



# Addressing the **Roots**

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



# Mobile Polling Platform

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Scan the QR code with your mobile device to answer polling questions throughout the presentation



# Presenter Disclosure

Name	Credentials and Affiliations
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## Relationships With Financial Sponsors

<b>SPEAKERS BUREAU/HONORARIA:</b>	
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<b>OTHER:</b>	



# 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.

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# 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.

# Faculty



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

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# 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

# Pre-Program Polling Question

# 1



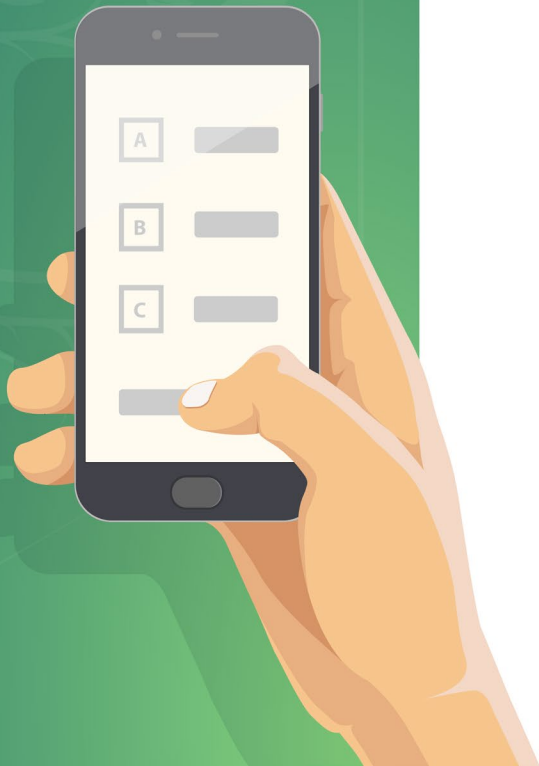
How familiar are you with the concept of adiposopathy (aka sick fat tissue) as a contributing cause of type 2 diabetes and its complications?

- 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

# 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

# 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



# Consider This Patient, Mihika

## History

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

## Physical examination

- Height: 160 cm
- Weight: 69 kg
- Body mass index: 27 kg/m<sup>2</sup>
- Waist circumference 85 cm
- BP 140/90 mmHg

## Investigations

- A1C 8.2%
- UACR 10 mg/mmol

## Medications

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





# Discussion

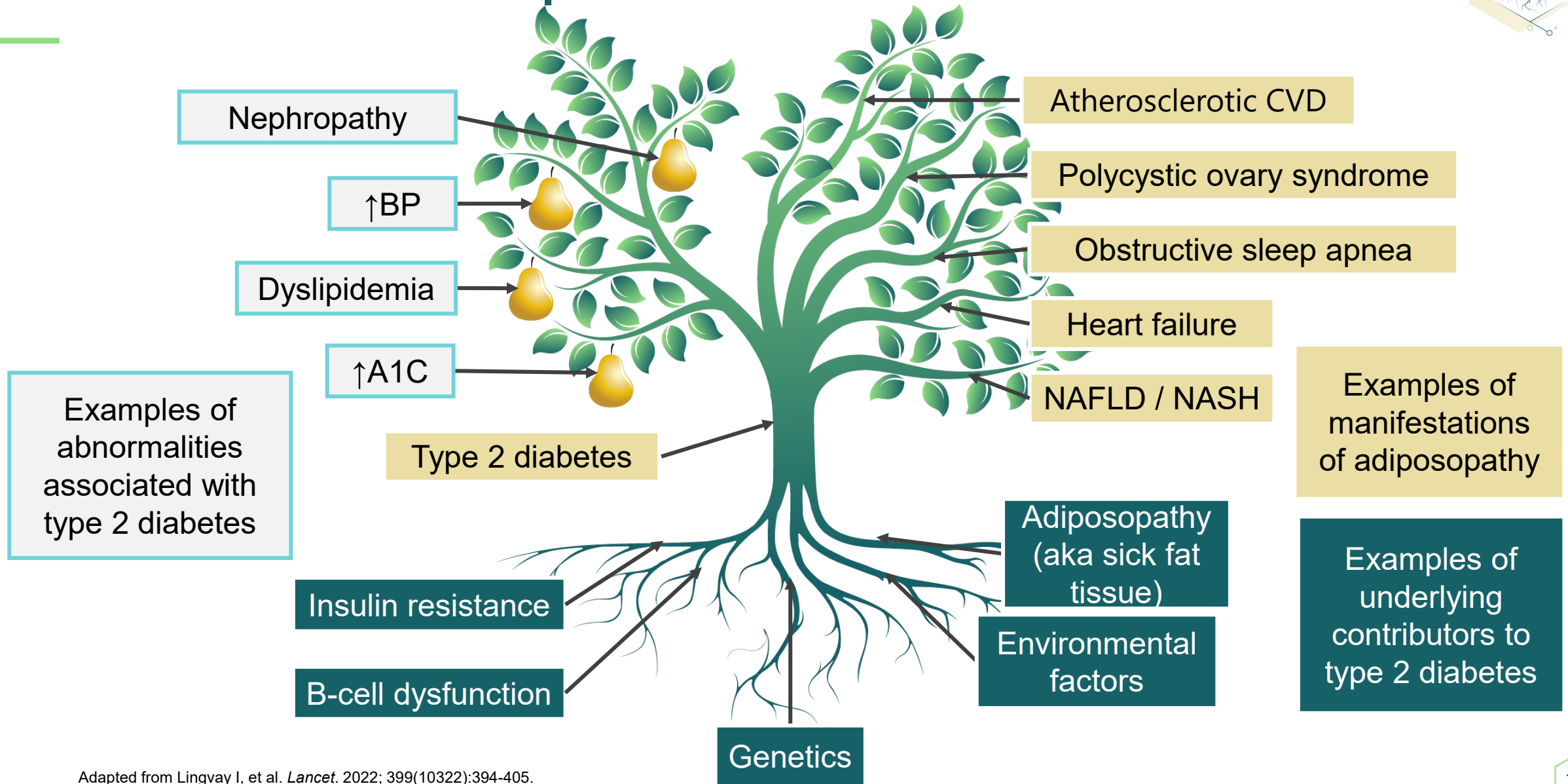
Why did this patient develop all these comorbidities (what are the likely underlying mechanisms)?



# 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



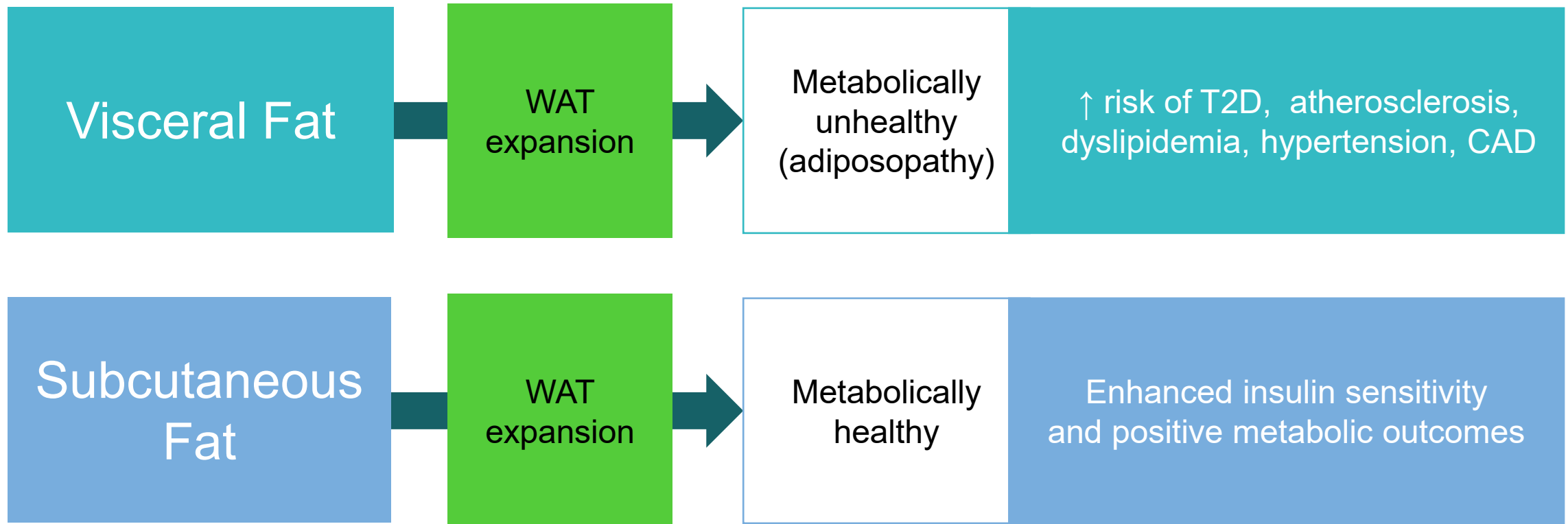
# What is “Adiposopathy”?

- 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<sup>1</sup>
- 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<sup>2</sup>

Obesity, as defined by BMI, does not necessarily equal adiposopathy<sup>1,3</sup>

People with T2D have adiposopathy... but not all people with adiposopathy have T2D<sup>3</sup>

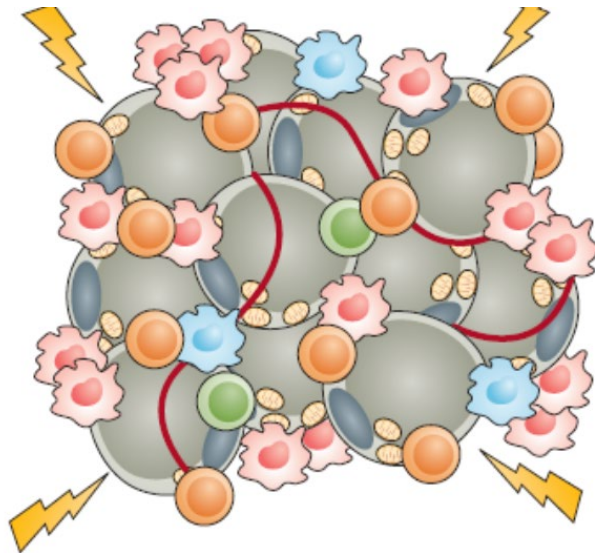
# Most Critical Aspect of White Adipose Tissue Expansion... Location, Location, Location<sup>1-7</sup>



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.:**

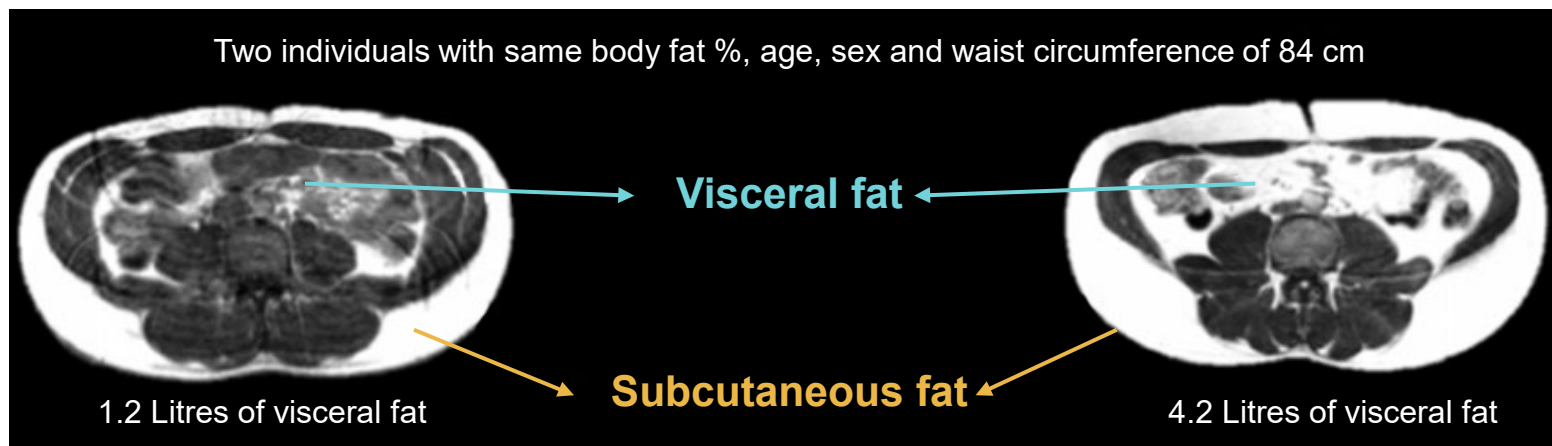
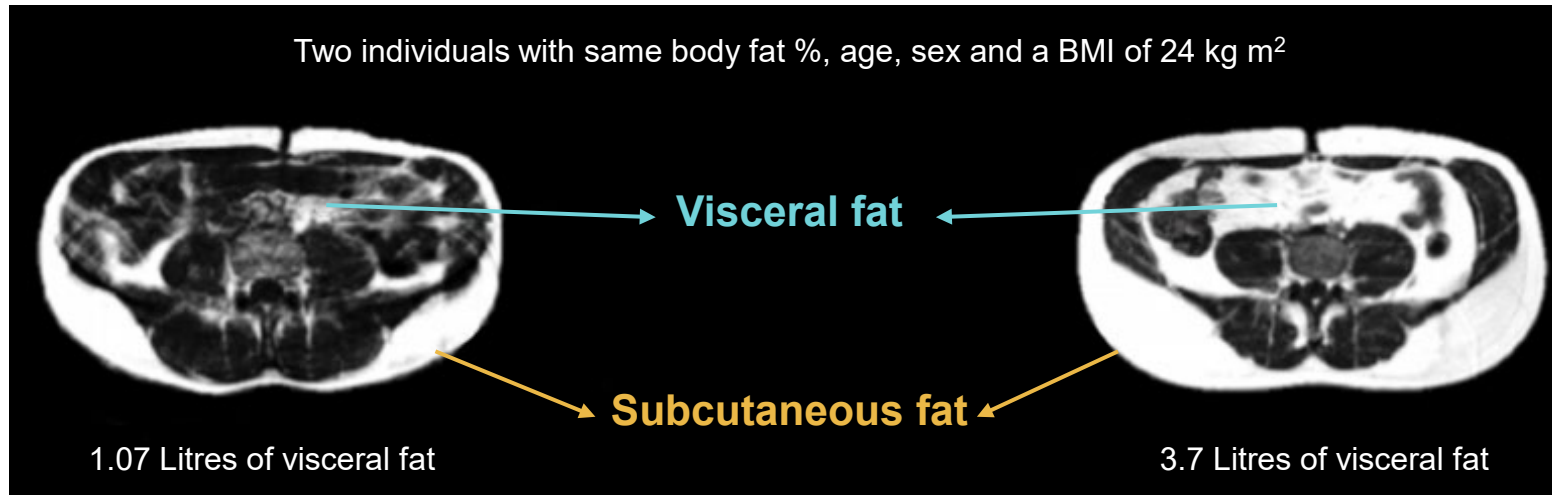
- TNF
- IL-1 $\beta$
- IL-6
- IL-8
- Leptin
- Resistin
- MCP1

