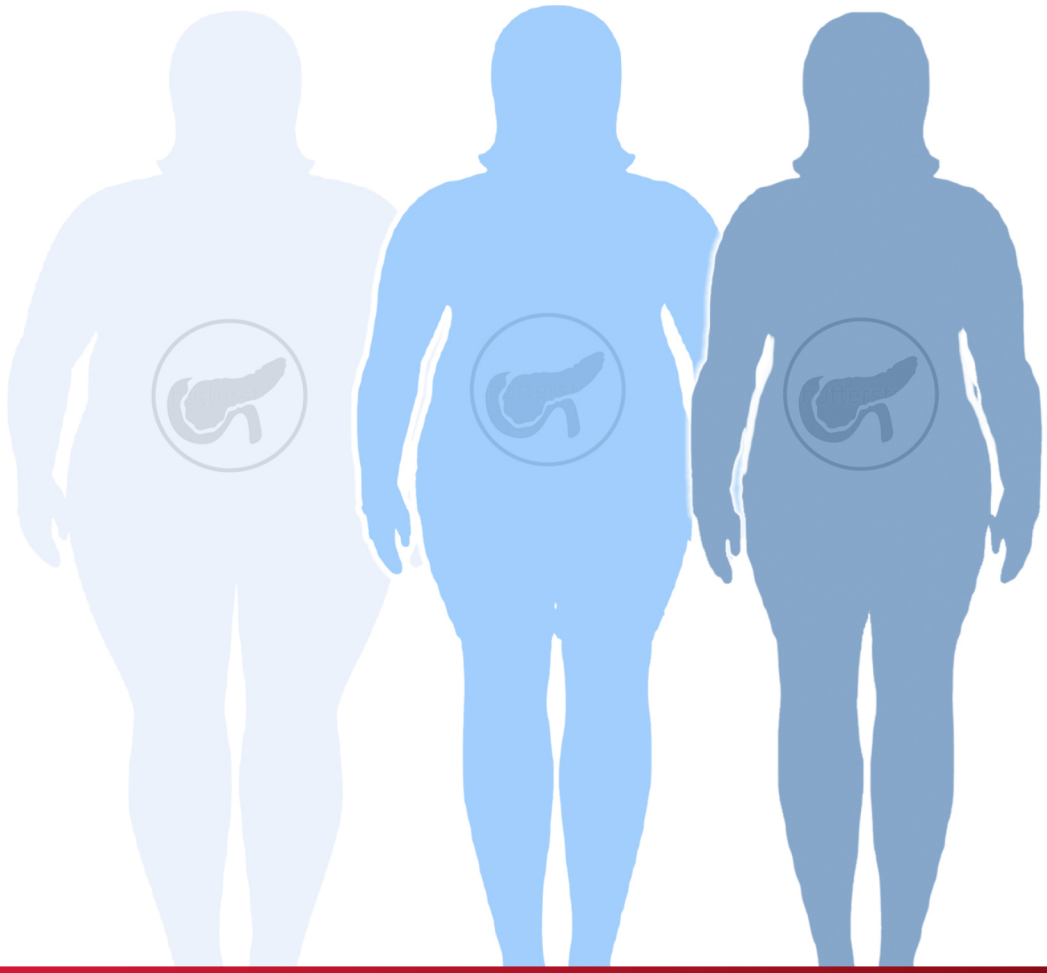

A HOLISTIC APPROACH TO **DIABETES CARE:**

Reducing HbA1c and Weight with Emerging Pharmacotherapies

SUMMIT MEETING
December 6, 2021
6:00 PM – 7:30 PM Eastern

FACULTY

Silvio E. Inzucchi, MD
Director, Yale Medicine Diabetes Center
Professor of Medicine, Endocrinology
Yale University School of Medicine
New Haven, CT

Anne L. Peters, MD
Professor of Medicine
Keck School of Medicine
University of Southern California
Westside Center for Diabetes
Los Angeles, CA

This activity is provided by Med Learning Group.
This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).
This activity is supported by an educational grant from Lilly.

A Holistic Approach to Diabetes Care: Reducing HbA1c and Weight with Emerging Pharmacotherapies

Time	Agenda
6:00-6:08 pm	**1. Type 2 Diabetes: An Overview** a. Epidemiology of type 2 diabetes (T2DM) b. Pathophysiological abnormalities in T2DM
6:09-6:28	2. **Diabetes Treatment and Complication Prevention** a. Complications of diabetes b. Treatment guidelines for T2DM c. Considering patient-specific factors when selecting therapies d. Holistic management of patients with T2DM i. Reducing cardiovascular events ii. Encouraging lifestyle changes iii. Managing hypertension and lipids
6:29-6:39	3. **Questions and answers**
6:40-6:55	**4. Improving Metabolic Outcomes** a. Case study b. Impact of obesity on patients with type 2 diabetes c. Strategies to encourage weight loss d. Effect of weight loss on glycemic outcomes e. Pharmacologic agents that reduce weight
6:56-7:05	**5. The Incretin System in Health and Disease** a. Review of the incretin hormones ***b. Whiteboard animation: Effects of GIP and GLP-1 in healthy individuals*** c. Clinical considerations for selecting between agents d. Adjusting other antihyperglycemic therapies when initiating GLP-1 RAs
7:06-7:18	**6. Emerging Incretin Therapy Options** ***a. Whiteboard animation: Pre-clinical data on the benefits of targeting both GIP and GLP-1*** b. Clinical trial data on the efficacy and safety of emerging dual GIP/GLP-1 receptor agonists **c.** Case study
7:18-7:20	**7. Conclusions**
7:21-7:30	**8. Questions and answers**

A Holistic Approach to Diabetes Care:

Reducing HbA1c and Weight with Emerging Pharmacotherapies

CO-CHAIRS

Silvio E. Inzucchi, MD
Director, Yale Medicine Diabetes Center
Professor of Medicine, Endocrinology
Yale University School of Medicine
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Anne L. Peters, MD
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LEARNING OBJECTIVES

- Select therapies for the improvement of glycemic and extra-glycemic outcomes in patients with T2DM.
- Determine the rationale for targeting GIP and GLP-1 receptors in the treatment of type2 diabetes and its metabolic comorbidities.
- Identify patients in their own practice who may potentially benefit from treatments targeting GIP and GLP-1 receptors in the future based on knowledge of recent clinical data

TARGET AUDIENCE

This educational activity is intended for a global audience of endocrinologists, primary care physicians, NPs, PAs, nurses, and other clinicians involved in the treatment of patients with type 2 diabetes mellitus (T2DM).

ACCREDITATION STATEMENT

Med Learning Group is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

CREDIT DESIGNATION STATEMENT

Med Learning Group designates this live activity for a maximum of 1.5 *AMA Category 1 Credit(s)*™. Physicians should claim only the credit commensurate with the extent of their participation in the virtual live activity.

NURSING CREDIT INFORMATION

Purpose: This program would be beneficial for nurses involved in the care of patients with type 2 diabetes mellitus. CNE Credits: 1.5 ANCC Contact Hours.

ACCREDITATION STATEMENT

Ultimate Medical Academy/Complete Conference Management (CCM) is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center's Commission on Accreditation. Awarded 1.5 contact hour(s) of continuing nursing education of RNs and APNs.

CNE ACCREDITATION STATEMENT

Ultimate Medical Academy/CCM is accredited as a provider of nursing continuing professional education development by the American Nurses Credentialing Center's Commission on Accreditation.

Awarded 1.5 contact hours of continuing nursing education of RNs and APNs.

COMMISSION ON DIETETIC REGISTRATION This program has received prior approval with the Commission on Dietetic Registration for Dietitians and Registered Dieticians.

DISCLOSURE POLICY STATEMENT In accordance with the Accreditation Council for Continuing Medical Education (ACCME) Standards for Commercial Support, educational programs sponsored by Med Learning Group must demonstrate balance, independence, objectivity, and scientific rigor. All faculty, authors, editors, staff, and planning committee members participating in a MLG-sponsored activity are required to disclose any relevant financial interest or other relationship with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services that are discussed in an educational activity.

DISCLOSURE OF FINANCIAL RELATIONSHIPS

Dr. Inzucchi discloses that he is consultant for Boehringer Ingelheim, AstraZeneca, Sanofi/Lexicon, Novo Nordisk, Merck, vTv Therapeutics, Zafgen, Abbott/Alere, Eisai (TIMI). He has also received royalties from McGraw-Hill and Uptodate and has received salary from Elsevier.

Dr. Peters discloses that she is on the speakers' bureau for Novo Nordisk. She is a consultant for Abbott Diabetes Care, Becton Dickinson, Boehringer Ingelheim, Eli Lilly and Company, Lexicon, Livongo, MannKind, Medscape, Merck, Novo Nordisk, Omada Health, OptumHealth, Sanofi, and Zafgen. Dr. Peters has also received research support from AstraZeneca, Dexcom, and MannKind and donated devices from Abbott Diabetes Care.

The independent reviewers, staff, planners, and managers reported the following financial relationships or relationships to products or devices they or their spouse/life partner have with commercial interests:

CME Content Review

The content of this activity was independently peer reviewed.

The reviewer of this activity has nothing to disclose.

CNE Content Review

The content of this activity was peer reviewed by a nurse reviewer.

Douglas Cox, MSN, MHA, RN

Ultimate Medical Academy/CCM – Lead Nurse Planner

The reviewer of this activity has nothing to disclose

Staff Planners and Managers

Douglas Cox, MSN, MHA, RN, UMA/CCM – LNP, has nothing to disclose.

This activity is co-provided by Ultimate Medical Academy/Complete Conference Management (CCM).

Staff, Planners and Managers

Matthew Frese, General Manager of Med Learning Group has nothing to disclose.

Christina Gallo, SVP, Educational Development for Med Learning Group has nothing to disclose.

Lauren Welch, MA, VP, Outcomes and Accreditation for Med Learning Group has nothing to disclose.

Russie Allen, Outcomes Coordinator for Med Learning Group has nothing to disclose.

Diana Tommasi, PhD, Medical Director, Scientific and Medical Services for Med Learning Group has nothing to disclose.

Melissa A. Johnson, Senior Program Manager for Med Learning Group has nothing to disclose.

Amanda Jenkins, Associate Program Manager for Med Learning Group has nothing to disclose.

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During the course of this lecture, the faculty may mention the use of medications for both FDA-approved and non-approved indications.

METHOD OF PARTICIPATION

There are no fees for participating and receiving CME/CNE credit for this web-based live activity. To receive CME/CNE credit participants must:

1. Read the CME/CNE information and faculty disclosures.
2. Participate in the web-based live activity.
3. Complete and submit the evaluation form to Med Learning Group.

You will receive your certificate after the web-based live activity.

DISCLAIMER

Med Learning Group makes every effort to develop CME activities that are scientifically based. This activity is designed for educational purposes. Participants have a responsibility to utilize this information to enhance their professional development in an effort to improve patient outcomes. Conclusions drawn by the participants should be derived from careful consideration of all available scientific information. The participant should use his/her clinical judgment, knowledge, experience, and diagnostic decision-making before applying any information, whether provided here or by others, for any professional use.

AMERICANS WITH DISABILITIES ACT

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For CME questions, please contact Med Learning Group at info@medlearninggroup.com

Contact this CME provider at Med Learning Group for privacy and confidentiality policy statement information at www.medlearninggroup.com/privacy-policy/

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A Holistic Approach to Diabetes Care: Reducing HbA1c and Weight with Emerging Pharmacotherapies

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Anne L. Peters, MD
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Los Angeles, CA

1

Program Resources

- **SUBMIT YOUR QUESTIONS.** Click on the QUESTIONS button at the bottom middle of your screen to submit your questions.
- **EMAIL ADDRESS.** Anytime after the program, send comments or questions for the faculty to info@medlearninggroup.com.
- **ANIMATIONS.** Access to the whiteboard animations are available as part of this program.
- **POSTER PORTAL.** Access to a complimentary POSTER PORTAL can be found at diabetescares.posterprogram.com
- **WEBSITE**. Find additional resources on our website caresdiabetes.com

You will receive an email that will remind you of these features after the program.

2

Disclosures

- Silvio Inzucchi, MD:
  - **Consultant / Clinical Trial Committees:** AstraZeneca, Boehringer-Ingelheim, Novo Nordisk, Merck/Pfizer, Lexicon, vTv Therapeutics, Abbott, Esperion
  - **Lectures:** AstraZeneca, Boehringer-Ingelheim
- Anne Peters, MD
  - Advisory Boards: Abbott, Astra-Zeneca, Lilly, NovoNordisk, Medscape, Zealand
  - Research: Abbott, Dexcom, Insulet
- During this lecture, faculty may mention the use of medications for both FDA-approved and non-approved indications.
- This activity is supported by an educational grant from Lilly.

3

Learning Objectives

- Select therapies for the improvement of glycemic and extra-glycemic outcomes in patients with type 2 diabetes mellitus (T2DM)
- Determine the rationale for targeting glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptors in the treatment of T2DM and its metabolic comorbidities
- Identify patients in your own practice who may potentially benefit from treatments targeting GIP and GLP-1 receptors in the future, based on knowledge of recent clinical data

4

Pre-test Question #1

Gus has an HbA1c of 8.7% despite treatment with metformin and insulin glargine. His past medical history is significant for hypertension, osteoarthritis of the knee, and obesity (BMI: 32). You recommend that Gus reduce his weight to improve his HbA1c. How much weight should Gus lose in order to improve his glycemia?

a. At least 15 pounds

b. 5%-10% of body weight

c. 15%-20% of body weight

d. To see any glycemic improvements, his BMI must be under 25.

5

Pre-test Question #2

Gus is interested in losing weight but has struggled with weight loss through diet and exercise alone. You recommend modifying Gus's treatment regimen to encourage weight loss and to reduce his HbA1c. Which of the following is LEAST likely to result in significant weight loss?

a. Liraglutide

b. Tirzepatide

c. Semaglutide

d. Exenatide

6

Pre-test Question #3

Which of the following statements regarding GLP-1 and GIP is TRUE?

a. GLP-1 and GIP agonism increases the risk of hypoglycemia.

b. GLP-1 and GIP stimulate insulin release only when blood glucose levels are elevated.

c. Patients with type 2 diabetes oversecrete incretin hormones to compensate for reduced insulin sensitivity.

d. Infusions of GIP alone are able to stimulate the release of insulin.

7

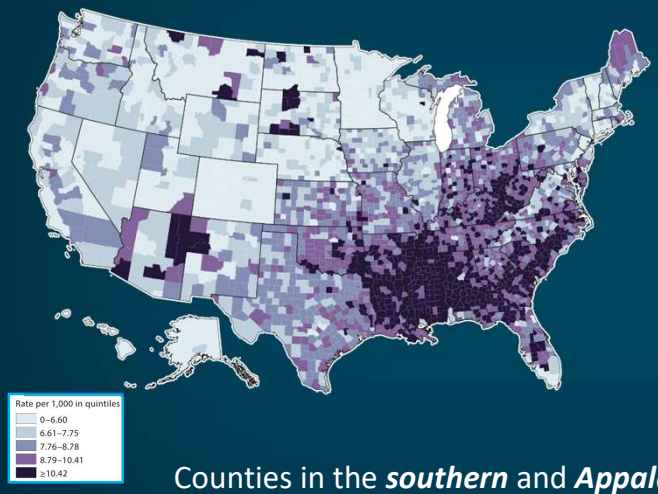
Epidemiology and Pathophysiology of Diabetes

Silvio Inzucchi, MD

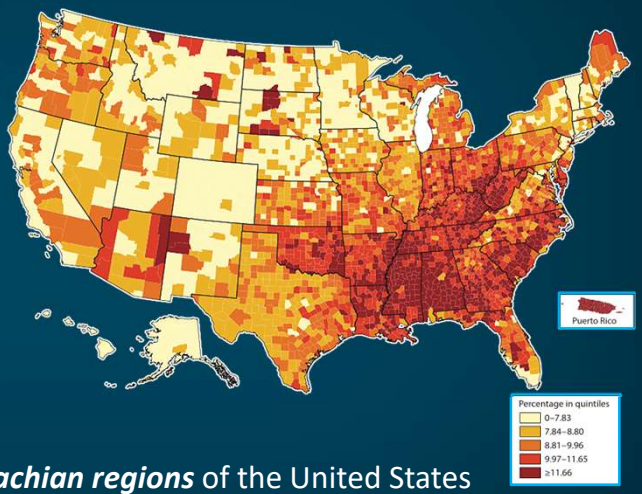
8

Incidence and Prevalence of Diabetes in United States by Region

Diagnosed diabetes **incidence** (2013)



