Addressing the Roots

Re-thinking the approach to type 2 diabetes management and the role of dual GIP/GLP-1 receptor agonism

GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Housekeeping Items

Camera
Please turn off your webcam

Mute your mic/phone
when not speaking

Chat Box
Please enter your questions in the chat box

Evaluation
You will be invited to complete the evaluation on your phone at the end of the presentation

Polling questions
Please scan the QR code with your phone to cast your vote

Presenter Disclosure

Name	Credentials and Affiliations

Relationships With Financial Sponsors

SPEAKERS BUREAU/HONORARIA:	
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Disclosure of Financial Support

This program has received:

- Financial support from Eli Lilly Canada Inc. in the form of an educational grant
- In-kind support from Eli Lilly Canada Inc in the form of logistical support

Potential for conflict of interest:

- Faculty members have received honoraria from the CPD Network
- Eli Lilly Canada Inc. benefits from the sale of products that may be discussed in this program

Mitigation of Potential Bias

The CPD Network is a not-for-profit physician organization that received an educational grant to develop this program. The CPD Network engaged the scientific planning committee and participated in the development of the program content and format.

The scientific planning committee was solely and fully responsible for developing the program content and was involved at all stages of CME development to achieve scientific integrity, objectivity and balance. Eli Lilly Canada Inc. provided funding for the content development and this CME event, but was not involved in any aspect of the program development process.

Any discussion of products outside of their indications represents the personal opinion of the presenter and unsolicited questions should be directed to the presenter.

Certification

College of Family Physicians of Canada (CFPC)

This 1-credit-per-hour Group Learning program has been certified by the College of Family Physicians of Canada and the province Chapter for 1.5 Mainpro+® credits.

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This educational event was organized in adherence to the guiding principles of *Diversity & Inclusion* as stated in:

www.theMedEdPledge.com

Learning Objectives

At the conclusion of this program, participants will be better able to:

- Discuss the role of adiposopathy in the pathophysiology of type 2 diabetes (T2D)
- Describe nonpharmacologic approaches to weight management in T2D
- Explain the rationale for the use of dual GIP/GLP-1 receptor agonist therapy in T2D

GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Pre-Program Polling Question

1

How familiar are you with the concept of adiposopathy (aka sick fat tissue) as a contributing cause of type 2 diabetes and its complications?

A. Not at all familiar

B. Not very familiar

C. Somewhat familiar

D. Very familiar

aka: also known as.

Pre-Program Polling Question

2

How comfortable would you be in describing the clinical trial record of efficacy and safety of dual GIP/GLP-1 receptor agonism in type 2 diabetes?

A. Not at all comfortable
B. Not very comfortable
C. Somewhat comfortable
D. Very comfortable

GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Pre-Program Polling Question

3

What is considered to be an ideal waist-to-height ratio (WHtR)?

A. <0.25
B. <0.5
C. <0.75
D. <1.0
E. None of the above

Pre-Program Polling Question

4

Which of these incretin hormones is thought to be associated with the greatest physiological contribution to post-prandial insulin secretion?

A. Glucose-dependent insulinotropic polypeptide (GIP)

B. Glucagon-like peptide-1 (GLP-1)

C. GIP and GLP-1 are thought to have roughly equivalent impact

GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Pre-Program Polling Question

5

A novel dual GIP/GLP-1 receptor agonist has demonstrated superiority in A1C lowering compared to which of the following antihyperglycemic agents in a head-to-head phase 3 clinical trial?

A. Sitagliptin
B. Semaglutide
C. Metformin
D. Gliclazide
E. Canagliflozin

A1C: glycated hemoglobin; GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Consider This Patient, Mihika

History
- 46-year-old female
- South Asian ethnicity
- Type 2 diabetes
- Hypertension
- Polycystic ovary syndrome

Investigations
- A1C 8.2%
- UACR 10 mg/mmol

Physical examination
- Height: 160 cm
- Weight: 69 kg
- Body mass index: 27 kg/m^2
- Waist circumference 85 cm
- BP 140/90 mmHg

Medications
- Metformin 1 g b.i.d.
- Ramipril 10 mg q.d.
- Rosuvastatin 10 mg q.d.

A1C: glycated hemoglobin; BP: blood pressure; UACR: urine albumin-to-creatinine ratio.

Opinion Polling Question

What do you think might be the most likely underlying cause of Mihika's type 2 diabetes, hypertension and polycystic ovary syndrome?

a) Overweight (27 kg/m^2)

b) Central adiposity (waist circumference 85 cm)

c) Family history / genetics

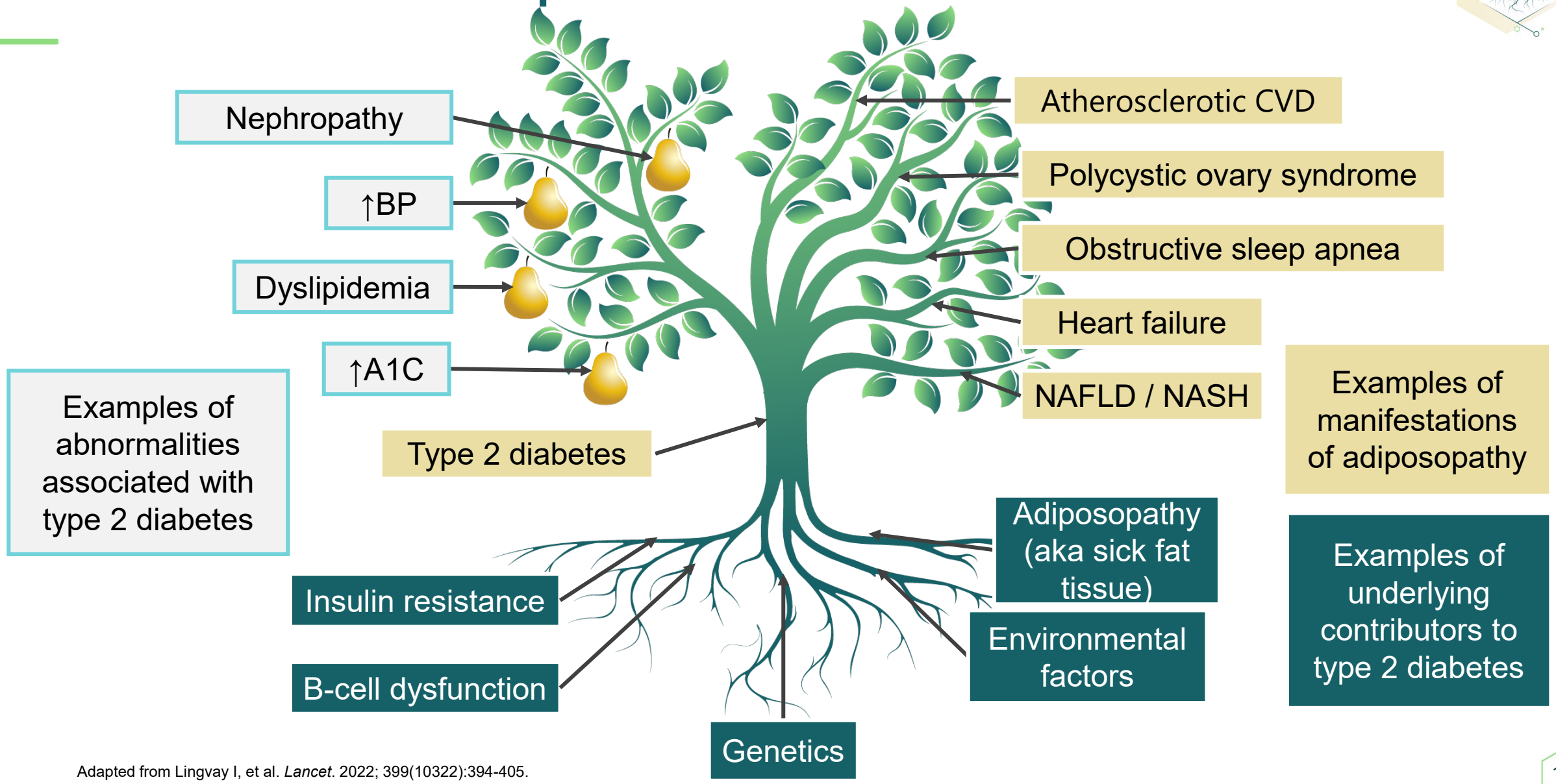
d) South Asian ethnicity

e) Something else

Stepping Back

What are the roots of type 2 diabetes pathophysiology?

The Pathological Roots of Type 2 Diabetes: A Horticultural Metaphor



Adapted from Lingvay I, et al. *Lancet*. 2022; 399(10322):394-405.
A1C: glycated hemoglobin; BP: blood pressure; CVD: cardiovascular disease; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis

What is “Adiposopathy”?

- Adiposopathy (*aka “Sick Fat Tissue”*) is anatomically manifested by adipocyte hypertrophy, visceral adiposity and/or ectopic fat deposition, which physiologically results in adverse endocrine and immune consequences leading to metabolic disease[1]
- White adipose tissue (WAT) is essential to human health, but its unhealthy expansion in certain areas of the body is thought to be the key mechanism behind adiposity-related pathologies[2]

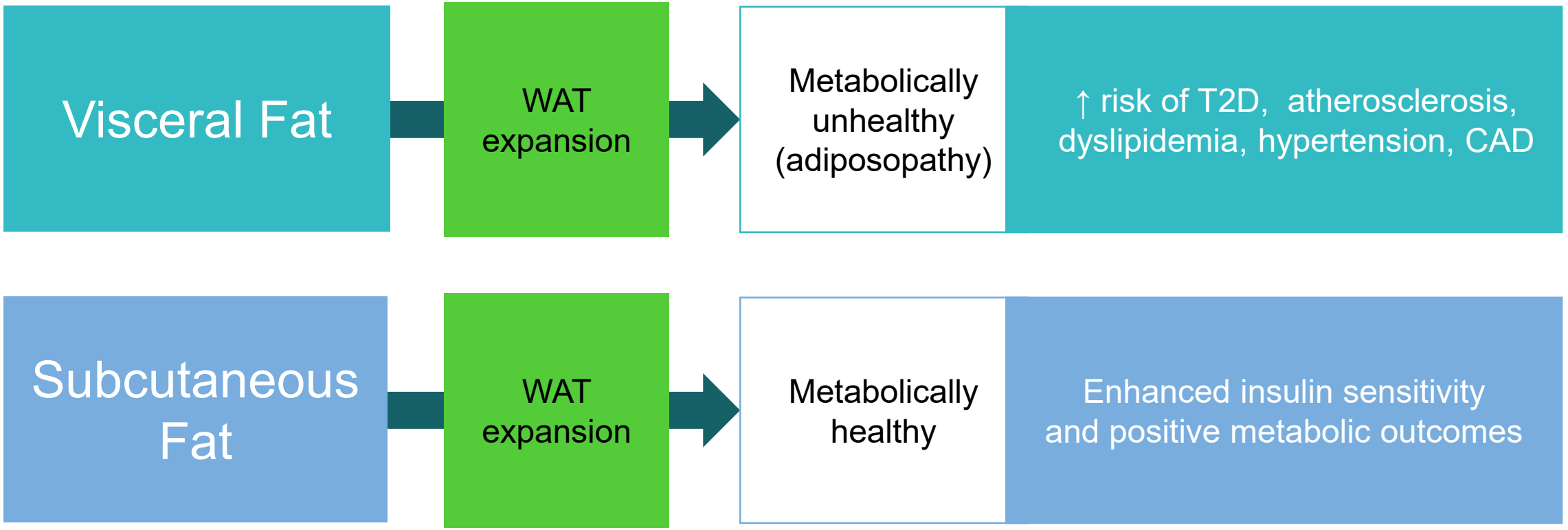
Obesity, as defined by BMI, does not necessarily equal adiposopathy[1,3]

People with T2D have adiposopathy… but not all people with adiposopathy have T2D[3]

BMI: body mass index; T2D: type 2 diabetes.

Adapted from 1. Bays HE, et al. *Int J Clin Pract.* 2008; 62(10):1474-83; 2. Cypess AM. *N Engl J Med*. 2022; 386(8):768-79; 3. Lingvay I, et al. *Lancet*. 2022; 399(10322):394-405.

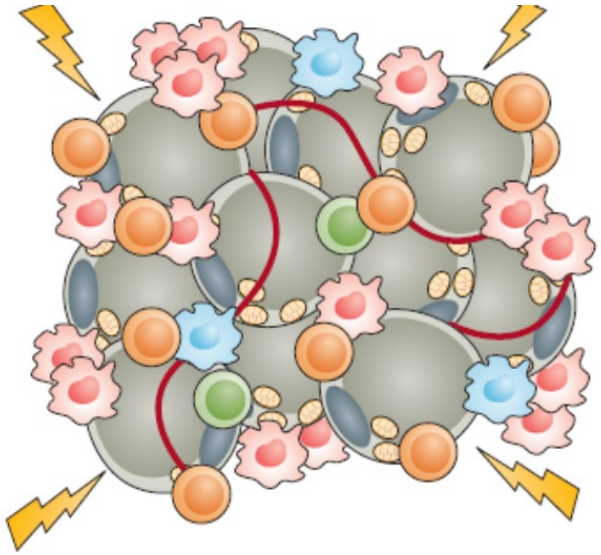
Most Critical Aspect of White Adipose Tissue Expansion… Location, Location, Location[1-7]



CAD: coronary artery disease; T2D: type 2 diabetes; WAT: white adipose tissue

1. Berg AH, et al. *Circ Res.* 2005; 96(9):939-49. 2. Despres JP, et al. *Arterioscler Thromb Vasc Biol.* 2008; 28(6):1039-49. 3. Hajer GR, et al. *Eur Heart J.* 2008; 29(24):2959-71;
4. Antuna-Puente B, et al. *Diabetes Metab.* 2008; 34(1):2-11. 5. Oikonomou EK, et al. *Nat Rev Cardiol.* 2019;16(2):83-99; 6. Bello-Chavolla OY, et al. *Clin Nutr.* 2020; 39(5):1613-21;
7. Kusminski CM, et al. *Nat Rev Drug Discov*. 2016; 15(9):639-60.

What Are the Pro-inflammatory Changes Associated with Unhealthy WAT Expansion?



WAT expansion through adipocyte hypertrophy

↓

Shift to an adverse adipokine secretory profile

↑ pro-inflammatory factors, e.g.:

- TNF
- IL-1β
- IL-6
- IL-8
- Leptin
- Resistin
- MCP1

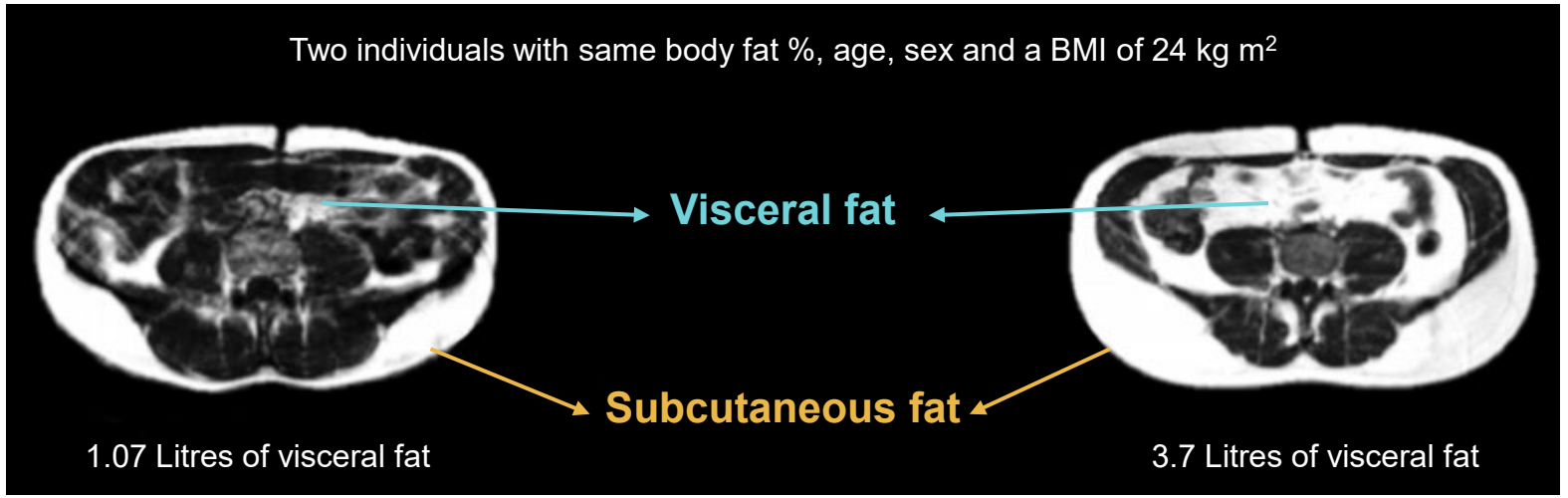
↓ anti-inflammatory factors, e.g.:

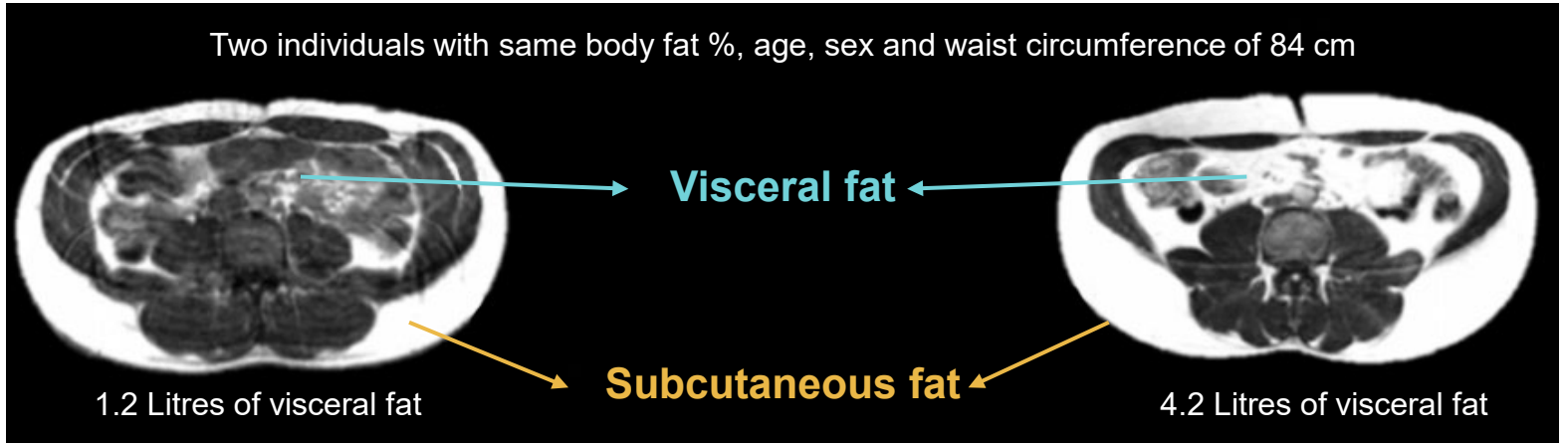
- IL-10
- Adiponectin

IL-1β: Interleukin 1 beta; IL-6: Interleukin-6; IL-8: Interleukin-8; IL-10: Interleukin-10; MCP1: monocyte chemoattractant protein-1; TNF: tumor necrosis factor.