↓ **anti-inflammatory factors, e.g.:**

- IL-10
- Adiponectin



# BMI Is Not An Accurate Predictor of Adiposopathy: Examples

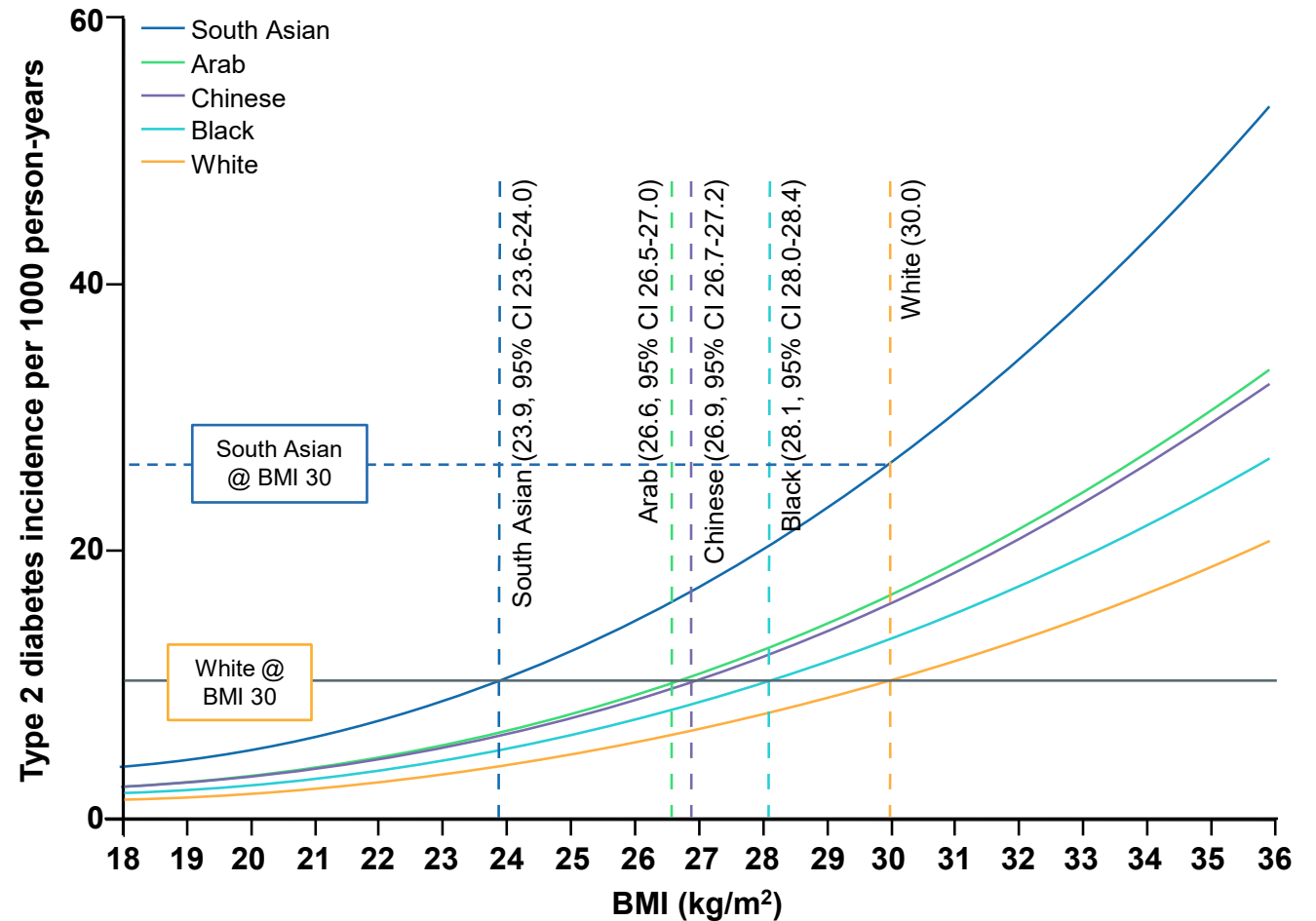




# People of Different Ethnicities Have Different Thresholds for BMI as a Risk Factor for T2D



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<sup>2</sup>

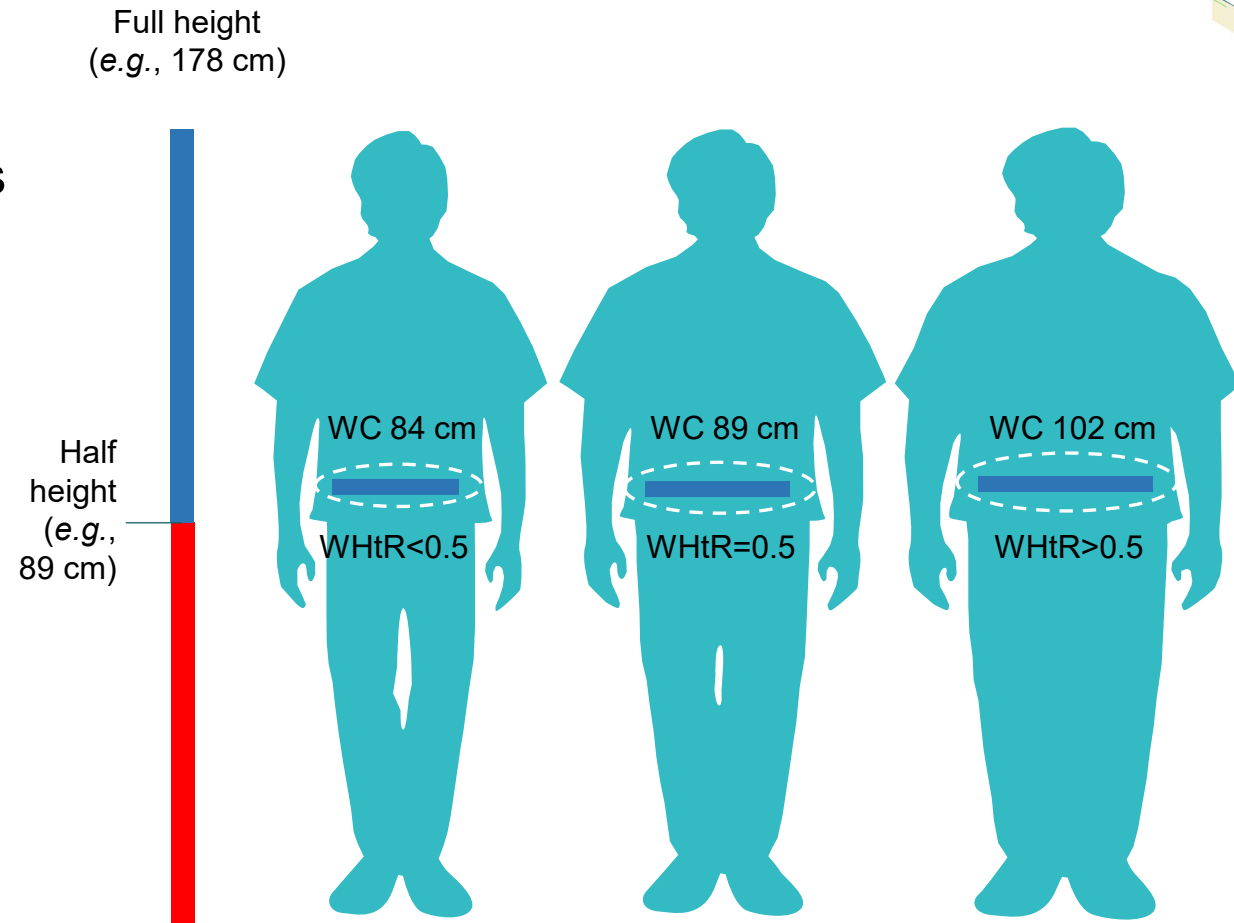


BMI: body mass index; CI: confidence interval; T2D: type 2 diabetes.  
Adapted from Caleyachetty R, et al. *Lancet Diabetes Endocrinol.* 2021; 9(7):419-26.

# 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<sup>1,2</sup>
- Ideal WHtR is  $<0.5$  (*i.e.*, waist circumference should be less than half height)<sup>2</sup>
- Ethnic-specific studies are still lacking, but there is some evidence that the 0.5 cutoff applies across ethnicities<sup>3</sup>



[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. Kazlauskaitė 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

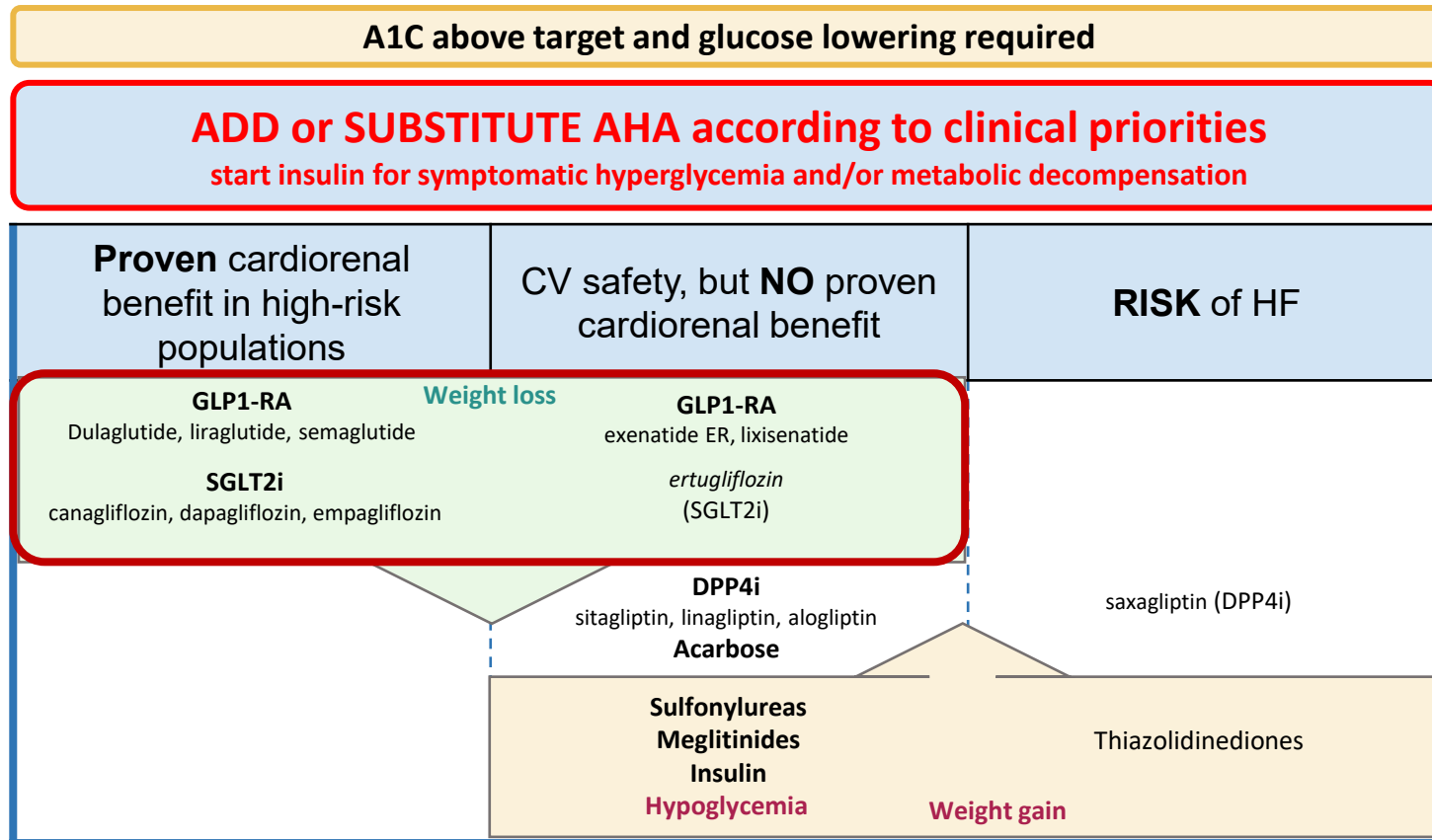
**So what should we do to help her and others like her?**



# Discussion

Should we expand our thinking and incorporate addressing adiposopathy into our treatment goals?