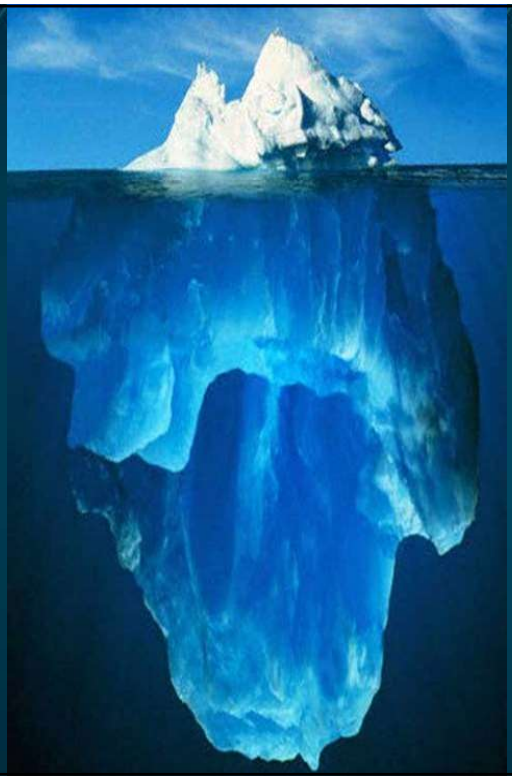
Diagnosed diabetes **prevalence** (2013)



Counties in the ***southern*** and ***Appalachian regions*** of the United States tend to have the highest rates of **incidence** and **prevalence**

Centers for Disease Control and Prevention (CDC). National Diabetes Statistics Report—2017 (https://dev.diabetes.org/sites/default/files/2019-06/cdc-statistics-report-2017.pdf)

9



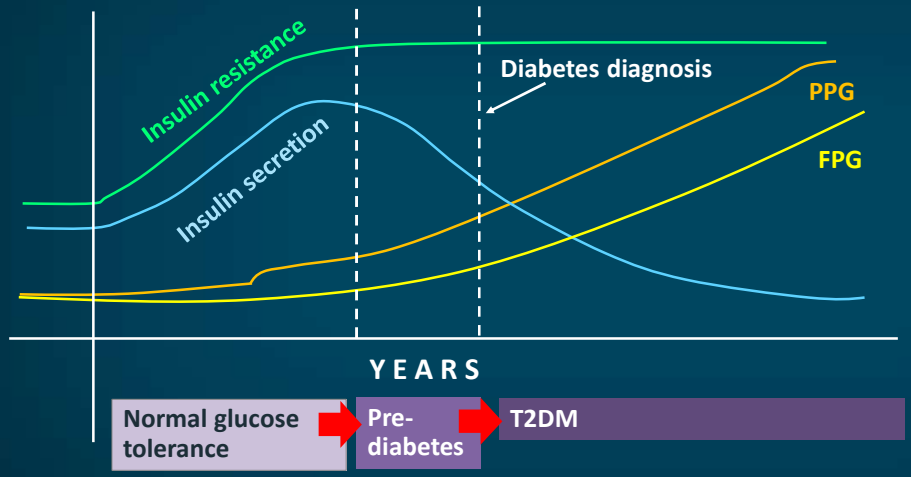
34.1 million US adults with diabetes

88 million US adults with prediabetes

CDC. National Diabetes Statistics Report—2020 (www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf). Accessed 9/14/2021.

10

Progressive β-Cell Dysfunction Is Key Driver of Progressive Dysglycemia in T2DM



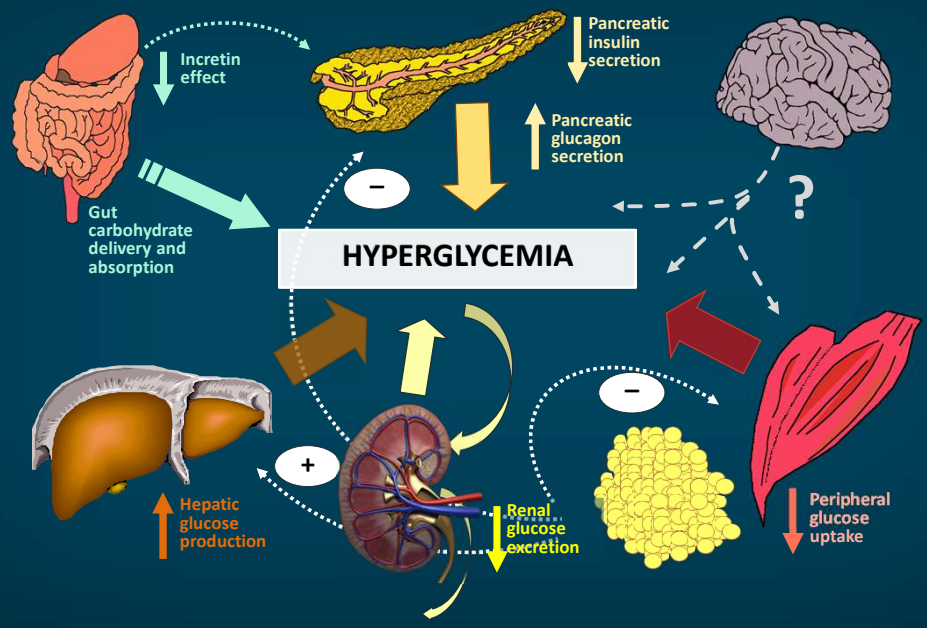
By time of diabetes diagnosis, up to 80% of β-cell function may be lost

T2DM = type 2 DM; PPG = postprandial plasma glucose; FPG = fasting plasma glucose.

Defronzo RA. *Diabetes*. 2009;58:773-795. Fehse F, et al. *J Clin Endocrinol Metab*. 2005;90:5991-5997. Figure modified from Kendall DM, et al. *Am J Med*. 2009;122(6 suppl):S37-S50.

11

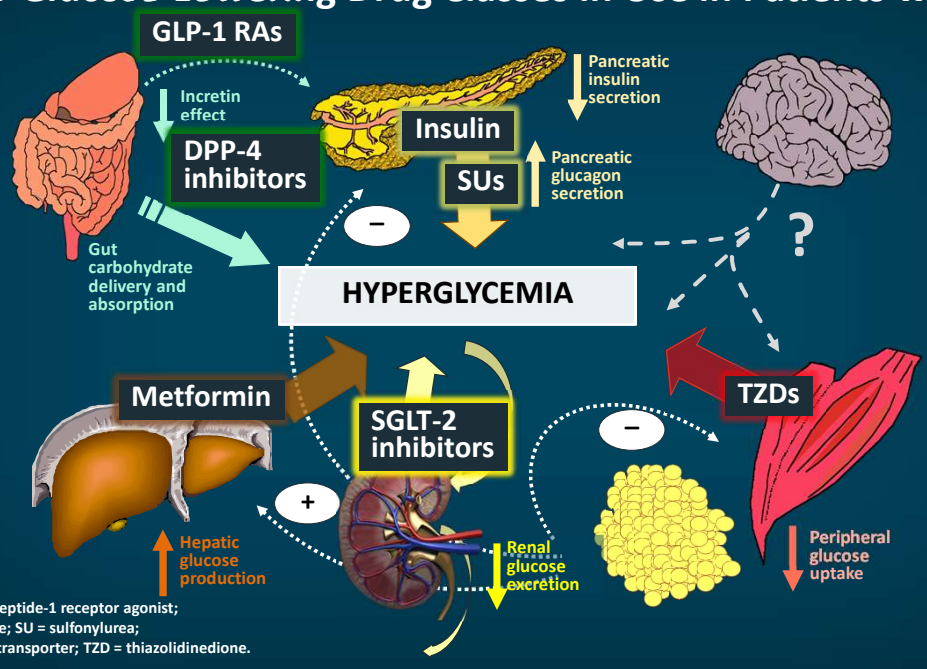
Multiple, Complex Pathophysiological Abnormalities in T2DM



Modified from Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI (eds). *Goldman's Cecil Medicine*, 24th edition. WB Saunders, 2011.

12

7 Major Glucose-Lowering Drug Classes in Use in Patients with T2DM



GLP-1RA = glucagon-like peptide-1 receptor agonist;
DPP = dipeptidyl peptidase; SU = sulfonylurea;
SGLT = sodium-glucose cotransporter; TZD = thiazolidinedione.

Modified from Inzucchi SE, Sherwin RS. Type 2 diabetes mellitus. In: Goldman L, Schafer AI (eds). *Goldman's Cecil Medicine*, 24th edition. WB Saunders, 2011.

13

Diabetes Treatment and Complication Prevention

14

Major Glucose-Lowering Agent Classes for T2DM

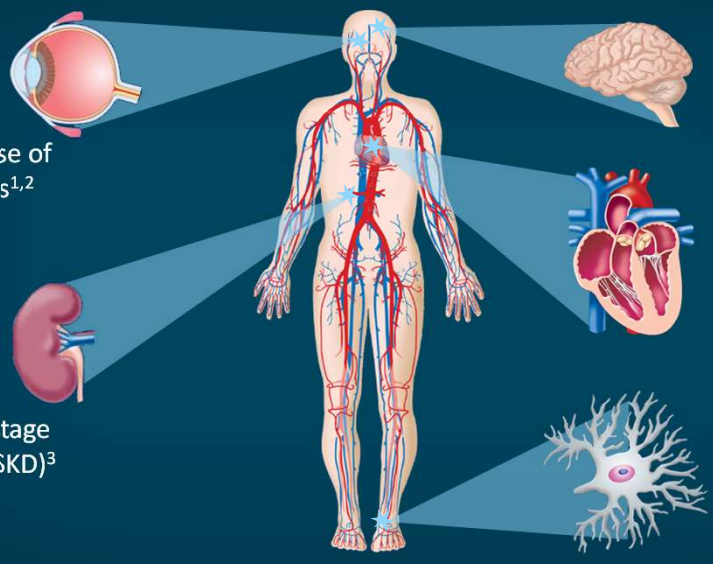
Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, glargine, detemir, NPH, regular, lispro, aspart, glulisine	No limit	Replaces deficient insulin supply	No ceiling; most titratable agent	Hypoglycemia, weight ↑	highly variable
SUs	Glyburide, glipizide, glimepiride	1–1.5%	↑ endogenous insulin production	Extensive experience	Hypoglycemia, weight ↑	$
Metformin	Metformin	1–1.5%	↓ hepatic glucose production (? others)	± weight loss, no hypoglycemia, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZDs	Rosiglitazone, pioglitazone	1–1.5%	Enhances peripheral insulin sensitivity	Durability, no hypoglycemia, ↓ CV events, ↓ NASH	Weight ↑, edema/HF, bone fractures, ? bladder cancer	$–$$$
DPP-4i	Sitagliptin, saxagliptin, alogliptin, linagliptin	0.5–1%	↓ DPP-4 activity, ↑ incretins (GLP-1, GIP)	Well-tolerated; no hypoglycemia	Urticaria, ? pancreatitis, ? HF	$$$$
GLP-1 RA	Exenatide, liraglutide, dulaglutide, lixisenatide, semaglutide	1–1.5%	↑ insulin, ↓ glucagon, ↓ gastromotility and hunger	Weight ↓, no hypoglycemia, ↓ BP, ↓ MACE	GI, ? pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT-2i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1%	↑ urinary glucose excretion	Weight ↓, ↓ BP, no hypoglycemia, ↓ MACE, HF, ↓ CKD	Polyuria, GU, DKA, bone fractures, amputations	$$$$

A1c = glycosylated hemoglobin; GIP = glucose-dependent insulinotropic polypeptide; NASH = nonalcoholic steatohepatitis; BP = blood pressure; MACE = major adverse CV event; HF = heart failure; CKD = chronic kidney disease; GI = gastrointestinal; ca = cancer; GU = genitourinary; DKA = diabetic ketoacidosis.

Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149. Buse JB, et al. *Diabetes Care*. 2020;43:487-493. Davies MJ, et al. *Diabetes Care*. 2018;41:2669-2701. Avogaro A, et al. *Cardiovasc Endocrinol Metab*. 2018;7:13-17. Tsapas A, et al. *Ann Intern Med*. 2020;173:278-286.

15

Complications of Diabetes



Diabetic retinopathy
An important cause of blindness in adults[1,2]

Diabetic nephropathy
Leading cause of chronic and end-stage kidney disease (ESKD)[3]

Stroke
Hypertension occurs in ~20–60% of patients with DM, increasing risk of stroke[4]

CVD
Major cause of morbidity and mortality in T2DM[5]

Diabetic neuropathy
Leading cause of non-traumatic lower extremity amputations[6,7]

CVD = cardiovascular disease.

1. Klein R, Klein BE. Chapter 21. In: *Diabetes in America, 3rd edition*. National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), 2016. 2. Fong DS, et al. *Diabetes Care*. 2003;26(suppl 1):S99-S102. 3. Afkarian M, et al. *JAMA*. 2016;316:602-610. 4. Arauz-Pacheco C, et al. *Diabetes Care*. 2003;26(suppl 1):S80-S82. 5. Barrett-Connor E, et al. Chapter 18. In: *Diabetes in America, 3rd edition*. NIDDK, 2016. 6. Mayfield JA, et al. *Diabetes Care*. 2003;26(suppl 1):S78-S79. 7. American Diabetes Association (ADA). *Diabetes Care*. 2021;44(suppl 1):S151-S167.

16

Summary of 25 Years of Diabetes Clinical Trials Linking Glucose Control to Vascular Complications

- **Glycemic control** (**HbA1c ~7%, perhaps even lower**) reduces ***micro***vascular complications in both T1DM and T2DM, with relative risk reduction (RRR) in the 25–60% range
- However, the **impact** of glycemic control itself on ***macrovascular*** complications in T2DM is **small to nonexistent**
  - Any benefit is on the order of a RRR of ~15%, which is mainly for non-fatal MI (not CV death) and seems to require long-term efforts before it can be appreciated
  - Benefit may be larger in T1DM

T1DM = type 1 diabetes mellitus; MI = myocardial infarction.

Inzucchi S. *Update on Diabetes Drugs and CVD Risk*. ADA 2017 (https://professional.diabetes.org/sites/professional.diabetes.org/files/media/inzucchi_update_on_diabetes_drugs_and_cvd_risk_final.pdf). Accessed 9/14/2021.

17

Impact of Intensive Glucose-Lowering Therapy in T2DM

Summary of Major Randomized Controlled Trials (RCTs)

RCT	Microvascular	Macrovascular	Mortality
T1DM DCCT[1–3] (A1c 7.4 vs 9.1%)	↓	↔	↔
T2DM UKPDS 34[4,5] (A1c 7.4 vs 8.0%)	↓	↔	↔
T2DM ACCORD[6] (A1c 6.4 vs 7.5%)	↓	↔	↑
T2DM ADVANCE[7] (A1c 6.5 vs 7.3%)	↓	↔	↔
T2DM VADT[8] (A1c 6.9 vs 8.4%)	↓	↔	↔

1. Diabetes Control and Complications Trial (DCCT) research group. *N Engl J Med.* 1993;329;977-986. 2. Nathan DM, et al. *N Engl J Med.* 2005;353:2643-2653. 3. DCCT group. *JAMA* 2015;313:45-53. 4. United Kingdom Prospective Diabetes Study (UKPDS) group. *Lancet*. 1998;352:854-865. 5. Holman RR, et al. *N Engl J Med.* 2008;359:1577-1589. 6. Gerstein HC, et al. *N Engl J Med.* 2008;358:2545-2559. 7. Patel A, et al. *N Engl J Med.* 2008;358:2560-2572. 8. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139. Kendall DM, Bergenstal RM. ©International Diabetes Center 2009, 2015.

18

Impact of Major Glucose-Lowering Agent Classes on CV Events

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, glargine, detemir, NPH, regular, lispro, aspart, glulisine	No	Replaces deficient	No ceiling; most titratable agent	Hypoglycemia, weight ↑	highly variable
SUs	Glyburide, glipizide, glimepiride		s insulin	Extensive experience	Hypoglycemia, weight ↑	$
Metformin	Metformin	1–1.5%	tic glucose tion ers)	± weight loss, no hypoglycemia, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZDs	Rosiglitazone, pioglitazone	1–1.5%	es peripheral sensitivity	Durability, no hypoglycemia, ↓ CV events, ↓ NASH	Weight ↑, edema, HF, bone fractures, ? bladder cancer	$–$$$
DPP-4i	Sitagliptin, saxagliptin, alogliptin, linagliptin	0.5–1%	↓ DPP-4 activity, ↑ incretins (GLP-1, GIP)	Well-tolerated; no hypoglycemia	Urticaria, ? pancreatitis, ? HF	$$$$
GLP-1 RA	Exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, semaglutide	1–1.5%	↑ insulin, ↓ glucagon, ↓ gastromotility and hunger	Weight ↓, no hypoglycemia, ↓ BP, ↓ MACE	GI, ? Pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT-2i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1%	↑ urinary glucose excretion	Weight ↓, ↓ BP, no hypoglycemia, ↓ MACE, HF, ↓ CKD	Polyuria, GU, DKA, bone fractures, amputations	$$$$

NEUTRAL

NEUTRAL

?