Guilherme A, et al. *Nat Rev Endocrinol*. 2019;15(4):207-25.

BMI Is Not An Accurate Predictor of Adiposopathy: Examples

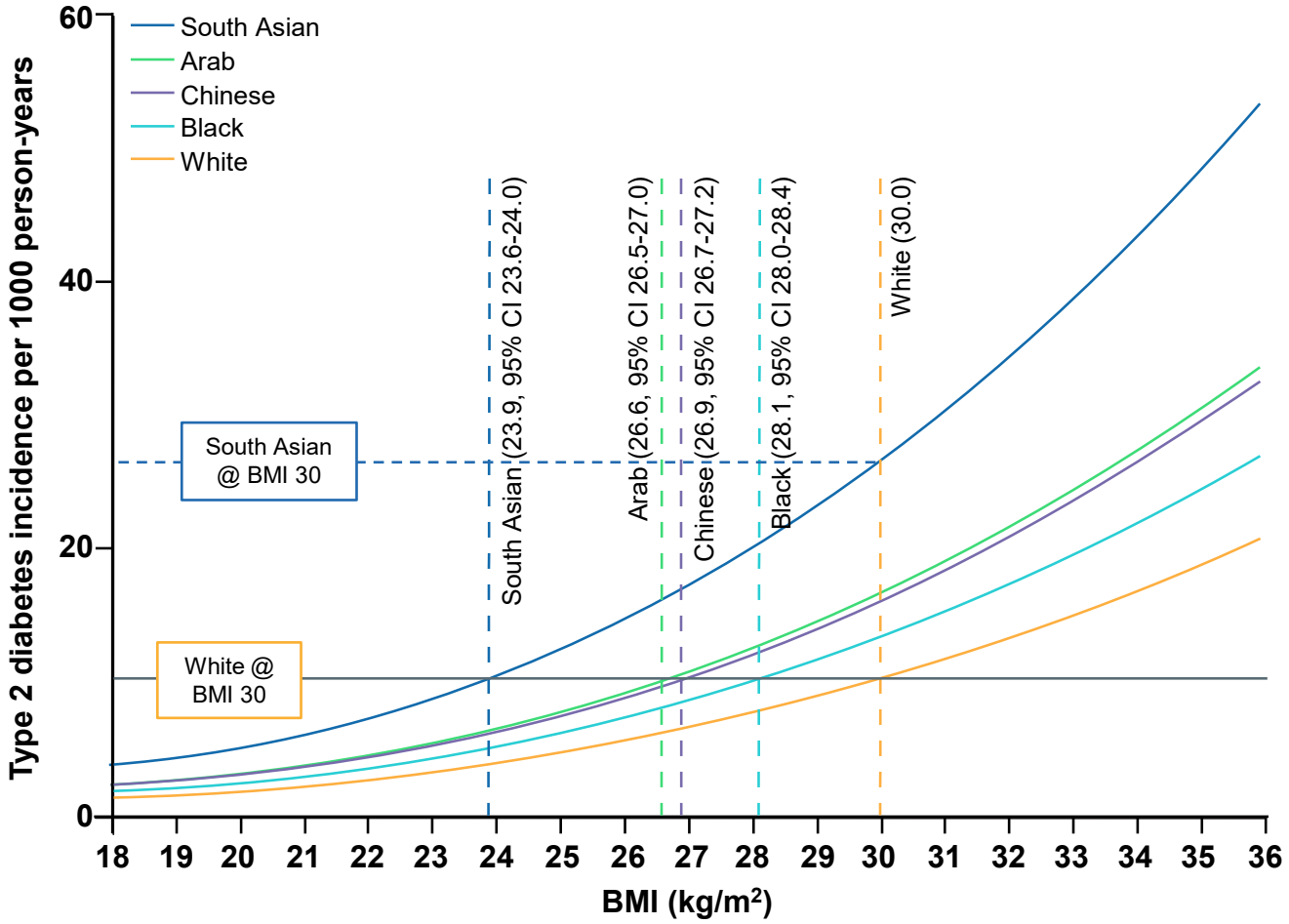




BMI: body mass index
Adapted from Yaghootkar H, et al. *J Intern Med*. 2020; 288(3):271-83.

People of Different Ethnicities Have Different Thresholds for BMI as a Risk Factor for T2D

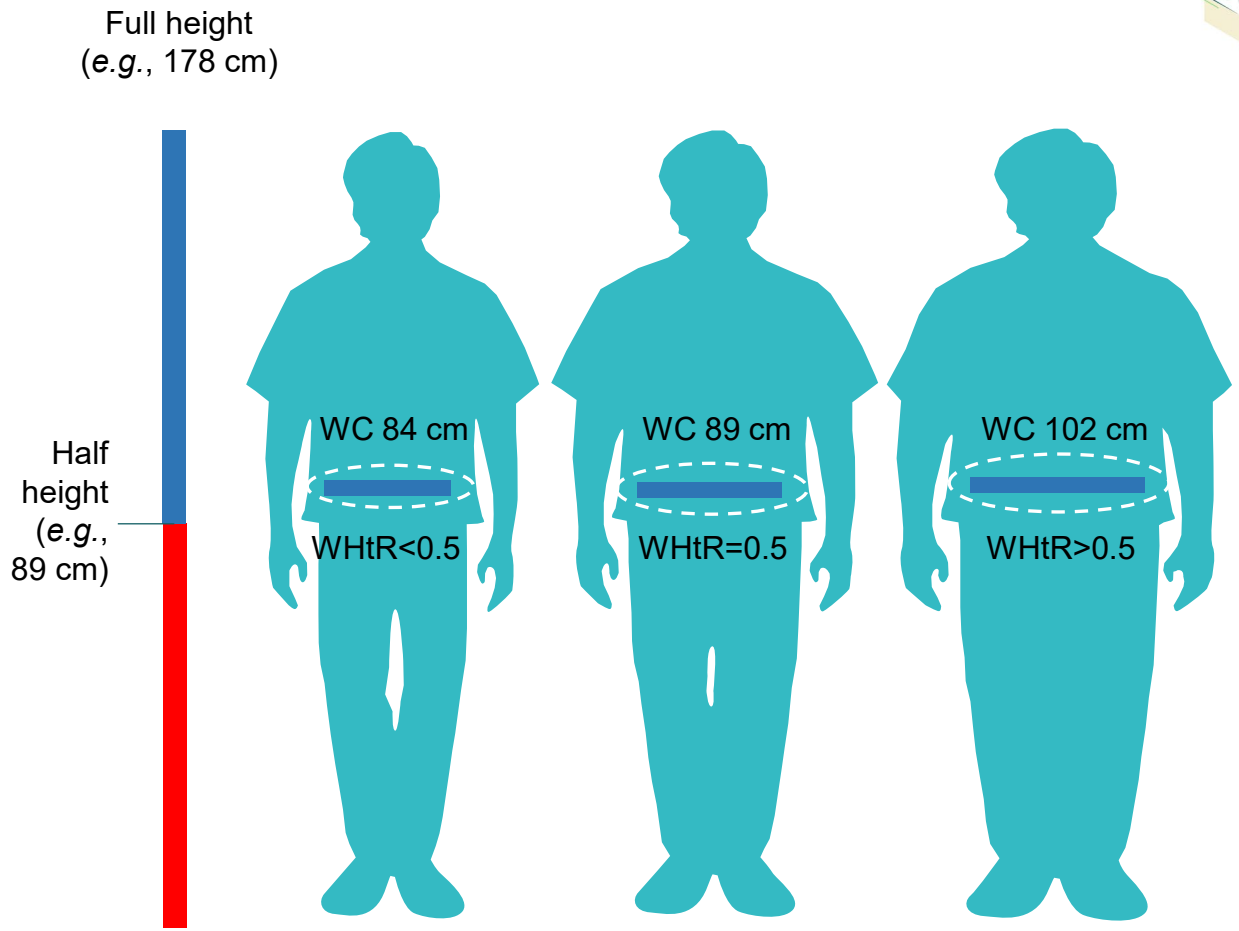
Thresholds were calculated based on equivalence in risk of developing type 2 diabetes compared to a White individual with a BMI of 30 kg/m^2



BMI: body mass index; CI: confidence interval; T2D: type 2 diabetes.
Adapted from Caleyachetty R, et al. *Lancet Diabetes Endocrinol*. 2021; 9(7):419-26.

Waist-to-Height Ratio (WHtR): A Simple Indicator of Adiposopathy

- Meta-analysis suggests that WHtR is a superior tool for discriminating obesity-related cardiometabolic risk compared with BMI or WC[1,2]
- Ideal WHtR is <0.5 (*i.e.*, waist circumference should be less than half height)[2]
- Ethnic-specific studies are still lacking, but there is some evidence that the 0.5 cutoff applies across ethnicities[3]



Click here to see proper WC measurement technique

BMI: body mass index; WC: waist circumference.

1. Ashwell M, et al. *Obes Rev*. 2012; 13(3):275-86; 2. Browning LM, et al. *Nutr Res Rev*. 2010; 23(2):247-69; 3. Kazlauskaite R, et al. *Am J Hum Biol*. 2017; 29(1):10.

Back to Mihika: Is There More We Can Do For Her?

- Some people, like our patient, may seem to have only modestly elevated BMI, yet they develop metabolic complications
  - Mihika's WHtR = 0.53
- This supports the concept that adiposopathy, rather than adipose tissue quantity, may be the primary driver of complications

BMI: body mass index; WHtR: Waist-to-Height Ratio.
Adapted from Lingvay I, et al. *Lancet*. 2022; 399(10322):394-405.

Discussion

So what should we do to help her and others like her?

Opinion Polling Question

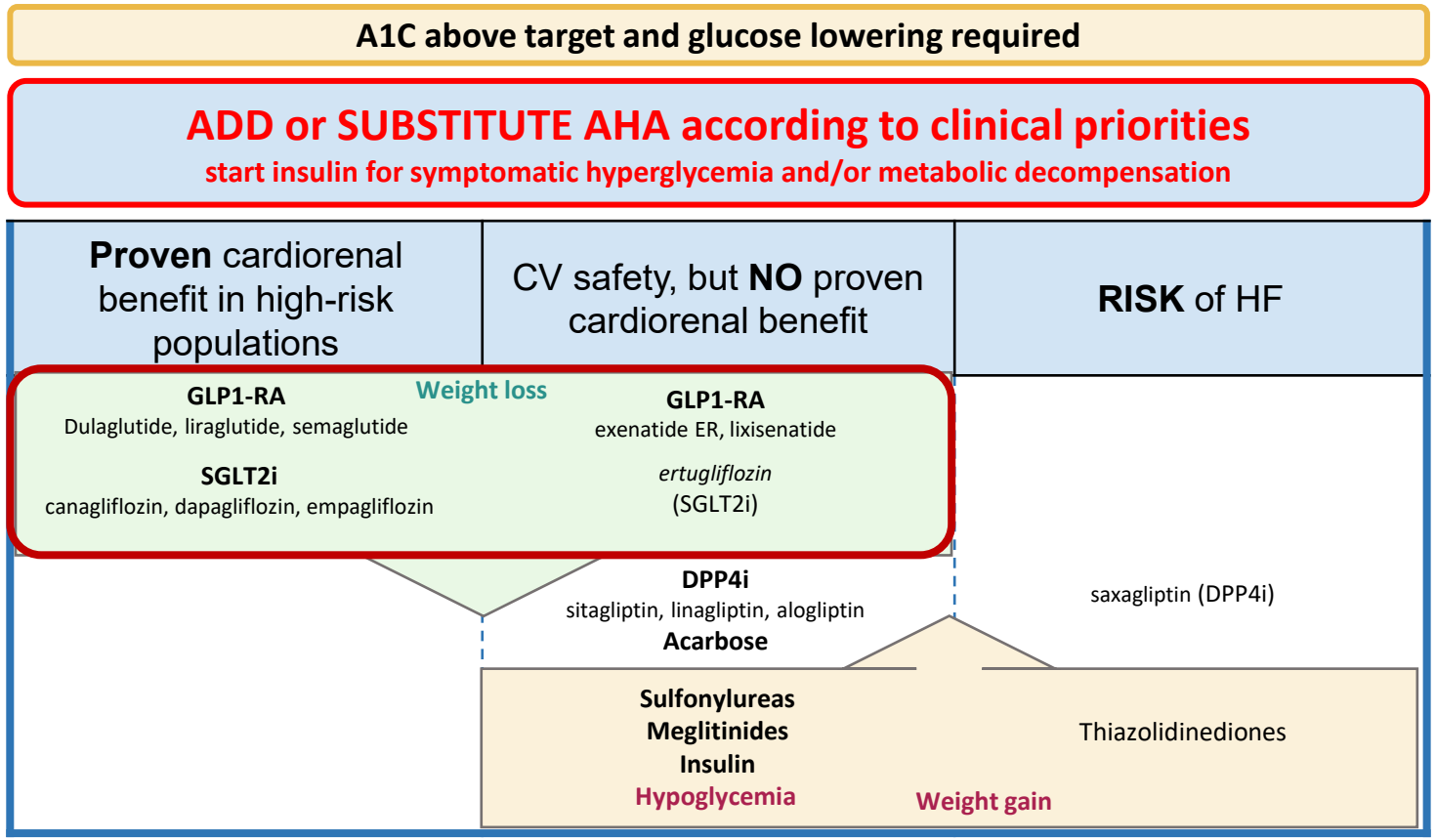
Should guidelines include addressing adiposopathy among the core treatment goals for patients with type 2 diabetes?

a) Yes

b) No

c) Maybe

2020 Diabetes Canada Update: Weight Management is a Key Clinical Priority When Adding or Substituting an Antihyperglycemic Agent



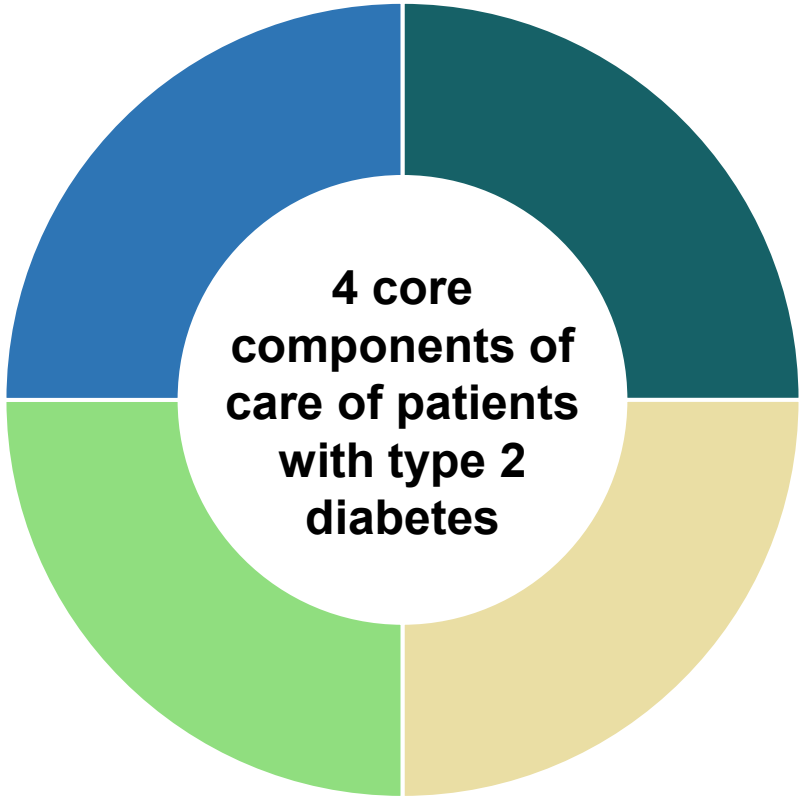
Fixed-dose combinations may be considered to reduce burden

A1C: glycated hemoglobin; AHA: antihyperglycemic agent; ASCVD: atherosclerotic cardiovascular diseases; CKD: chronic kidney disease; CV: cardiovascular disease; DPP4i: dipeptidyl peptidase-4 inhibitor; GLP1-RA: glucagon-like peptide 1 receptor agonist; HF: heart failure; HHF: hospitalization for heart failure; MACE: major adverse cardiovascular events; SGLT2i: sodium glucose co-transporter 2 inhibitor.