# 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.

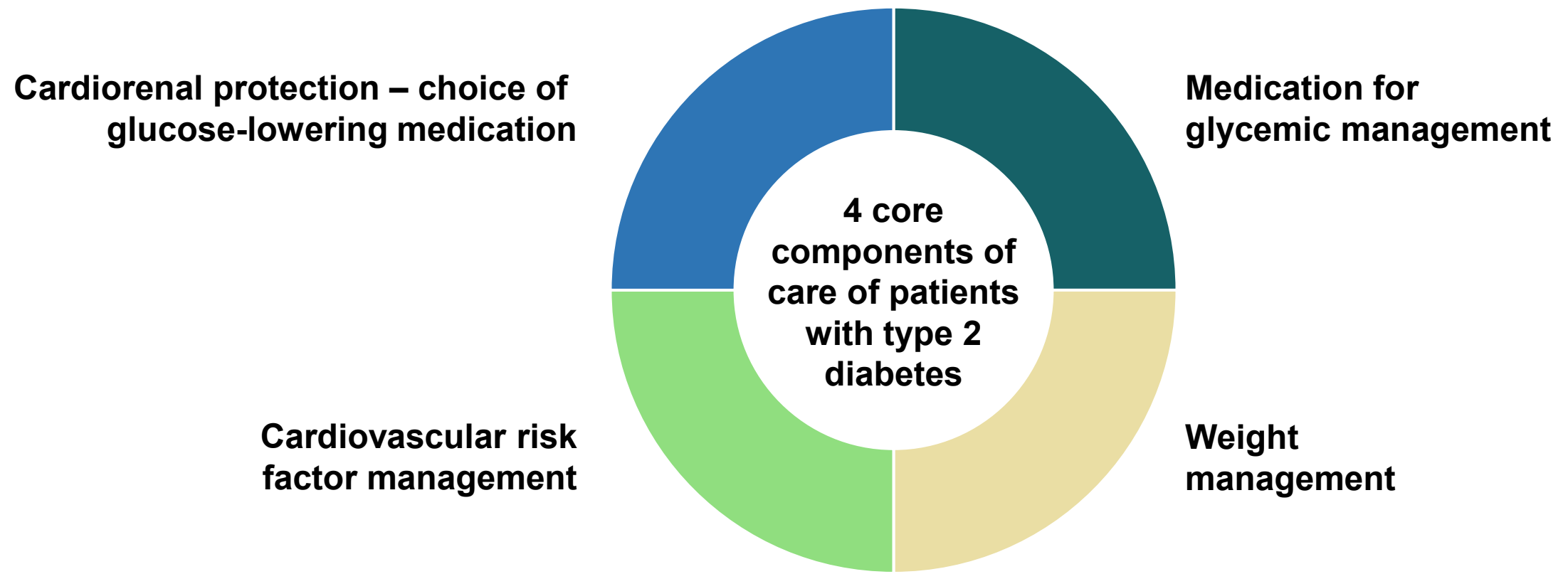
Lipscombe L, et al. Can J Diabetes. 2020; 44:575-91.



# 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)





# Comprehensive Management of Type 2 Diabetes

Should We Incorporate Modulation of Adiposopathy as a Treatment Goal?



# Nonpharmacologic Approaches

Can These Influence Adiposopathy?

# 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



# Lifestyle Modifications With Evidence of Benefit in T2D

## Food Intake

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

## Physical Activity

- Reduced amount of time sitting<sup>12-15</sup>
- “Exercise snacking”- small amount of activity whenever possible<sup>16</sup>
- Physical activity after meals<sup>17</sup>

Improved sleep is also associated with evidence of benefit<sup>18-21</sup>

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.

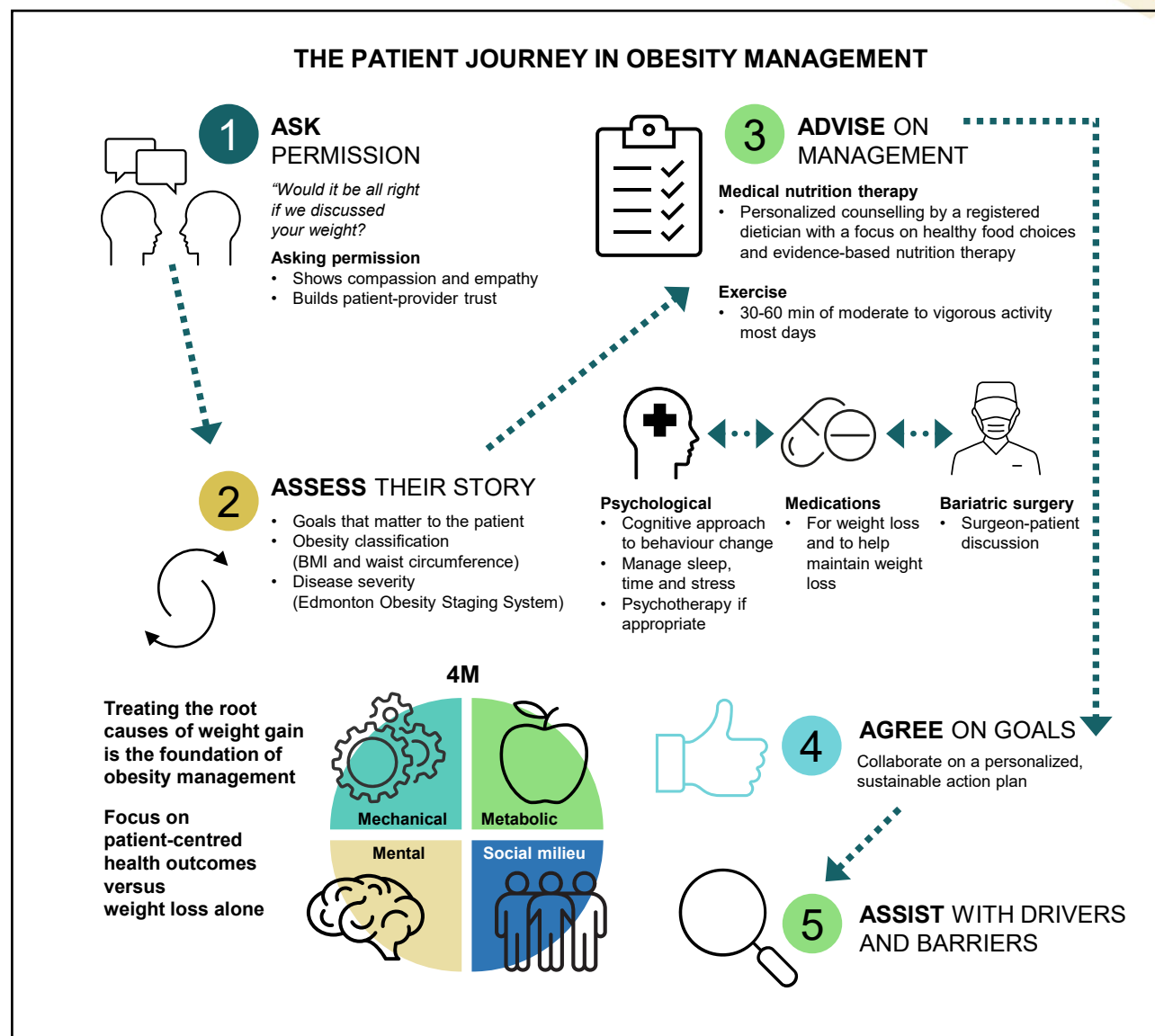
CHO, carbohydrate; GI, glycemic index; T2D, type 2 diabetes

# 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:

- **Ask**
- **Assess**
- **Advise**
- **Agree**
- **Assist**





# 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.”



# Canadian Obesity Guidelines Recommendations on Bariatric Surgery



**Bariatric surgery can be considered for people with BMI  $\geq 40$  kg/m<sup>2</sup> or BMI  $\geq 35$  kg/m<sup>2</sup> 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

# 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  $\geq 35$  kg/m<sup>2</sup>, 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<sup>2</sup>.”

“BMI thresholds should be adjusted in the Asian population such that a BMI  $\geq 25$  kg/m<sup>2</sup> suggests clinical obesity, and individuals with BMI  $\geq 27.5$  kg/m<sup>2</sup> should be offered MBS.”

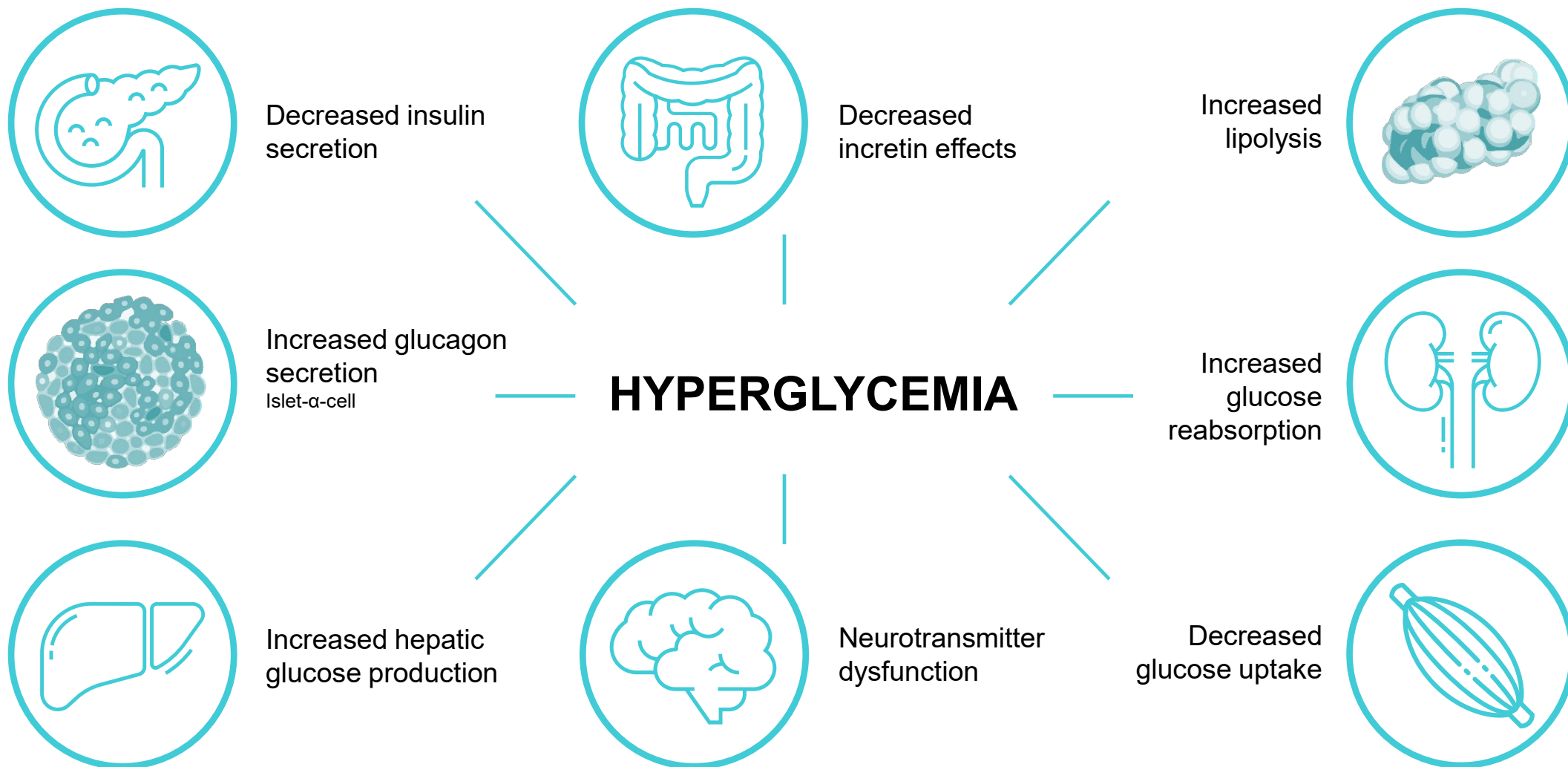
“Long-term results of MBS consistently demonstrate safety and efficacy.”