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Inzucchi SE, et al. *Diabetes Care*. 2015;38:140-149. Buse JB, et al. *Diabetes Care*. 2020;43:487-493. Davies MJ, et al. *Diabetes Care*. 2018;41:2669-2701. Avogaro A, et al. *Cardiovasc Endocrinol Metab*. 2018;7:13-17. Tsapas A, et al. *Ann Intern Med*. 2020;173:278-286.

19

The 2008 FDA Guidance Prompts Large CV Outcome Trials in T2DM

Study	SAVOR[1]	EXAMINE[2]	TECOS[3]	CARMELINA[4]	CAROLINA[5]
DPP4-i	saxagliptin	alogliptin	sitagliptin	linagliptin	linagliptin
Comparator	pl	pl	pl	pl	glime SU)
N	,492	380	,071	079	042
Results	2013	2013	2015	2018	2019

NEUTRAL NEUTRAL NEUTRAL NEUTRAL NEUTRAL

Study	ELIXA[6]	LEADER[7]	SUSTAIN 6[8]	EXSCEL[9]	REWIND[10]	HARMONY[11]
GLP1-RA	lixisenatide	liraglutide	semaglutide	exenatide ER	dulaglutide	~~albiglutide~~
Comparator	pl	pl bo	pl	pl	pl bo	pla ebo
N	68	9 0	32	,752	01	
Results	2015	2016	2016	2017	2019	2018

NEUTRAL

Study	EMPA-REG[12]	CANVAS*[13]	CREDENCE[14]	DECLARE[15]	VERTIS CV[16]
SGLT2-i	empagliflozin	canagliflozin	canagliflozin	dapagliflozin	ertugliflozin
Comparator	bo	pl bo	pl	pl bo	pl
N	20	4 0	44	160	246
Results	2015	2017	2019	2018	2020

NEUTRAL

*canagliflozin had greater risk of amputation in this study.
ER = extended release.

1. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326. 2. White WB, et al. *N Engl J Med*. 2013;369:1327-1335. 3. Green JB, et al. *N Engl J Med*. 2015;373:232-242. 4. Rosenstock J, et al. *JAMA*. 2019;321:69-79. 5. Rosenstock J, et al. *JAMA*. 2019;322:1155-1166. 6. Pfeffer MA, et al. *N Engl J Med*. 2015;373:2247-2257. 7. Marso SP, et al. *N Engl J Med*. 2016;375:311-322. 8. Marso SP, et al. *N Engl J Med*. 2016;375:1834-1844. 9. Holman RR, et al. *N Engl J Med*. 2017;377:1228-1239. 10. Gerstein HC, et al. *Lancet*. 2019;394:121-130. 11. Hernandez AF, et al. *Lancet*. 2018;392:1519-1529. 12. Zinman B, et al. *N Engl J Med*. 2015;373:2117-2128. 13. Neal B, et al. *N Engl J Med*. 2017;377:644-657. 14. Perkovic V, et al. *N Engl J Med*. 2019;380:2295-2306. 15. Wiviott SD, et al. *N Engl J Med*. 2019;380:347-357. 16. Cannon CP, et al. *N Engl J Med*. 2020;383:1425-1435.

20

Impact of Major Glucose-Lowering Agent Classes on CV Events

Classes	Generic Names	↓A1c	Mechanism(s)	Positive(s)	Negative(s)	Cost
Insulin	Degludec, glargine, detemir, NPH, regular, lispro, aspart, glulisine	No	Replaces deficient	No ceiling; most titratable agent	Hypoglycemia, weight ↑	highly variable
SUs	Glyburide, glipizide, glimepiride		s insulin	Extensive experience	Hypoglycemia, weight ↑	$
Metformin	Metformin	1–1.5%	tic glucose tion iers)	± weight loss, no hypoglycemia, ↓ CV events (?)	GI, lactic acidosis, B-12 deficiency	$
TZDs	Rosiglitazone, pioglitazone	1–1.5%	es peripheral sensitivity	Durability, no hypoglycemia, ↓ CV events, ↓ NASH	Weight ↑, edema, HF, bone fractures, ? bladder cancer	$–$$$
DPP-4i	Sitagliptin, saxagliptin, alogliptin, linagliptin	0.5	↓ DPP-4 activity, ↑ 1, GIP)	Well-tolerated; no hypoglycemia	Urticaria, ? pancreatitis, ? HF	$$$$
GLP-1 RA	Exenatide, liraglutide, dulaglutide, albiglutide, lixisenatide, semaglutide	1–1.5%	↓ glucagon, motility and ger	Weight ↓, no hypoglycemia, ↓ BP, ↓ MACE	GI, ? Pancreatic/ biliary disease, ? medullary thyroid ca	$$$$
SGLT-2i	Canagliflozin, dapagliflozin, empagliflozin, ertugliflozin	0.5–1%	y gl n	Weight ↓, ↓ BP, no hypoglycemia, ↓ MACE, HF, ↓ CKD	Polyuria, GU, DKA, bone fractures, amputations	$$$$

NEUTRAL

NEUTRAL

?

+/–

NEUTRAL

✓

✓ ✓

Inzucchi SE, et al. *Diabetes Care.* 2015;38:140-149. Buse JB, et al. *Diabetes Care.* 2020;43:487-493. Davies MJ, et al. *Diabetes Care.* 2018;41:2669-2701. Avogaro A, et al. *Cardiovasc Endocrinol Metab.* 2018;7:13-17.

21

Impact of Lifestyle Changes

- Ideal cardiovascular health based on 7 of the 10 most costly risk factors—**Life's Simple 7®**—that can be improved through lifestyle changes
- Studies have shown:
  - Annual employer healthcare cost were $2021 less with at least 6 risk factors in optimal ranges
  - 78% risk reduction for heart-related death with at least 5 risk factors in optimal ranges

Manage weight | Eat better | Get active | Stop smoking

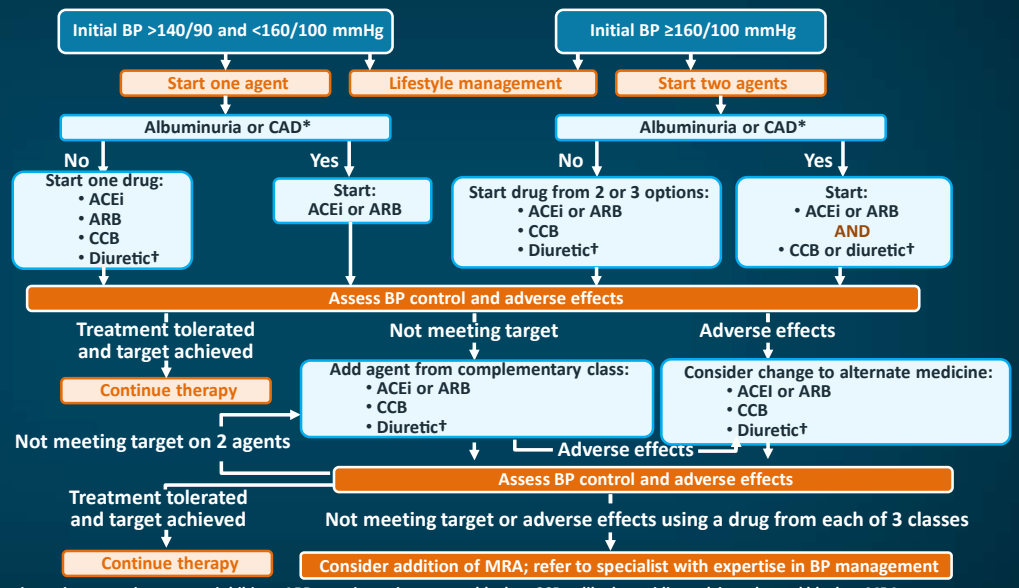
Manage BP | Lipid control | Reduce BG

BG = blood glucose.

American Heart Association (AHA). *Life's simple 7*, 2020 (www.heart.org/en/professional/workplace-health/lifes-simple-7). Accessed 9/14/2021.

22

Recommendations: Treating Confirmed Hypertension in People with DM



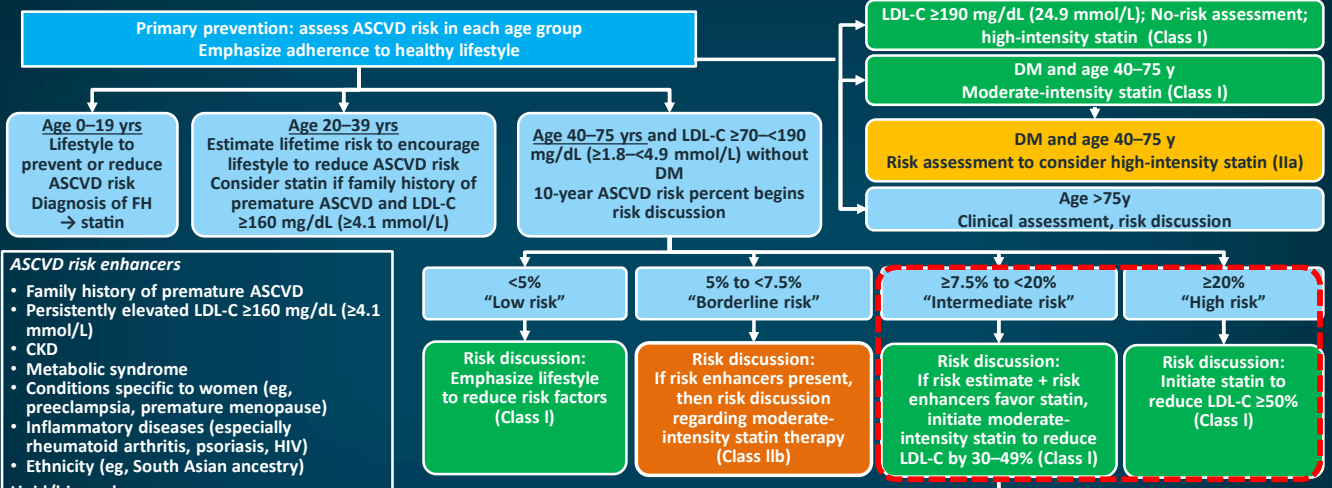
*ACEi or ARB suggested to treat hypertension for patients with CAD or urine albumin-to-creatinine ratio 30–299 mg/g creatinine and strongly recommended for patients with urine albumin-to-creatinine ratio ≥300 mg/g creatinine; †Thiazide-like diuretic; long-acting agents shown to reduce CV events.

CAD = coronary artery disease; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCB = dihydropyridine calcium channel blocker; MRA = mineralocorticoid receptor agonist.

ADA. *Diabetes Care.* 2021;44(suppl 1):S125-S150.

23

AHA/ACC Guidelines on Management of Blood Cholesterol: Primary Prevention



Grundy SM, et al. *Circulation* 2018;139:e1082-e1143.

yr(s) = year(s); FH = familial hypercholesterolemia; CAC = coronary artery calcium; hsCRP = high-sensitivity C-reactive protein; Lp(a) = lipoprotein (a); apoB = apolipoprotein B; ABI = ankle-brachial index; CHD = coronary heart disease.

24

Diabetes Treatment and Complication Prevention

Improving Other Metabolic Outcomes

Anne Peters, MD

25

Case Study #1: Alice

- Alice is a 51-year-old woman with a 10-year history of T2DM
- History of retinopathy and peripheral neuropathy
- Insulin treatment initiated 2 years ago
- PMH significant for a prior hospitalization for severe hypoglycemia
- Last HbA1c measurement was 9.1%
- BMI of 34
- Current therapy: metformin 1000 mg BID and insulin glargine 50 U QHS

How would you manage this patient?

Did you take Alice's weight into account when considering treatment options?

PMH = prior medical history; QHS = each bedtime.

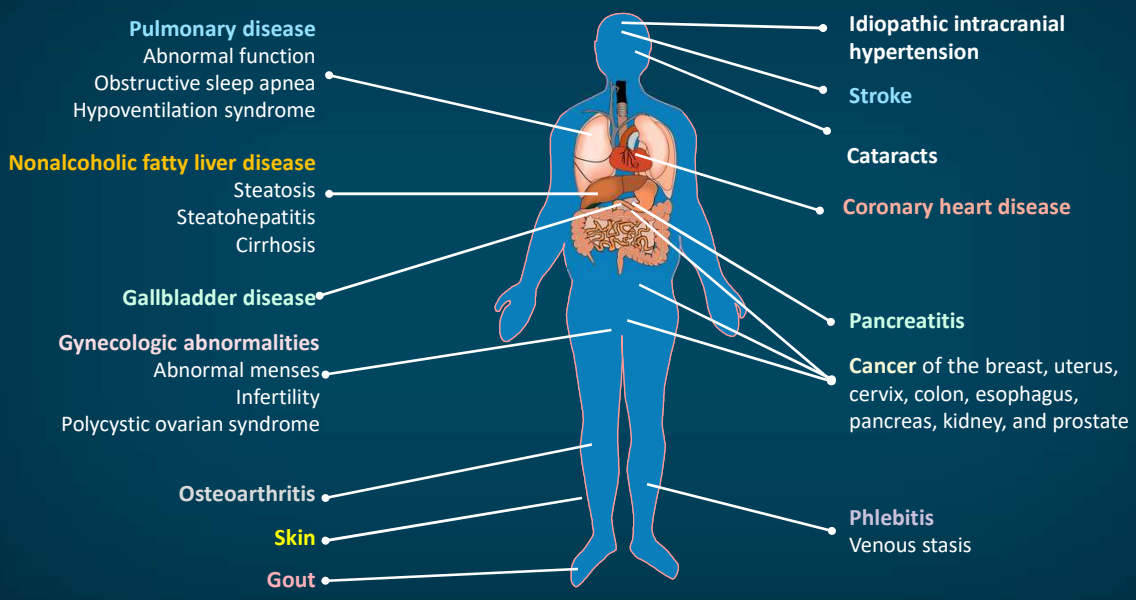
26

Audience Poll

- How often do you consider weight when selecting treatment options for patients with T2DM and overweight/obesity?
  1. Never
  2. Rarely
  3. Occasionally
  4. Most of the time
  5. Every time

27

Obesity Is Associated With 236 Other Disease States



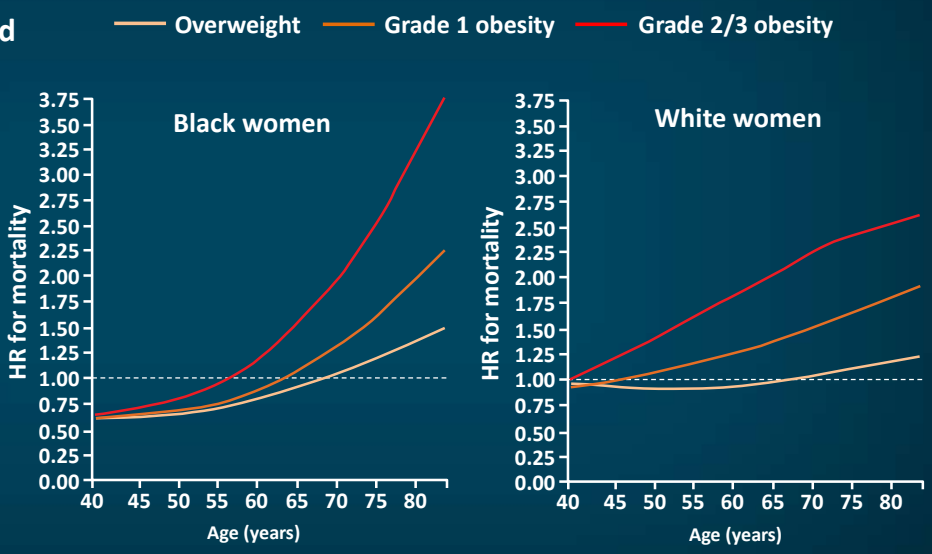
Yuen MM, et al. *Obesity Week*, 2016: poster T-P-3166.

28

Mortality Attributable to Overweight/Obesity

US adult deaths associated with overweight/obesity (1986–2006)

- White men = 15.6%
- Black men = 5.0%
- White women = 21.7%
- Black women = 26.8%



US = United States; HR = hazard ratio.

Masters RK, et al. *Am J Public Health*. 2013;103:1895-1901.

29

Approaches to Managing Obesity

- Lifestyle change
  - Diet
  - Exercise
- Anti-obesity medication
- Bariatric surgery
- Endoscopic procedures
- Managing complications
  - Metabolic
  - Cardiovascular
  - Obstructive sleep apnea
  - Osteoarthritis
  - Others

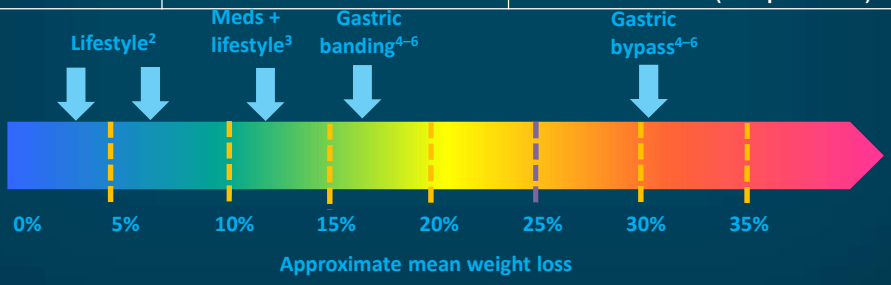
CV = cardiovascular; OSA = obstructive sleep apnea; OA = osteoarthritis.