Lipscombe L, et al. Can J Diabetes. 2020; 44:575-91.

Weight Management: Recognized by Experts as a Key Component of Diabetes Care

From a 2022 Consensus Report on the Management of Hyperglycemia by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)



Cardiorenal protection – choice of glucose-lowering medication

Medication for glycemic management

Cardiovascular risk factor management

Weight management

Adapted from Davies MJ, et al. *Diabetologia*. 2022; 65(12):1925-66.

Comprehensive Management of Type 2 Diabetes

Should We Incorporate Modulation of Adiposopathy as a Treatment Goal?

Nonpharmacologic Approaches

Can These Influence Adiposopathy?

T2D: type 2 diabetes.

Healthy Behaviour Interventions are the Cornerstone of Treatment: Key Messages from the Diabetes Canada Clinical Practice Guidelines

- Sustained weight loss of >5% of initial body weight can improve glycemic control and CV risk factors

- In people with diabetes and obesity, weight loss and A1C lowering can be achieved with healthy behaviour interventions as the cornerstone of treatment

A1C, glycated hemoglobin; CV, cardiovascular
Adapted from Diabetes Canada Clinical Practice Guidelines Expert Committee; Can J Diabetes. 2018;42 Suppl 1:S124-S129.

Lifestyle Modifications With Evidence of Benefit in T2D

Food Intake

- Reduced carbohydrate intake / foods with lower glycemic index favoured[1]
- Calorie-restricted balanced diet with adequate intake of micronutrients, aligned with circadian rhythm (i.e., not eating close to bedtime)[2-11]

Physical Activity

- Reduced amount of time sitting[12-15]
- "Exercise snacking"- small amount of activity whenever possible[16]
- Physical activity after meals[17]

Improved sleep is also associated with evidence of benefit[18-21]

T2D: type 2 diabetes.

Adapted from 1. Sievenpiper JL, et al. *Can J Diabetes.* 2018; 42:S64-S79; 2. Patterson RE, et al. *Ann Rev Nutr.* 2017; 37(1):371-93; 3. Farshchi HR, et al. *Am J Clin Nutr*. 2005; 81(1):16-24; 4. Poggiogalle E, et al. *Metabolism*. 2018; 84:11-27; 5. Jamshed H, *et al. Nutrients.* 2019; 11:1234; 6. Peeke PM, *et al. Nutr Diabetes.* 2021; 11:6; 7. Oosterman JE, et al. *Endocrinology.* 2020; 161:bqaa180; 8. Bonnet JP, et al. *Obesity* (Silver Spring). 2020; 28:1098-109; 9. Gu C, et al. *J Clin Endocrinol Metab.* 2020; 105:2789-802; 10. Hutchison AT, et al. *Obesity* (Silver Spring). 2019; 27:724-32; 11. Liu D, et al. *N Engl J Med*. 2022; 386:1495-504; 12. Dempsey PC, et al. *Diabetes Care.* 2016; 39:964-72; 13. Duvivier BM, et al. *Diabetologia*. 2016; 60:490-8; 14. Winkler EA, et al. *Med Sci Sports Exerc*. 2018; 50(3):516-24; 15. Dempsey PC, et al. *Curr Diab Rep*. 2016; 16(11):114; 16. Francois ME, *et al*. *Diabetologia*. 2014; 57(7):1437-45; 17. Colberg SR, et al. *J Am Med Dir Assoc*. 2009; 10(6):394-7; 18. Mesarwi O, et al. *Endocrinol Metab Clin North Am*. 2013; 42(3):617-34; 19. Donga E, et al. *J Clin Endocrinol Metab*. 2010; 95(6):2963-8; 20. Antza C, et al. *J Endocrinol*. 2021; 252(2):125-41; 21. Koren D, et al. *Metabolism*. 2018; 84:67-75.

Stage-targeted Nutrition for Type 2 Diabetes: 2018 Diabetes Canada Clinical Practice Guidelines

Early T2D
- Weight loss or maintenance*
- Portion control
- Low-GI CHO
- High fibre
- CHO distribution
- Dietary pattern of choice†
- Physical activity

T2D NOT on Insulin
- Weight loss or maintenance*
- Portion control
- CHO distribution
- Low-GI CHO
- High fibre
- Dietary pattern of choice†
- Physical activity

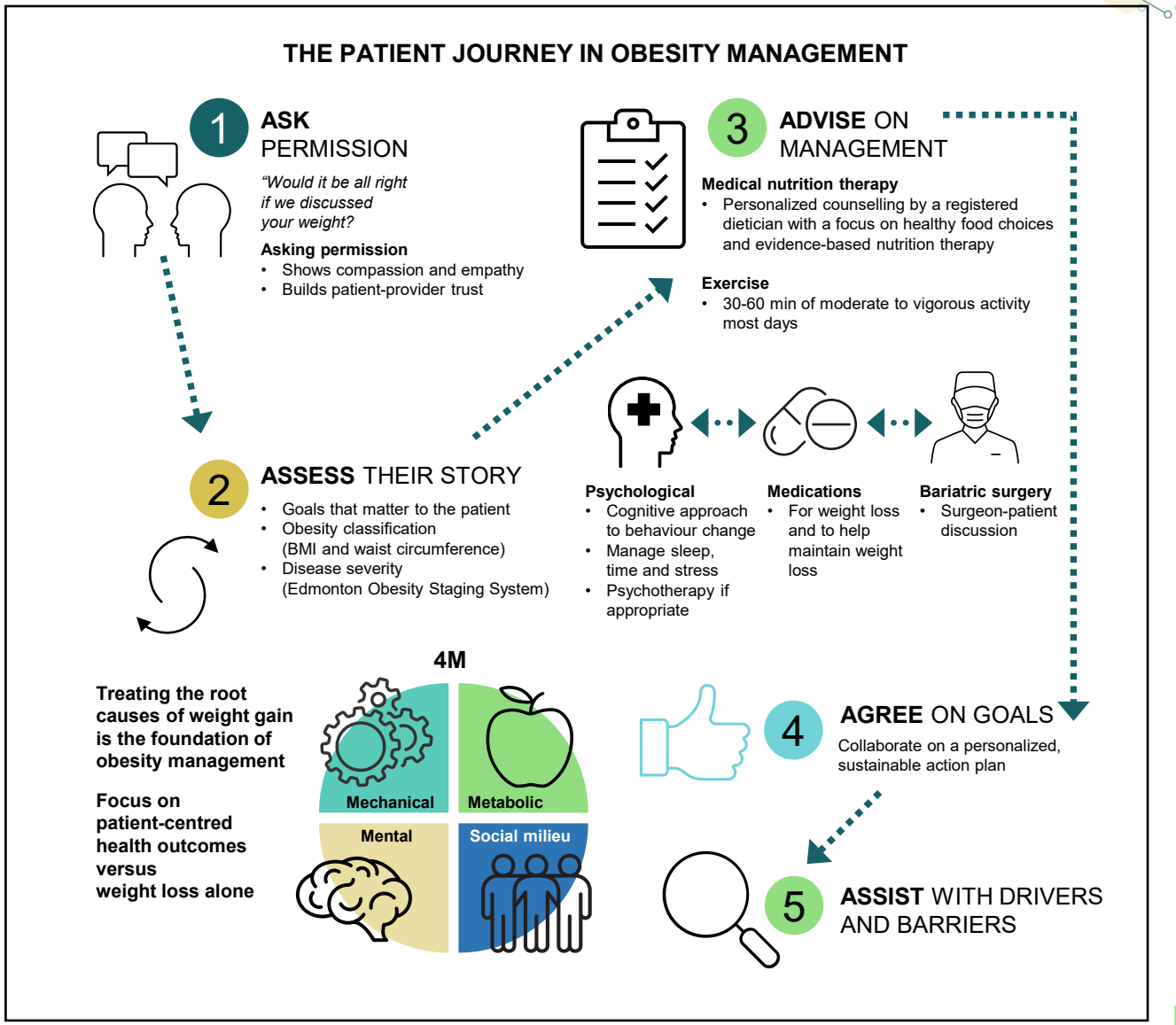
T2D on Basal Insulin Only
- Portion control
- Weight loss or maintenance*
- CHO consistency
- Low-GI CHO
- High fibre
- Dietary pattern of choice†
- Physical activity

T2D on Basal-bolus Insulin
- Portion control
- Weight loss or maintenance*
- CHO consistency initially, then learn CHO counting
- Low-GI CHO
- High fibre
- Dietary pattern of choice†
- Physical activity

*As appropriate
†Dietary patterns include Mediterranean, vegetarian, DASH, Portfolio and Nordic dietary patterns, as well as diets emphasizing specific foods (i.e., dietary pulses, fruits and vegetables, nuts, whole grains and dairy products) which have evidence of benefit for people with diabetes.
CHO, carbohydrate; GI, glycemic index; T2D, type 2 diabetes

Recognition and Respect of the Patient with Obesity

- Canadian obesity guidelines describe a system of “five As” for clinicians to keep in mind when caring for a patient with obesity:
- **A**sk
- **A**ssess
- **A**dvise
- **A**gree
- **A**ssist



Wharton S, et al. CMAJ 2020; 192:E875-91.
Diagram is reproduced, with no changes made, under license CC BY-NC-ND 4.0.

Canadian Obesity Guidelines (2020): Importance of Attitudes, Beliefs and Biases

"Healthcare providers should assess their own attitudes and beliefs regarding obesity and consider how their attitudes and beliefs may influence care delivery"

"Healthcare providers should recognize that internalized weight bias (bias towards oneself) in people living with obesity can affect behavioural and health outcomes"

"We recommend that healthcare providers avoid making assumptions that an ailment or complaint a patient presents with is related to their body weight."

"Healthcare providers should avoid using judgmental words, images and practices when working with patients living with obesity."

Kirk SFL, et al. Canadian Adult Obesity Clinical Practice Guidelines: Reducing Weight Bias in Obesity Management, Practice and Policy. Available from: https://obesitycanada.ca/guidelines/weightbias. Accessed March 2, 2022.

Canadian Obesity Guidelines Recommendations on Bariatic Surgery

Bariatric surgery can be considered for people with BMI ≥ 40 kg/m^2 or BMI ≥ 35 kg/m^2 with at least 1 adiposity-related disease to:

- Reduce long-term overall mortality
- Induce significantly better long-term weight loss compared with medical management alone
- Induce control and remission of type 2 diabetes, in combination with best medical management, over best medical management alone
- Significantly improve quality of life
- Induce long-term remission of most adiposity-related diseases, including dyslipidemia, hypertension, liver steatosis and nonalcoholic steatohepatitis

BMI: body mass index

Wharton S, *et al. CMAJ.* 2020; 192:E875-91.

2022 Joint Statement of the American Society for Metabolic & Bariatric Surgery and the International Federation for the Surgery of Obesity and Metabolic Disorders

Indications for Metabolic and Bariatric Surgery (MBS)

"Metabolic and bariatric surgery (MBS) is recommended for individuals with a BMI ≥35 kg/m^2, regardless of presence, absence, or severity of co-morbidities."

"MBS should be considered for individuals with metabolic disease and BMI of 30-34.9 kg/m^2."

"BMI thresholds should be adjusted in the Asian population such that a BMI ≥25 kg/m^2 suggests clinical obesity, and individuals with BMI ≥27.5 kg/m^2 should be offered MBS."

"Long-term results of MBS consistently demonstrate safety and efficacy."

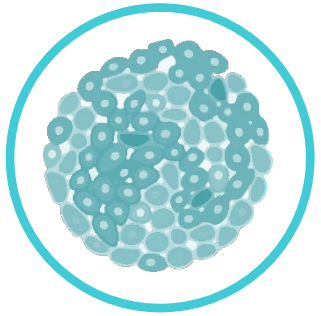
Adapted from Eisenberg D, et al. Obes Surg. 2023;33(1):3-14.

Pharmacologic Approaches

T2D: type 2 diabetes.

Key Historic Focus of Diabetes Management: Glycemic Control and The Ominous Octet

Decreased insulin secretion



Increased glucagon secretion
Islet-α-cell

Increased hepatic glucose production

Decreased incretin effects

Neurotransmitter dysfunction

HYPERGLYCEMIA

Increased lipolysis

Increased glucose reabsorption

Decreased glucose uptake

Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; and Abdul-Ghani M, et al. *Diabetes Care.* 2017; 40:1121-7.

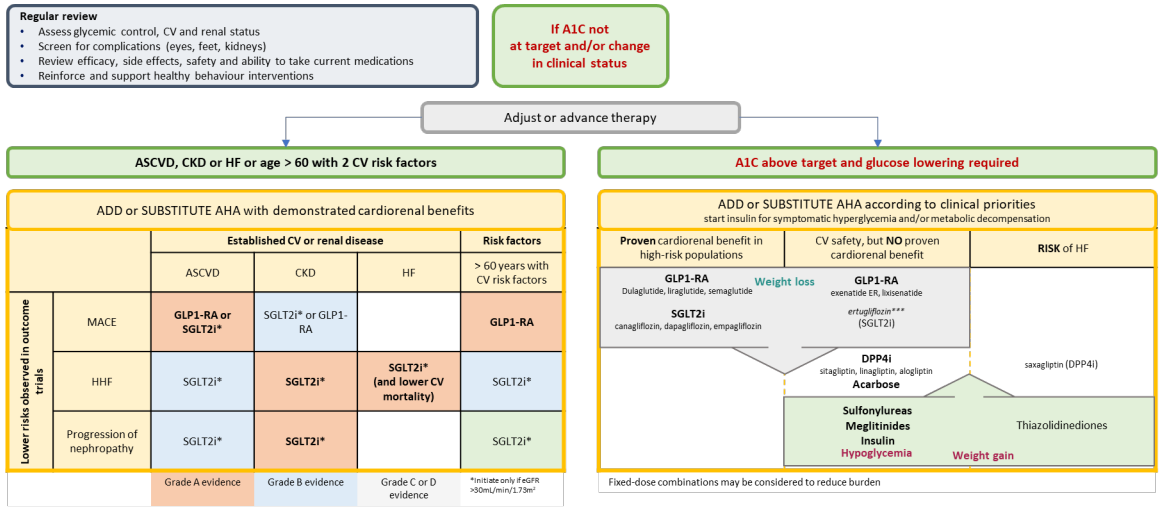
Common Antihyperglycemic Therapies and How They Address the Ominous Octet

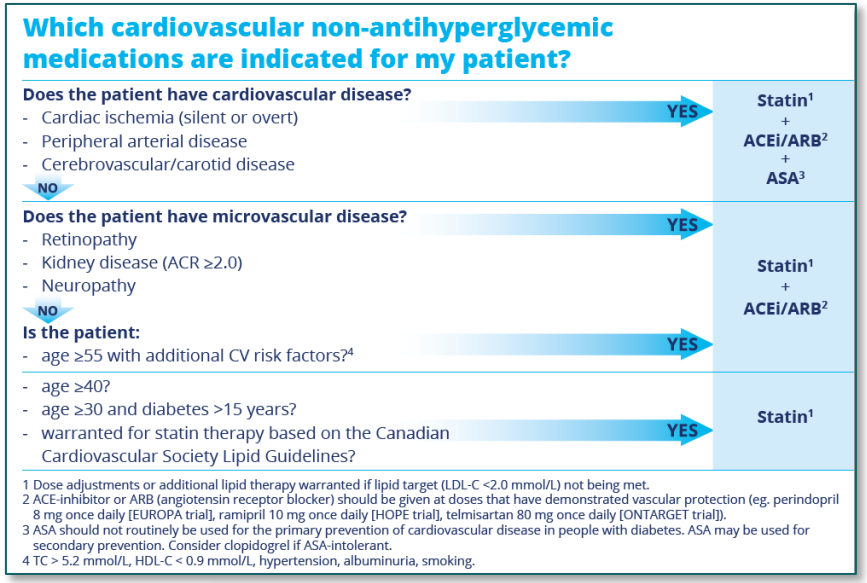
Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i
 ↑ insulin secretion		✓	✓	✓	✓	
 ↓ glucagon secretion				✓	✓	
 ↓ hepatic glucose production	✓		✓	✓	✓	
 Incretin pathways				✓	✓	
 ↓ lipolysis			✓			
 ↓ glucose reabsorption						✓
 ↑ glucose uptake	✓		✓	✓	✓	
 ↓ neurotransmitter dysfunction					?	