# Pharmacologic Approaches











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



# Common Antihyperglycemic Therapies and How They Address the Ominous Octet



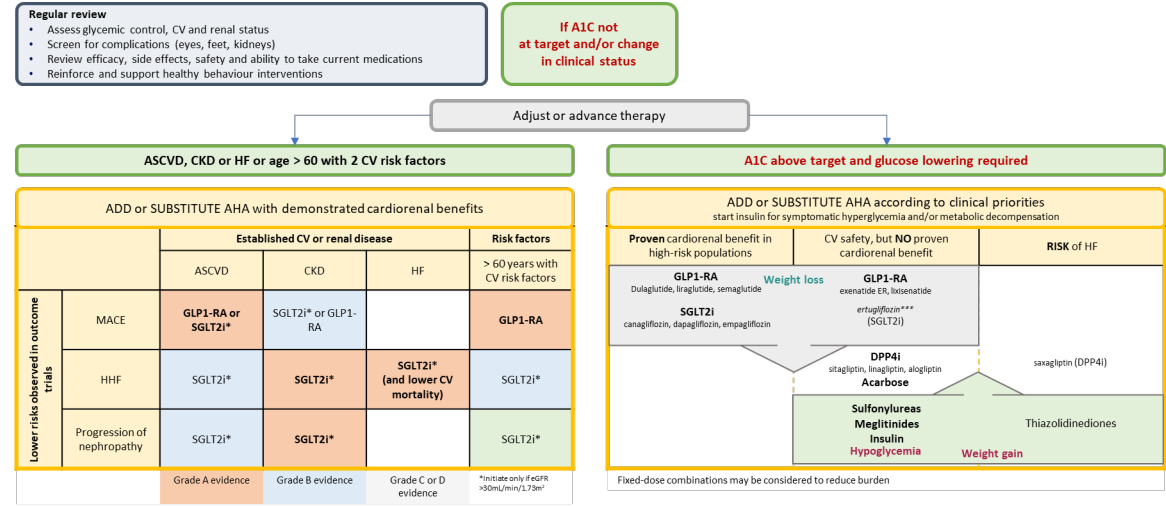
Mechanism	Metformin	SU / glinide	TZD	DPP4i	GLP1-RA	SGLT2i
 ↑ insulin secretion		✓	✓	✓	✓	
 ↓ glucagon secretion				✓	✓	
 ↓ hepatic glucose production	✓		✓	✓	✓	
 Incretin pathways				✓	✓	
 ↓ lipolysis			✓			
 ↓ glucose reabsorption						✓
 ↑ glucose uptake	✓		✓	✓	✓	
 ↓ neurotransmitter dysfunction				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

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)<sup>1,2</sup>



### Which cardiovascular non-antihyperglycemic medications are indicated for my patient?

<b>Does the patient have cardiovascular disease?</b> - Cardiac ischemia (silent or overt) - Peripheral arterial disease - Cerebrovascular/carotid disease YES	<b>Statin<sup>1</sup> + ACEi/ARB<sup>2</sup> + ASA<sup>3</sup></b>
NO	
<b>Does the patient have microvascular disease?</b> - Retinopathy - Kidney disease (ACR ≥2.0) - Neuropathy YES	<b>Statin<sup>1</sup> + ACEi/ARB<sup>2</sup></b>
NO	
<b>Is the patient:</b> - age ≥55 with additional CV risk factors? <sup>4</sup> - age ≥40? - age ≥30 and diabetes >15 years? - warranted for statin therapy based on the Canadian Cardiovascular Society Lipid Guidelines? YES	<b>Statin<sup>1</sup></b>

1 Dose adjustments or additional lipid therapy warranted if lipid target (LDL-C <2.0 mmol/L) not being met.  
 2 ACE-inhibitor or ARB (angiotensin receptor blocker) should be given at doses that have demonstrated vascular protection (eg. perindopril 8 mg once daily [EUROPA trial], ramipril 10 mg once daily [HOPE trial], telmisartan 80 mg once daily [ONTARGET trial]).  
 3 ASA should not routinely be used for the primary prevention of cardiovascular disease in people with diabetes. ASA may be used for secondary prevention. Consider clopidogrel if ASA-intolerant.  
 4 TC > 5.2 mmol/L, HDL-C < 0.9 mmol/L, hypertension, albuminuria, smoking.










ABCDEs of diabetes care		2020
	<b>GUIDELINE TARGET</b> (or personalized goal)	
<b>A</b>	<b>A1C targets</b>	A1C ≤7.0% (or ≤6.5% to ↓ risk of CKD and retinopathy)
<b>B</b>	<b>BP targets</b>	BP <130/80 mmHg If on treatment, assess for risk of falls
<b>C</b>	<b>Cholesterol targets</b>	LDL-C <2.0 mmol/L (or >50 % reduction from baseline)
<b>D</b>	<b>Drugs for CV and/or Cardiorenal protection</b>	(non-AHA) • ACEi/ARB (if CVD, age ≥55 with risk factors, OR diabetes complications) • Statin (if CVD, age ≥40 for type 2, OR diabetes complications) • ASA (if CVD) (Antihyperglycemic Agents) • SGLT2i/GLP1-RA with demonstrated cardiorenal benefits in high risk type 2 with ASCVD, CKD or HF, OR Age >60 with 2 CV risk factors
<b>E</b>	<b>Exercise goals and healthy eating</b>	• 150 minutes of moderate to vigorous aerobic activity/ week and resistance exercises 2-3 times/week • Follow healthy dietary pattern (eg Mediterranean diet, low glycemic index)
<b>S</b>	<b>Screening for complications</b>	• Cardiac: ECG every 3-5 years if age >40 OR diabetes complications • Foot: Monofilament/Vibration yearly or more if abnormal • Kidney: Test eGFR and ACR yearly, or more if abnormal • Retinopathy: type 1 - annually; type 2 - q1-2 yrs
<b>S</b>	<b>Smoking cessation</b>	If smoker: Ask permission to give advice, arrange therapy and provide support
<b>S</b>	<b>Self-management, stress, other barriers</b>	• Set personalized goals (see "individualized goal setting" panel) • Assess for stress, mental health and financial or other concerns that might be barriers to achieving goals

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](http://guidelines.diabetes.ca/CDACPG/media/documents/CPG/CPG_Quick_Reference_Guide_PRINT_EN_2021.pdf) Accessed September 2022.

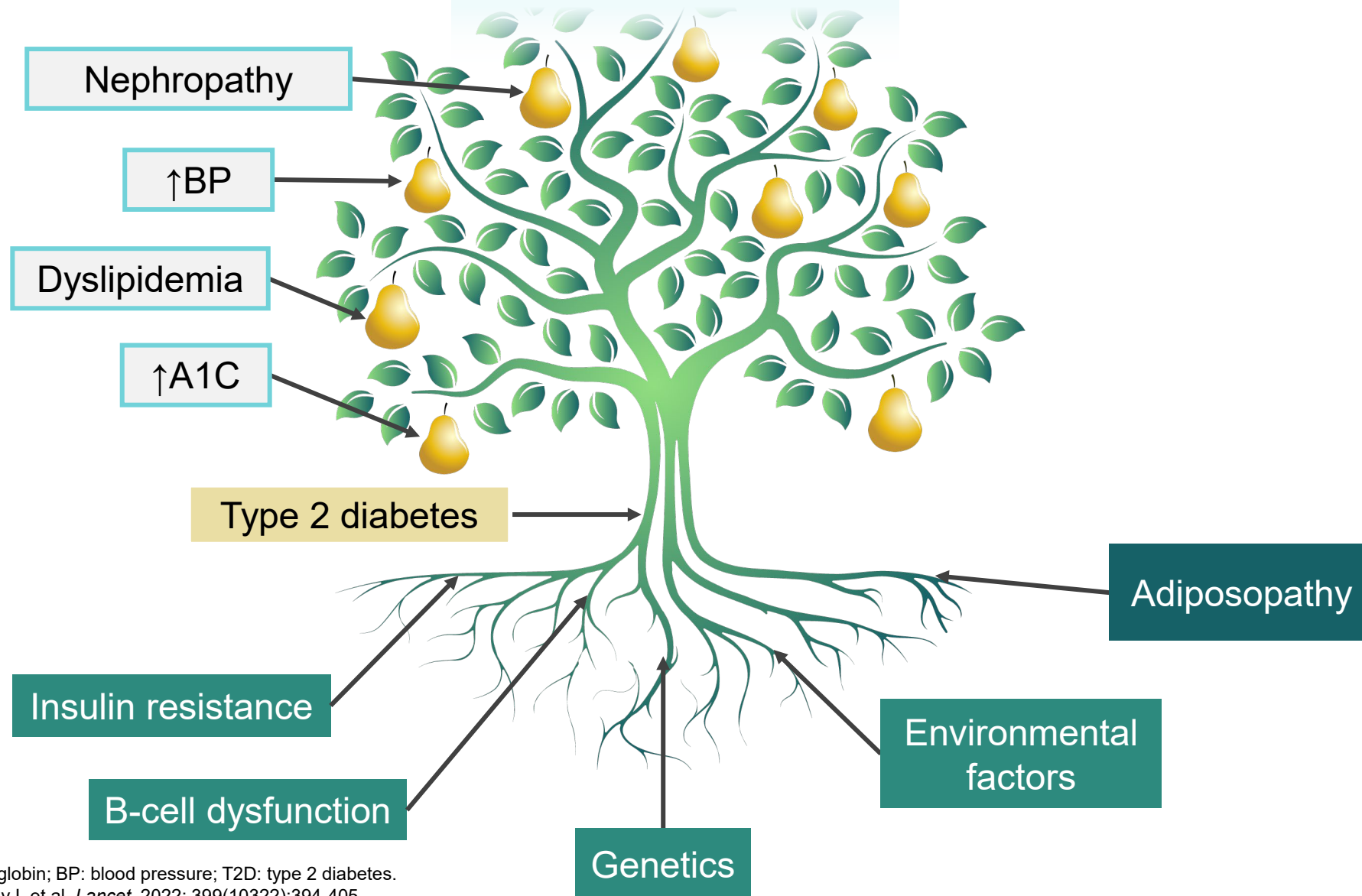
# Evolving View of Antihyperglycemic Therapies, Including Cardiorenal Protection



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.



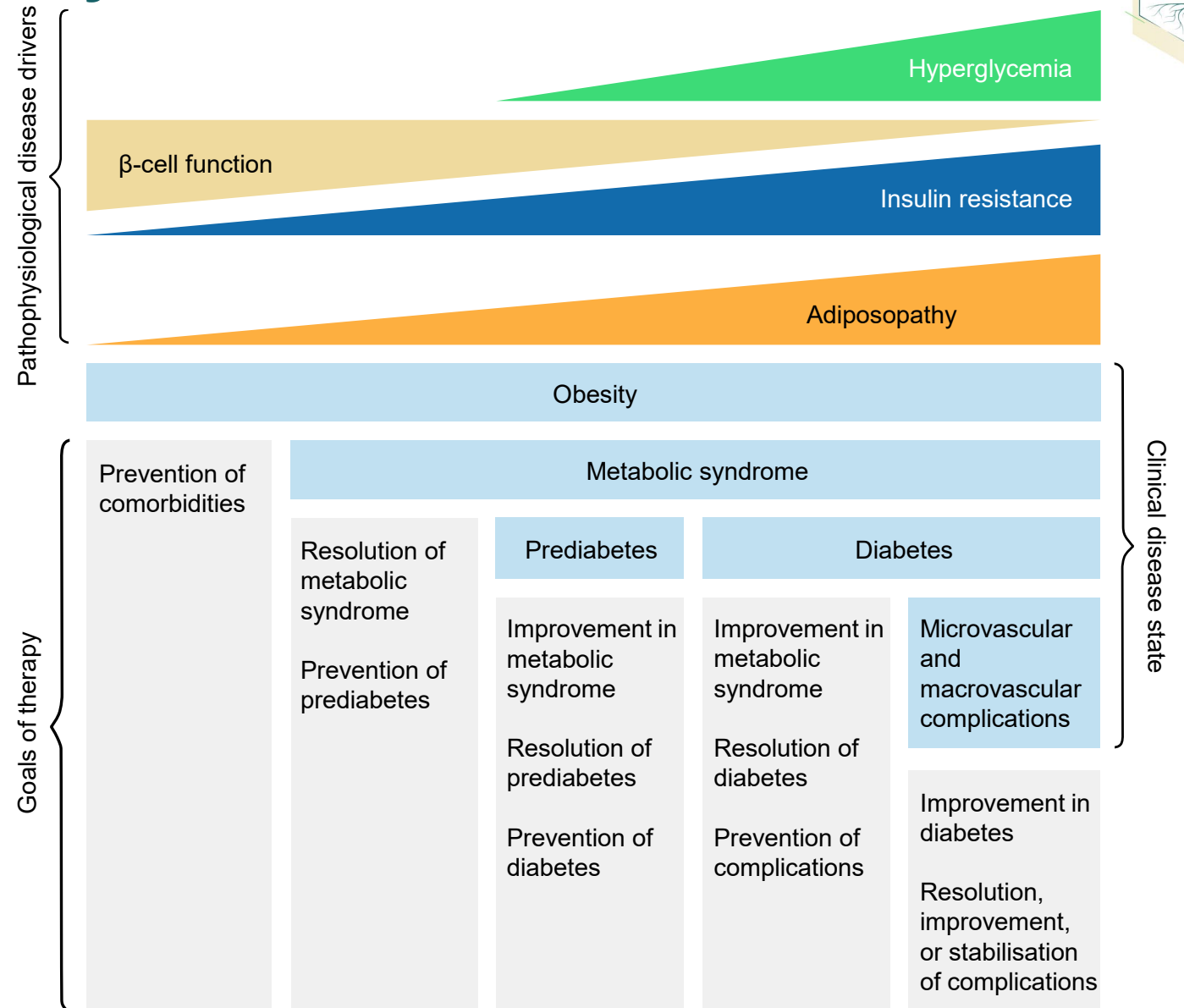
# Discussion

Which of the currently available antihyperglycemics would be most likely to positively influence adiposopathy? How?



