 5. Dahl D et al. Poster presented at ADA 2021. Poster LB-20. 6. NIH. Accessed 8/17/21. https://clinicaltrials.gov/ct2/show/NCT04537923 (accessed Aug 17, 2021). 7. NIH. Accessed 8/17/21. https://clinicaltrials.gov/ct2/show/study/NCT04255433

39

SURPASS: HbA1c Change from Baseline

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Duration	40 weeks	40 weeks	52 weeks	52 weeks	40 weeks
Baseline HbA1c	7.9%	8.3%	8.2%	8.5%	8.3%
N	478	1,878	1,437	1,995	475



Superiority vs	Placebo	SEMA 1 mg	Insulin degludec	Insulin glargine	Placebo
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET

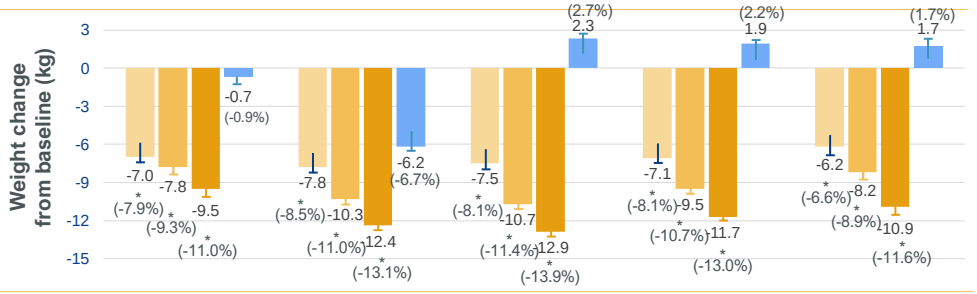
*$P<0.001$ vs placebo or active comparator. Data are LSM (SE). mITT population (efficacy analysis set). MMRM analysis. Data labels are % HbA1c. LSM, least squares mean; mITT, modified intent-to-treat; MMRM, mixed model repeated measures; SEMA, semaglutide

1. Rosenstock J et al. *Lancet*. 2021;398(10295):143-155. 2. Frias JP et al. *N Eng J Med*. 2021;385(6):503-515. 3. Ludvik B et al. *Lancet*. 2021;398(10300):583-598. 4. Del Prato S et al. *Lancet*. 2021;(Accepted). 5. Dahl D et al. Poster presented at: *ADA* 2021. Poster LB-20. Graph adapted Eli Lilly and Company, 2021.

40

SURPASS: Body Weight Change from Baseline

Study	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Duration	40 weeks	40 weeks	52 weeks	52 weeks	40 weeks
Baseline Weight (kg)	85.9	93.7	94.3	90.3	95.3



Superiority vs	Placebo	Semaglutide 1 mg	Insulin degludec	Insulin glargine	Placebo
Background therapy	Monotherapy	Add-on to MET	Add-on to MET or MET + SGLT2i	Add-on to MET, SGLT2i, or SU	Add-on to insulin glargine ± MET

*P<0.001 vs placebo or active comparator. Data are LSM (SE); mITT population (efficacy analysis set). MMRM analysis.

1. Rosenstock J et al. *Lancet.* 2021;398(10295):143-155. 2. Frias JP et al. *N Eng J Med.* 2021;385(6):503-515. 3. Ludvik B et al. *Lancet.* 2021;398(10300):583-598.
4. Del Prato S et al. *Lancet.* 2021;(Accepted). 5. Dahl D et al. Poster presented at: *ADA* 2021. Poster LB-20. Graph adapted from Eli Lilly and Company, 2021.