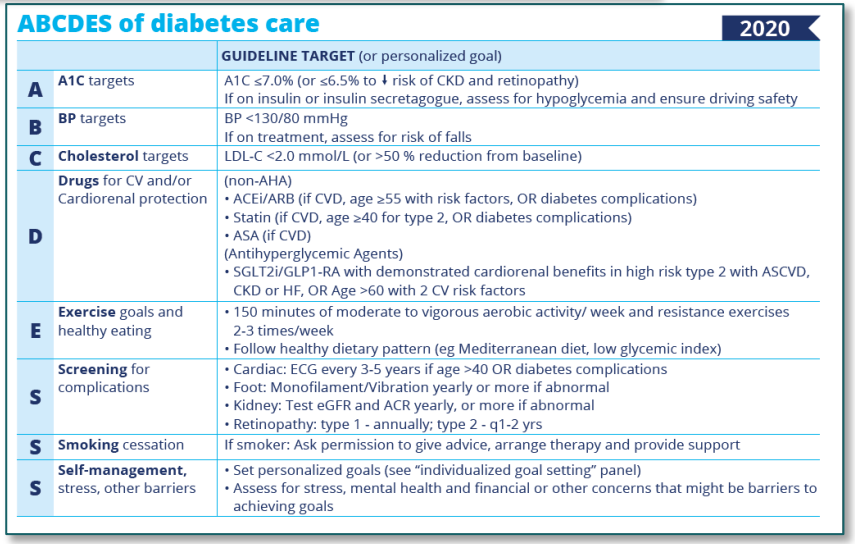
DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas.
Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; and Abdul-Ghani M, *et al. Diabetes Care.* 2017; 40:1121-7.

Beyond Glucose: Adding Cardiorenal Protection As a Key Focus in T2D

Diabetes Canada guidelines now incorporate multiple key goals, including selection of therapies proven to reduce cardiorenal risk (*e.g.*, SGLT2is, some GLP1-RAs)[1,2]







GLP1-RA: glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor ; T2D: type 2 diabetes.

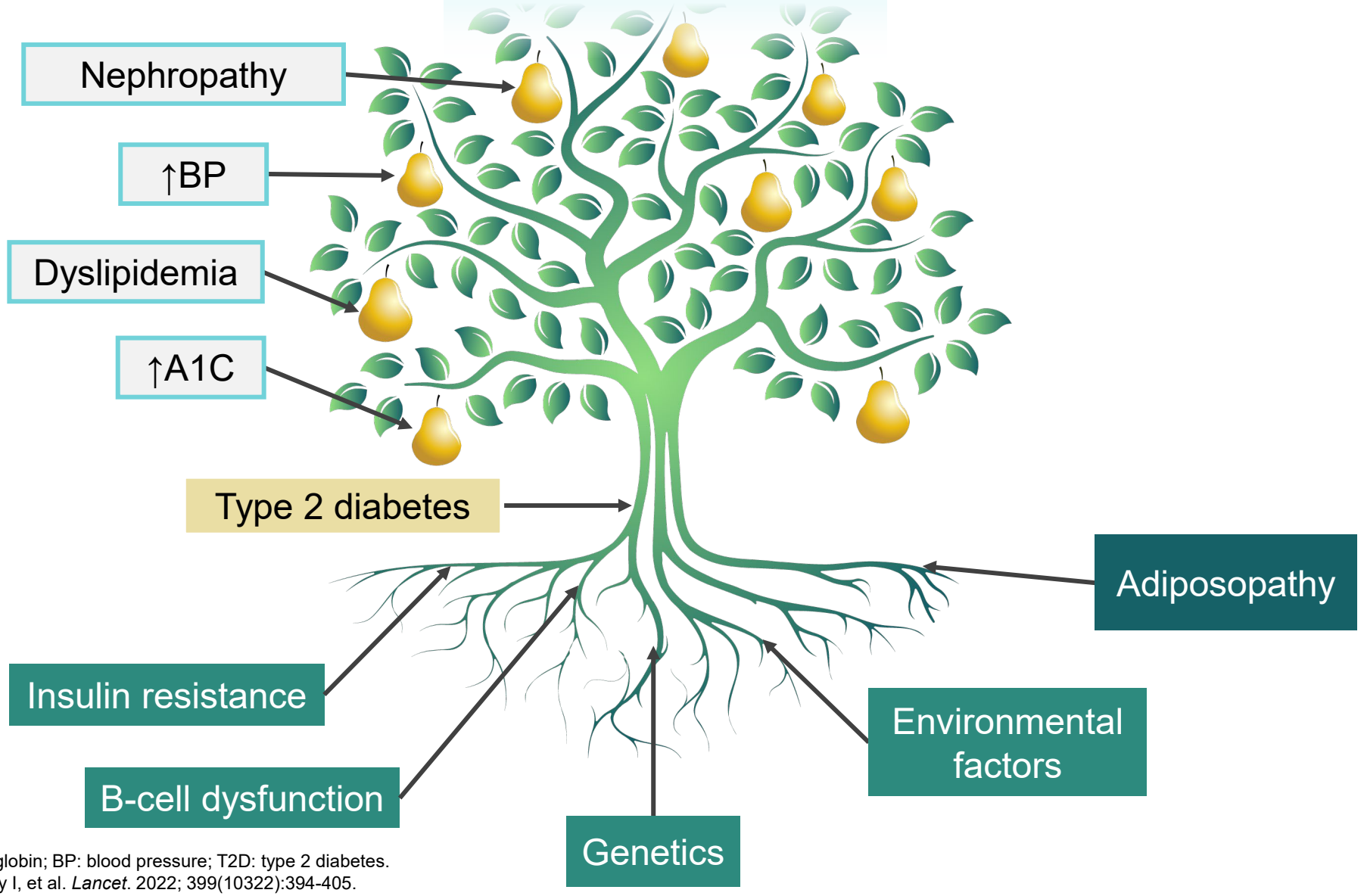
1. Lipscombe L, et al. *Can J Diabetes*. 2020; 44(7):575-91.
2. Diabetes Canada 2020 Quick Reference Guide. Online at http://guidelines.diabetes.ca/CDACPG/media/documents/CPG/CPG_Quick_Reference_Guide_PRINT_EN_2021.pdf Accessed September 2022.

Evolving View of Antihyperglycemic Therapies, Including Cardiorenal Protection

Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i
↑ insulin secretion		✓	✓	✓	✓	
↓ glucagon secretion				✓	✓	
↓ hepatic glucose production	✓		✓	✓	✓	
Incretin pathways				✓	✓	
↓ lipolysis			✓			
↓ glucose reabsorption						✓
↑ glucose uptake	✓		✓	✓	✓	
↓ neurotransmitter dysfunction					?	
↓ cardiorenal risk					✓	✓

DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas.
Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; Abdul-Ghani M, *et al. Diabetes Care.* 2017; 40:1121-7; and Lipscombe L, et al. *Can J Diabetes*. 2020; 44(7):575-91.

Even with Cardiorenal Protection, We Are Still Not Getting to All the Root Contributors to T2D



A1C: glycated hemoglobin; BP: blood pressure; T2D: type 2 diabetes.
Adapted from Lingvay I, et al. *Lancet*. 2022; 399(10322):394-405.

What if We Added Targeting Adiposopathy to Our Treatment Goals?

Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i
↑ insulin secretion		✓	✓	✓	✓	
↓ glucagon secretion				✓	✓	
↓ hepatic glucose production	✓		✓	✓	✓	
Incretin pathways				✓	✓	
↓ lipolysis			✓			
↓ glucose reabsorption						✓
↑ glucose uptake	✓		✓	✓	✓	
↓ neurotransmitter dysfunction					?	
↓ cardiorenal risk					✓	✓
Modulation of adiposopathy	?	?	?	?	?	?

DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas.
Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; Abdul-Ghani M, *et al. Diabetes Care.* 2017; 40:1121-7; and Lipscombe L, et al. *Can J Diabetes*. 2020; 44(7):575-91.

Opinion Polling Question

Which of the currently available antihyperglycemic classes / agents would be most likely to positively influence adiposopathy?

a) DPP4 inhibitors

b) GLP-1 receptor agonists

c) Metformin

d) SGLT2 inhibitors

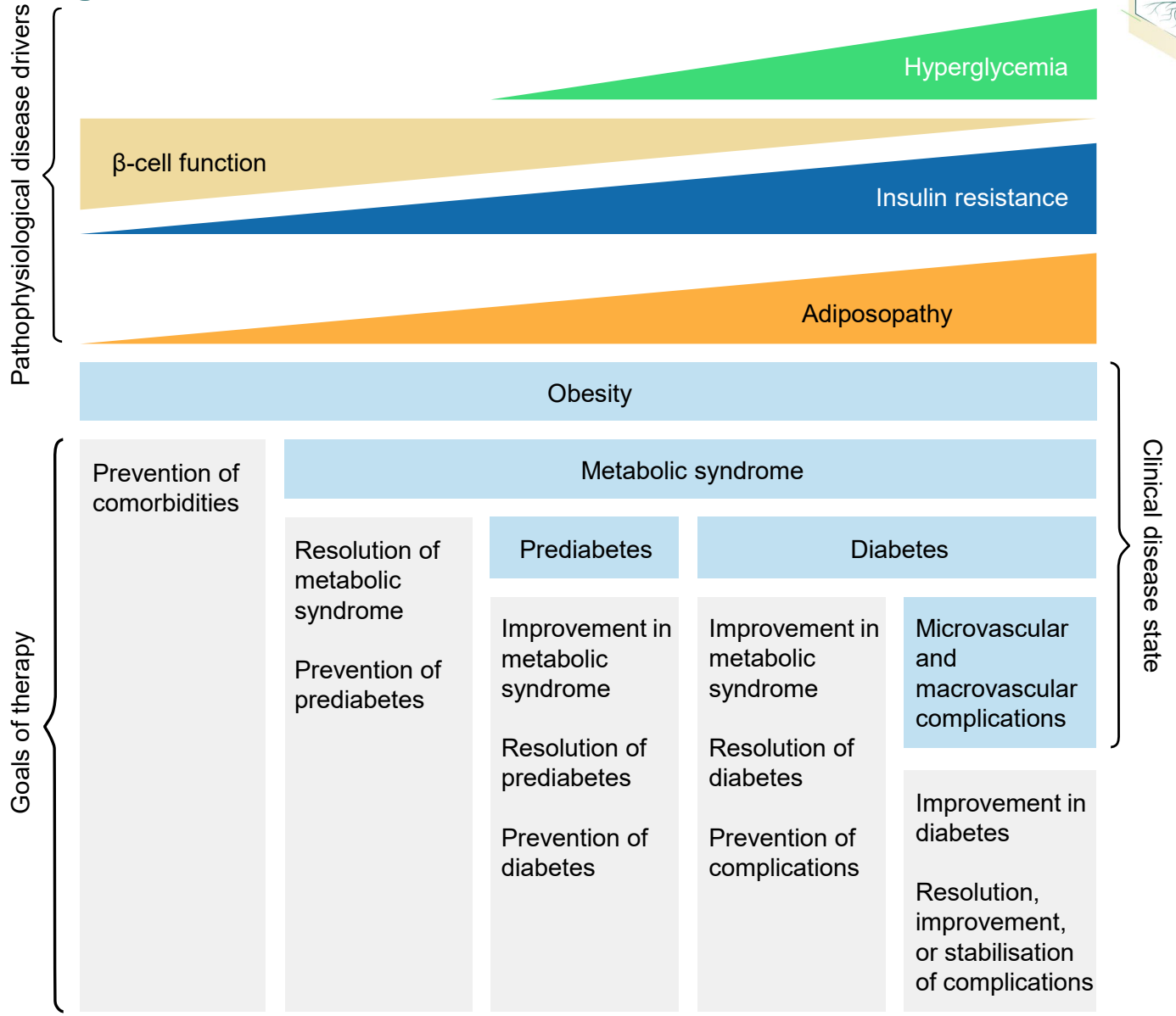
e) Sulfonylureas

f) Thiazolidinediones

DPP4, dipeptidyl peptidase-4; GLP-1: glucagon-like peptide-1; SGLT2: sodium glucose co-transporter-2.

Addressing Adiposopathy Not Just a Consideration for T2D

- Underlying metabolic abnormalities (*e.g.,* adiposopathy) are typically present decades before T2D develops
- Possible benefits of successfully targeting these abnormalities:
  - In the prediabetes stage: remission of prediabetes, prevention of progression to overt diabetes
  - In T2D: diabetes remission or improvement of T2D



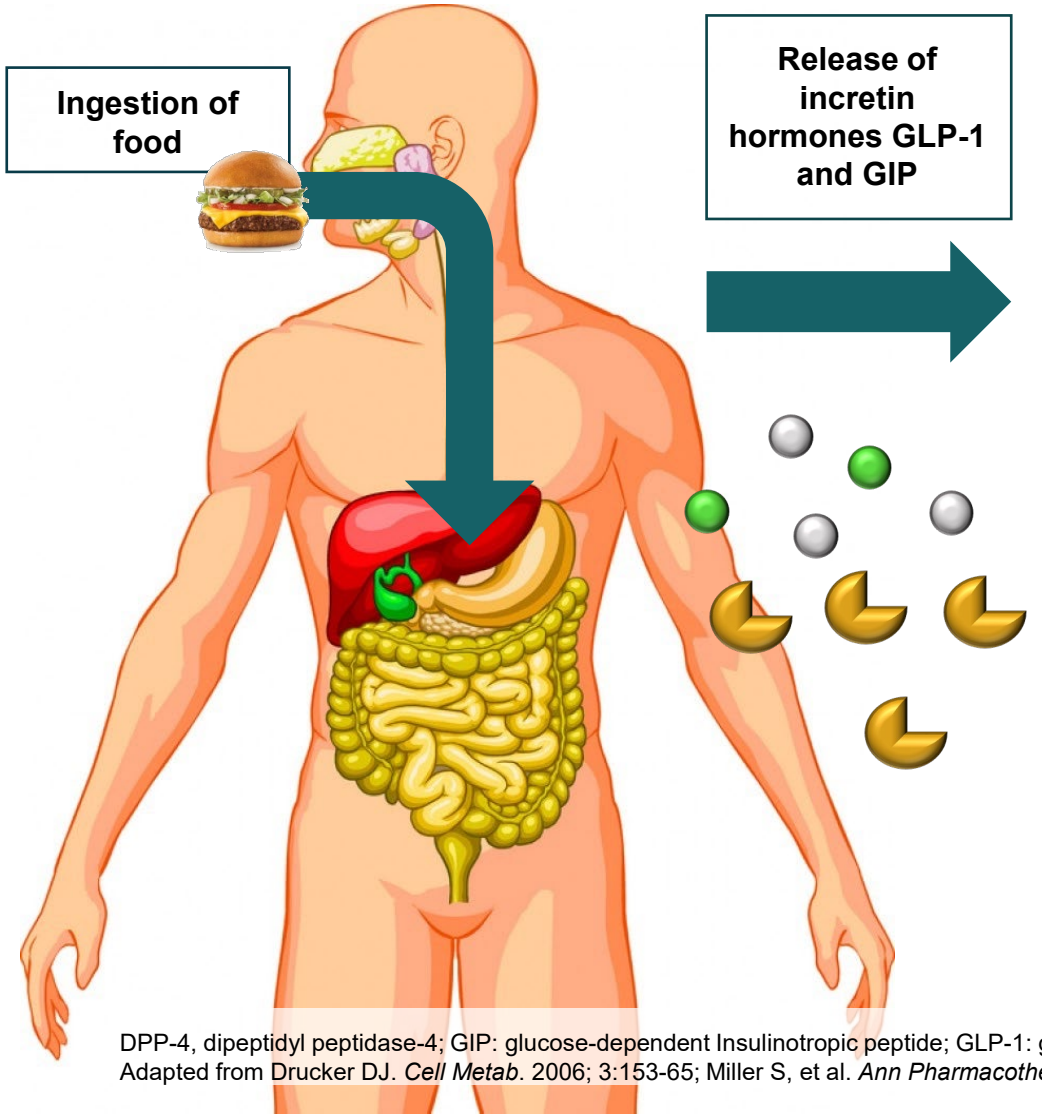
T2D: type 2 diabetes.
Adapted from Lingvay I, et al. *Lancet*. 2022; 399(10322):394-405.