# 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



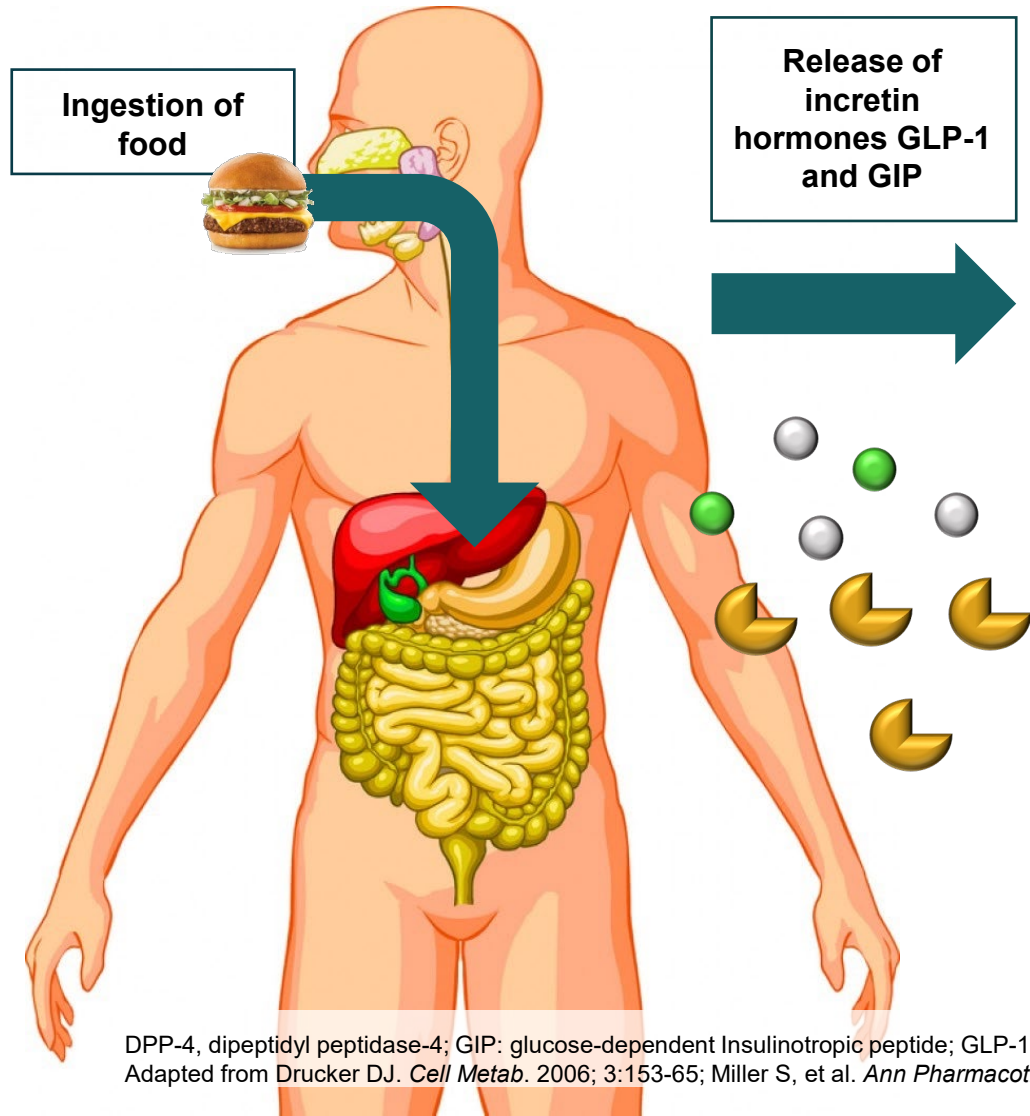


# *Moving Forward* Evolving Pharmacotherapy for Comprehensive T2D Management

Focusing on novel approaches to modulating  
the incretin pathways



# 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

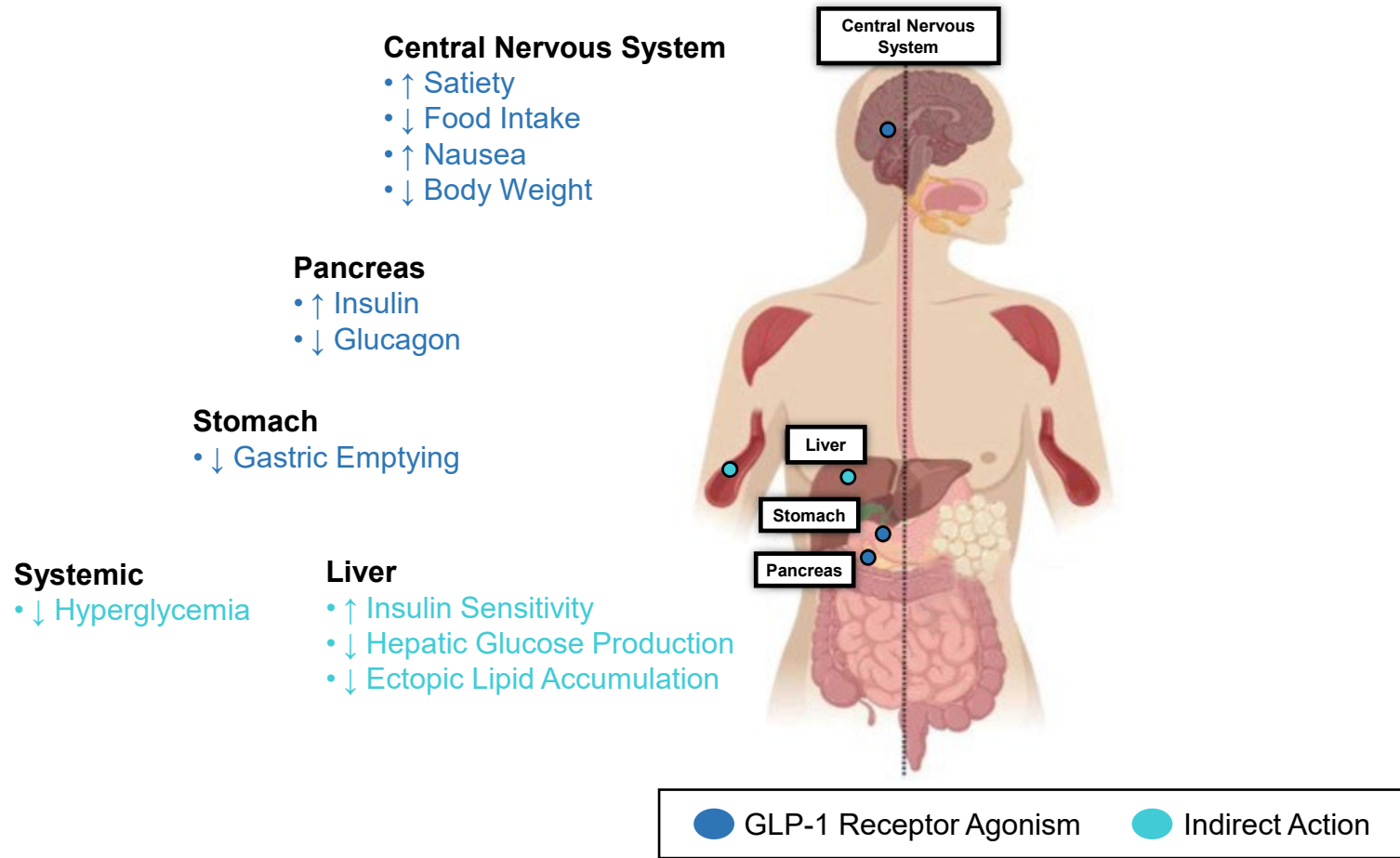
The incretin effect is diminished in patients with type 2 diabetes compared to healthy individuals

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

# Effects of GLP-1 Receptor Agonism Extend Beyond Glycemic Control



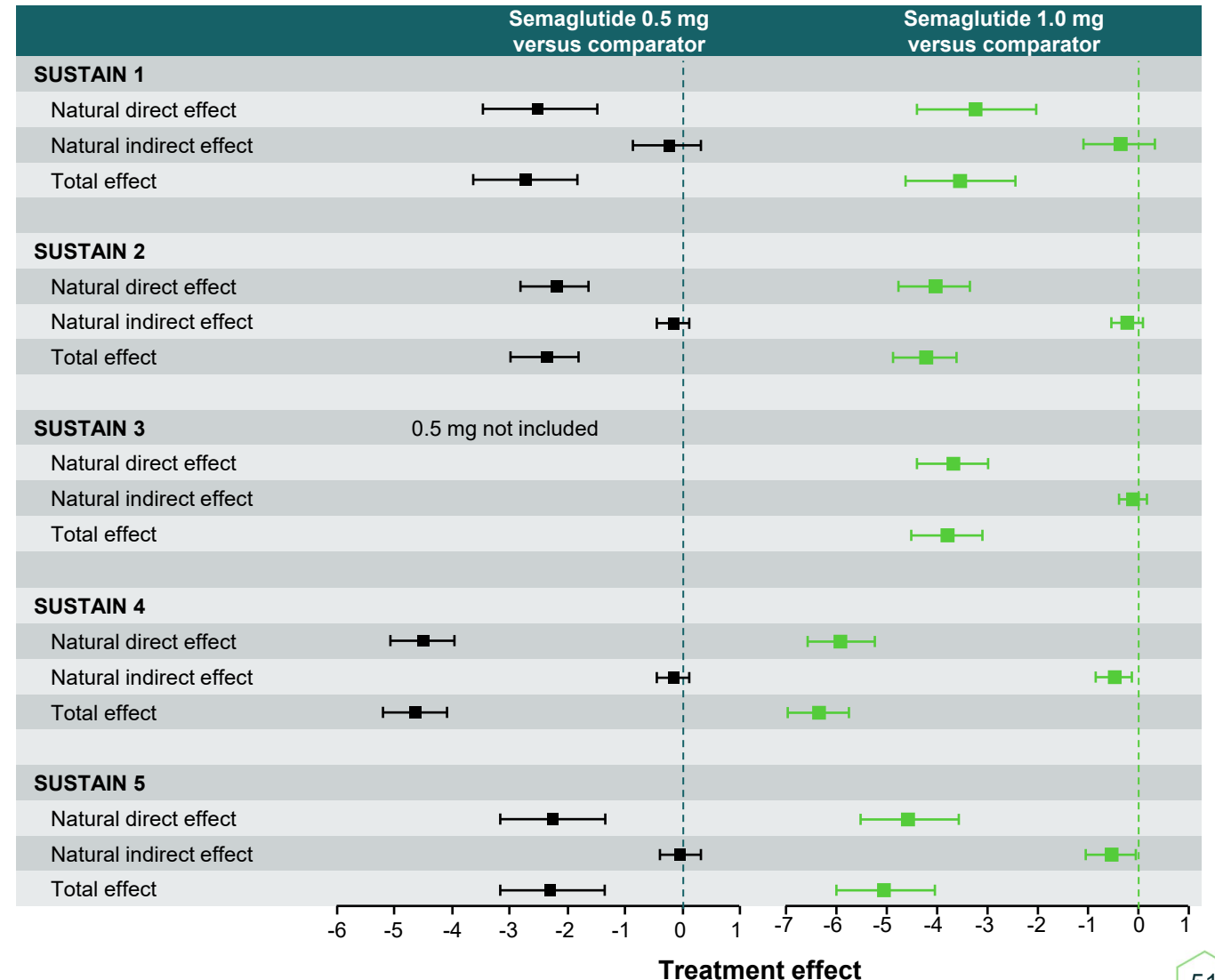
## Glucagon-like Peptide-1 Receptor Agonism



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

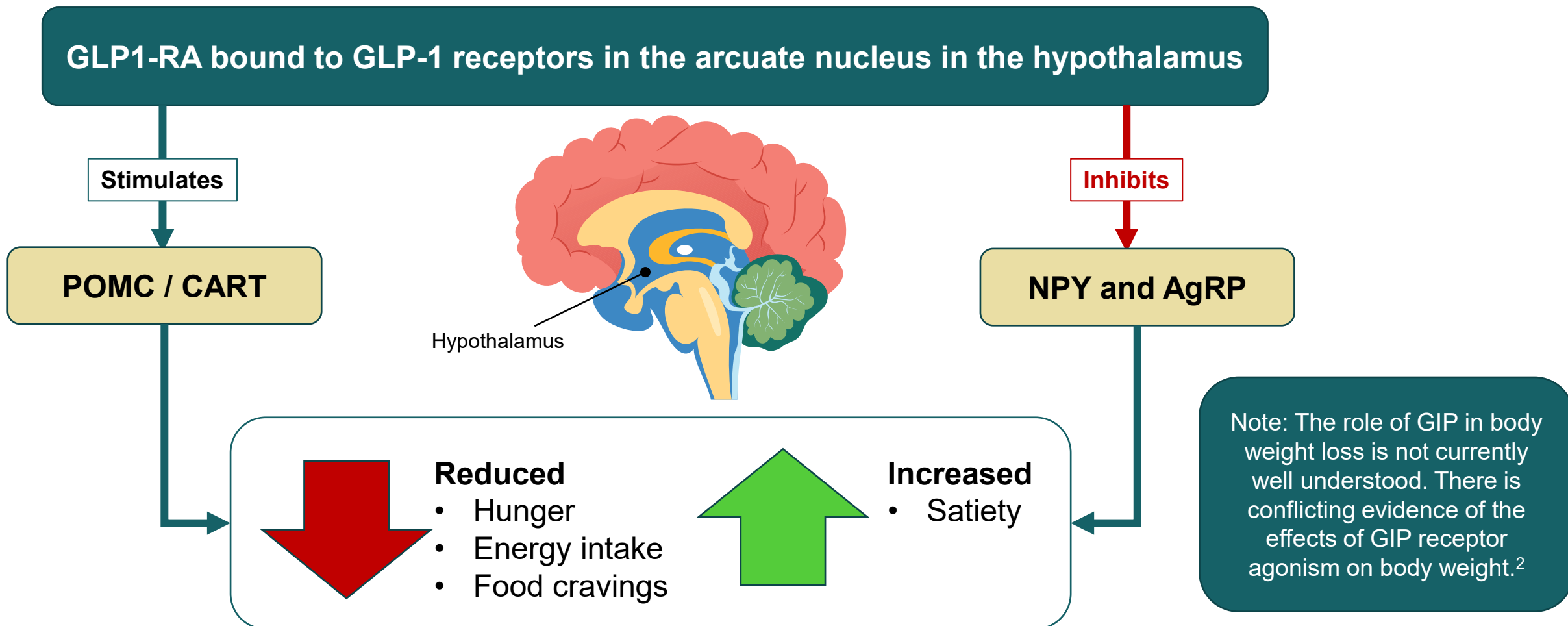


- Mediation analyses of direct vs. indirect (gastrointestinal) effects on weight loss with semaglutide 0.5 and 1.0 mg in SUSTAIN 1-5
- Only 0.07 to 0.5 kg of the weight loss could be attributed to nausea/vomiting
- Therefore, large proportion of the weight loss observed is due to effects other than nausea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