41

Tirzepatide Safety and Tolerability

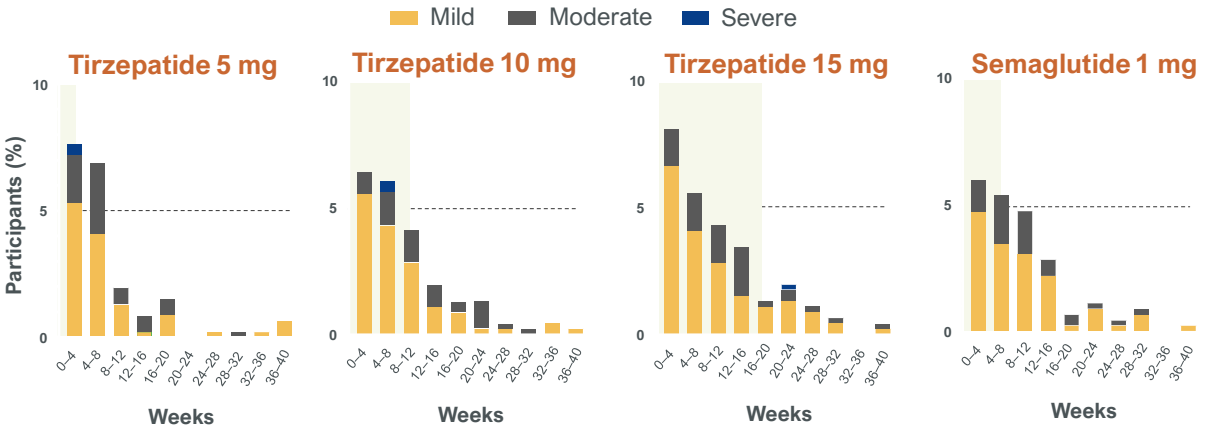
Parameters	SURPASS-1[1]	SURPASS-2[2]	SURPASS-3[3]	SURPASS-4[4]	SURPASS-5[5]
Pancreatitis[a]	0	2 (TZP 10 mg) 2 (TZP 15 mg) 3 (SEMA 1 mg)	0	3 (TZP 5 mg) 2 (TZP 10 mg) 1 (TZP 15 mg) 1 (insulin glargine)	0
Cholelithiasis	1 (TZP 5 mg)	4 (TZP 5 mg) 4 (TZP 10 mg) 4 (TZP 15 mg) 2 (SEMA 1 mg)	2 (TZP 5 mg) 1 (TZP 10 mg) 1 (TZP 15 mg)	3 (TZP 5 mg) 1 (TZP 10 mg) 1 (TZP 15 mg) 4 (insulin glargine)	1 (TZP 5 mg)
Medullary thyroid carcinoma	0	0	0	0	0
Diabetic retinopathy	0	2 (TZP 10 mg)	2 (TZP 5 mg) 1 (TZP 10 mg)	2 (TZP 5 mg) 1 (TZP 10 mg) 1 (TZP 15 mg) 1 (insulin glargine)	0

[a]Adjudication-Confirmed.

1. Rosenstock J et al. *Lancet.* 2021;398(10295):143-155. 2. Frias JP et al. *N Eng J Med.* 2021;385(6):503-515. 3. Ludvik B et al. *Lancet.* 2021;398(10300):583-598.
4. Del Prato S et al. *Lancet.* 2021;398(10313):1811-1824. 5. Dahl D et al. *JAMA*. 2022;327(6):534-545.

42

SURPASS-2: Time Course of Nausea During Trial



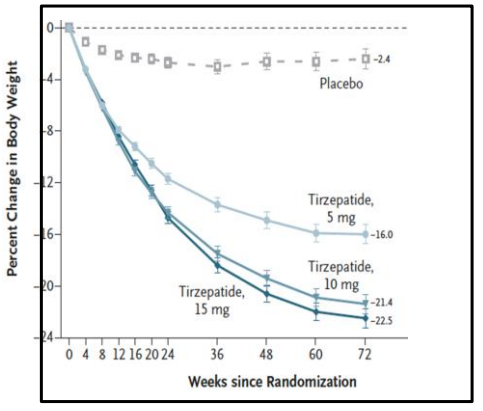
Most cases of nausea were mild to moderate, transient, and occurred during the dose-escalation period in all groups

mITT population (safety analysis set); shaded areas show the time before reaching the maintenance dose of the study treatments.
Frias JP et al. *N Engl J Med*. 2021;385:503-515 and supplement.