Bray GA, et al. *Endocri Rev*. 2018;39:79-132.

30

Recommendations for Comprehensive Lifestyle Management

Reduced caloric intake[1,2]	Increased activity[1,2]	Behavioral interventions[1,2]
• Set calorie limits or cut calories or restrict certain food types (eg, dietary fat) • Many dietary approaches work • Consider patient health status and preferences	• Moderate aerobic activity >150 min/wk • Resistance training to preserve lean mass • 200–300 min/wk moderate aerobic activity for maintenance	Weight loss • On-site, high-intensity intervention (eg, ≥14 sessions—group or individual—in 6 mo)*† • Provide strategies‡ Weight maintenance • Continued contact (≥1 × per month) for ≥1 year*

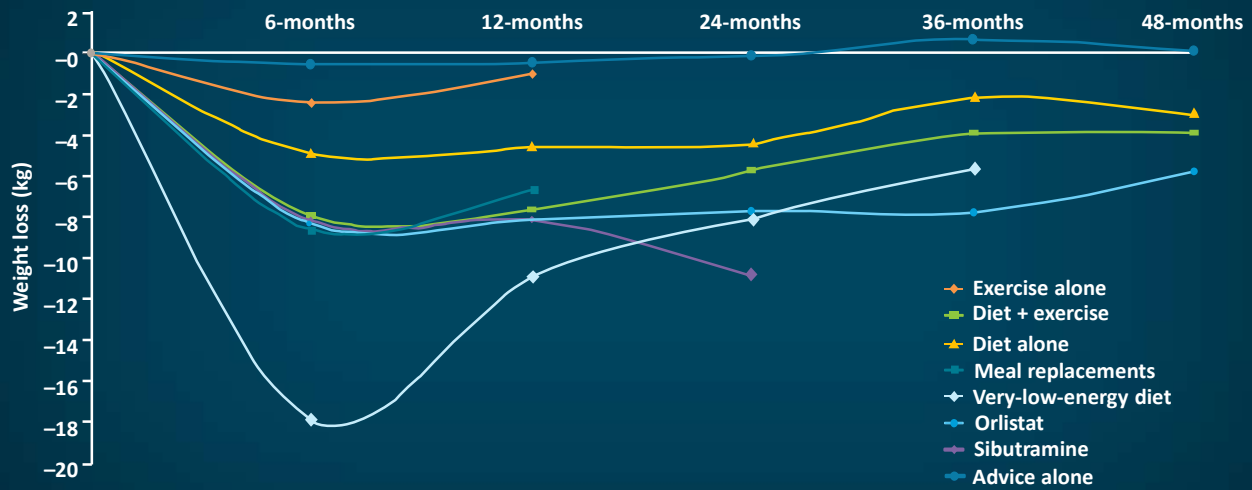


*With trained interventionist; †Face-to-face preferred; telephone or electronic counseling are options but may produce less weight loss than face-to-face counseling; ‡Includes goals, self-monitoring.

1. Bays HE, et al; ObMA. Obesity algorithm (www.obesityalgorithm.org). Accessed 10/20/2020. 2. Jensen MD, et al. *Obesity*. 2014;22(suppl 2):S5-S39. 3. Colman E, et al. *N Engl J Med*. 2012;367:1577-1579. 4. LABS Consortium. *N Engl J Med*. 2009;361:445-454. 5. Courcoulas AP, et al. *JAMA*. 2013;310:2416-2425. 6. Courcoulas AP, et al. *JAMA Surg*. 2018;153:427-434.

31

Weight Maintenance Is Challenging



Franz MJ, et al. *J Am Diet Assoc*. 2007;107:1755-1767.

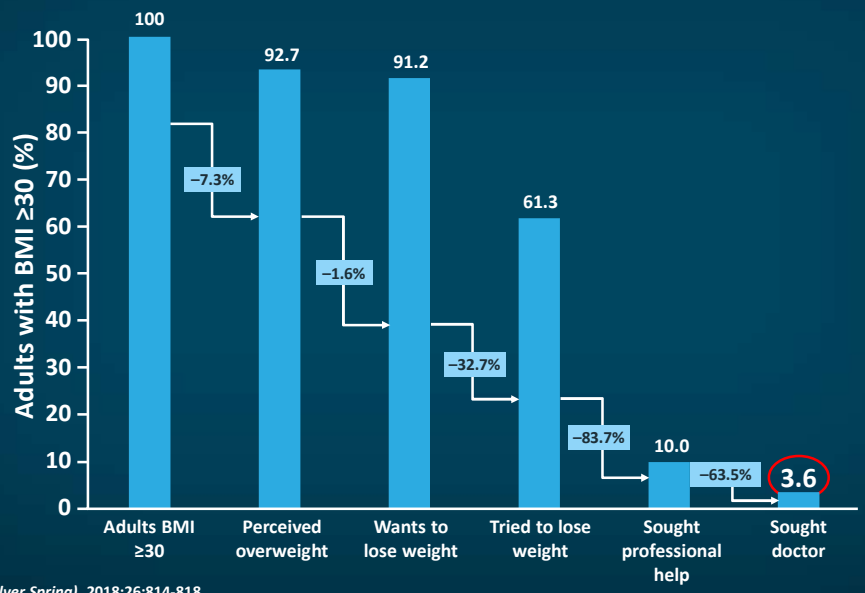
32

Audience Poll

- How often do you discuss weight loss with your patients with T2DM and overweight/obesity?
  1. Only when the patient asks for help with weight loss
  2. Very rarely
  3. Occasionally
  4. At least once with each patient
  5. At every clinic appointment

33

What % of Patients With BMI ≥30 Sought Help from an HCP for Weight Loss?

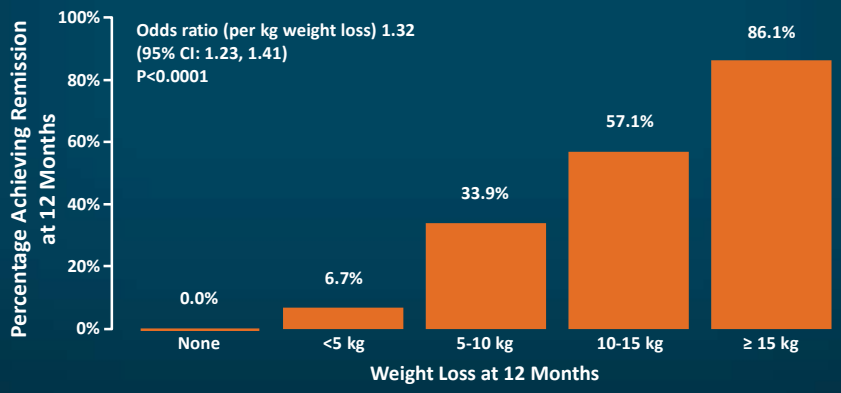


Stokes A, et al. *Obesity (Silver Spring)*. 2018;26:814-818.

34

What Effect Does Weight Loss Have on Diabetes?

- At 12 months, 46% of participants who lost weight achieved diabetes remission (HbA1c <6.5% after at least 2 months off all antidiabetic medications) in the DiRECT open-label trial
- Greater weight loss was associated with greater odds of remission

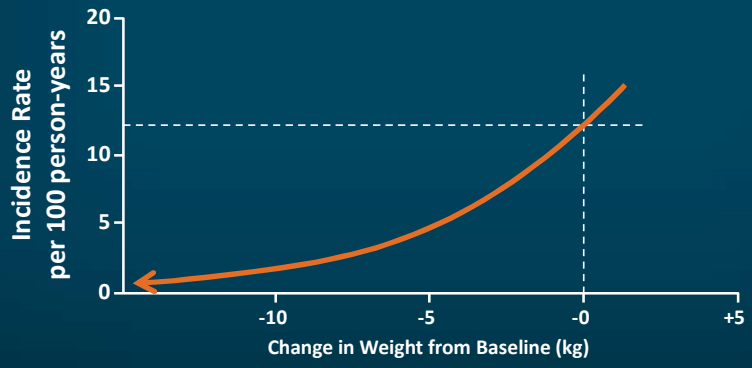


Lean MEJ, et al. *Lancet.* 2018;391:541-551.

35

How Much Weight Loss Is Needed to Provide Benefit?

- Modest weight loss (5%-10%) improves glycemia, blood pressure, lipids, the need for medications, mobility and quality of life
- In the Diabetes Prevention Program, weight loss averaged 5.5 kg and reduced the risk of conversion from impaired glucose tolerance to T2DM by 58%



Bray GA, Ryan DH. *Diabetes Obes Metab.* 2021;23(Suppl 1):50-62.

36

Antiobesity Medications (AOMs)

Sympathomimetics
- Phentermine
- Diethylpropion
- Phendimetrazine

Orlistat

~~Lorcaserin~~
~~Fenfluramine/phentermine~~
~~Sibutramine~~
~~Rimonabant~~

Naltrexone/ bupropion

Phentermine/ topiramate

GLP-1 receptor agonists
*Higher doses than used for T2DM management

Ahmad NN, et al. *Obesity Rev.* 2021;e13326. US Food and Drug Administration (FDA). Lorcaserin withdrawal. (www.fda.gov/drugs/drug-safety-and-availability/fda-requests-withdrawal-weight-loss-drug-belviq-belviq-xr-lorcaserin-market). Accessed 9/14/2021.

37

Weight Loss with Liraglutide

Trial	Participant characteristics	Placebo-corrected weight loss	≥5% body weight loss		≥10% body weight loss	
			Liraglutide 3.0 mg	Placebo	Liraglutide 3.0 mg	Placebo
Astrup et al	76% women stable body weight, BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2	-4.4 kg	76.1%	29.6%	28.3%	2.0%
Astrup et al	76% women stable body weight, BMI ≥ 30 kg/m^2 and ≤ 40 kg/m^2	-5.8 kg	73%	28%	37%	10%
Wadden et al	81% women, stable body weight, BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 with dyslipidemia or hypertension, lost ≥5 % of the initial body weight in low caloric diet run-in period (4 to 12 weeks)	-5.9 kg	50.5%	21.8%	26.1%	6.3%
Pi-Sunyer et al	78% women, stable body weight, BMI ≥ 30 kg/m^2 or ≥ 27 kg/m^2 if with dyslipidemia or hypertension	-5.6 kg	63.2%	27.1%	33.1%	10.6%
Davies et al	50% women, stable body weight, BMI ≥ 27 kg/m^2, type 2 diabetes (HbA1c 7.0-10.0%) treated with diet and exercise alone or in combination with one to three oral hypoglycemic agents	-4.2 kg	54.3%	21.4%	25.2%	6.7%
Blackman et al	28% women, stable body weight, BMI ≥ 30 kg/m^2, moderate to severe OSA, unwilling or unable to use CPAP	-4.9 kg	46.4%	18.1%	22.4%	1.5%

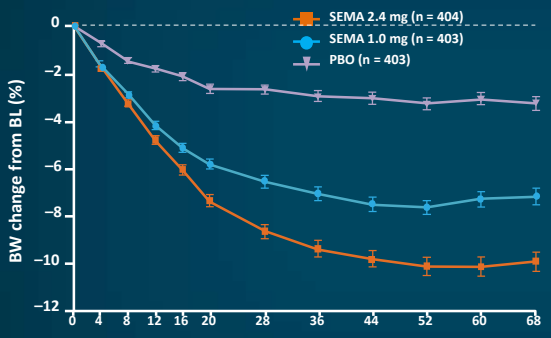
Mehta A, et al. *Obes Sci Pract.* 2017;3:3-14.

38

STEP 2: Semaglutide 2.4 mg QW in Overweight/Obese Adults With T2DM

Randomized, double-blind, double-dummy, placebo-controlled, phase 3 trial

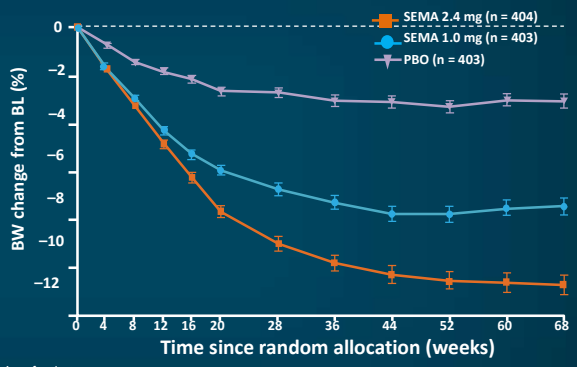
Change in BW over time during in-trial



Number of patients

SEMA 2.4 mg	404	395	397	390	388	392	386	383	381	381	378	388
SEMA 1.0 mg	403	394	392	385	383	383	378	377	373	370	374	380
PBO	403	398	394	389	387	383	381	377	371	367	366	376

Change in BW over time on treatment



Number of patients

SEMA 2.4 mg	404	393	390	376	369	369	363	360	358	361	356	351
SEMA 1.0 mg	403	392	385	374	367	366	363	359	355	352	355	353
PBO	403	392	391	383	379	369	365	359	352	347	348	340

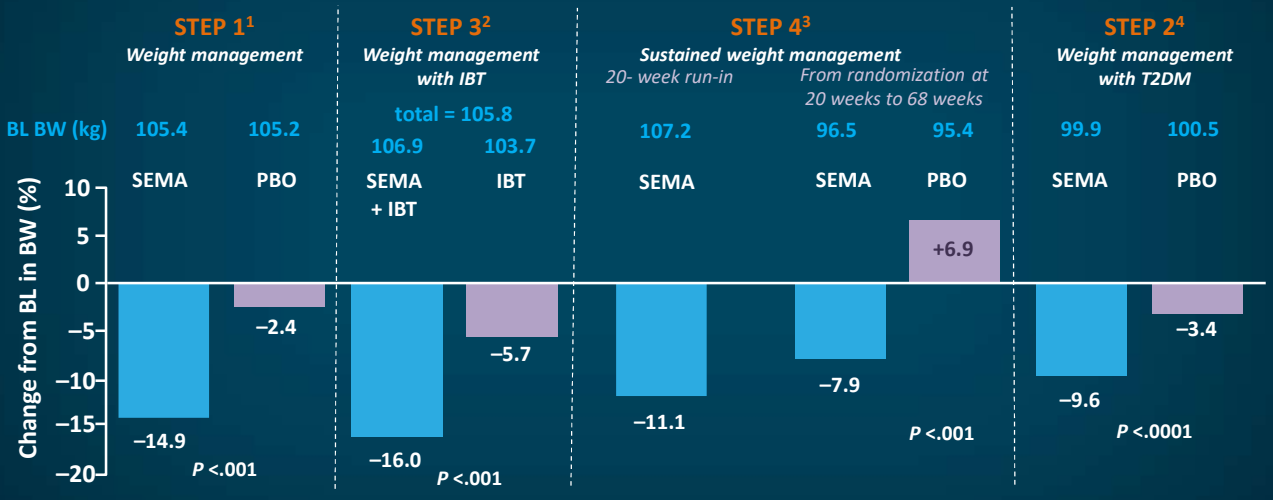
BW = bodyweight.

Davies M, et al. *Lancet.* 2021;397:971-984.

39

The STEP Trials: Higher-Dose Semaglutide in Obesity

Semaglutide is a GLP-1 receptor agonist approved for management of T2DM

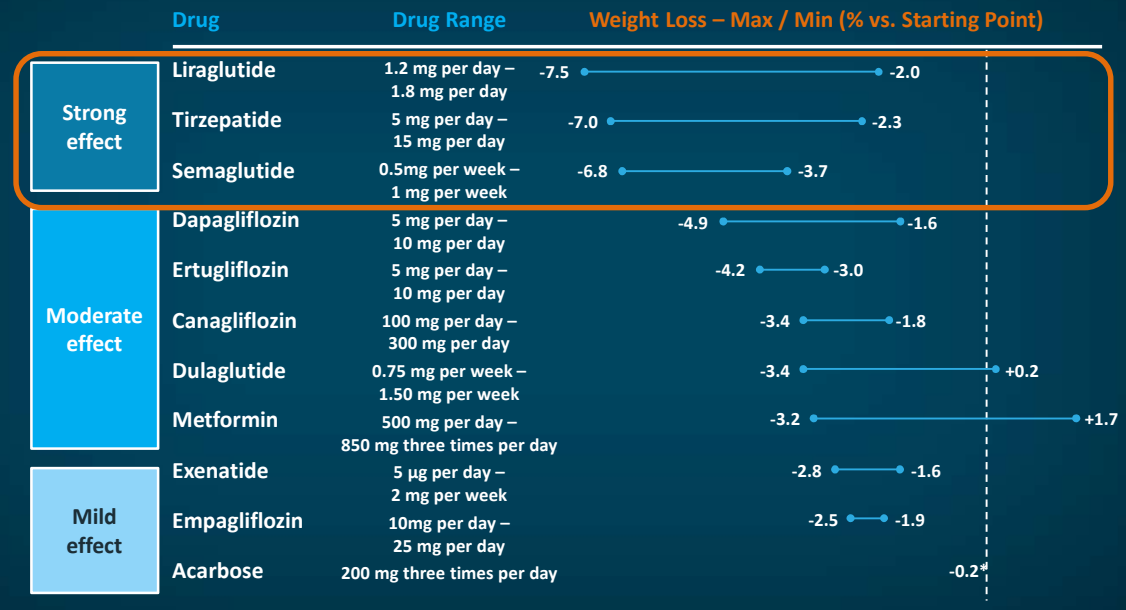


IBT = intensive behavioral therapy.