Moving Forward Evolving Pharmacotherapy for Comprehensive T2D Management

Focusing on novel approaches to modulating the incretin pathways

T2D: type 2 diabetes.

The Incretin Effect and its Impairment in T2D



Endogenous GLP-1 and GIP have multiple actions in the body, including impact on glycemic control and satiety

Natural GLP-1 and GIP are both *rapidly* broken down by DPP-4

In T2D

The incretin effect is diminished in patients with type 2 diabetes compared to healthy individuals

GLP1-RAs and DPP4is are currently approved agents that favourably modulate the incretin pathways

DPP-4, dipeptidyl peptidase-4; GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1; GLP-1-RA: glucagon-like peptide-1 receptor agonist; T2D: type 2 diabetes.
Adapted from Drucker DJ. *Cell Metab*. 2006; 3:153-65; Miller S, et al. *Ann Pharmacother*. 2006; 40:1336-43.

Effects of GLP-1 Receptor Agonism Extend Beyond Glycemic Control

Glucagon-like Peptide-1 Receptor Agonism

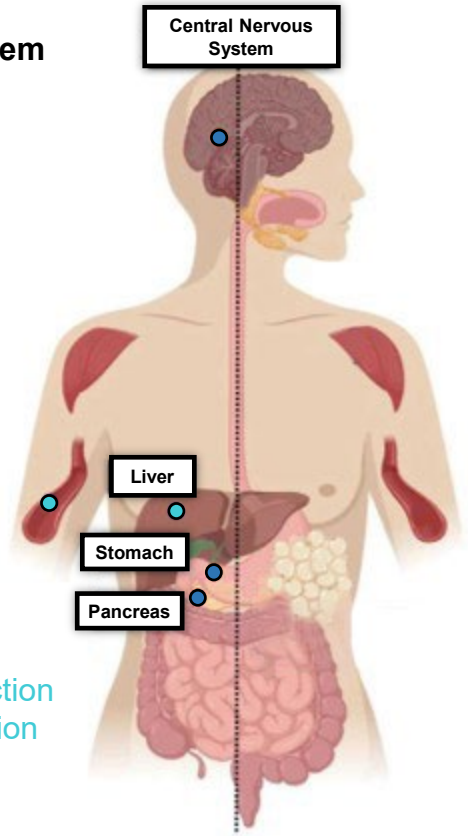
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation

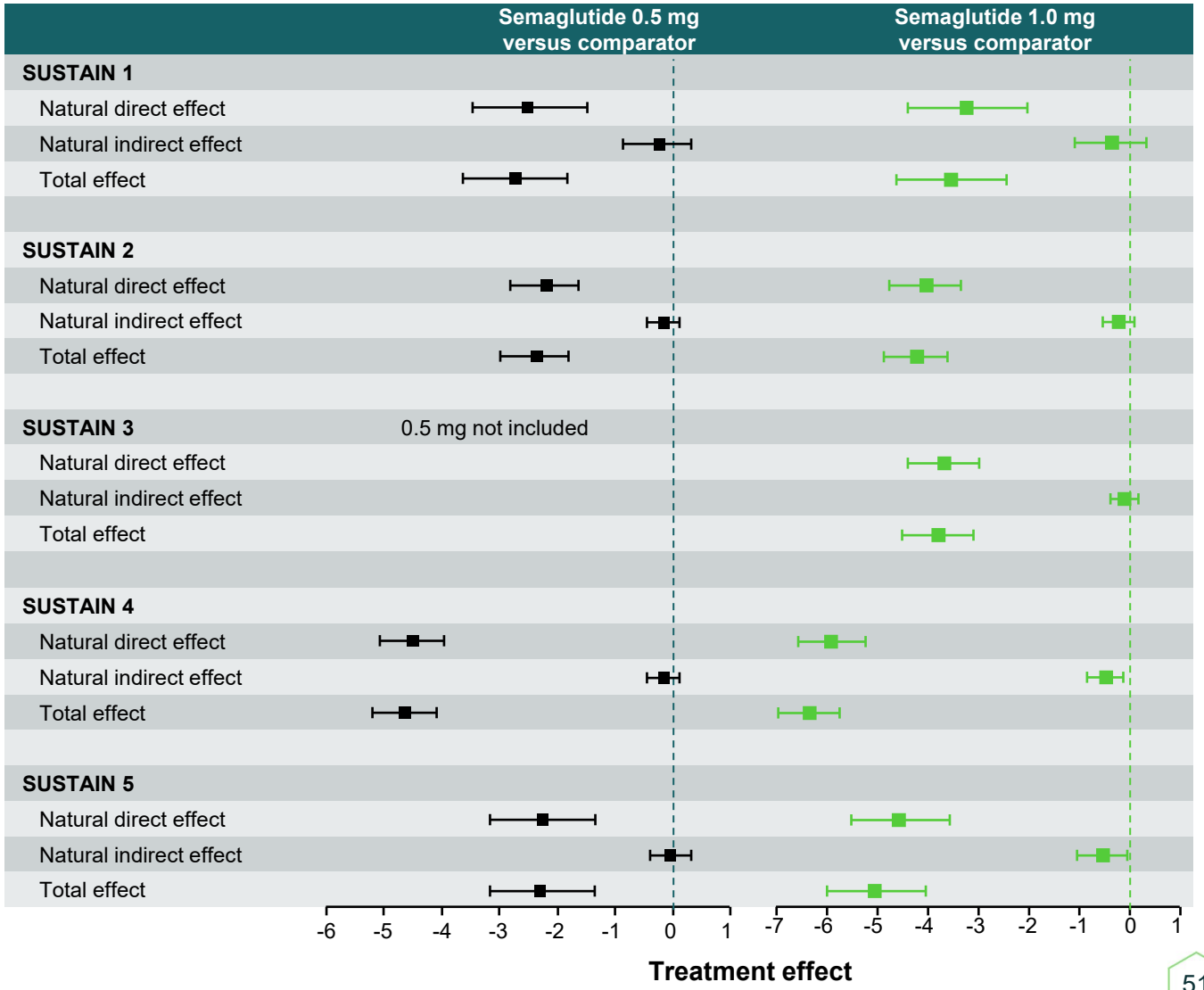


GLP-1 Receptor Agonism Indirect Action

GLP-1: glucagon-like peptide-1.
Adapted from Samms RJ, et al. *Trends Endocrinol Metab*. 2020; 31(6):410-21.

Only a Small Portion of Weight Loss from GLP-1 RA Could Be Attributed to Nausea / Vomiting (Mediation Analysis)

- Mediation analyses of direct *vs*. indirect (gastrointestinal) effects on weight loss with semaglutide 0.5 and 1.0 mg in SUSTAIN 1-5
- Only 0.07 to 0.5 kg of the weight loss could be attributed to nausea/vomiting
- Therefore, large proportion of the weight loss observed is due to effects other than nausea / vomiting



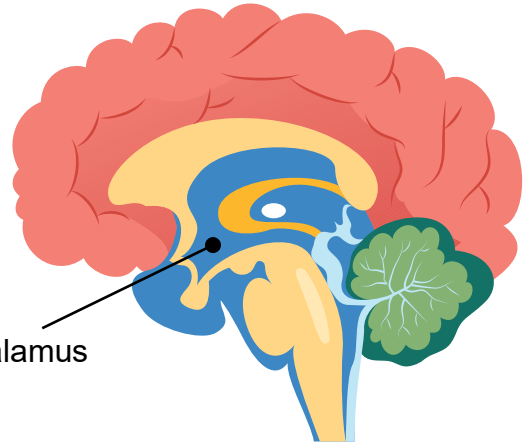
GLP-1-RA: glucagon-like peptide-1 receptor agonist.
Adapted from Ahren B, et al *Diabetes Obes Metab.* 2018; 20:2210-9.

How Can GLP1-RA Therapy Lead to Body Weight Loss?[1]

GLP1-RA bound to GLP-1 receptors in the arcuate nucleus in the hypothalamus

Stimulates → **POMC / CART**

Inhibits → **NPY and AgRP**



Reduced
- Hunger
- Energy intake
- Food cravings

Increased
- Satiety

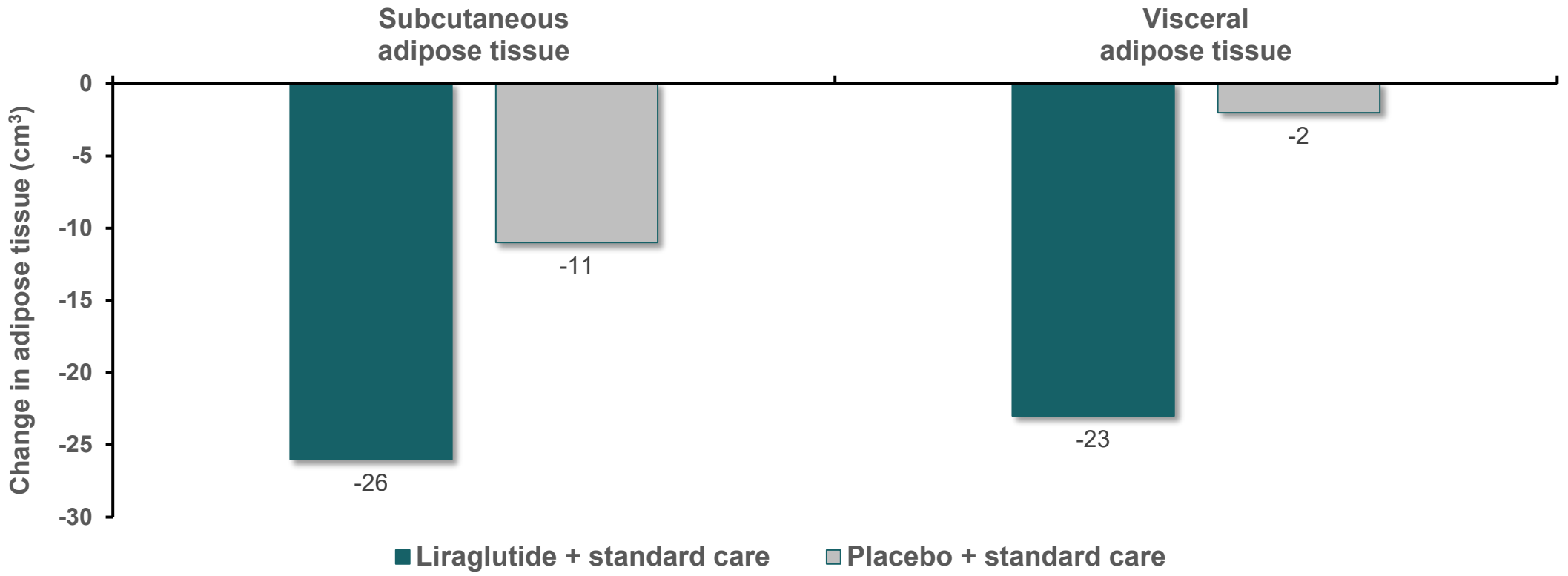
Note: The role of GIP in body weight loss is not currently well understood. There is conflicting evidence of the effects of GIP receptor agonism on body weight.[2]

AgRP: agouti-related peptide; GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1; GLP-1-RA: glucagon-like peptide-1 receptor agonist; NPY: neuropeptide Y; POMC / CART: proopiomelanocortin and cocaine- and amphetamine-regulated transcript

Adapted from 1. Ard J, et al. *Adv Ther*. 2021; 38(6):2821-39; and 2. Holst JJ, et al. *J Clin Endocrinol Metab*. 2020; 105(8):e2710–6.

Changes in Adiposity with GLP1-RA: MRI Assessment of South Asian Subjects with T2D

- N=47 South Asian subjects with T2D
- Adipose tissue assessed by MRI at baseline and after 26 weeks of treatment with liraglutide 1.8 mg/d or placebo added to standard care



Per protocol analysis
GLP-1-RA: glucagon-like peptide-1 receptor agonist; MRI: magnetic resonance imaging; T2D: type 2 diabetes.
Adapted from van Eyk HJ, et al. *Cardiovasc Diabetol*. 2019; 18(1):87.

Current Agents Targeting the Incretin Pathway

Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i
↑ insulin secretion		✓	✓	✓	✓	
↓ glucagon secretion				✓	✓	
↓ hepatic glucose production	✓		✓	✓	✓	
Incretin pathways				✓	✓	
↓ lipolysis			✓			
↓ glucose reabsorption						✓
↑ glucose uptake	✓		✓	✓	✓	
↓ neurotransmitter dysfunction					?	
↓ cardiorenal risk					✓	✓
Decrease body weight					✓	✓

DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas.
Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; Abdul-Ghani M, et al. *Diabetes Care.* 2017; 40:1121-7; and Lipscombe L, et al. *Can J Diabetes*. 2020; 44(7):575-91.

Effects of GLP-1 and GIP Receptor Agonism Extend Beyond Glycemic Control

Glucagon-like Peptide-1 (GLP-1) Receptor Agonism

Glucose-dependent Insulinotropic Polypeptide (GIP) Receptor Agonism

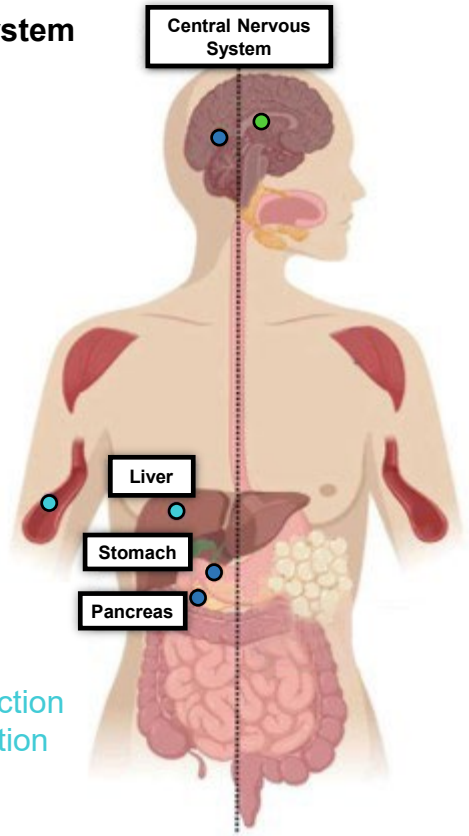
Central Nervous System
- ↑ Satiety
- ↓ Food Intake
- ↑ Nausea
- ↓ Body Weight

Pancreas
- ↑ Insulin
- ↓ Glucagon

Stomach
- ↓ Gastric Emptying

Systemic
- ↓ Hyperglycemia

Liver
- ↑ Insulin Sensitivity
- ↓ Hepatic Glucose Production
- ↓ Ectopic Lipid Accumulation



Based on preclinical investigations, a number of potential actions of GIP receptor agonism have been proposed which are being studied.

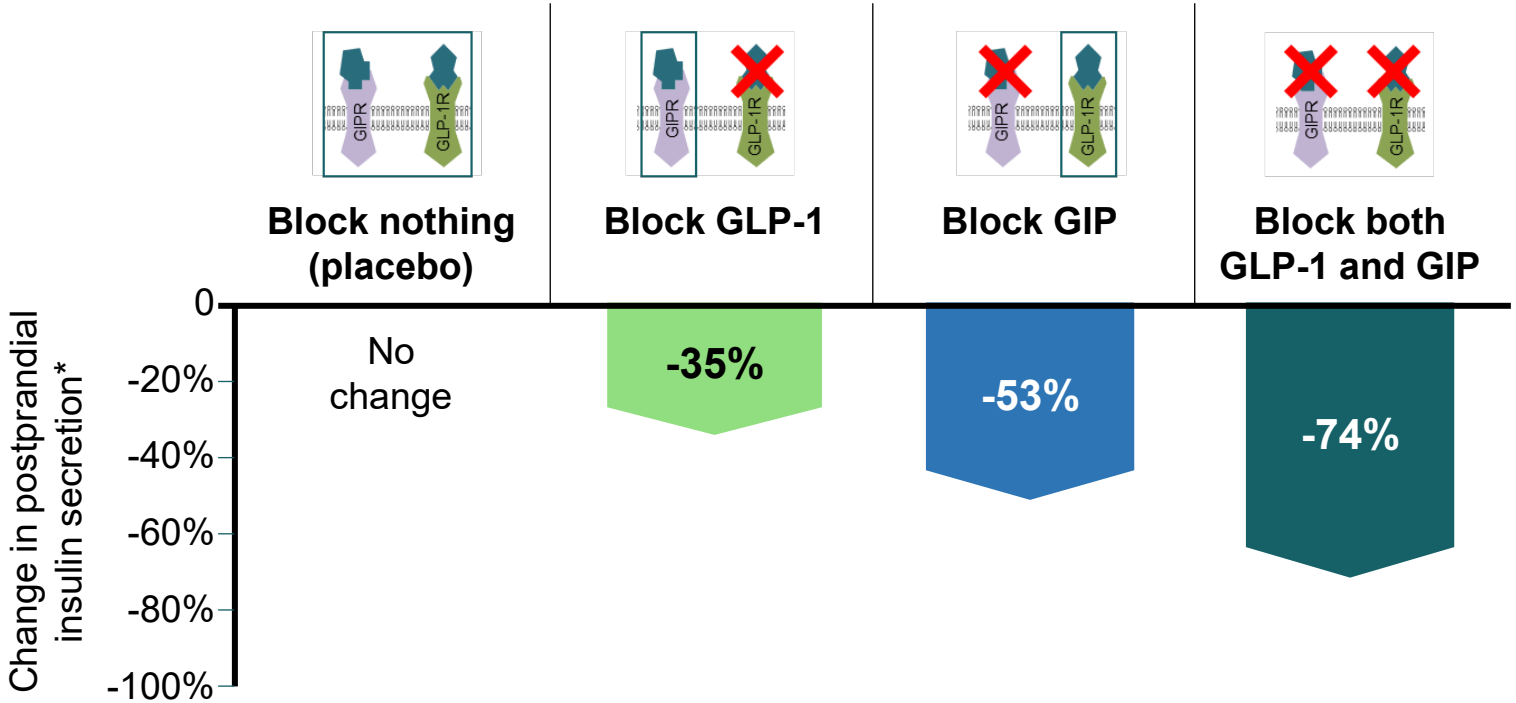
GLP-1 Receptor Agonism Indirect Action

GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.
Adapted from Samms RJ, et al. *Trends Endocrinol Metab*. 2020; 31(6):410-21.