43

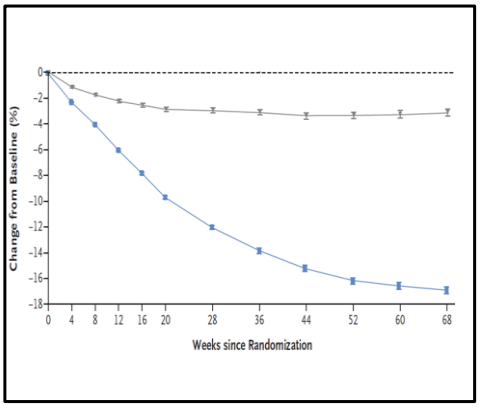
Dual Incretin Therapy in Obesity

Tirzepatide



A Jastreboff, NEJM 2022

Semaglutide



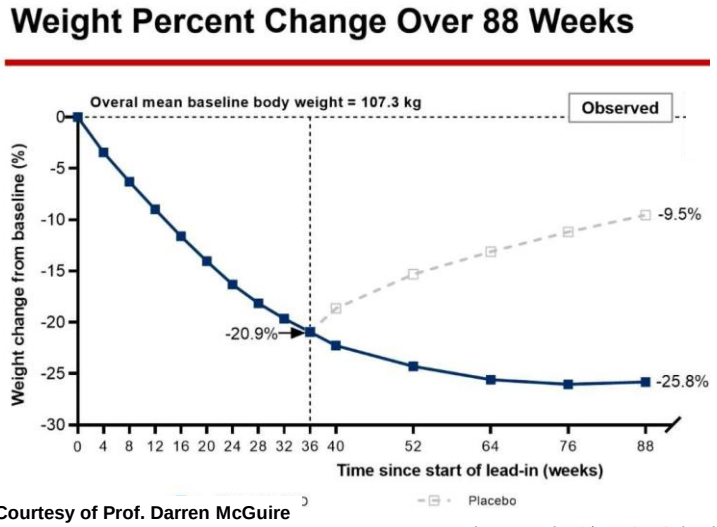
J Wilding, NEJM 2021

44

SURMOUNT-4 Topline Results: Randomized Withdrawal of Tirzepatide

N=783
BMI >30kg/m^2; or >27kg/m^2 + ≥comorbidity

Without Diabetes



UTSouthwestern Medical Center Parkland

Courtesy of Prof. Darren McGuire

Holst JJ et al. 59th EASD Scientific Sessions 2023; NCT04660643

45

GLP-1 RA vs Dual Incretin Therapy in T2DM

GLP-1 receptor agonists

- Dosing daily or weekly options
- Subcutaneous injection or oral options
- Some can significantly reduce risk of CV death, heart attack, and stroke
- Some approved for ages 10 years and older
- Liraglutide and semaglutide also approved for overweight and obesity
- Common side effects: nausea, vomiting, diarrhea, injection site reactions

Dual GLP-1/GIP receptor agonist

- Dosing once weekly
- Subcutaneous injection
- Cardiovascular outcomes trial ongoing
- Approved for adults
- Tirzepatide now approved for overweight and obesity
- Common side effects: nausea, diarrhea, injection site reactions