1. Wilding JPH, et al. *N Engl J Med.* 2020;384:989-1002. 2. Wadden TA, et al. *JAMA.* 2021;325:1403-1413.
3. Rubino D, et al. *JAMA.* 2021;325:1414-1425. 4. Davies M, et al. *Lancet.* 2021;397:971-984.

40

Weight Loss with Antidiabetic Agents



Lazzaroni E, et al. *Pharmacol Res.* 2021;171:105782.

41

Q&A

42

Current Type 2 Diabetes Treatment Guidelines

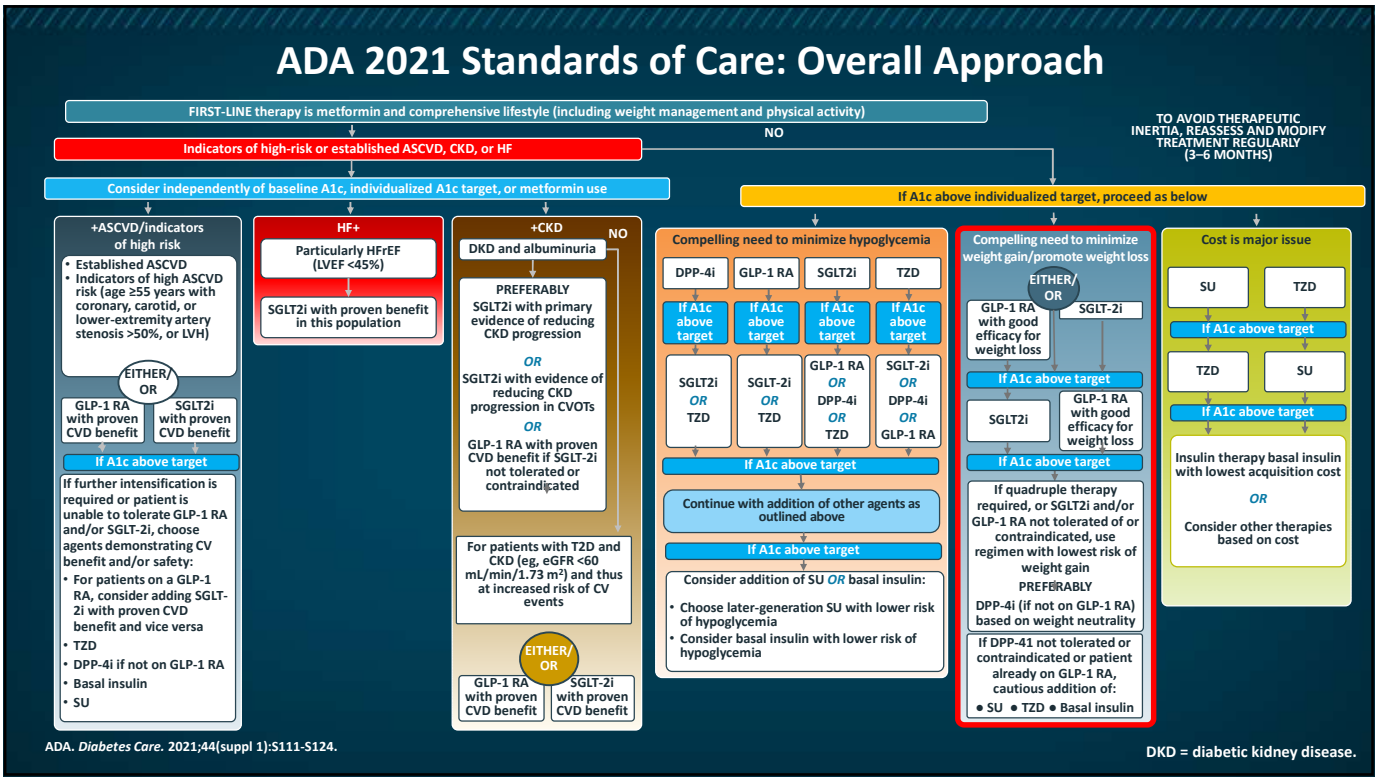
Silvio Inzucchi, MD

43

Audience Poll

- How would you manage a patient with T2DM and overweight/obesity?
  1. Recommend lifestyle changes
  2. Prescribe a GLP-1 RA
  3. Prescribe an SGLT-2i
  4. Prescribe a DPP-4i
  5. Weight loss is usually not a priority in my patients

44



45

CV, Mortality, and Kidney Outcomes with GLP-1 RAs in Patients with T2DM: Systematic Review and Meta-analysis of RCTs

	GLP-1 RA n/N (%)	PBO n/N (%)	HR (95% CI)	NNT (95% CI)	*P*-value
Three-point MACE					
ELIXA	400/3034 (13%)	392/3034 (13%)	1.02 (0.89–1.17)		.78
LEADER	608/4668 (13%)	694/4672 (15%)	0.87 (0.78–0.97)		.01
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)	0.74 (0.58–0.95)		.016
EXSCEL	839/7356 (11%)	905/7396 (12%)	0.91 (0.83–1.00)		.061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)	0.78 (0.68–0.90)		.0006
REWIND	594/4949 (12%)	663/4952 (13%)	0.88 (0.79–0.99)		.026
PIONEER 6	61/1591 (4%)	76/1592 (5%)	0.79 (0.57–1.11)		.17
AMPLITUDE-O	189/2717 (7%)	125/1359 (9%)	0.73 (0.58–0.92)		.0069
Subtotal (I^2=44.5%, *P*= .08)			**0.86 (0.80–0.93)**	**65 (45–130)**	<.0001
CV death					.85
ELIXA	156/3034 (5%)	158/3034 (5%)	**0.98 (0.78–1.22)**		
LEADER	219/4668 (5%)	278/4672 (6%)	0.78 (0.66–0.93)		.007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)	0.98 (0.65–1.48)		.92
EXSCEL	340/7356 (5%)	383/7396 (5%)	0.88 (0.76–1.02)		.096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)	0.93 (0.73–1.19)		.58
REWIND	317/4949 (6%)	346/4952 (7%)	0.91 (0.78–1.06)		.21
PIONEER 6	15/1591 (1%)	30/1592 (2%).	0.49 (0.27–0.92)		.021
AMPLITUDE-O	75/2717 (3%)	50/1359 (4%)	0.72 (0.50–1.03)		.07
Subtotal (I^2=13.4%, *P*= .33)			**0.87 (0.80–0.94)**	**163 (103–353)**	.001
Fatal or non-fatal MI					
ELIXA	270/3034 (9%)	261/3034 (9%)	1.03 (0.87–1.22)		.71
LEADER	292/4668 (6%)	339/4672 (7%)	0.86 (0.73–1.00)		.046
SUSTAIN-6	54/1648 (3%)	67/1649 (4%)	0.81 (0.57–1.16)		.26
EXSCEL	483/7356 (7%)	493/7396 (7%)	0.97 (0.85–1.10)		.62
Harmony Outcomes	181/4731 (4%)	240/4732 (5%)	0.75 (0.61–0.90)		.003
REWIND	223/4949 (5%)	231/4952 (5%)	0.96 (0.79–1.15)		.63
PIONEER 6	37/1591 (2%)	35/1592 (2%)	1.04 (0.66–1.66)		.49
AMPLITUDE-O	91/2717 (3%)	58/1359 (4%)	0.75 (0.54–1.05)		.09
Subtotal (I^2=26.9%, *P*= .21)			**0.90 (0.83–0.98)**	**175 (103–878)**	.02
Fatal or non-fatal stroke					
ELIXA	67/3034 (2%)	60/3034 (2%)	1.12 (0.79–1.58)		.54
LEADER	173/4668 (4%)	199/4672 (4%)	0.86 (0.71–1.06)		.16
SUSTAIN-6	30/1648 (2%)	46/1649 (3%)	0.65 (0.41–1.03)		.066
EXSCEL	187/7356 (3%)	218/7396 (3%)	0.85 (0.70–1.03)		.095
Harmony Outcomes	94/4731 (2%)	108/4732 (2%)	0.86 (0.66–1.14)		.30
REWIND	158/4949 (3%)	205/4952 (4%)	0.76 (0.62–0.94)		.010
PIONEER 6	13/1591 (1%)	17/1592 (1%)	0.76 (0.37–1.56)		.43
AMPLITUDE-O	47/2717 (2%)	31/1359 (2%)	0.74 (0.47–1.17)		.19
Subtotal (I^2=0.0%, *P*= .64)			**0.83 (0.76–0.92)**	**198 (140–421)**	.0002

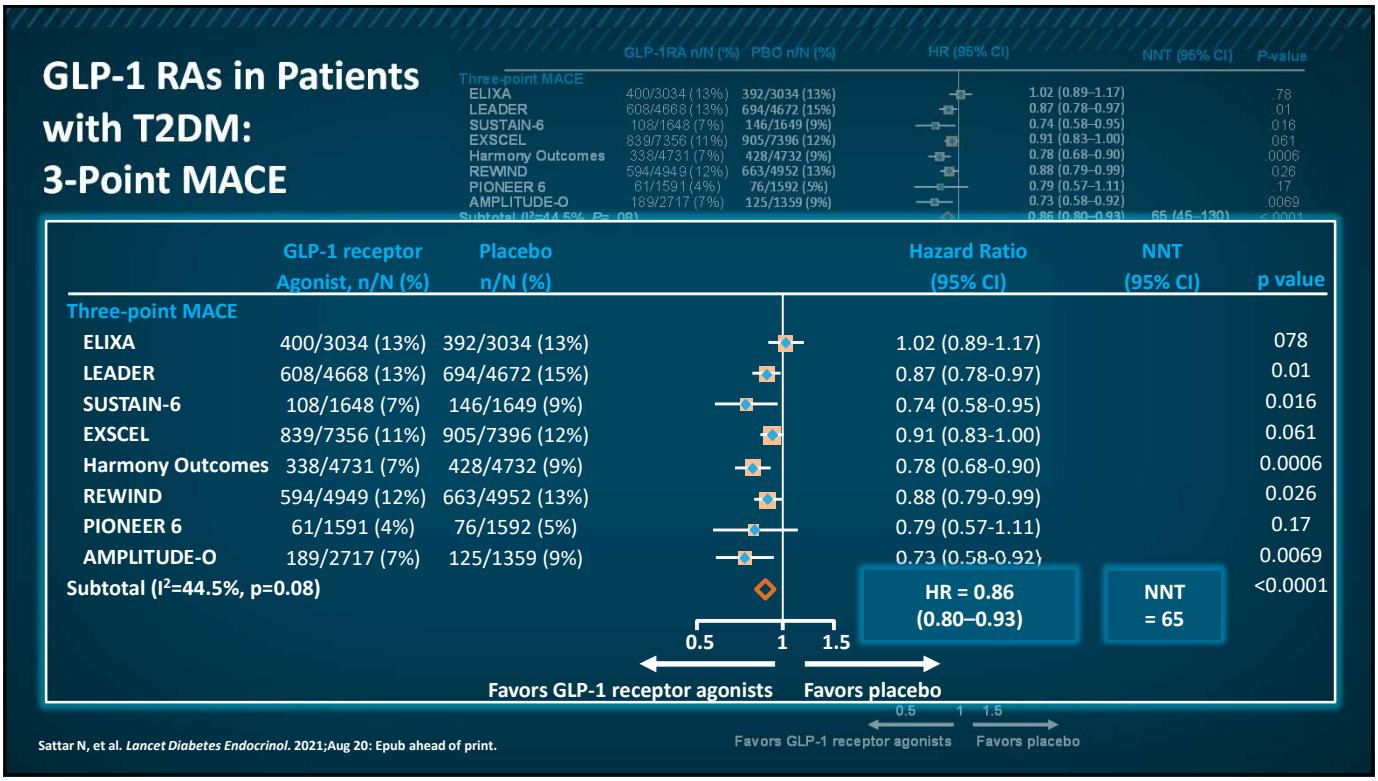
0.5 1 1.5

Favors GLP-1 receptor agonists | Favors placebo

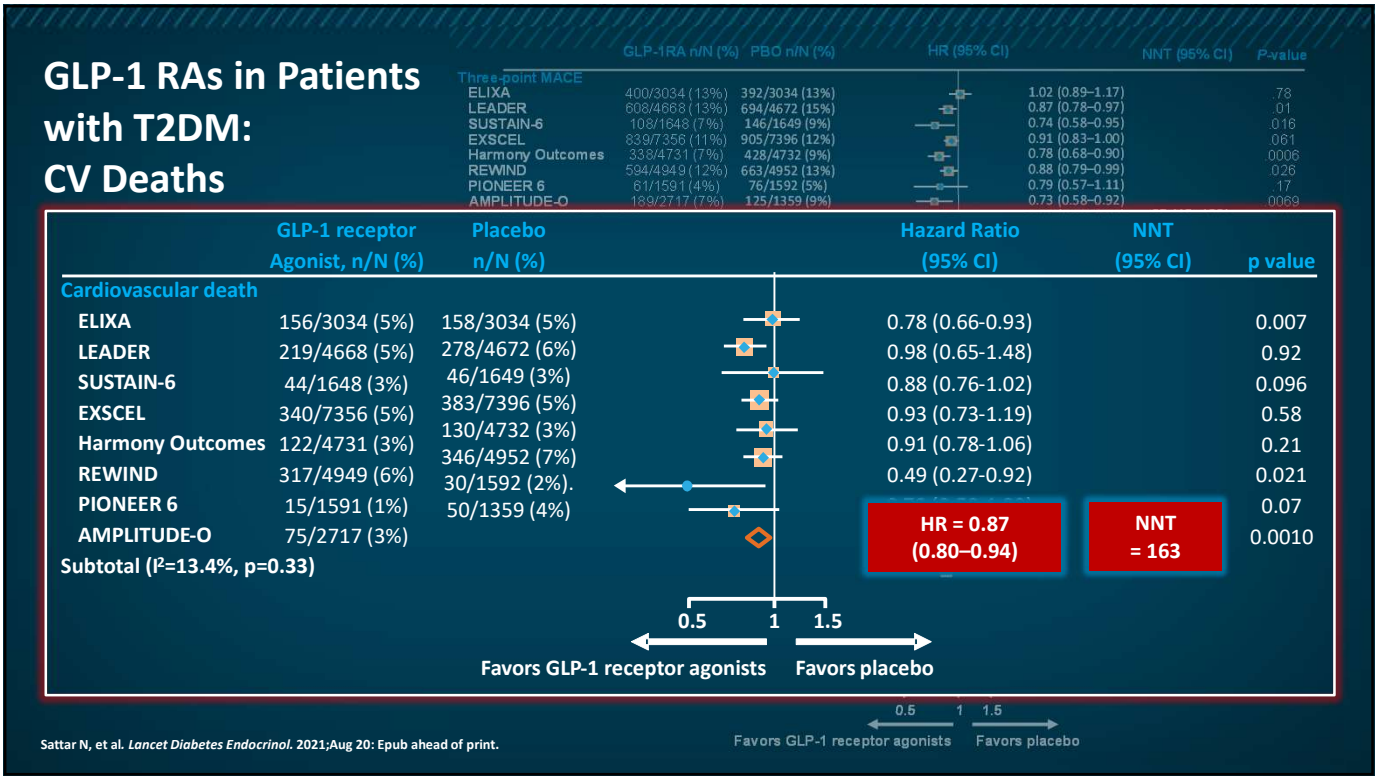
PBO = placebo; NNT = number needed to treat.

Sattar N, et al. *Lancet Diabetes Endocrinol*. 2021;Aug 20: Epub ahead of print.