GIP May Contribute More to Postprandial Insulin Secretion than GLP-1: Evidence from 2 Studies in People Without T2D

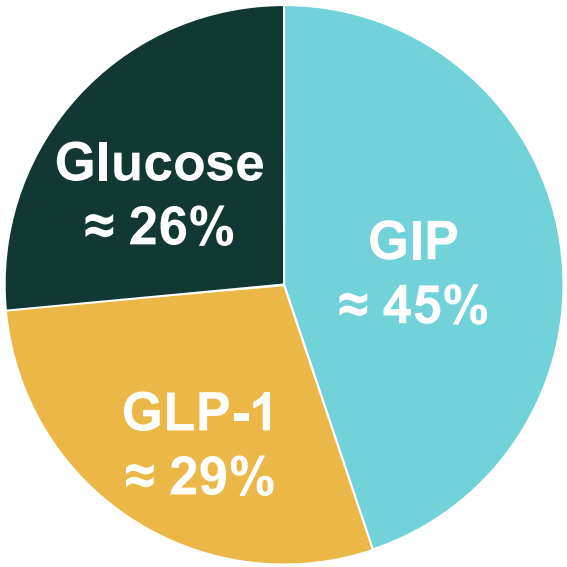
What happens to post-prandial insulin secretion if you block the activity of GIP, GLP-1 or both?

During oral glucose tolerance test in 18 men without T2D, using specific antagonists[1†]



Stimulators of Postprandial Insulin Secretion

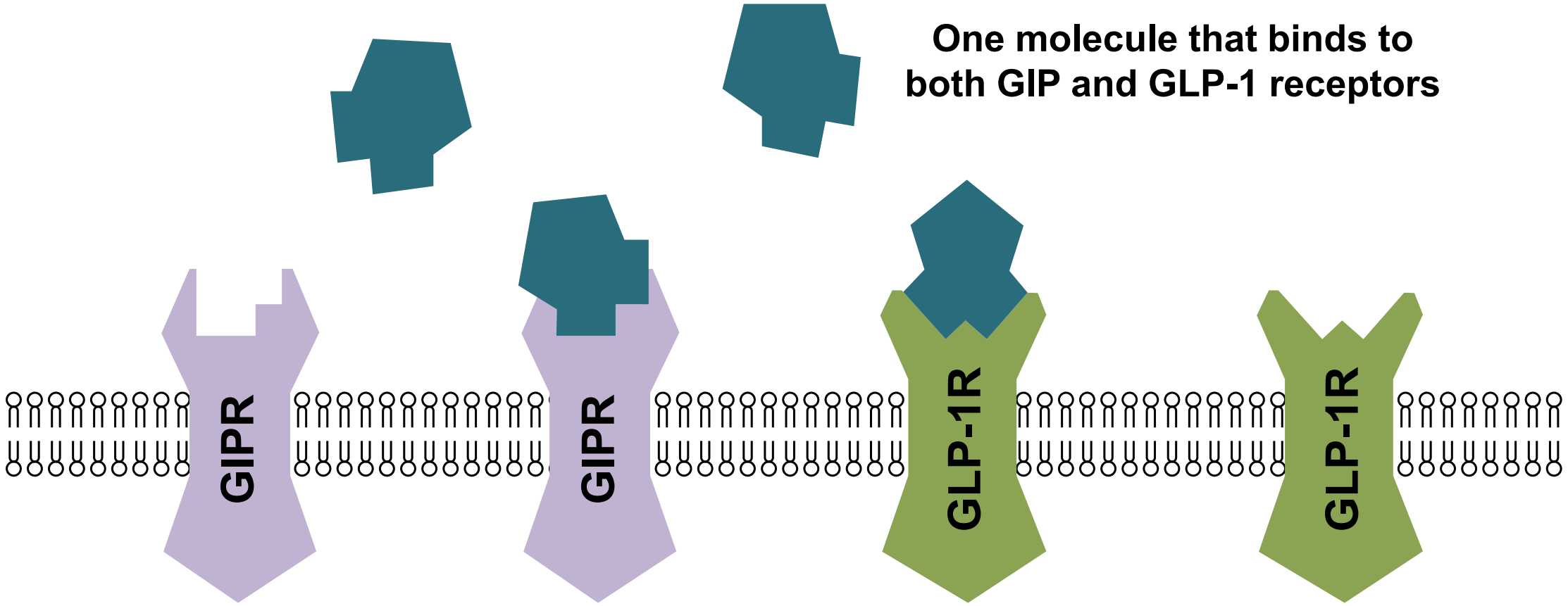
Based on incretin receptor antagonist studies in individuals without T2D[2]



*Measured by basal-substracted area under the curve of ISR:glucose, adjusted for fold-difference in glucose of placebo; †Antagonists used: For GLP-1: Exendin(9-39)NH_2; for GIP: GIP(3-30)NH_2; GIP: glucose-dependent insulinotropic polypeptide; GIPR: glucose-dependent insulinotropic polypeptide receptor; GLP-1: glucagon-like peptide-1; ISR: insulin secretion rate; T2D type 2 diabetes.

1. Gasbjerg LS, et al. *Diabetes Obes Metab.* 2021; 23(1):68-74; 2. Holst JJ, et al. *Endocrinology*. 2021;162(7):bqab065.

New Method of Modulating the Incretin Pathway: Dual GIP/GLP-1 Receptor Agonism

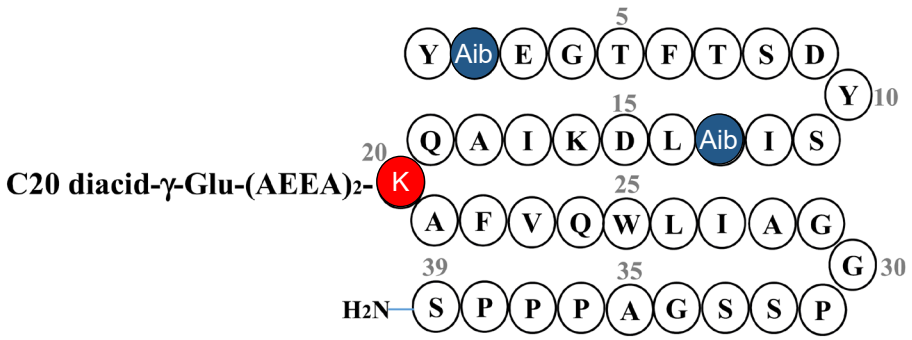


GIPR: glucose-dependent insulinotropic polypeptide receptor; GLP-1R: glucagon-like peptide-1 receptor

Skow MA, et al. *Diabetes Obes Metab*. 2016; 18(9):847-54.

Dual GIP/GLP-1 Receptor Agonist: Tirzepatide[1]

Molecular Sequence of Tirzepatide



Aib — **Positions 2 and 13**: Non-coded amino acid residues (Aib: α-amino isobutyric acid)

K — **Position 20**: Site of conjugation via a linker connected to the lysine residue

- Based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
- 39 amino acid linear peptide, includes a C20 fatty diacid moiety
- *In vitro*, higher potency to native GIP, less potent to native GLP-1
- Mean half-life: ~5 days (116.7 h), enabling once-weekly dosing
- Rationale: ↑ glycemic efficacy, ↑ durable effect, ↑ glucagon secretion, ↑ body weight loss

Approved by Health Canada in November 2022 for once-weekly administration as an adjunct to diet and exercise to improve glycemic control for the treatment of adult patients with type 2 diabetes.[2]

GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1

1. Coskun T, et al. *Mol Metab*. 2018; 18:3-14; 2. Eli Lilly Canada Inc. MOUNJARO product monograph. November 23, 2022.

Tirzepatide's Clinical Trial Program: SURPASS

Monotherapy	2-Drug Combination	2-3-Drug Combinations	2-4-Drug Combinations	Combination With Insulin

SURPASS-1
vs placebo[1]
Drug-naïve or washout from any OAM
Baseline A1C: 7.9%
Duration of T2D: 4.7 yrs

SURPASS-2
vs semaglutide[2]
Add-on to metformin
Baseline A1C: 8.3%
Duration of T2D: 8.6 yrs

SURPASS-3
vs insulin degludec[3]
Add-on to metformin with or without SGLT2i
Baseline A1C: 8.2%
Duration of T2D: 8.4 yrs

SURPASS-4
vs insulin glargine[4]
Add-on to ≥ 1 and ≤ 3 OAMs (metformin, SGLT2i, or SU)
Baseline A1C: 8.5%
Duration of T2D: 11.8 yrs

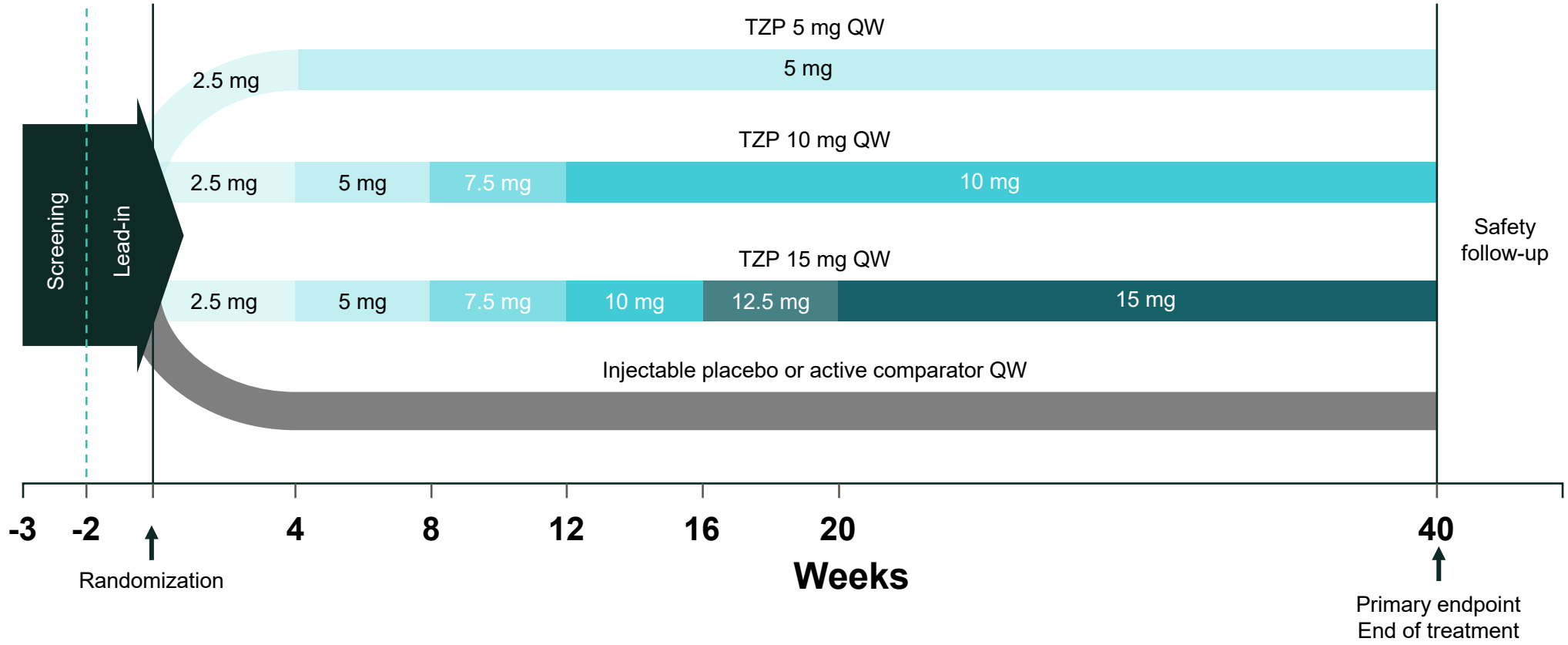
SURPASS-5
vs placebo[5]
Both with insulin glargine with or without metformin
Baseline A1C: 8.3%
Duration of T2D: 13.3 yrs

SURPASS-6
vs insulin lispro (TID)[6]
Both with insulin glargine with or without metformin
Baseline A1C: 8.8%
Duration of T2D: 14 yrs

Cardiovascular Outcome Trial (ongoing)
SURPASS-CVOT vs dulaglutide, each added to standard of care[7]
Baseline A1C: NR; Duration of T2D: NR

A1C: glycated hemoglobin; NR: Not reported; OAM: oral antihyperglycemic medication; SGLT2i: sodium glucose co-transporter-2 inhibitor; SU: sulfonylureas; T2D: type 2 diabetes; TID: thrice daily.
1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45; 6. Rosenstock J et al. Presented at American Diabetes Association – 83rd Annual Scientific Sessions; 2023. Poster 750-P; 7. Clinicaltrials.gov. NCT04255433.

SURPASS Study Design[1-5]



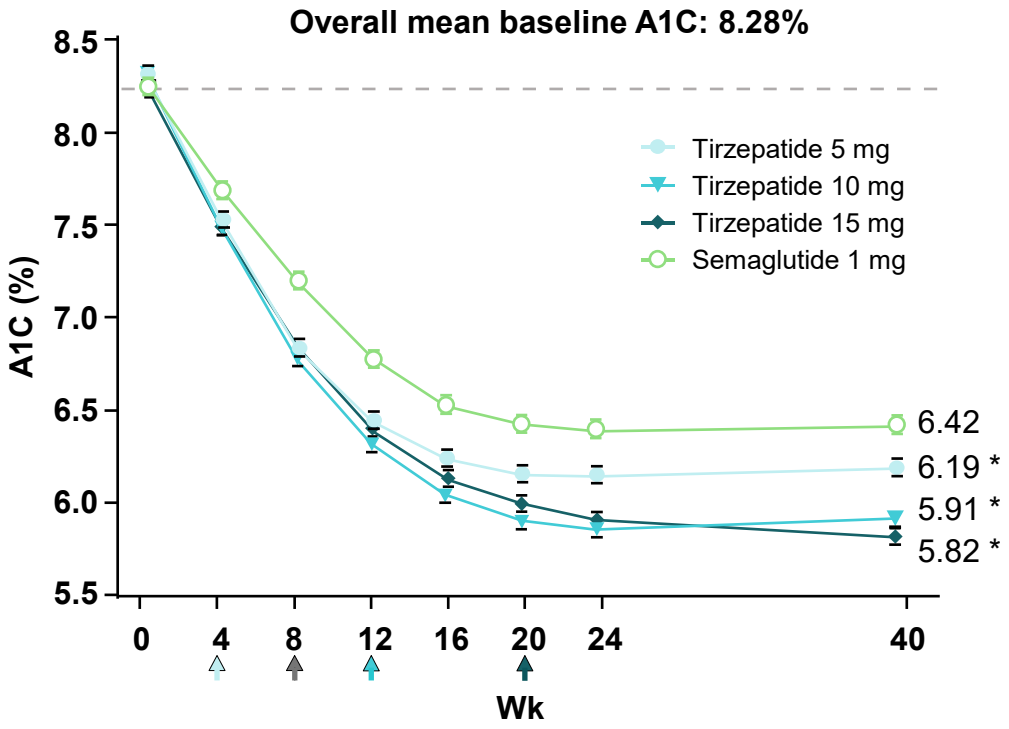
Primary objective: superiority and/or noninferiority of TZP 5 mg and/or 10 mg and/or 15 mg vs placebo or active comparator in mean change in A1C from baseline at 40 or 52 weeks.

A1C: glycated hemoglobin; QW: once weekly; TZP: tirzepatide.