46

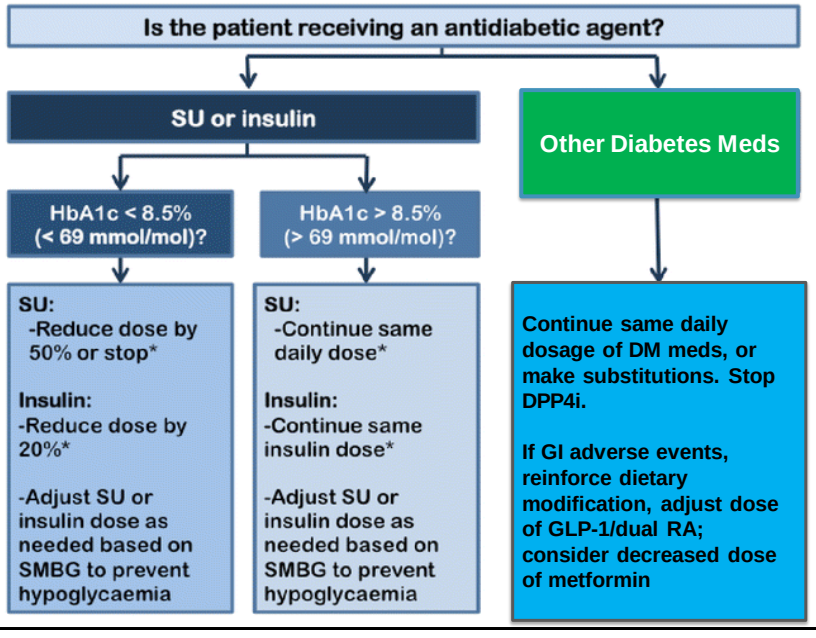
Key Considerations in Use Of GLP-1RA or Combination Rx

- Should not be used in those with MEN2, MTC, or family history of MTC
- Should not be combined with other GLP-1 RAs, insulin/GLP-1 combinations, or DPP4 inhibitors
- Higher risk of hypoglycemia when used concomitantly with insulin or sulfonylureas

MEN2, multiple endocrine neoplasia syndrome type 2; MTC, medullary thyroid carcinoma

47

Adding GLP-1/Dual RA to Other Diabetes Medications



Do not use DPP4i, GLP-1RA, dual incretin agents together

Gomez-Peralta F et al. Diabetes Ther 2017

48

Question #2

A patient with type 2 diabetes and obesity has recently started the GLP-1 receptor agonist semaglutide in addition to her existing metformin therapy. The patient reports that she has been experiencing some nausea since she has up-titrated the dose to 1 mg weekly. However, the nausea is mild with no associated vomiting or diarrhea.

Wharton S, Davies M, Dicker D et al. Managing the Gastrointestinal Side Effects of GLP-1 Receptor Agonists in Obesity: Recommendations for Clinical Practice. Postgrad Med. 2022;134(1):14-19. https://www.tandfonline.com/doi/full/10.1080/00325481.2021.2002616

What Do You Recommend?

A. Change from semaglutide to tirzepatide
B. Eat something at all mealtimes even if not hungry
C. Use ondansetron as needed for the next two weeks
D. Avoid meals with a high fat content

Wharton S, Davies M, Dicker D et al. Managing the Gastrointestinal Side Effects of GLP-1 Receptor Agonists in Obesity: Recommendations for Clinical Practice. Postgrad Med. 2022;134(1):14-19. https://www.tandfonline.com/doi/full/10.1080/00325481.2021.2002616

Managing GI Side Effects from Incretin Agonists

- Most common are nausea, vomiting, and diarrhea or constipation
- Typically occur during initiation and up-titration
- Counsel patients on potential for these side effects when prescribing
- Follow gradual dose escalation per prescribing instructions
  - (ok to go more slowly!)
- If symptoms are persistent or severe, pause dose escalation and rule out any other underlying GI disorders
- If lower dose not tolerated, consider switching to alternative agent
- Stop treatment if none of the above have worked to ease side effects

Wharton S et al. *Postgrad Med.* 2022;134(1):14-19.

51

Managing GI Side Effects from Incretin Agonists

Dietary modifications for all GI side effects:

- Reduce meal size, stop eating once full
- Avoid eating when not hungry
- Avoid high fat or spicy food
- Moderate alcohol intake

Constipation: increase fiber and water intake, consider stool softeners

Gastroesophageal reflux disease (GERD): consider proton pump inhibitor (PPI) or H2 blockers

Nausea: an antiemetic could be considered for short-term use

Wharton S et al. *Postgrad Med.* 2022;134(1):14-19.