46

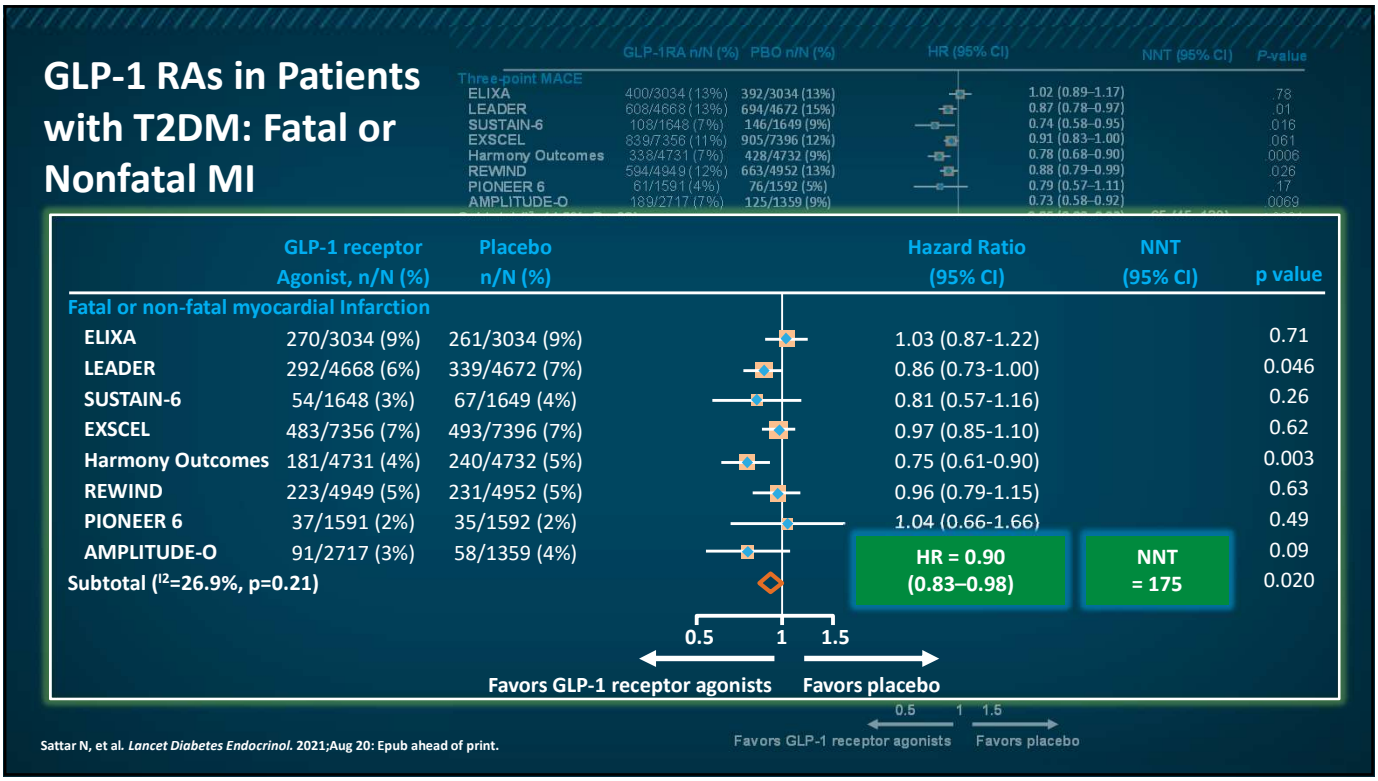

GLP-1 RAs in Patients with T2DM: 3-Point MACE
GLP-1 receptor Agonist, n/N (%)
Placebo n/N (%)
Hazard Ratio (95% CI)
NNT (95% CI)
p value
Three-point MACE
ELIXA 400/3034 (13%) 392/3034 (13%) 1.02 (0.89-1.17) 078
LEADER 608/4668 (13%) 694/4672 (15%) 0.87 (0.78-0.97) 0.01
SUSTAIN-6 108/1648 (7%) 146/1649 (9%) 0.74 (0.58-0.95) 0.016
EXSCEL 839/7356 (11%) 905/7396 (12%) 0.91 (0.83-1.00) 0.061
Harmony Outcomes 338/4731 (7%) 428/4732 (9%) 0.78 (0.68-0.90) 0.0006
REWIND 594/4949 (12%) 663/4952 (13%) 0.88 (0.79-0.99) 0.026
PIONEER 6 61/1591 (4%) 76/1592 (5%) 0.79 (0.57-1.11) 0.17
AMPLITUDE-O 189/2717 (7%) 125/1359 (9%) 0.73 (0.58-0.92) 0.0069
Subtotal (I²=44.5%, p=0.08) <0.0001
HR = 0.86 (0.80–0.93)
NNT = 65
0.5 1 1.5
Favors GLP-1 receptor agonists
Favors placebo
Sattar N, et al. Lancet Diabetes Endocrinol. 2021;Aug 20: Epub ahead of print.

47


GLP-1 RAs in Patients with T2DM: CV Deaths
GLP-1 receptor Agonist, n/N (%)
Placebo n/N (%)
Hazard Ratio (95% CI)
NNT (95% CI)
p value
Cardiovascular death
ELIXA 156/3034 (5%) 158/3034 (5%) 0.78 (0.66-0.93) 0.007
LEADER 219/4668 (5%) 278/4672 (6%) 0.98 (0.65-1.48) 0.92
SUSTAIN-6 44/1648 (3%) 46/1649 (3%) 0.88 (0.76-1.02) 0.096
EXSCEL 340/7356 (5%) 383/7396 (5%) 0.93 (0.73-1.19) 0.58
Harmony Outcomes 122/4731 (3%) 130/4732 (3%) 0.91 (0.78-1.06) 0.21
REWIND 317/4949 (6%) 346/4952 (7%) 0.49 (0.27-0.92) 0.021
PIONEER 6 15/1591 (1%) 30/1592 (2%). 0.07
AMPLITUDE-O 75/2717 (3%) 50/1359 (4%) 0.0010
Subtotal (I²=13.4%, p=0.33)
HR = 0.87 (0.80–0.94)
NNT = 163
0.5 1 1.5
Favors GLP-1 receptor agonists
Favors placebo
Sattar N, et al. Lancet Diabetes Endocrinol. 2021;Aug 20: Epub ahead of print.

48

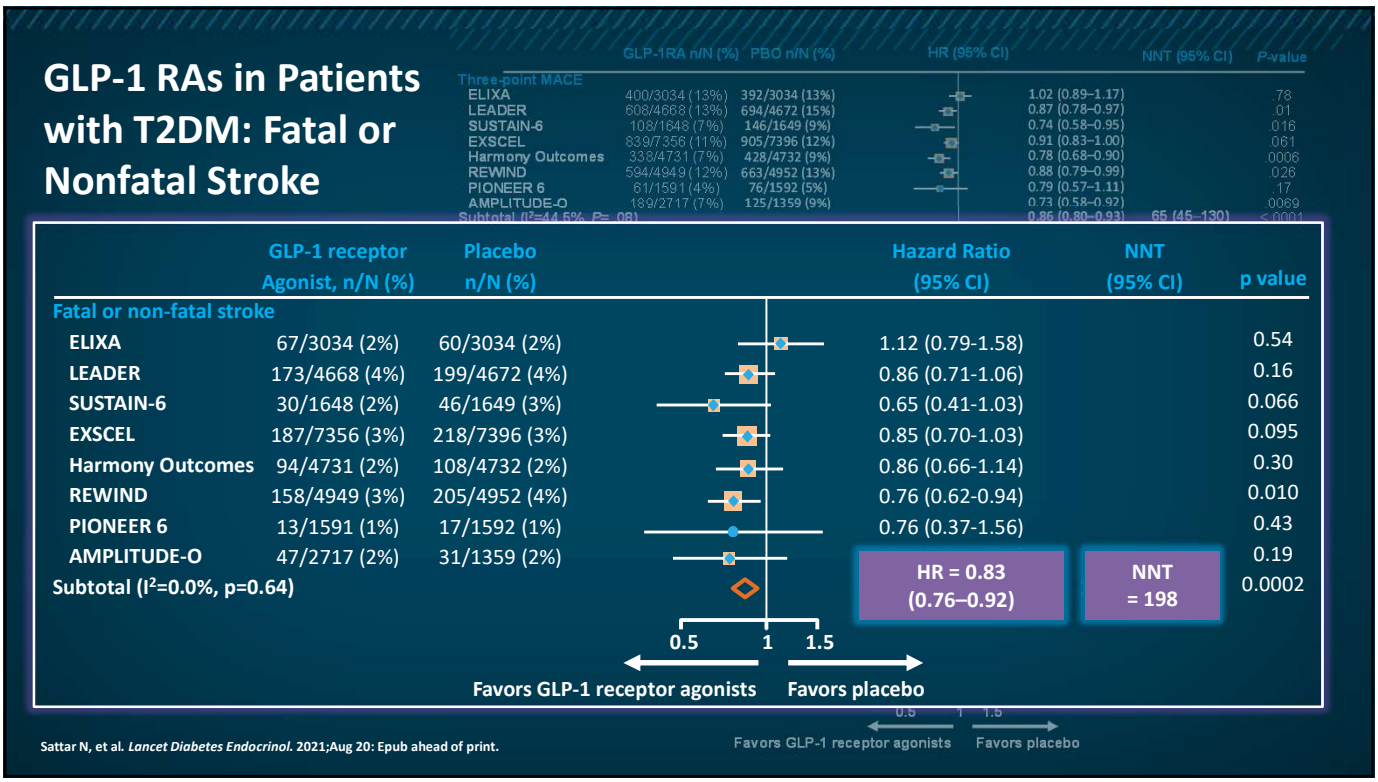
GLP-1 RAs in Patients with T2DM: Fatal or Nonfatal MI



Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;Aug 20: Epub ahead of print.

49

GLP-1 RAs in Patients with T2DM: Fatal or Nonfatal Stroke



Sattar N, et al. *Lancet Diabetes Endocrinol.* 2021;Aug 20: Epub ahead of print.

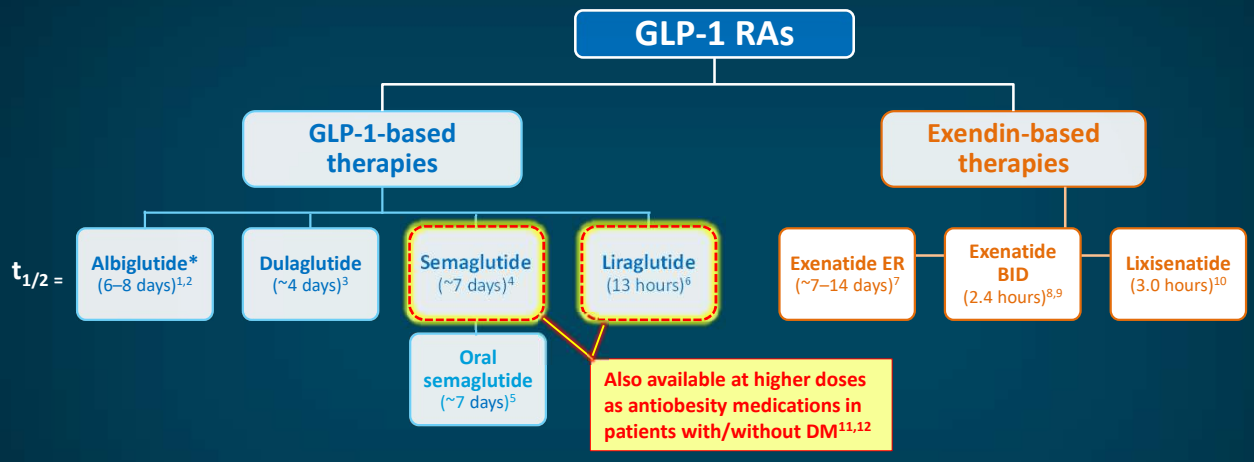
50

The Incretin System in Health and Disease

Silvio Inzucchi, MD

51

GLP-1 RA Landscape



*Albiglutide was withdrawn from market in 2018.

$t_{1/2}$ = elimination half-live; BID = twice daily.

1. Bush MA, et al. *Diabetes Obes Metab.* 2009;11:498-505. 2. Matthews JE, et al. *J Clin Endocrinol Metab.* 2008;93:4810-4817. 3. Barrington P, et al. *Diabetes Obes Metab.* 2011;13:434-438. 4. Semaglutide [Ozempic®] prescribing information (PI) 2021 (www.novo-pi.com/ozempic.pdf). 5. Semaglutide oral [Rybelsus®] PI 2021 (www.novo-pi.com/rybelsus.pdf). 6. Liraglutide [Victoza®] PI 2020 (www.novo-pi.com/victoza.pdf). 7. Exenatide. Drugs.com (www.drugs.com/ppa/exenatide.html). 8. Fineman M, et al. *Clin Pharmacokinet.* 2011;50:65-74. 9. Exenatide (Byetta®) (https://odprod65-origin-medical-affairs-us.digital-astrazeneca.com/home/prescribing-information/byetta-pi.html). 10. Lixisenatide (Adlyxin®) PI 2021 (https://products.sanofi.us/Adlyxin/Adlyxin.pdf). 11. Semaglutide (Wegovy™) PI 2021 (www.novo-pi.com/wegovy.pdf). 12, Liraglutide (Saxenda®) PI 2021 (www.novo-pi.com/saxenda.pdf). URLs accessed 9/14/2021.

52

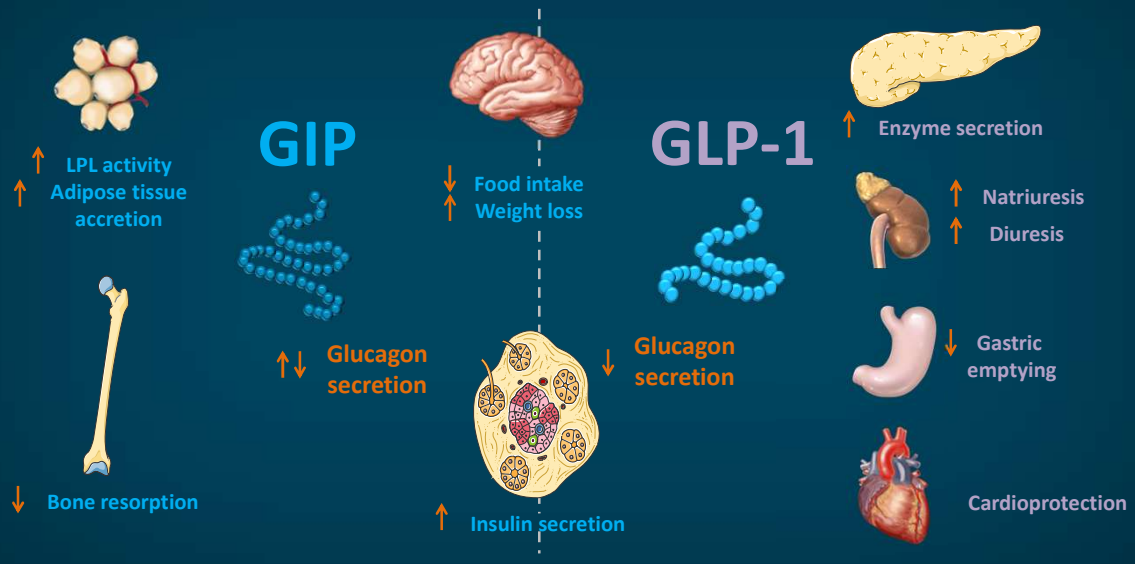
Whiteboard animation

https://youtu.be/hWXqU8oe-Ps

Effects of GIP and GLP-1 in Healthy Individuals

53

Dual Effects of GIP + GLP-1 Partnership on Biology



Baggio LL, Drucker DJ. *Mol Metab*. 2021;Apr: Epub ahead of print. Courtesy of Daniel Drucker, MD

54

GLP-1 RA Pharmacokinetic Profiles

Increasing half-life

GLP-1 RAs	Half-life	T_{max}
Exenatide BID[1]	2.4 hours	2.1 hours
Lixisenatide QD[2]	3 hours	1.0–3.5 hours
Liraglutide QD[3]	13 hours	8–12 hours
Dulaglutide QW[4]	~5 days	24–48 hours (1–2 days)
Semaglutide QW[5]	~1 week	1–3 days
Albiglutide QW[6]	~5 days	3–5 days
Exenatide QW[7,8]	~2 weeks	6–7 weeks

QD = once daily; QW = once weekly; T_{max} = time to reach maximum concentration.

1. Exenatide (Byetta®) PI (https://den8dhaj6zs0e.cloudfront.net/50fd68b9-106b-4550-b5d0-12b045f8b184/ce8afab9-2b45-436d-957c-a73978d09e93/ce8afab9-2b45-436d-957c-a73978d09e93_viewable_rendition__v.pdf). 2. Lixisenatide (Adlyxin®) PI 2021 (https://products.sanofi.us/Adlyxin/Adlyxin.pdf). 3. Liraglutide [Victoza®] PI 2020 (www.novo-pi.com/victoza.pdf). 4. Dulaglutide (Trulicity®) PI 2021 (http://pi.lilly.com/us/trulicity-uspi.pdf). 5. Semaglutide [Ozempic®] prescribing information (PI) 2021 (www.novo-pi.com/ozempic.pdf). 6. Albiglutide (Tanzeum) PI 2017 (www.accessdata.fda.gov/drugsatfda_docs/label/2017/125431s019lbl.pdf). 7. Exenatide ER [Bydureon®] PI 2021 (www.accessdata.fda.gov/drugsatfda_docs/label/2021/022200s031lbl.pdf). Exenatide. Drugs.com (www.drugs.com/ppa/exenatide.html). URLs accessed 9/14/2021.