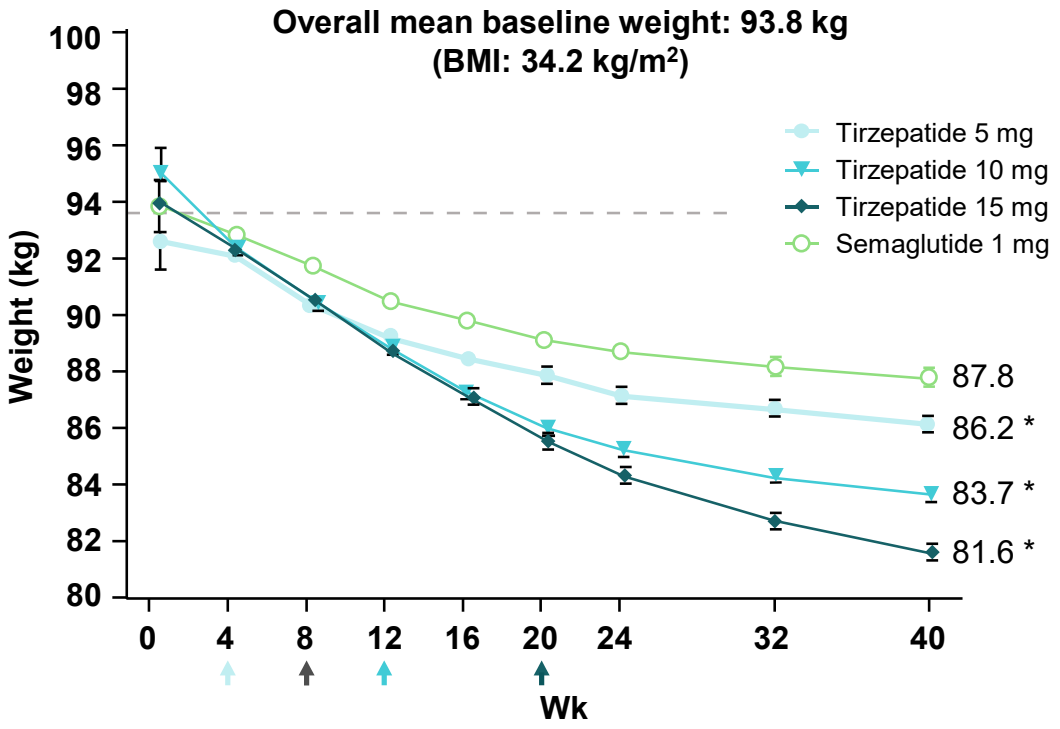
1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45.

SURPASS-2: A1C and Body Weight Reductions *vs.* Semaglutide 1 mg (Selective GLP1-RA)

A1C Reductions from Baseline

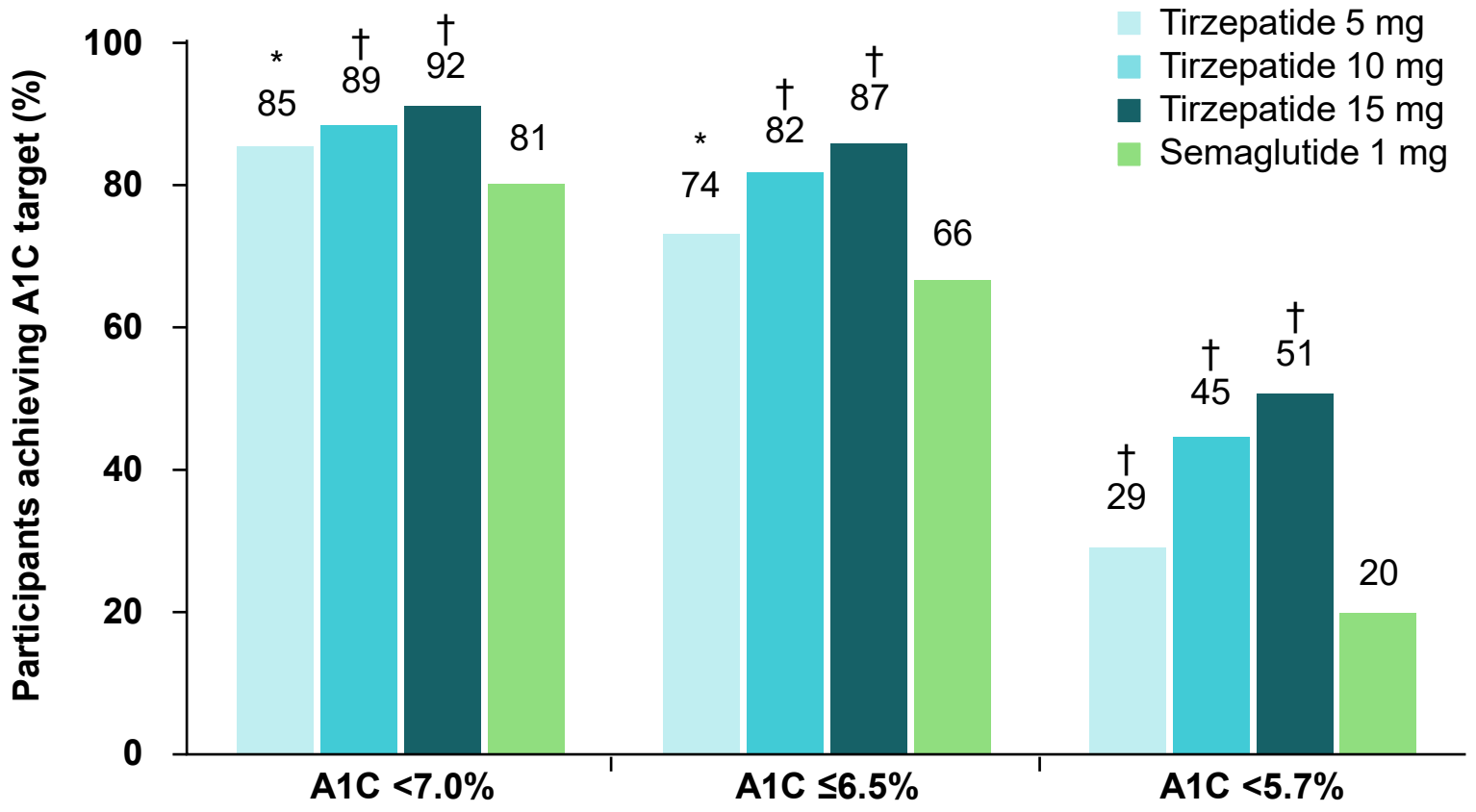


Body Weight Changes from Baseline



*p<0.001 vs. semaglutide; Arrows on the x-axes indicate where maintenance doses were achieved
A1C: glycated hemoglobin; BMI: body mass index; GLP1-RA: glucagon-like peptide-1 receptor agonist; Wk: week
Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15.

SURPASS-2: Proportion of Participants Achieving A1C Target Thresholds at 40 Weeks

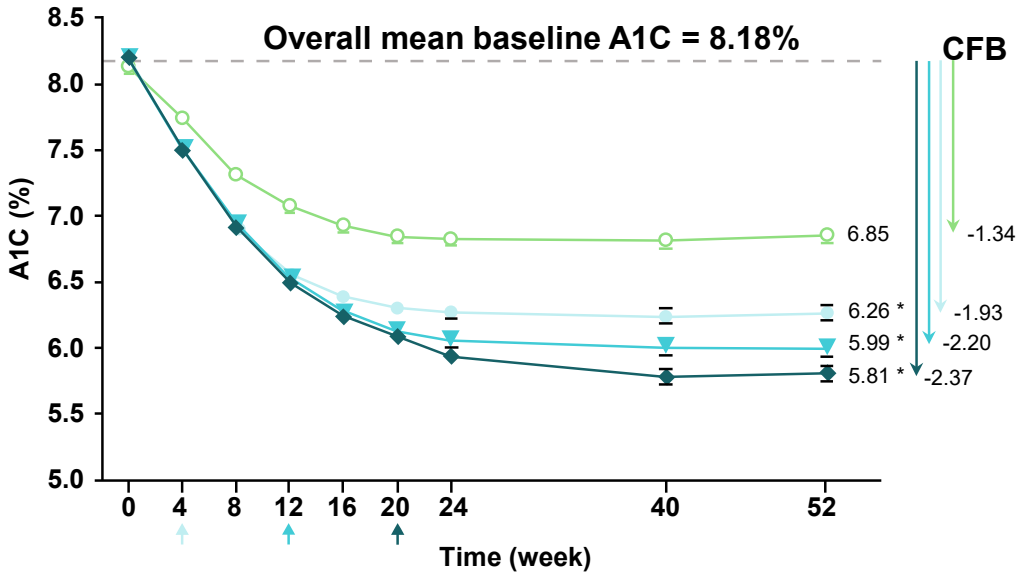


With tirzepatide 15 mg:
92% reached A1C of <7.0%,
51% reached A1C of <5.7%

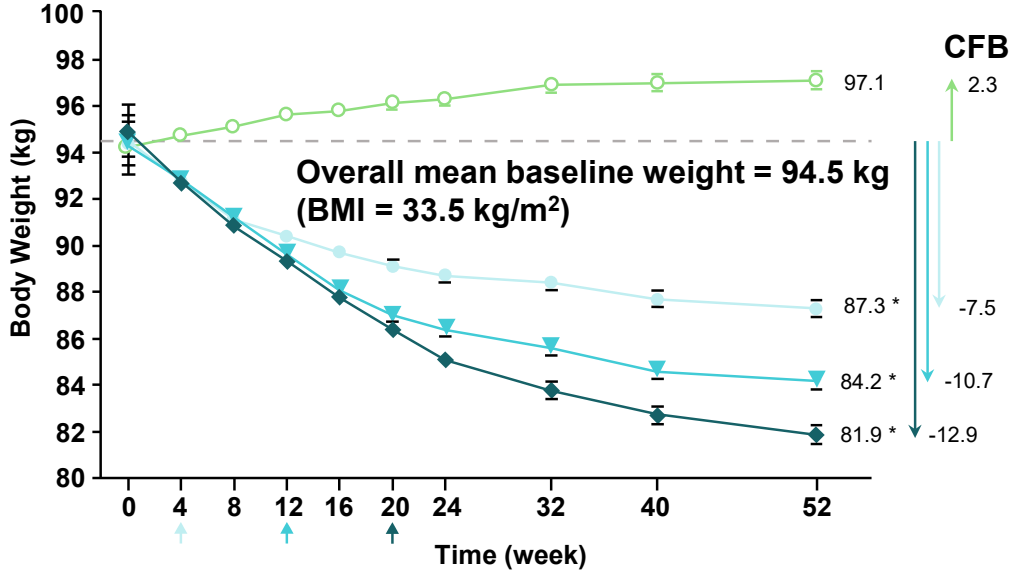
*p<0.05 vs semaglutide 1 mg. †p<0.001 vs semaglutide 1 mg.
A1C: glycated hemoglobin
Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15.

SURPASS-3: A1C and Body Weight Reductions vs. Insulin Degludec

A1C Reductions from Baseline



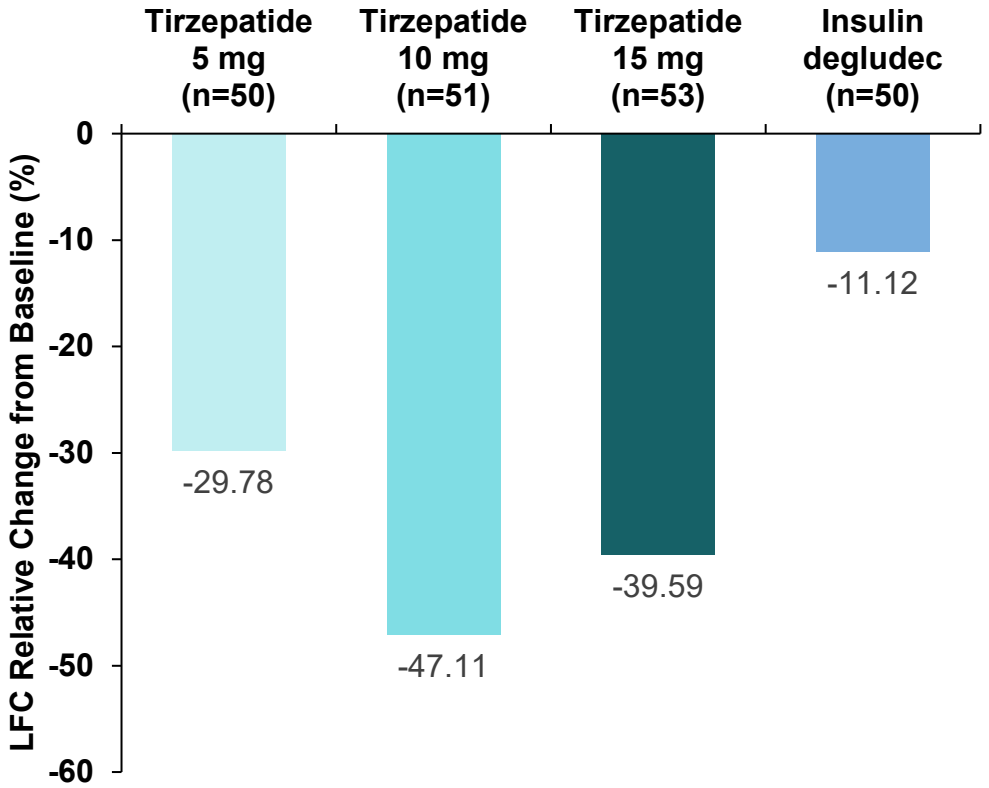
Body Weight Changes from Baseline



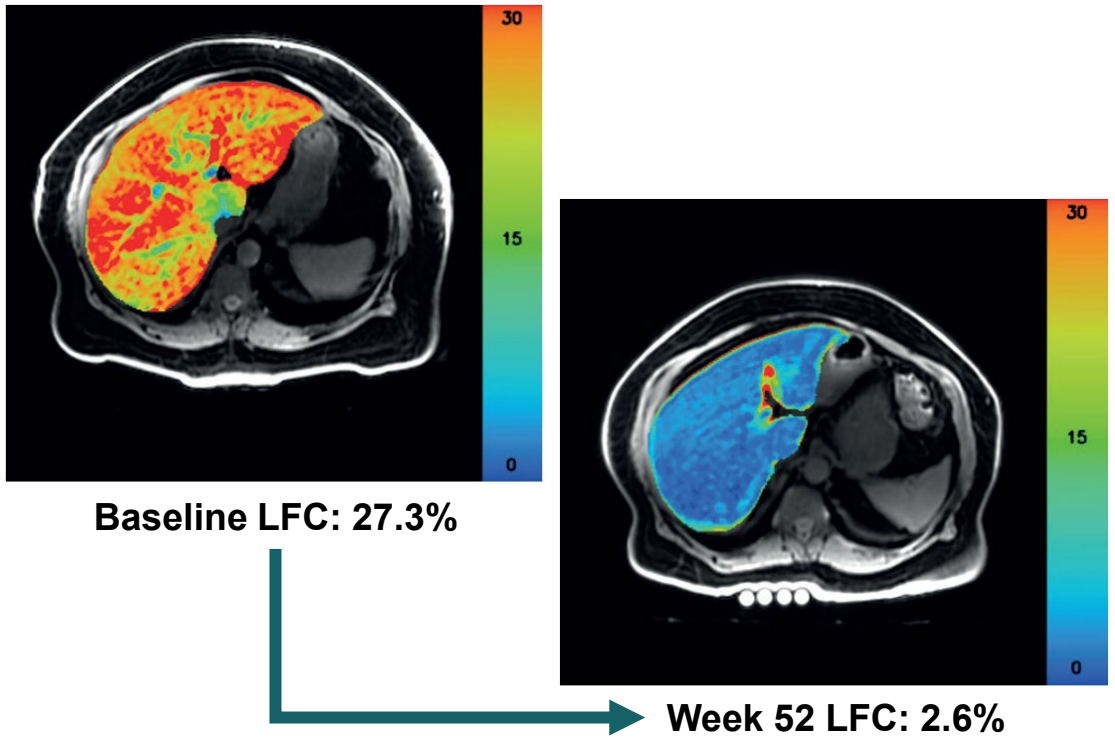
*p<0.001 vs. insulin degludec; Arrows on the x-axes indicate where maintenance doses were achieved
A1C: glycated hemoglobin; BMI: body mass index; CFB: change from baseline;
Adapted from Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98.

SURPASS-3 Sub-study in Liver Fat Content

Relative Changes in Liver Fat Content from Baseline to Week 52



Example of Change in Liver Fat Content: Individual Patient Randomized to TZP 5 mg



LFC: liver fat content; TZP: tirzepatide

Gastaldelli A, et al. *Lancet Diabetes Endocrinol*. 2022; 10(6):393-406.