# How Can GLP1-RA Therapy Lead to Body Weight Loss?<sup>1</sup>

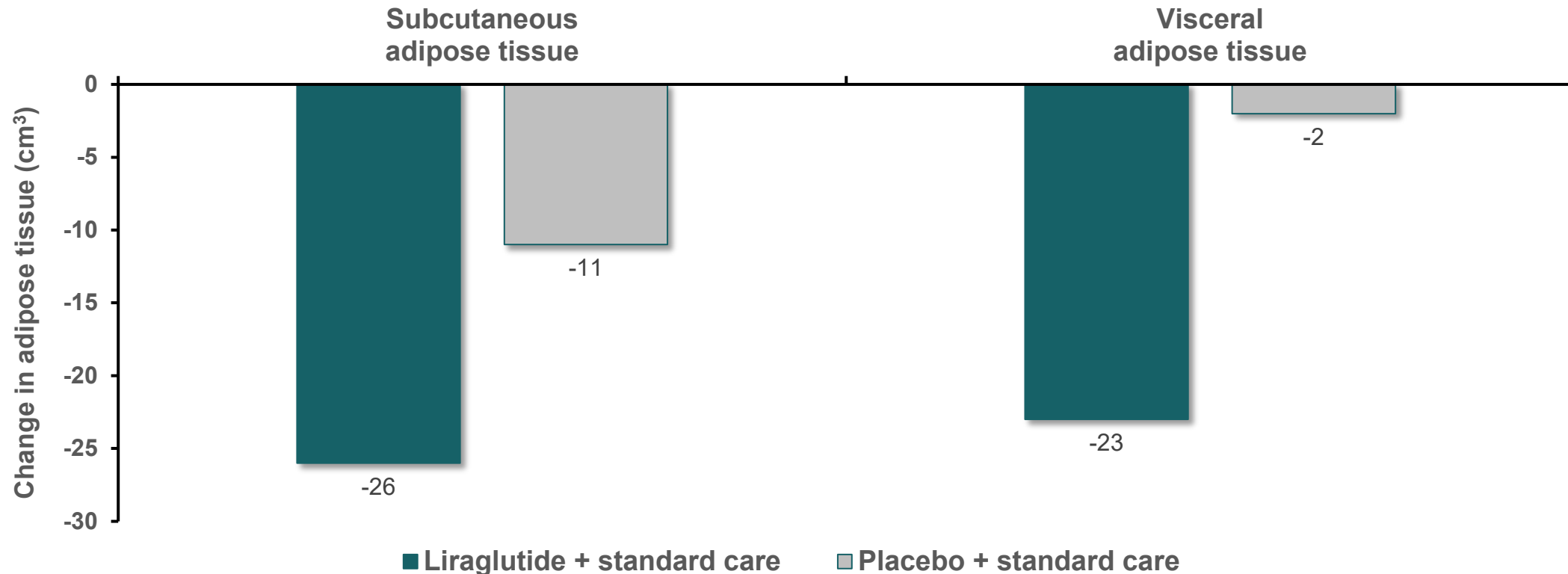


AgRP: agouti-related peptide; GIP: glucose-dependent Insulinotropic peptide; GLP-1: glucagon-like peptide-1; GLP-1-RA: glucagon-like peptide-1 receptor agonist; NPY: neuropeptide Y; POMC / CART: proopiomelanocortin and cocaine- and amphetamine-regulated transcript  
Adapted from 1. Ard J, et al. *Adv 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





# Current Agents Targeting the Incretin Pathway

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

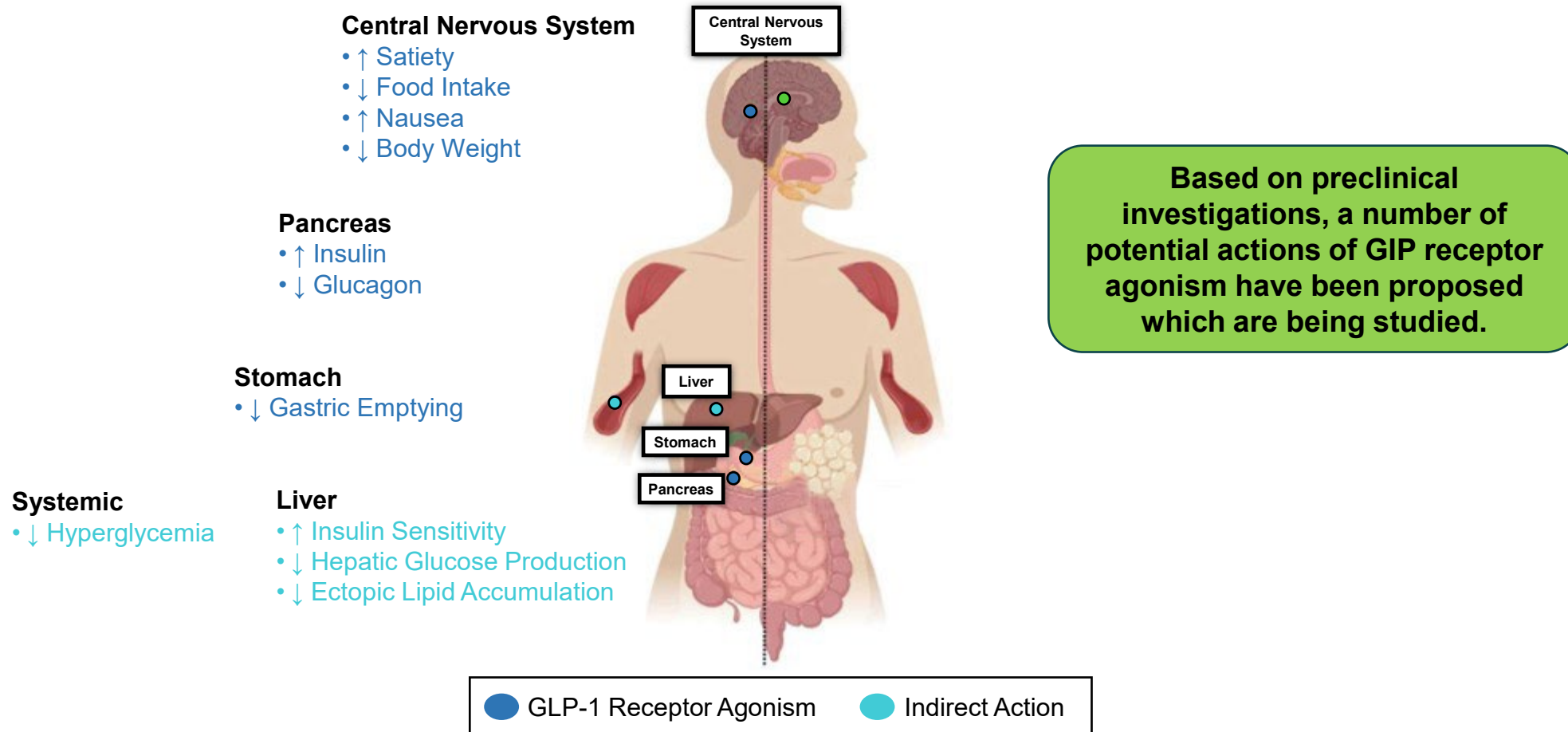
DPP4i: Dipeptidyl peptidase-4 inhibitor; GLP-1-RA: Glucagon-like peptide-1 receptor agonist; SGLT2i: sodium glucose co-transporter-2 inhibitor; TZD: Thiazolidinedione; SU: sulfonylureas. Adapted from: DeFronzo RA. *Diabetes*. 2009; 58(4):773-95; Abdul-Ghani M, et al. *Diabetes Care*. 2017; 40:1121-7;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

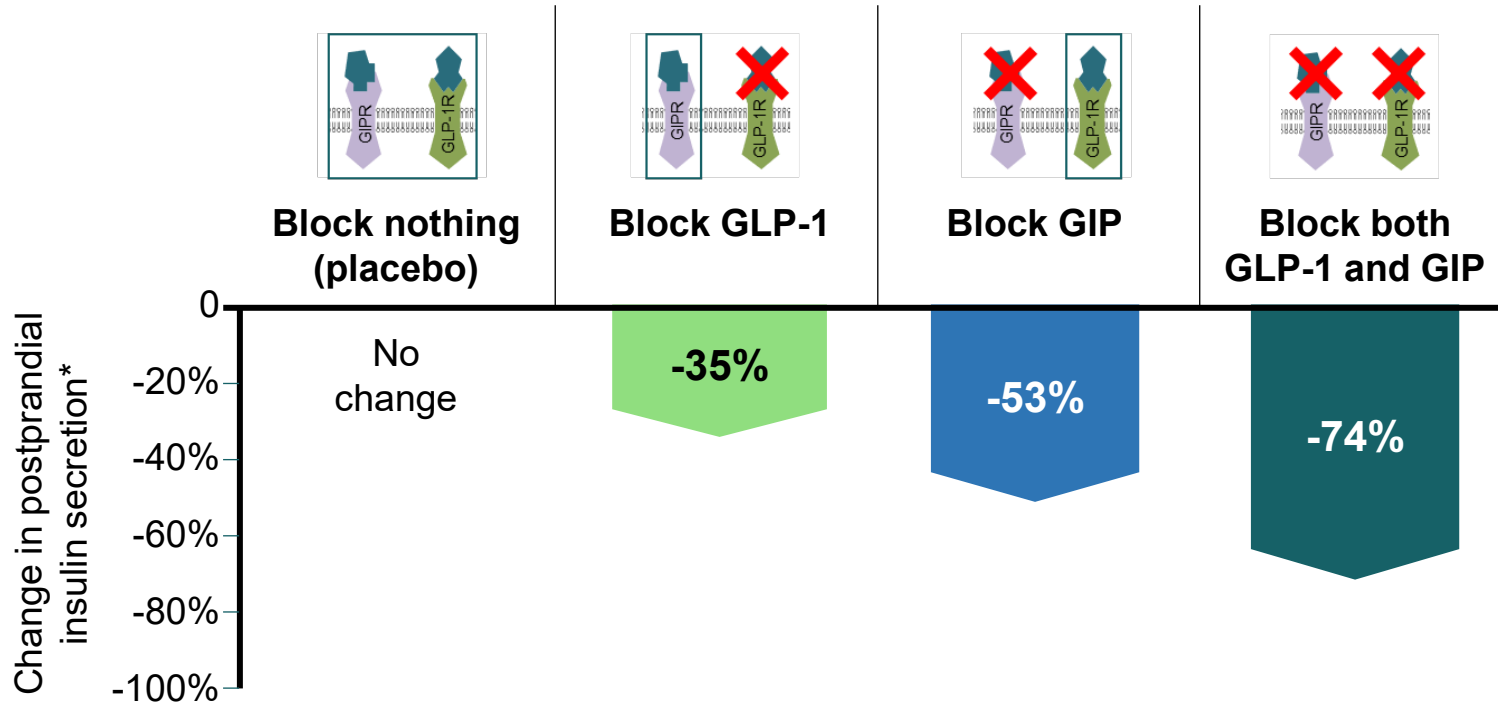


# GIP May Contribute More to Postprandial Insulin Secretion than GLP-1: Evidence from 2 Studies in People Without T2D



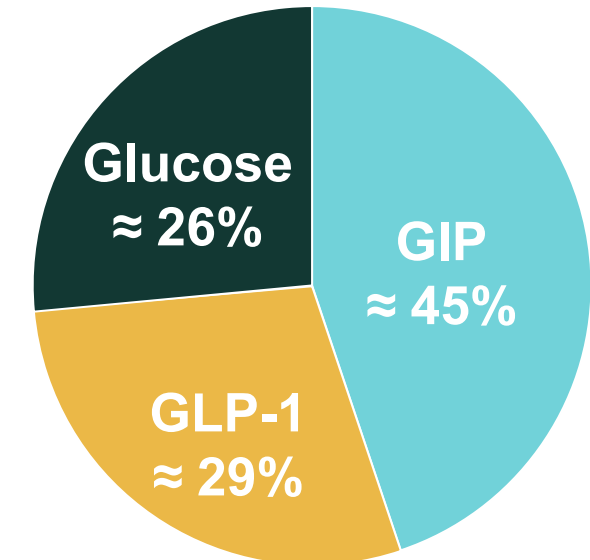
## What happens to post-prandial insulin secretion if you block the activity of GIP, GLP-1 or both?