55

Clinical Considerations for Selecting Between GLP-1 RAs and SGLT2 Inhibitors

Considerations	GLP-1RAs may be the better choice…	SGLT2 inhibitors may be the better choice…
Cardiorenal	Established atherosclerotic CVD and/or cerebrovascular disease; eGFR <30 mL/min/1.73 m^2	HF or CKD dominates
Glycemic control and DKA	More HbA1c reduction needed; history of DKA	
Comorbidities	Obesity; frequent genital mycotic infections; frequent or complicated UTIs, ? osteoporosis or history of fractures; ? advanced PVD, lower-limb ulcers or amputations	Active gallbladder disease; h/o pancreatitis; gastroparesis or delayed gastric emptying; personal or family history of MTC or MEN-2; ? h/o proliferative retinopathy
Other	Patient preference (most are injectables)	Patient preference

UTI = urinary tract infection; PVD = peripheral vascular disease; h/o = history of; MTC = medullary thyroid cancer; MEN-2 = multiple endocrine neoplasia type 2.

Modified from Honigberg MC, et al. *JAMA Cardiol.* 2020;5:1182-1190.

56

Adjusting Other Antihyperglycemic Therapies at Initiation of GLP-1 RAs

- Sulfonylureas
  - If HbA1c is ≤7.5% or hypoglycemic episodes, stop sulfonylurea medication
  - If HbA1c is 7.6–8.5%, decrease sulfonylurea medication by 50%
  - If HbA1c is >8.5%, continue sulfonylurea medication with possibility of future weaning
- Insulin
  - If HbA1c is at or below individualized target or hypoglycemic episodes, decrease basal insulin by 20–30%
  - Coordination amongst providers is key (i.e, if clinician who is not managing diabetes/insulin is the one adding the GLP-1 RA)
- Dipeptidyl peptidase-4 inhibitors
  - Discontinue after starting GLP-1 RA (no interaction, but waste since no longer effective)
- Other agents do not require adjustment

Modified from Honigberg MC, et al. *JAMA Cardiol.* 2020;5:1182-1190.

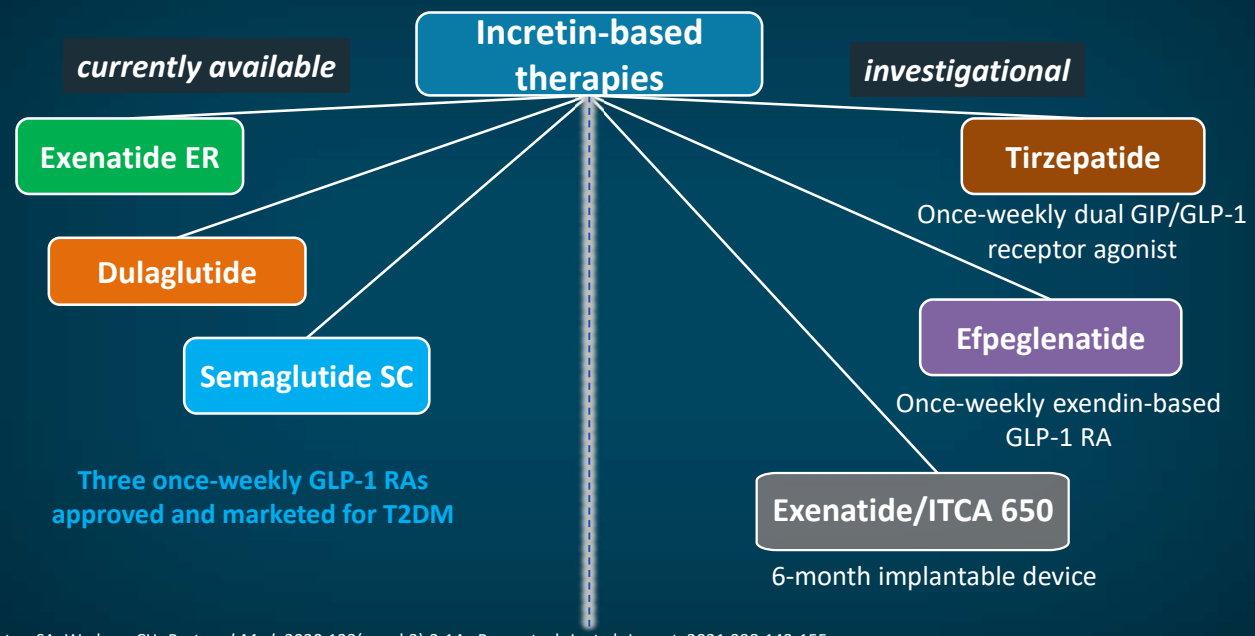
57

Emerging Incretin Therapy Options

Anne Peters, MD

58

Current And Possibly Future Weekly+ Incretin-Based Options



Brunton SA, Wysham CH. *Postgrad Med.* 2020;132(suppl 2):3-14. Rosenstock J, et al. *Lancet.* 2021;398:143-155. Gerstein HC, et al. *N Engl J Med.* 2021;385:896-907. Bertsch T, McKeirnan K. *Clin Diabetes.* 2018;36:265-267.

59

Considering Weight When Selecting Therapy

- International guidelines recommend choice of anti-hyperglycemic therapy based on presence or absence of CV disease, renal disease, and obesity
- With increasing prevalence of both diabetes and obesity, agents with potent weight loss are increasingly important
  - Weight gain worsens insulin resistance
- Existing need for anti-hyperglycemic agents with greater HbA1c reduction and weight loss

Min T, Bain SC. *Diabetes Ther.* 2021;12:143-157.

60

Whiteboard animation

https://youtu.be/mBMUzT2P7Uk

Pre-clinical data on the benefits of targeting both GIP and GLP-1

References:

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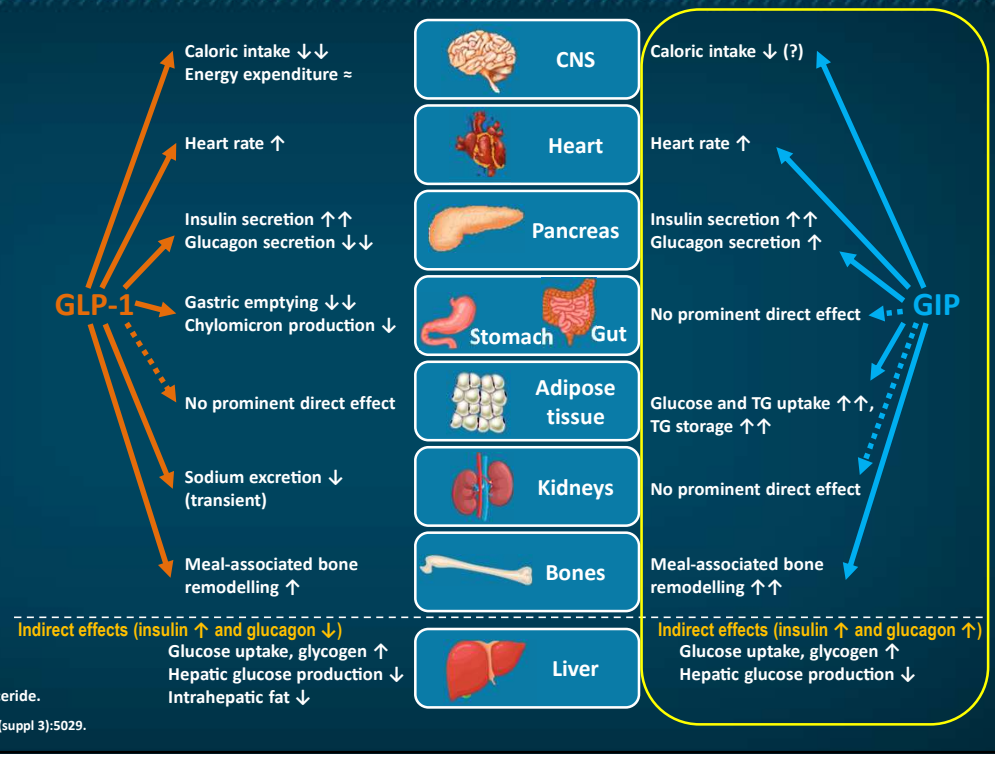
- Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: The SURPASS clinical trials. Diabetes Ther. 2021;12:143-157.
- Lim GE, Brubaker PL. Glucagon-like peptide 1 secretion by the L-cell: The view from within. Diabetes. 2006;55(Suppl 2):S70-S77.
- Willard FS, Douros JD, Gabe MBN, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI Insight. 2020;5:e140532.

61

Overview of Biological GIP and GLP-1 Effects at the Organ/Tissue Level



CNS = central nervous system; TG = triglyceride.

Nauck MA. et al. *Diabetes Obes Metab.* 2021;23(suppl 3):5029.

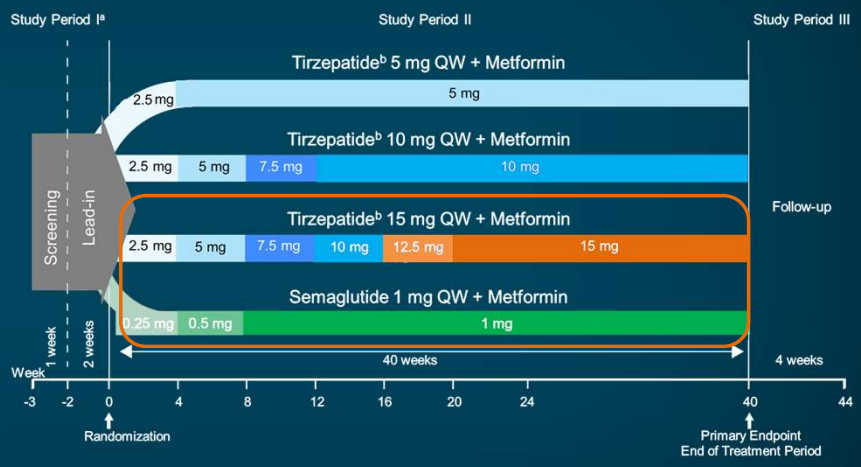
62

SURPASS 2: Study Design

Randomized, open-label, active-controlled, parallel group, multicenter, multinational trial

Key inclusion criteria
- T2DM
- HbA1c ≥7.0% to ≤10.5% at screening
- BMI ≥25 kg/m^2 with stable weight
- Have been on stable T2DM treatment with metformin ≥1500 mg/day in 3 months prior to screening and between screening and randomization

Key exclusion criteria
- T1DM
- History of acute pancreatitis
- eGFR <45 mL/min/1.73 m^2
- Use of any antihyperglycemic treatment other than metformin in 3 months prior to screening



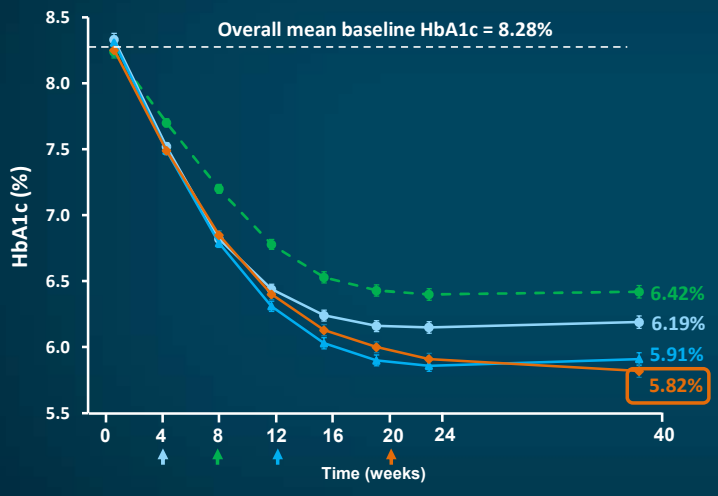
[a]Stable doses of metformin ≥1500 mg/day for at least 3 months prior to visit 1 and during screening lead-in period; [b]all tirzepatide doses were double-blinded.

Frias JP, *et al. N Engl J Med.* 2021;385:503-515 and supplement.

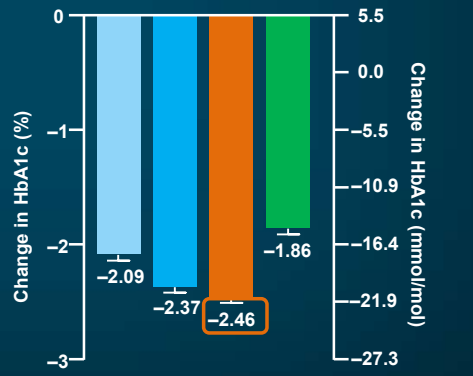
63

SURPASS 2: HbA1c Over Time and Change from Baseline at 40 Weeks

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide



TZP vs SEMA: ETD in HbA1c (LSM ± SE)		
Tirzepatide	ETD (95% CI)	*P*-value
5 mg dose	–0.23 (–0.36 to –0.10)	<.001
10 mg dose	–0.51 (–0.64 to –0.38)	<.001
15 mg dose	–0.60 (–0.73 to–0.47)	<.001



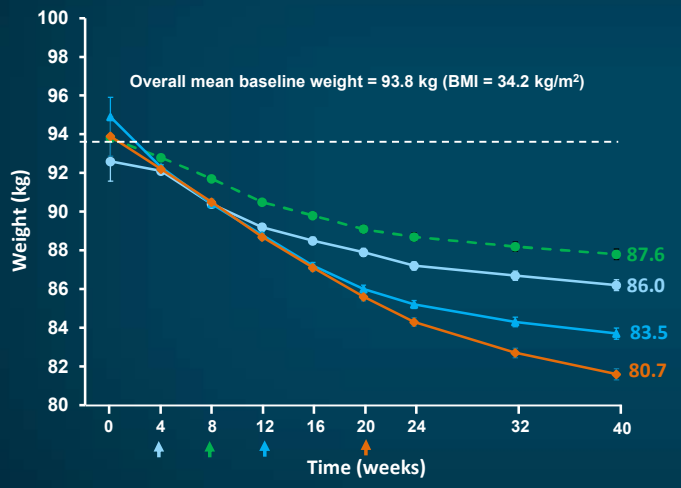
ETD = estimated treatment difference; LSM = least squares mean; SE = standard error.

Frias JP, *et al. N Engl J Med.* 2021;385:503-515 and supplement.

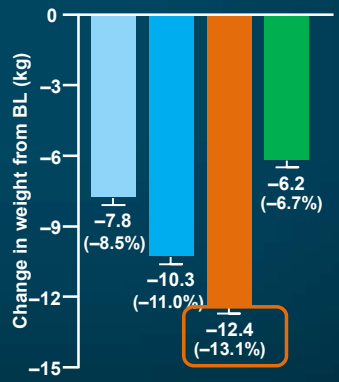
64

SURPASS 2: Body Weight Over Time and Change from BL at 40 Weeks

Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Semaglutide



TZP vs SEMA: ETD in weight (LSM ± SE)		
Tirzepatide	ETD (95% CI)	*P*-value
5 mg dose	–1.7 (–2.6 to –0.7)	<.001
10 mg dose	–4.1 (–5.0 to –3.2)	<.001
15 mg dose	–6.2 (–7.1 to–5.3)	<.001

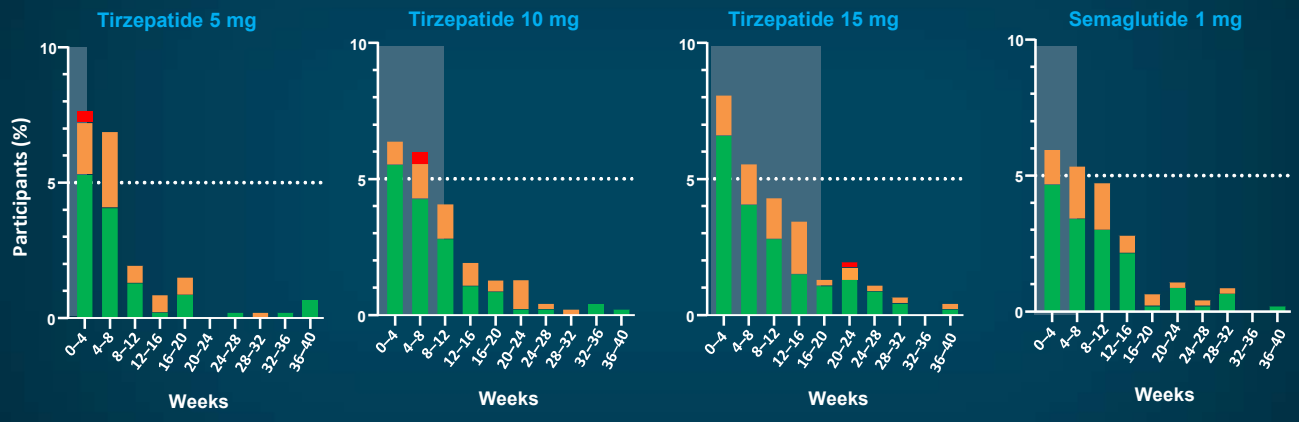


Frias JP, *et al. N Engl J Med.* 2021;385:503-515 and supplement.