SURPASS Program: Summary of A1C Lowering*

SURPASS-1[1]
vs. placebo
40 weeks
No background OAMs
Baseline A1C: 7.9%
N = 478

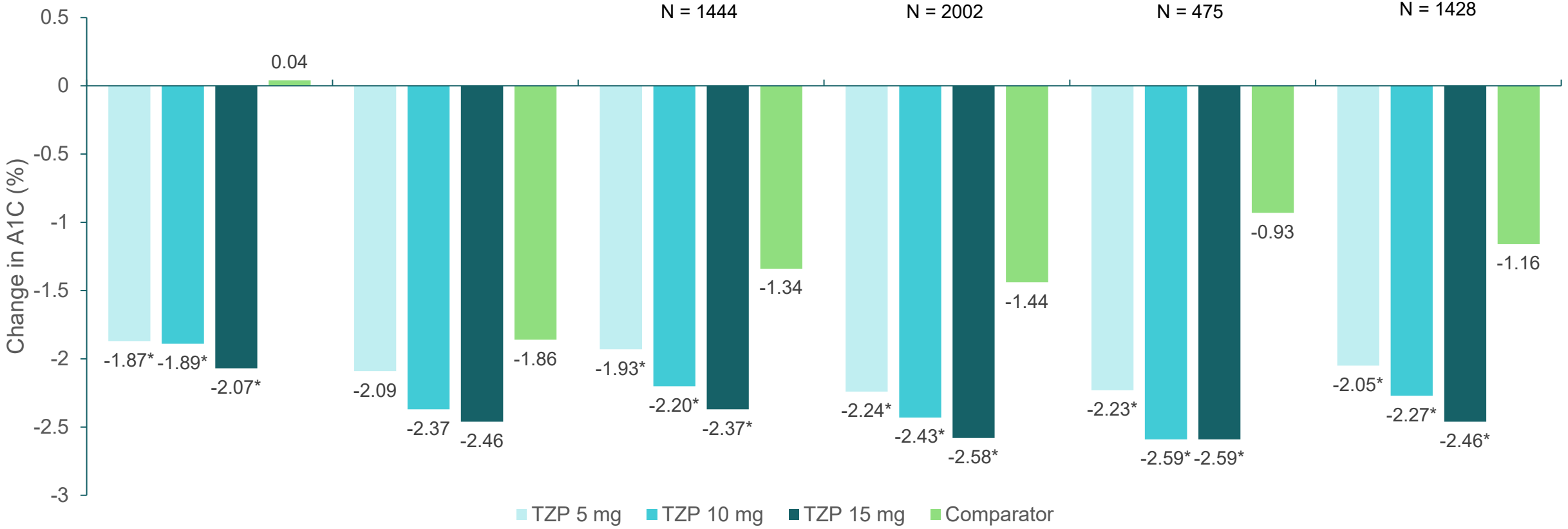
SURPASS-2[2]
vs. Semaglutide 1 mg
40 Weeks
Background metformin
Baseline A1C: 8.3%
N = 1879

SURPASS-3[3]
vs. Insulin degludec
52 Weeks
Background metformin ± SGLT2i
Baseline A1C: 8.2%
N = 1444

SURPASS-4[4]
vs. Insulin glargine
52 Weeks
Background metformin ± SGLT2i or SU
Baseline A1C: 8.52%
N = 2002

SURPASS-5[5]
vs. Placebo
40 Weeks
Background iGlargine ± metformin
Baseline A1C: 8.3%
N = 475

SURPASS-6[6]
vs. Insulin lispro t.i.d.
52 Weeks
Background iGlargine ± metformin
Baseline A1C: 8.8%
N = 1428



*All Statistically significant vs. comparator
A1C: glycated hemoglobin; OAM: Oral antihyperglycemic medication; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylureas; TZP: tirzepatide; Wk: week.

1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45; 6. Rosenstock J et al. Presented at American Diabetes Association – 83rd Annual Scientific Sessions; 2023. Poster 750-P.

SURPASS Program: Summary of Body Weight Loss

SURPASS-1[1]
vs. placebo
40 weeks
No background OAMs
Baseline weight: 85.9 kg
N = 478

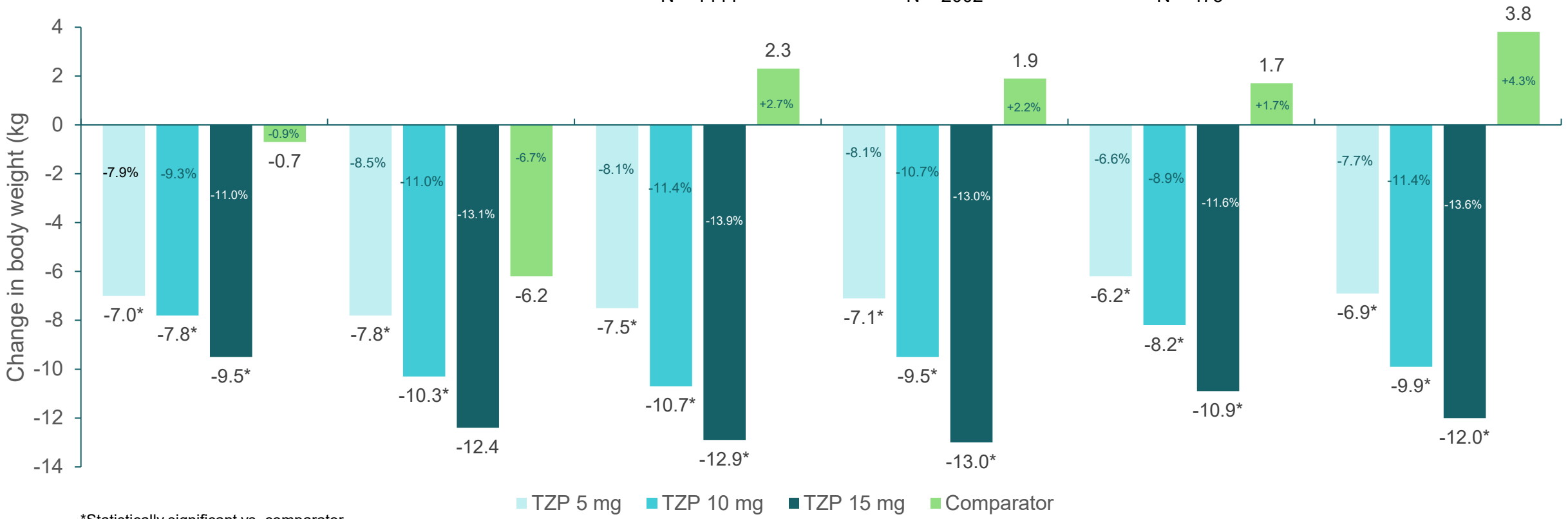
SURPASS-2[2]
vs. Semaglutide 1 mg
40 Weeks
Background metformin
Baseline weight: 93.7 kg
N = 1879

SURPASS-3[3]
vs. Insulin degludec
52 Weeks
Background metformin ± SGLT2i
Baseline weight: 94.3 kg
N = 1444

SURPASS-4[4]
vs. Insulin glargine
52 Weeks
Background metformin ± SGLT2i or SU
Baseline weight: 90.3 kg
N = 2002

SURPASS-5[5]
vs. Placebo
40 Weeks
Background iGlargine ± metformin
Baseline weight: 95.2 kg
N = 475

SURPASS-6[6]
vs. Insulin lispro t.i.d.
52 Weeks
Background iGlargine ± metformin
Baseline weight: 90.4 kg
N = 1428



*Statistically significant vs. comparator
OAM: Oral antihyperglycemic medication; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylureas; TZP: tirzepatide

1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45; 6. Rosenstock J et al. Presented at American Diabetes Association – 83rd Annual Scientific Sessions; 2023. Poster 750-P.

SURPASS-2: Tolerability of Tirzepatide vs. Semaglutide (Selective GLP1-RA)

Parameter, n (%)	TZP 5 mg (N = 470)	TZP 10 mg (N = 469)	TZP 15 mg (N = 470)	SEMA 1 mg (N = 469)
Participants with ≥1 TEAE	299 (63.6)	322 (68.7)	324 (68.9)	301 (64.2)
SAEs	33 (7.0)	25 (5.3)	27 (5.7)	13 (2.8)
Deaths*	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)
TEAEs with ≥5% frequency				
Nausea	82 (17.4)	90 (19.2)	104 (22.1)	84 (17.9)
Diarrhea	62 (13.2)	77 (16.4)	65 (13.8)	54 (11.5)
Vomiting	27 (5.7)	40 (8.5)	46 (9.8)	39 (8.3)
Dyspepsia	34 (7.2)	29 (6.2)	43 (9.1)	31 (6.6)
Decreased appetite	35 (7.4)	34 (7.2)	42 (8.9)	25 (5.3)
Constipation	32 (6.8)	21 (4.5)	21 (4.5)	27 (5.8)
Abdominal pain	14 (3.0)	21 (4.5)	24 (5.1)	24 (5.1)

*Also included as SAEs
GLP1-RA: glucagon-like peptide-1 receptor agonist; SAE: serious adverse event; SEMA: semaglutide; TEAE: treatment-emergent adverse event; TZP: tirzepatide
Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15.

SURPASS-2: Adverse Events of Special Interest

AE, n (%)	TZP 5 mg (N = 470)	TZP 10 mg (N = 469)	TZP 15 mg (N = 470)	SEMA 1 mg (N = 469)
Pancreatitis	0	2 (0.4)	2 (0.4)	3 (0.60
Thyroid cancer	0	0	0	0
Cholelithiasis	4 (0.9)	4 (0.9)	4 (0.9)	1 (0.2)
Complications of diabetic retinopathy	5 (1.1)	3 (0.6)	2 (0.4)	2 (0.4)
Macular edema	3 (0.6)	2 (0.4)	0	0
Vision blurred	1 (0.2)	1 (0.2)	1 (0.2)	1 (0.20
Diabetic hypertensive	1 (0.2)	0	1 (0.2)	0
Maculopathy	0	0	0	1 (0.2)
Retinal vein occlusion	1 (0.2)	0	0	0

SEMA: semaglutide; TZP: tirzepatide

Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15 (and online supplementary appendix).

What About Cardiorenal Risk? Study Underway with Tirzepatide (SURPASS-CVOT)

- **Subjects** (N = 12,500):
  - T2D
  - Confirmed CVD
  - A1C ≥7.0% to ≤10.5%
  - BMI ≥25 kg/m^2
- **Interventions:** Dulaglutide or tirzepatide
- **Primary outcome:** 1st occurrence of CV death, MI or stroke (3-point MACE)
- **Expected completion**: October 2024

A1C: glycated hemoglobin; BMI: body mass index; CV: cardiovascular; CVD: cardiovascular disease; MACE: major adverse cardiovascular events; MI: myocardial infarction; T2D: type 2 diabetes
ClinicalTrials.gov Identifier: NCT04255433.

Dual GIP/GLP-1 Receptor Agonist Tirzepatide: Summary of Clinical Trial Findings in T2D

Studied across spectrum of people living with T2D[1-5]

Superior A1C and body weight reduction compared to placebo, semaglutide 1mg, insulin degludec, insulin glargine U100[1-4]

The data on the safety and tolerability of tirzepatide showed that its side effects are comparable to those of GLP-1RA alone[2]

Awaiting results of SURPASS-CVOT (estimated completion date 2024)[6]

A1C: glycated hemoglobin; CVOT: cardiovascular outcome trial; GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; GLP-1RA: glucagon-like peptide-1 receptor agonist; T2D: type 2 diabetes.

1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frías JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45; 6. Clinicaltrials.gov. NCT04255433.

Opinion Polling Question

Where do you see dual GIP/GLP-1 receptor agonist therapy best fitting in treatment algorithms for T2D?

a) As one of several possible choices for add-on therapy to metformin

b) As the favored class for add-on therapy among people who are not candidates for cardiorenal protection with GLP1-RAs and/or SGLT2 inhibitors

c) As a replacement for GLP1-RAs wherever those agents are currently recommended

d) As the favored class as first add-on to metformin for all patients with T2D

e) As the favored class for any people with T2D and obesity / overweight

f) Not sure

GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; GLP1-RA: glucagon-like peptide-1 receptor agonist: SGLT2: sodium glucose co-transporter-2; T2D: type 2 diabetes.

Where Could Dual GIP/GLP-1 Receptor Agonist Therapy Fit? Summary of Effects

Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i	GIP/ GLP-1RA
↑ insulin secretion		✓	✓	✓	✓		✓
↓ glucagon secretion				✓	✓		✓
↓ hepatic glucose production	✓		✓	✓	✓		✓
Incretin pathways				✓	✓		✓
↓ lipolysis			✓				?
↓ glucose reabsorption						✓	
↑ glucose uptake	✓		✓	✓	✓		✓
↓ neurotransmitter dysfunction					?		?
↓ cardiorenal risk					✓	✓	?
Decrease Body Weight					✓	✓	✓

DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas.
Adapted from: Defronzo RA. *Diabetes.* 2009; 58(4):773-95; Abdul-Ghani M, et al. *Diabetes Care* 2017; 40:1121-7; Lipscombe L, et al. *Can J Diabetes*. 2020; 44(7):575-91.

What Else Might the Future Hold? Investigational Therapies for Type 2 Diabetes

Class	Agent(s)	Status in T2D
GIPR/GLP-1R dual agonist	NNC 0090-2746	Phase 2 completed
GLP-1R/GCGR dual agonists	Cotadutide	Phase 3 ongoing
	Mazdutide (IBI362)	Phase 3 ongoing
	BI 456906	Phase 2 completed
GIPR/GCGR/GLP-1R triagonists	Retatrutide	Phase 3 in development
Co-formulated GLP1-RA + amylin analogue	Semaglutide - cagrilintide	Phase 3 in development
Monoclonal antibody	Bimagrumab	Phase 2 completed

GCGR: glucagon receptor; GIP: glucose-dependent insulinotropic polypeptide; GIPR: glucose-dependent insulinotropic polypeptide receptor; GLP-1: glucagon-like peptide-1; GLP-1R: glucagon-like peptide-1 receptor; T2D type 2 diabetes
Adapted from Bailey CJ, et al. Peptides. 2023;161:170939 and clinicaltrials.gov, accessed April 2023.

Overall Conclusions

While glycemic control remains a cornerstone of diabetes management, overall treatment goals are more comprehensive, including reduction of cardiorenal risk

Adiposopathy is an underlying mechanism for many disease states, including T2D

Therapies for T2D address different components of the pathophysiology – an ideal therapy would address multiple components, including glycemic control, cardiorenal risk reduction and adiposopathy

Dual GIP/GLP-1 receptor agonism has demonstrated A1C and body weight reductions superior to placebo, to GLP-1 receptor agonism and to basal insulin in clinical trials.

GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1; T2D: type 2 diabetes.

Post-Program Polling Question

1

How familiar are you with the concept of adiposopathy (aka sick fat tissue) as a contributing cause of type 2 diabetes and its complications?

A. Not at all familiar

B. Not very familiar

C. Somewhat familiar

D. Very familiar

aka: also known as.

Post-Program Polling Question

2

How comfortable would you be in describing the clinical trial record of efficacy and safety of dual GIP/GLP-1 receptor agonism in type 2 diabetes?

A. Not at all comfortable

B. Not very comfortable

C. Somewhat comfortable

D. Very comfortable

GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1.

Post-Program Polling Question

3

What is considered to be an ideal waist-to-height ratio (WHtR)?

A. <0.25

B. <0.5

C. <0.75

D. <1.0

E. None of the above

Post-Program Polling Question

4

Which of these incretin hormones is thought to be associated with the greatest physiological contribution to post-prandial insulin secretion?

A. Glucose-dependent insulinotropic polypeptide (GIP)

B. Glucagon-like peptide-1 (GLP-1)

C. GIP and GLP-1 are thought to have roughly equivalent impact

GIP: glucose-dependent insulinotropic polypeptide; GLP-1: glucagon-like peptide-1.

Post-Program Polling Question

5

A novel dual GIP/GLP-1 receptor agonist has demonstrated superiority in A1C lowering compared to which of the following antihyperglycemic agents in a head-to-head phase 3 clinical trial?

A. Sitagliptin

B. Semaglutide

C. Metformin

D. Glyburide

E. Rosiglitazone

A1C: glycated hemoglobin; DDP-4: dipeptidyl peptidase 4; GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1.

Thank you for your participation!

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If you haven’t scanned the QR code during the presentation, please use the one below.

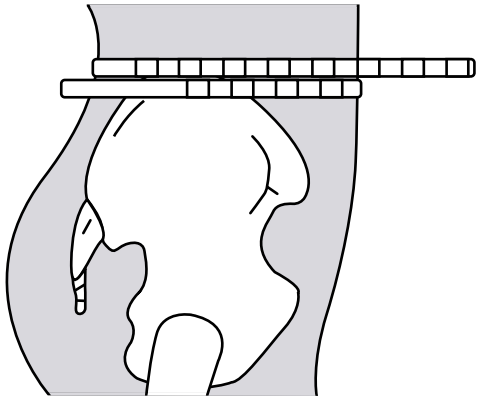
Upon completion of the evaluation, you will be able to download the **certificate of attendance.**

End of Program

Hyperlinks

Measurement of Waist Circumference

- WC is measured in a horizontal plane around the abdomen at the level of the iliac crest
- The tape should fit snugly without compressing underlying soft tissues and should be parallel to the floor
- Record to the nearest 0.5 cm at the end of a normal expiration



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WC: waist circumference.
Adapted from The Practical Guide, *NIH*, 2000; and Douketis JD, et al. *CMAJ.* 2005; 172(8):995-8.

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