During oral glucose tolerance test in 18 men without T2D, using specific antagonists<sup>1†</sup>



## Stimulators of Postprandial Insulin Secretion

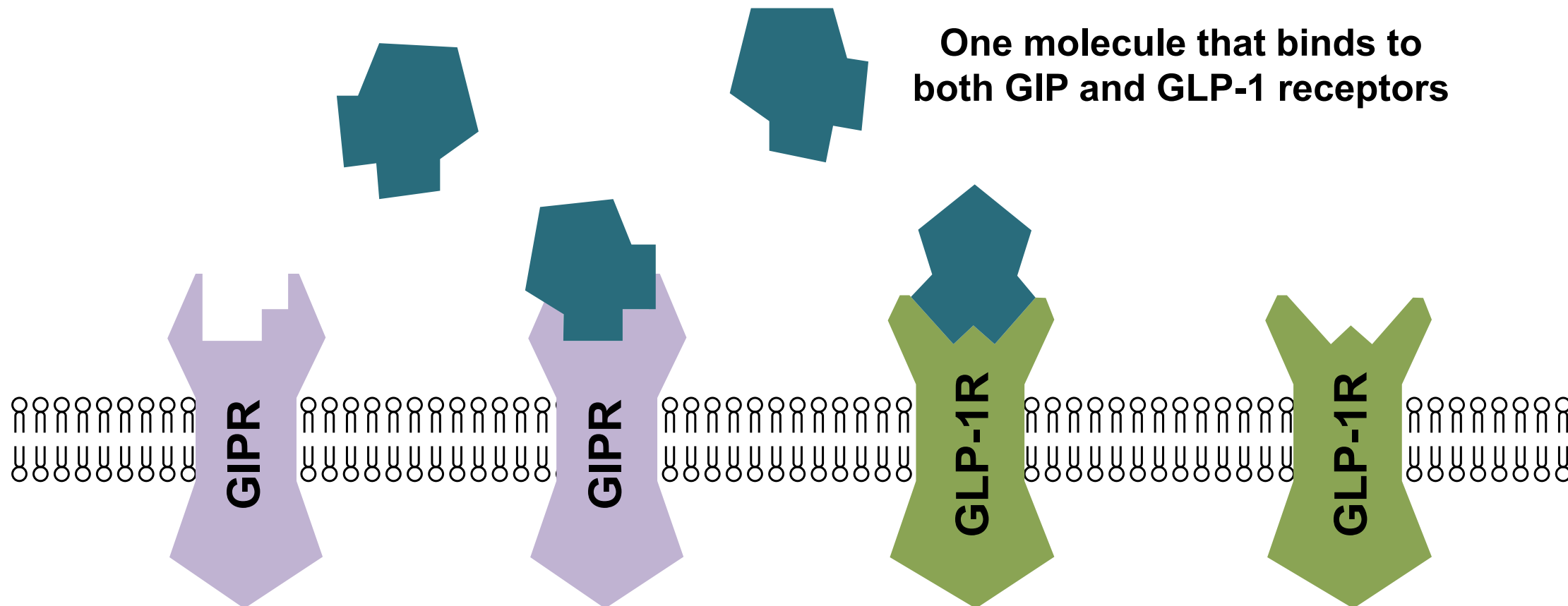
Based on incretin receptor antagonist studies in individuals without T2D<sup>2</sup>



\*Measured by basal-subtracted area under the curve of ISR:glucose, adjusted for fold-difference in glucose of placebo; †Antagonists used: For GLP-1: Exendin(9-39)NH<sub>2</sub>; for GIP: GIP(3-30)NH<sub>2</sub>; GIP: glucose-dependent insulintropic polypeptide; GIPR: glucose-dependent insulintropic 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.



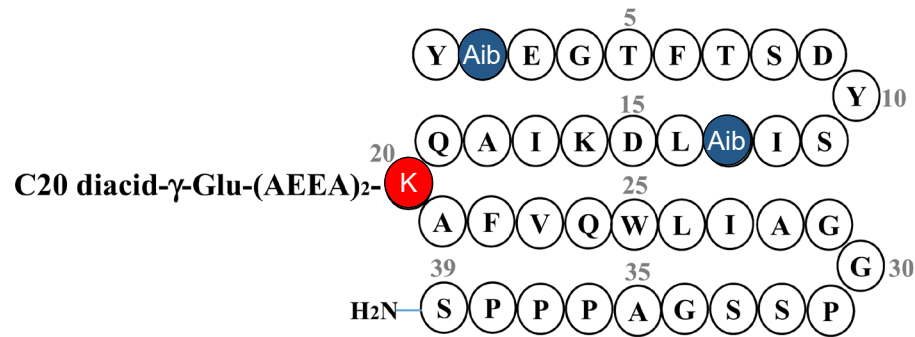
# New Method of Modulating the Incretin Pathway: Dual GIP/GLP-1 Receptor Agonism





# Dual GIP/GLP-1 Receptor Agonist: Tirzepatide<sup>1</sup>

## Molecular Sequence of Tirzepatide



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



**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

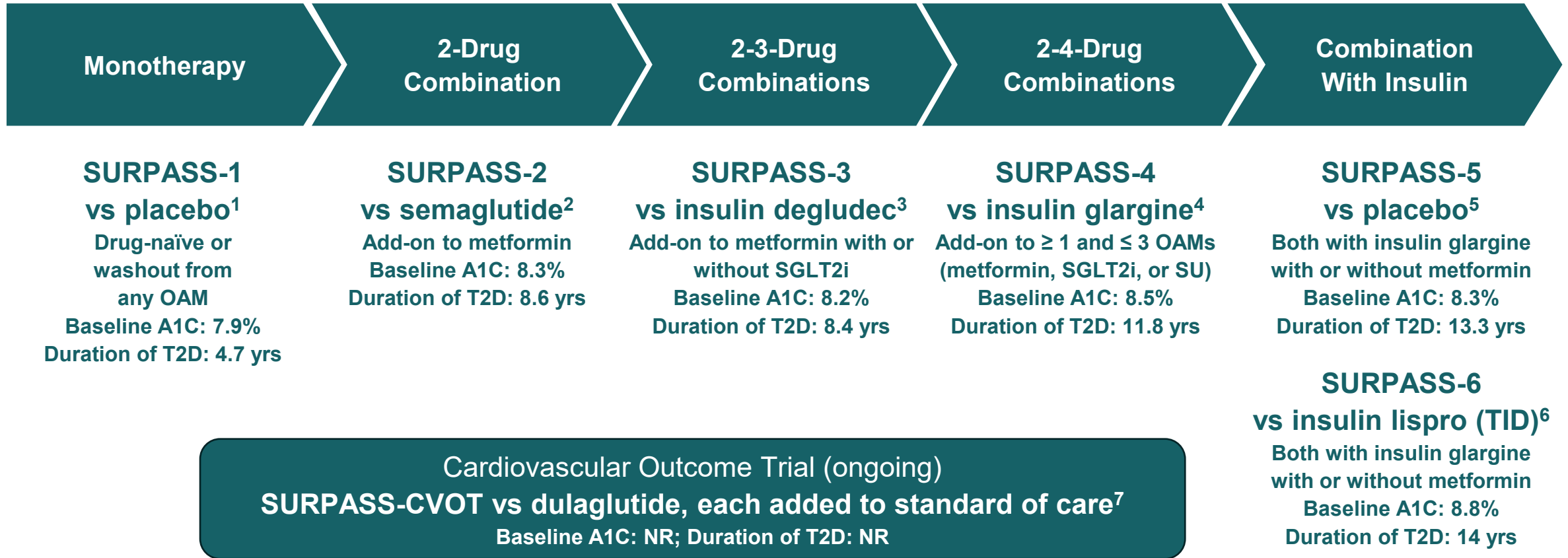
**Approved by Health Canada in November 2022 for once-weekly administration as an adjunct to diet and exercise to improve glycemic control for the treatment of adult patients with type 2 diabetes.<sup>2</sup>**

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.

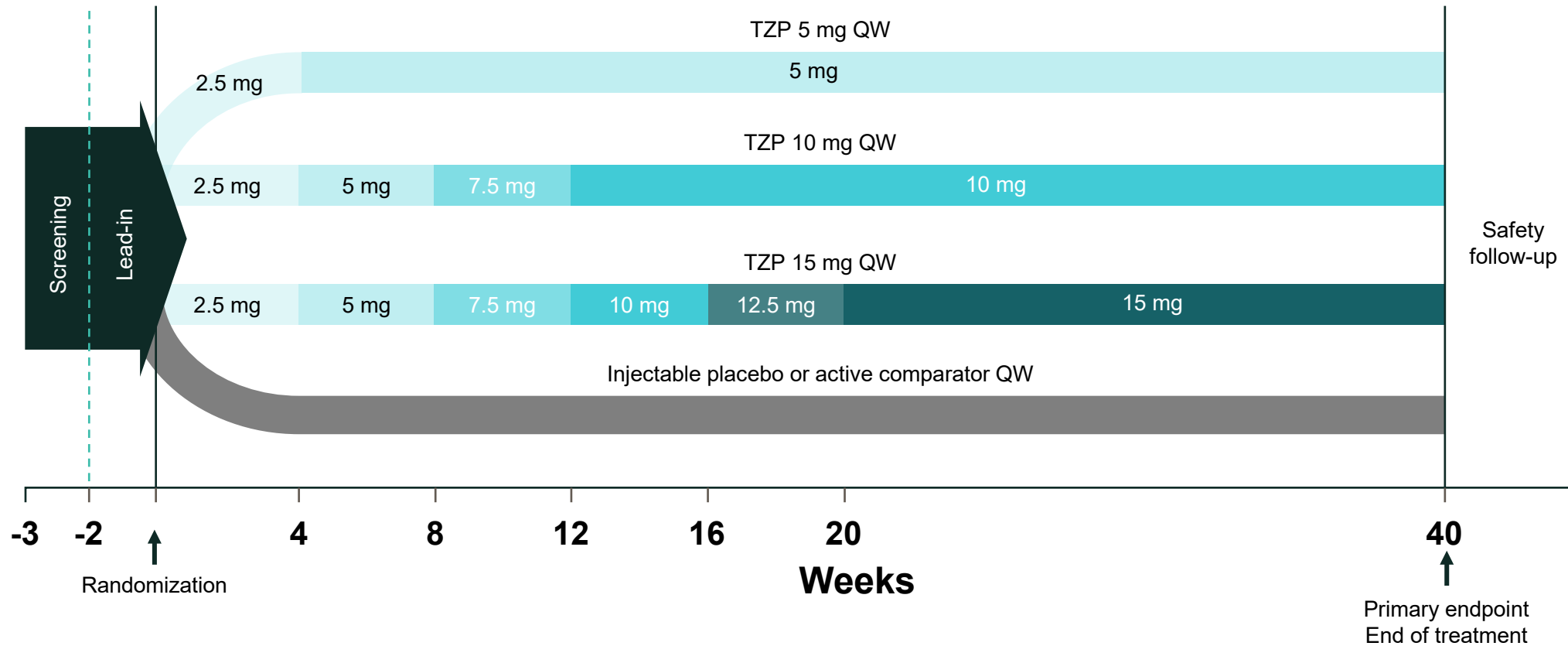


# Tirzepatide's Clinical Trial Program: SURPASS



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<sup>1-5</sup>



**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.

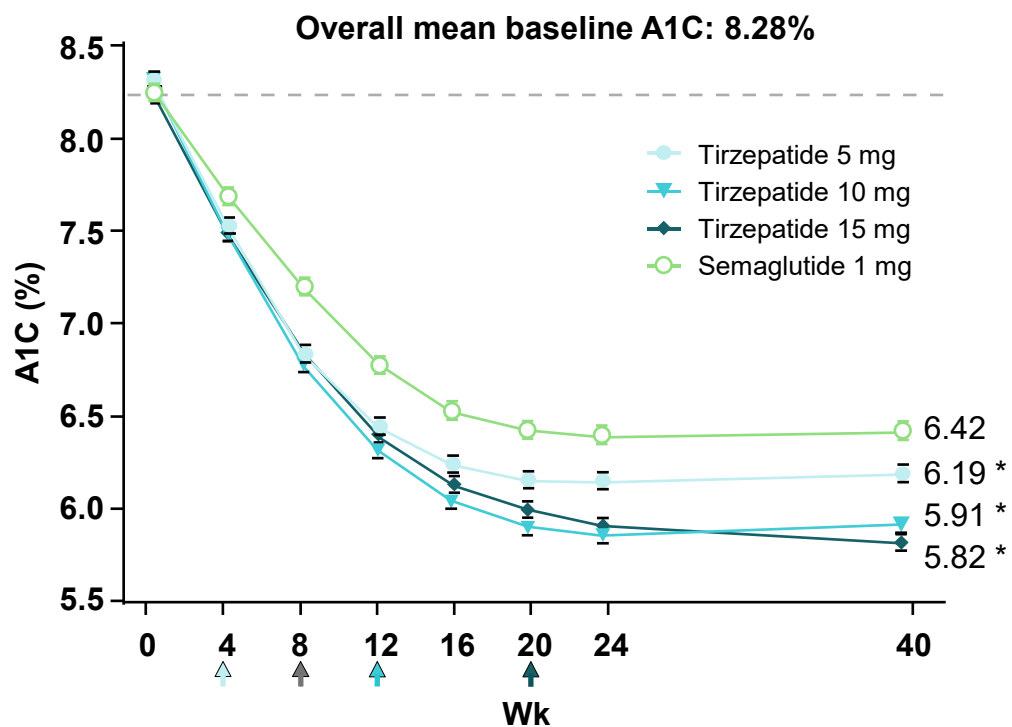
1. Rosenstock J, et al. *Lancet*. 2021; 398(10295):143-55; 2. Frias JP, et al. *N Engl J Med*. 2021; 385(6):503-15; 3. Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98; 4. Del Prato S, et al. *Lancet*. 2021; 398(10313):1811-24; 5. Dahl D, et al. *JAMA*. 2022; 327(6):534-45.