65

SURPASS 2: Time Course of Nausea During Trial

Mild Moderate Severe



mITT population (safety analysis set). Shaded areas indicate the period of time before reaching the maintenance dose of the study treatments.

Frias JP, *et al. N Engl J Med.* 2021;385:503-515 and supplement.

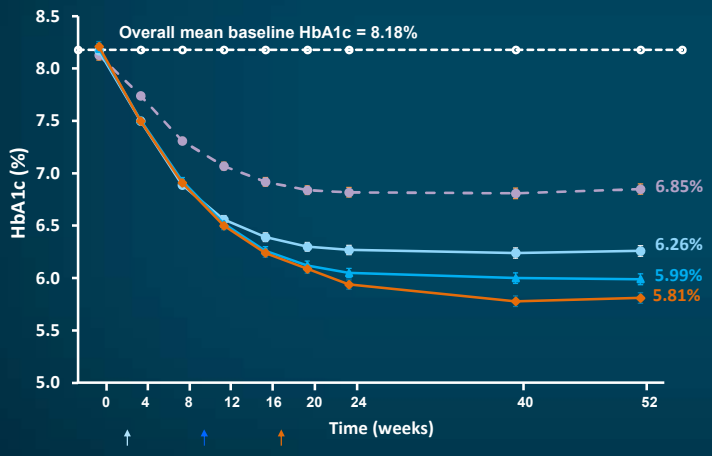
66

SURPASS 3: Tirzepatide vs Insulin Degludec

Patients received study drug (tirzepatide 5 mg, 10 mg, or 15 mg or insulin degludec) plus metformin ± SGLT-2i

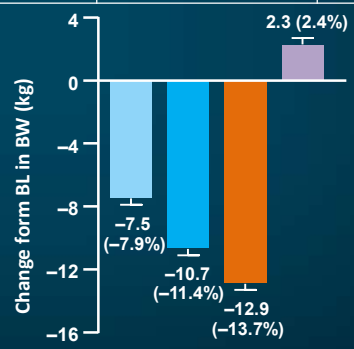
Tirzepatide 5 mg Tirzepatide 10 mg Tirzepatide 15 mg Insulin degludec

Change in HbA1c from Baseline



Change in Body Weight from Baseline

TZP vs Degludec: ETD in BW (LSM ± SE)		
Tirzepatide	ETD (95% CI)	*P*-value
5 mg dose	–9.8 (–10.8 to –8.8)	<.0001
10 mg dose	–13.0 (–14.0 to –11.9)	<.0001
15 mg dose	–15.2 (–16.2 to –14.2)	<.0001



Data are LSM (SE) over time and at 52 weeks.

Ludvik B, et al. *Lancet*. 2021;398:583-598 and supplement.

67

SURPASS 3: Overview of Adverse Events Through 52 Weeks

Parameter, n (%)	TZP 5 mg n = 358	TZP 10 mg n = 360	TZP 15 mg n = 359	Insulin Degludec n = 360
TEAEs	219 (61)	248 (69)	263 (73)	193 (54)
SAEs	29 (8)	20 (6)*	26 (7)	22 (6)
Deaths*	1 (<1)	2 (1)	1 (<1)	1 (<1)
TEAE with ≥5% frequency in any arm				
Nausea	41 (12)	81 (23)	85 (24)	6 (2)
Diarrhea	55 (15)	60 (17)	56 (16)	14 (4)
Decreased appetite	22 (6)	37 (10)	43 (12)	2 (1)
Vomiting	21 (6)	34 (9)	36 (10)	4 (1)
Dyspepsia	15 (4)	32 (9)	18 (5)	0
Lipase increased	21 (6)	16 (4)	20 (6)	7 (2)
Nasopharyngitis	11 (3)	14 (4)	15 (4)	22 (6)
Abdominal pain	7 (2)	17 (5)	23 (6)	4 (1)
Hypertension	11 (3)	7 (2)	11 (3)	21 (6)

- Hypoglycemia (<54 mg/dL or severe) was reported in ≤2% of participants on tirzepatide vs 7% of participants on insulin degludec

*Deaths are included as SAEs; one SAE is nonvalid because it occurred before randomization. Note: Patients may be counted in more than 1 category.

Ludvik B, et al. *Lancet*. 2021;398:583-598 and supplement.

68

Managing Advanced Disease

- Approximately a decade after diagnosis, patients with T2DM tend to become resistant to multiple pharmacologic agents and become increasingly insulin-dependent

29.1% **Percentage of people with T2DM who use insulin**

38.8% **Percentage of people with T2DM who have HbA1c values ≥8% despite insulin therapy**

Selvin E, et al. *Diabetes Care*. 2016;39:e33-35. Hodish I. *Diabetes Obes Metab*. 2018;20:2085-2092.

69

SURPASS 5: Tirzepatide Added to Basal Insulin

- 40-week phase 3 trial comparing tirzepatide vs placebo as add-on to titrated insulin glargine ± metformin
  - Mean baseline characteristics: 13.3 year disease duration; 60.6 years of age; HbA1c 8.31%; BMI 33.4 kg/m^2

Parameter, n (%)	TZP 5 mg n = 116	TZP 10 mg n = 119	TZP 15 mg n = 120	Placebo n = 120
% of people achieving HbA1c targets, n (%)				
<7.0%	107 (93%)	110 (97.4%)	110 (94.0%)	40 (33.9%)
≤6.5%	92 (80.0%)	107 (94.7%)	108 (92.4%)	20 (17.0%)
<5.7%	30 (26.1%)	54 (47.8%)	73 (62.4%)	2 (2.5%)
% of people achieving weight loss, n (%)				
≥5%	62 (53.9%)	73 (64.6%)	99 (84.6%)	7 (5.9%)
≥10%	26 (22.6%)	53 (46.9%)	60 (51.3%)	1 (0.9%)
≥15%	8 (7.0%)	30 (26.6%)	37 (31.6%)	0 (0.0%)

Dahl D, et al. *Diabetes*. 2021 Jun;70(Suppl 1):80-LB.

70

Tirzepatide: Clinical Implications

- Once weekly dosing
- Significant reductions in HbA1c and body weight
  - Superior to semaglutide in SURPASS-2 trial
  - Significant reduction in HbA1c and body weight when administered with insulin glargine (SURPASS-5)
- Overall safety profile similar to that of GLP-1 RAs
  - Mild to moderate GI side effects most common but decreased with continued dosing
  - Low risk of hypoglycemia
- Awaiting results of trial assessing cardiovascular outcomes

71

Case Study #2: Sal

- Sal is a 63-year-old man with a 5-year-history of diabetes
- He began gaining weight 15 years ago, and his current BMI is 36
- He reports difficulty losing weight with diet and exercise
- His past medical history is significant for obstructive sleep apnea and osteoarthritis of the knee
- Current medications: metformin 500 mg QD, insulin glargine 20 U every evening, glyburide 5 mg QD
- His current HbA1c is 6.9%

How would you manage this patient?

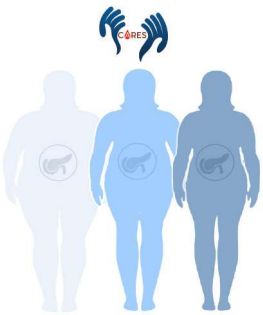
72

Reducing HbA1c and Weight with Emerging Pharmacotherapies

Summary

- Incretin-based therapy is an increasingly popular strategy for T2DM patients, especially those who are obese and desire weight loss
- Many of the GLP-1 based formulations have also been associated with improvement in CV outcomes, predominately ASCVD
- As a result of these relatively recent data, the latest T2DM guidelines from both diabetes and cardiology societies endorse GLP-1 RA use in those patients with CVD or at high risk for developing it
- One investigational agent, tirzepatide, activates both GLP-1 and GIP receptors and appears to have an even greater effect in reducing HbA1c and body weight

73



A HOLISTIC APPROACH TO DIABETES CARE:

Reducing HbA1c and Weight with Emerging Pharmacotherapies

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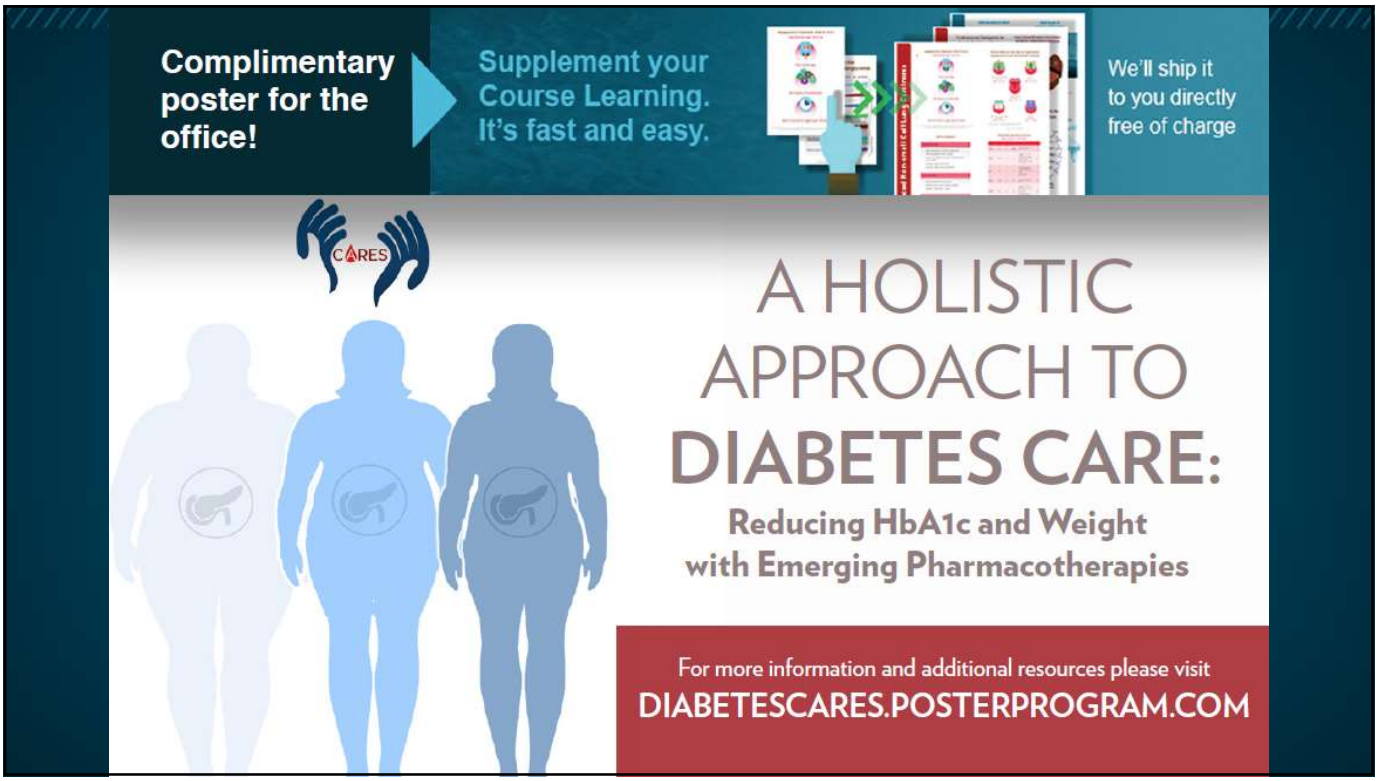
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A HOLISTIC APPROACH TO DIABETES CARE:
Reducing HbA1c and Weight with Emerging Pharmacotherapies
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DIABETESCARES.POSTERPROGRAM.COM

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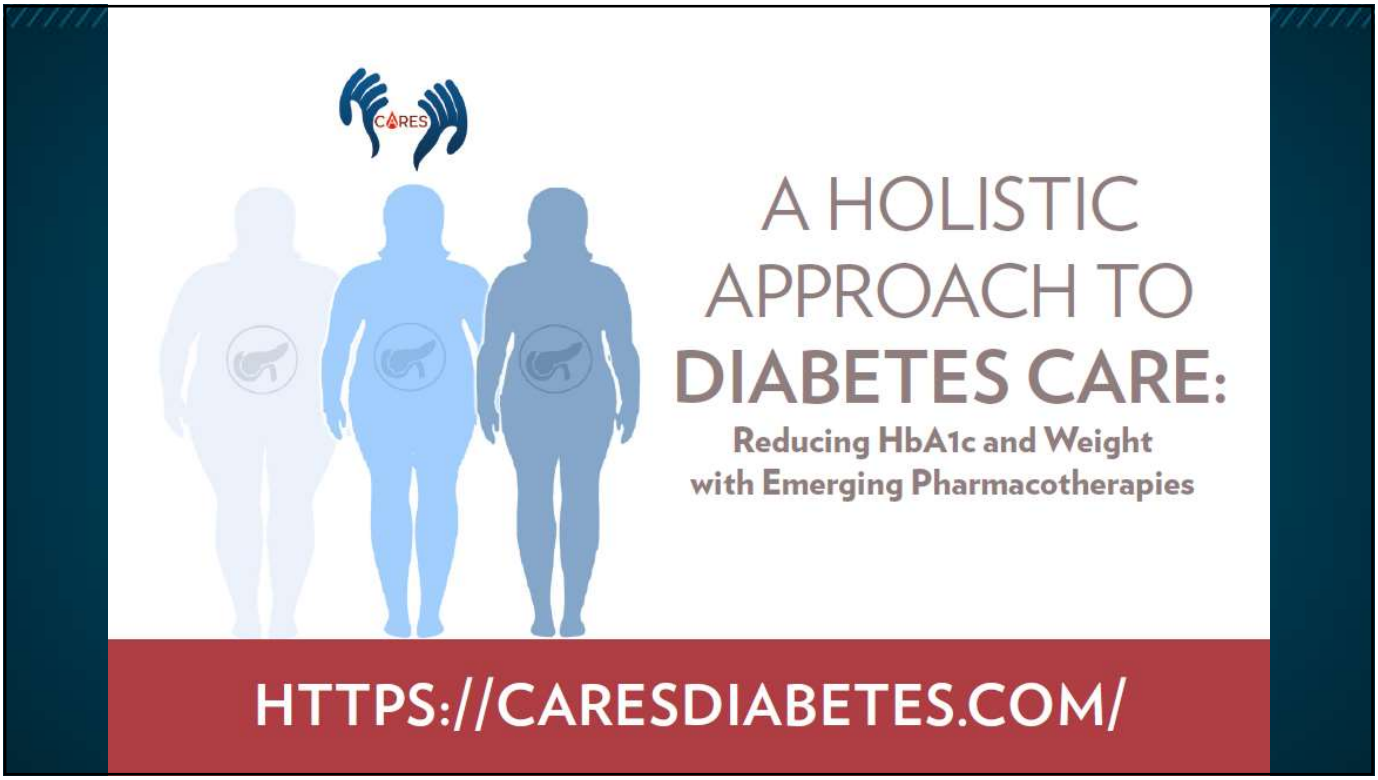
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76

Post-test Question #1

Gus has an HbA1c of 8.7% despite treatment with metformin and insulin glargine. His past medical history is significant for hypertension, osteoarthritis of the knee, and obesity (BMI: 32). You recommend that Gus reduce his weight to improve his HbA1c. How much weight should Gus lose in order to improve his glycemia?

a. At least 15 pounds

b. 5%-10% of body weight

c. 15%-20% of body weight

d. To see any glycemic improvements, his BMI must be under 25.

77

Post-test Question #2

Gus is interested in losing weight but has struggled with weight loss through diet and exercise alone. You recommend modifying Gus's treatment regimen to encourage weight loss and to reduce his HbA1c. Which of the following is LEAST likely to result in significant weight loss?

a. Liraglutide

b. Tirzepatide

c. Semaglutide

d. Exenatide

78

Post-test Question #3

Which of the following statements regarding GLP-1 and GIP is TRUE?

a. GLP-1 and GIP agonism increases the risk of hypoglycemia.

b. GLP-1 and GIP stimulate insulin release only when blood glucose levels are elevated.

c. Patients with type 2 diabetes oversecrete incretin hormones to compensate for reduced insulin sensitivity.

d. Infusions of GIP alone are able to stimulate the release of insulin.

79

Thank You!

Q & A

80