52

Managing GI Side Effects from Incretin Agonists

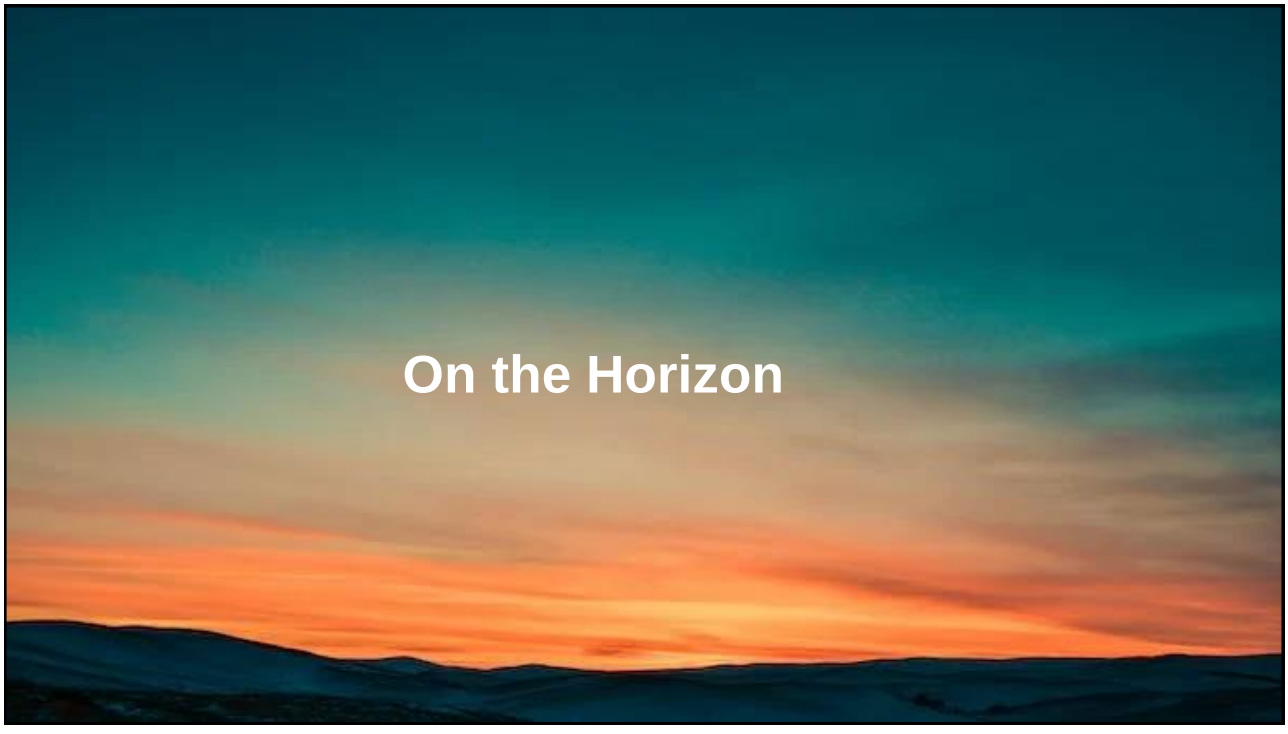
Some anesthesiology societies have recommended that GLP-1RA/dual incretin agonists be held prior to surgery.

However, subsequent analyses of large claims databases have found no association between GLP-1RA use and adverse respiratory events in patients undergoing emergency surgery.

One such example analyzed outcomes in 23 679 patients, 3502 (14.8%) of whom had a GLP-1 RA fill in the Merative MarketScan Commercial Database. Overall incidence of postoperative respiratory complications was 3.5% for those with a GLP-1 RA fill and 4.0% for those without, with no significant difference in outcomes (both overall and following adjustment).

JAMA. 2024 May 21;331(19):1672-1673. doi: 10.1001/jama.202

53



54

More Incretin and Other Combination Drugs

Other combination treatments are in development

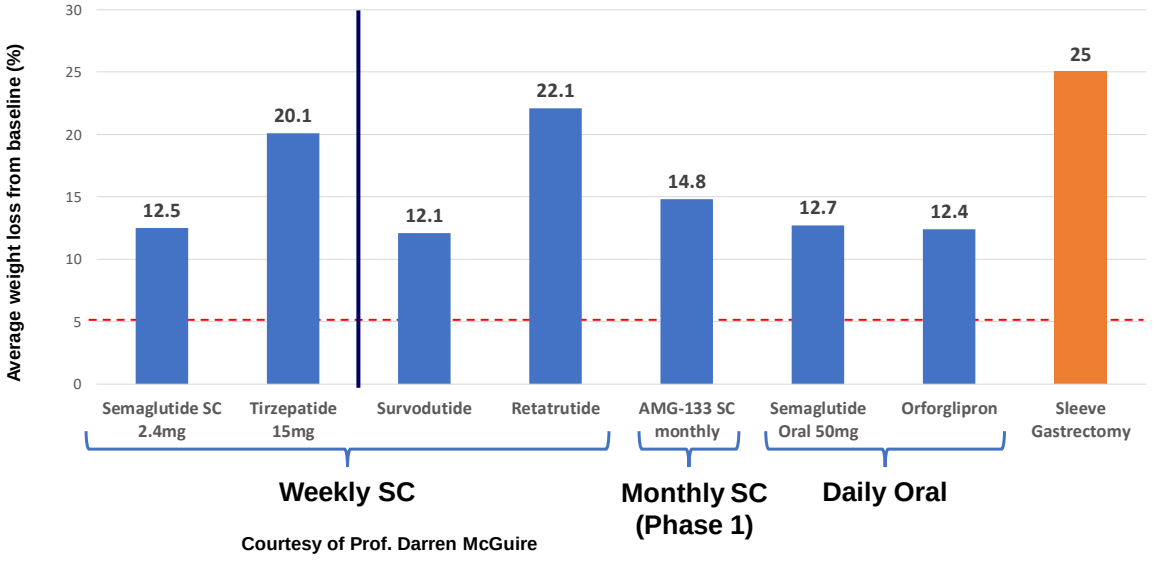
- GLP-1/glucagon dual agonist
- GLP-1 and amylin analogue combination
- GLP-1/GIP/glucagon tri-agonist (*data on retatrutide presented at ADA*)
- GLP-1 RA, oxyntomodulin and peptide YY combination

GLP-1, glucagon-like peptide 1; GIP, glucose-dependent insulinotropic polypeptide; RA, receptor agonist

Kakouri A et al. *Pharmaceuticals (Basel)*. 2021;14(9):869.

55

Average Weight Loss Achieved with Obesity Pharmacotherapies and Sleeve Gastrectomy



Courtesy of Prof. Darren McGuire

56

Upcoming Trials

- **SURPASS-CVOT**[1]: Head-to-head trial comparing tirzepatide (dual GLP-1+ GIP RA) vs dulaglutide >12,000 participants
- **SOUL**[2]: CV outcomes trial of oral semaglutide
- **PRECIDENT D**[3]: Outcomes trial comparing impact of SGLT2i, GLP-1RA, or both in patients with T2DM and ASCVD

(1)https://clinicaltrials.gov/ct2/show/study/NCT04255433 (2) https://clinicaltrials.gov/ct2/show/NCT03914326 (3) https://clinicaltrials.gov/ct2/show/NCT05254002

57

Conclusions

- Incretin-based therapies are important tools in the management of T2D
- GLP-1RA have significant efficacy in both weight loss and glucose-lowering
- Certain GLP-1RA provide cardiorenal outcomes benefit to:
  - T2D patients with or at high risk for ASCVD, or with CKD
  - People with overweight/obesity and established ASCVD
- Dual incretin therapy with a GLP/GIP RA provides very high potency in glucose, weight lowering. The CVOT of tirzepatide is ongoing, but CV and kidney outcomes data available to date are reassuring.

58