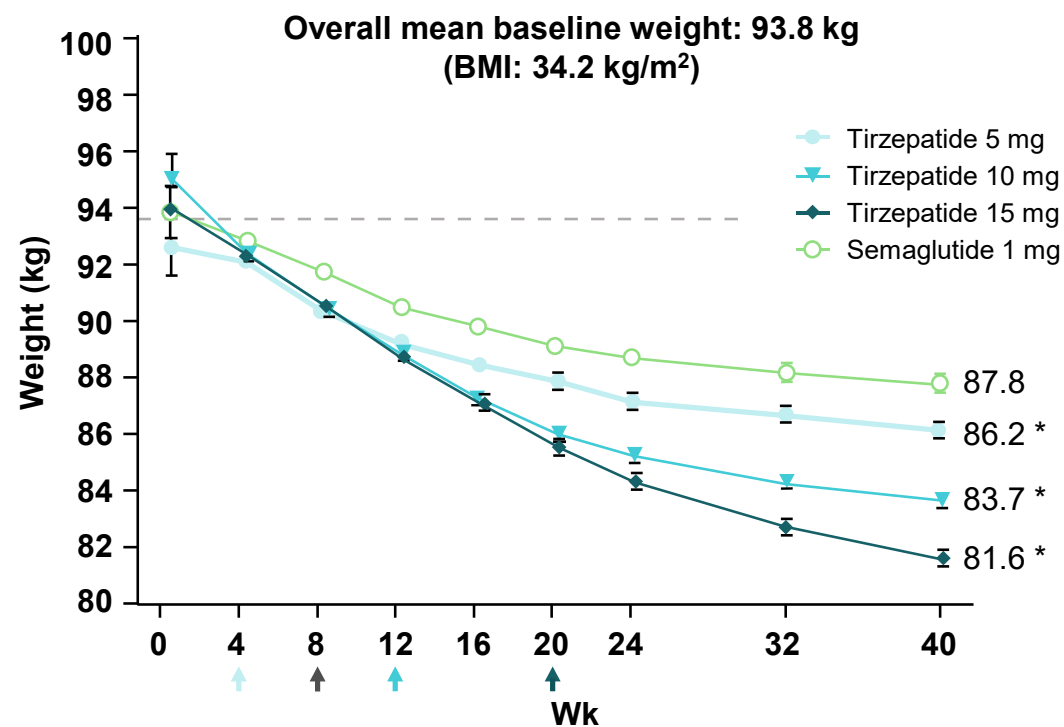
# SURPASS-2: A1C and Body Weight Reductions vs. Semaglutide 1 mg (Selective GLP1-RA)



## A1C Reductions from Baseline



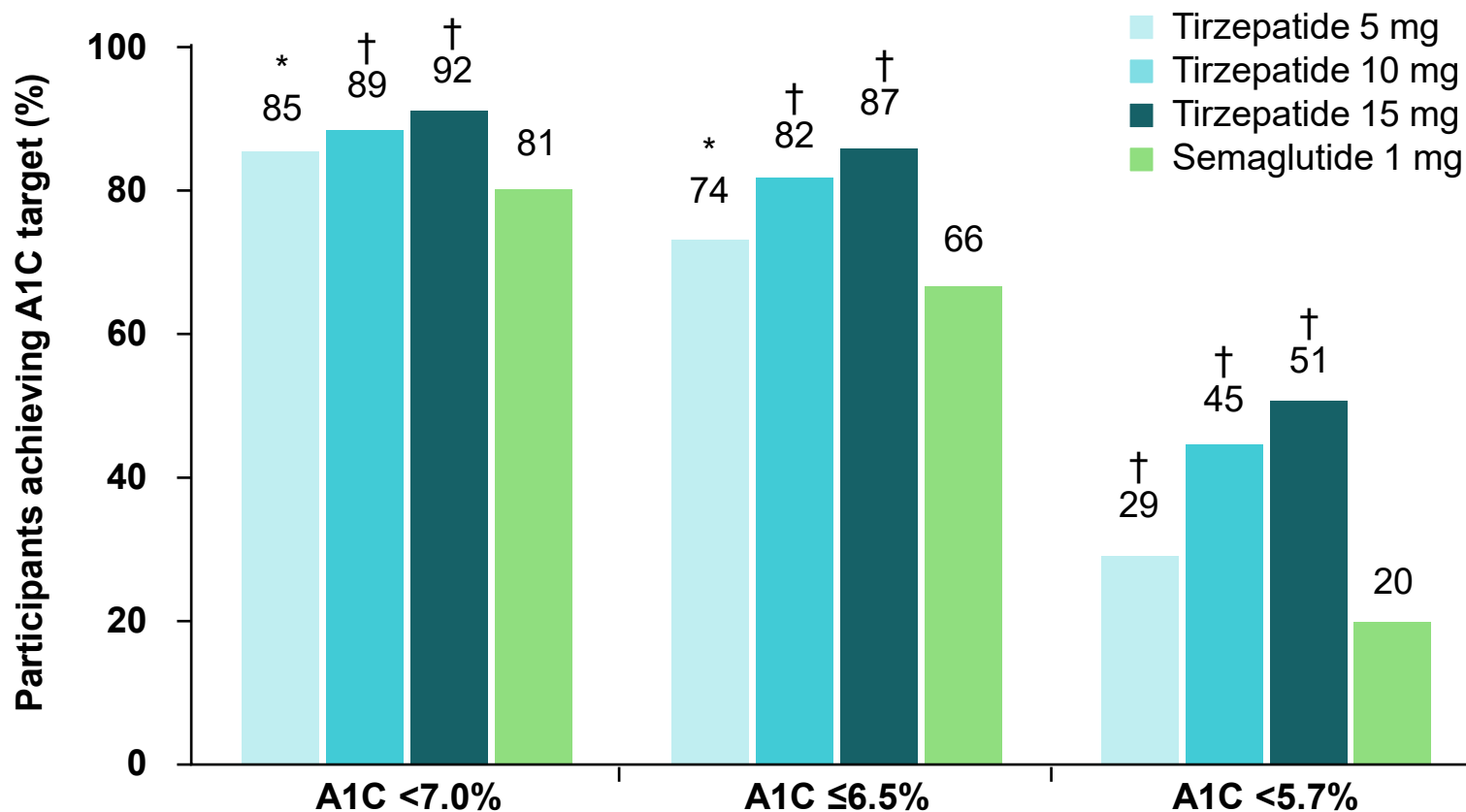
## Body Weight Changes from Baseline



\* $p < 0.001$  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%

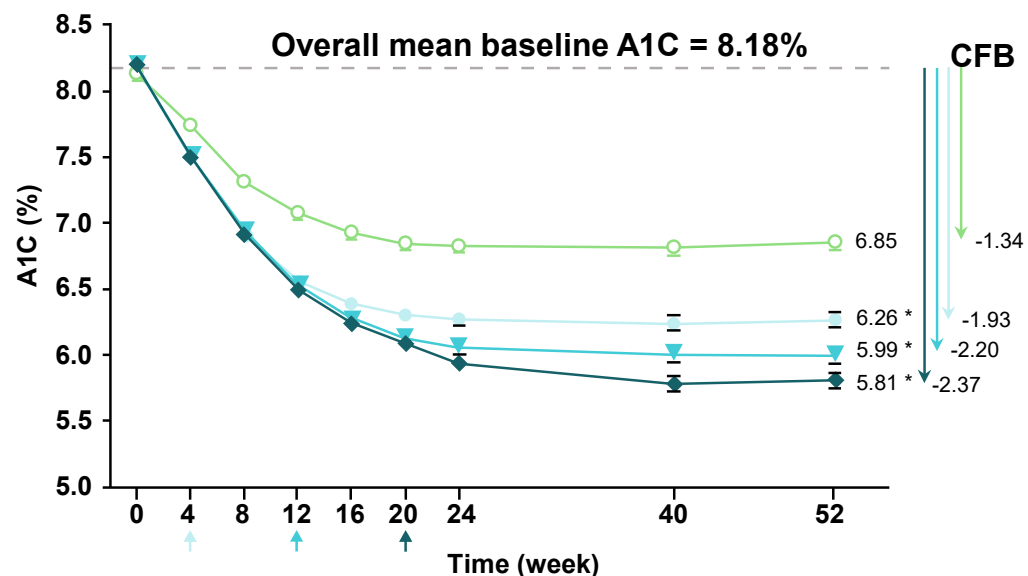
\* $p < 0.05$  vs semaglutide 1 mg. † $p < 0.001$  vs semaglutide 1 mg.  
A1C: glycated hemoglobin  
Frías JP, et al. *N Engl J Med.* 2021; 385(6):503-15.



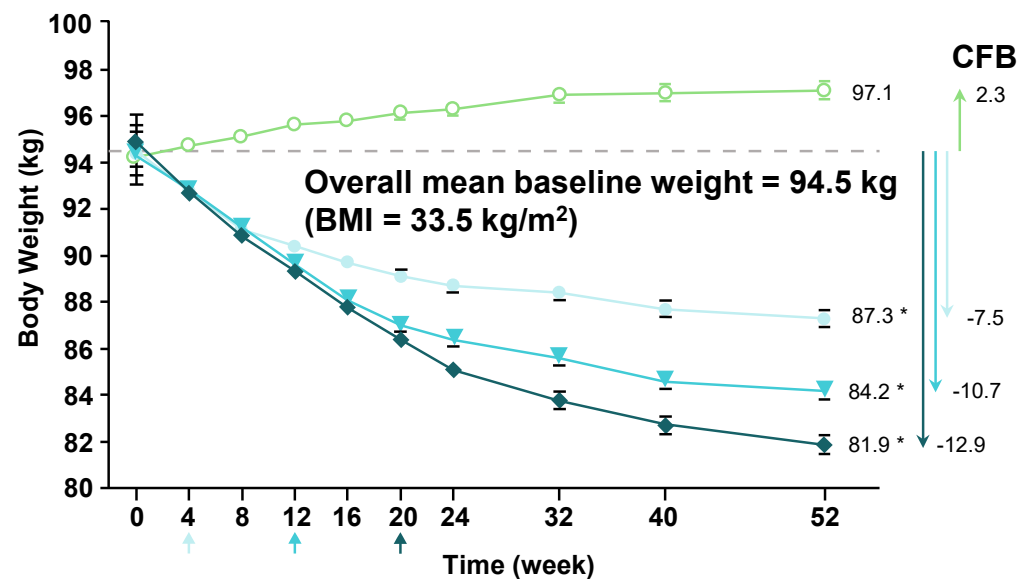
# SURPASS-3: A1C and Body Weight Reductions vs. Insulin Degludec



## A1C Reductions from Baseline



## Body Weight Changes from Baseline

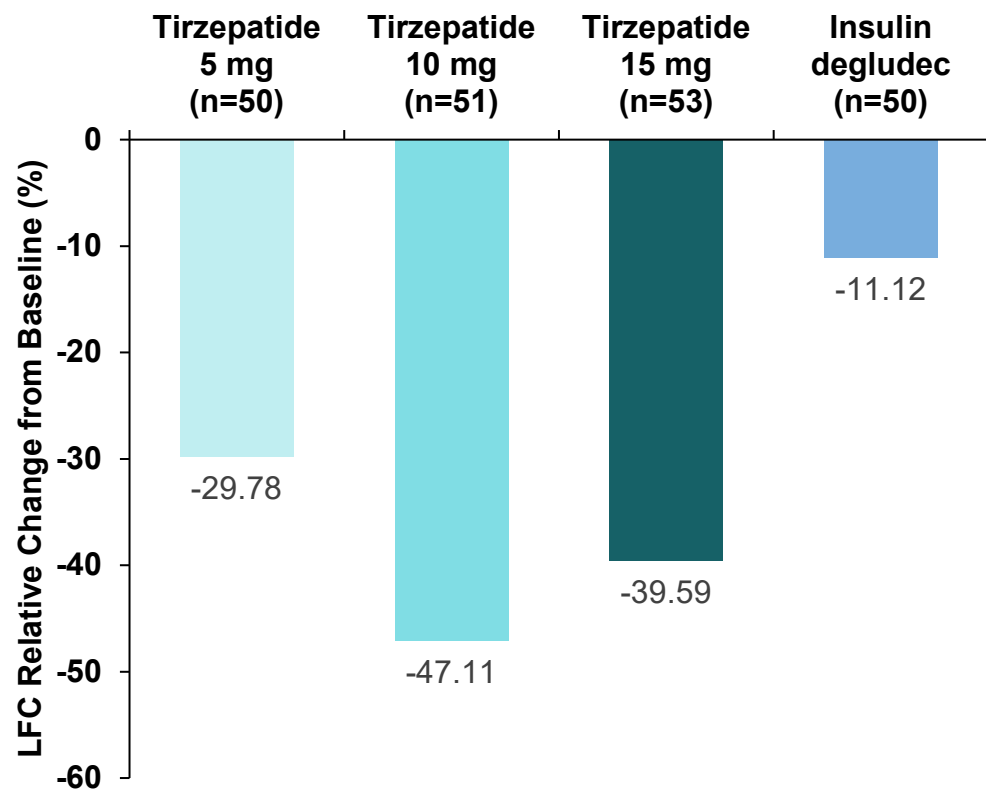


\* $p < 0.001$  vs. insulin degludec; Arrows on the x-axes indicate where maintenance doses were achieved  
A1C: glycated hemoglobin; BMI: body mass index; CFB: change from baseline;  
Adapted from Ludvik B, et al. *Lancet*. 2021; 398(10300):583-98.

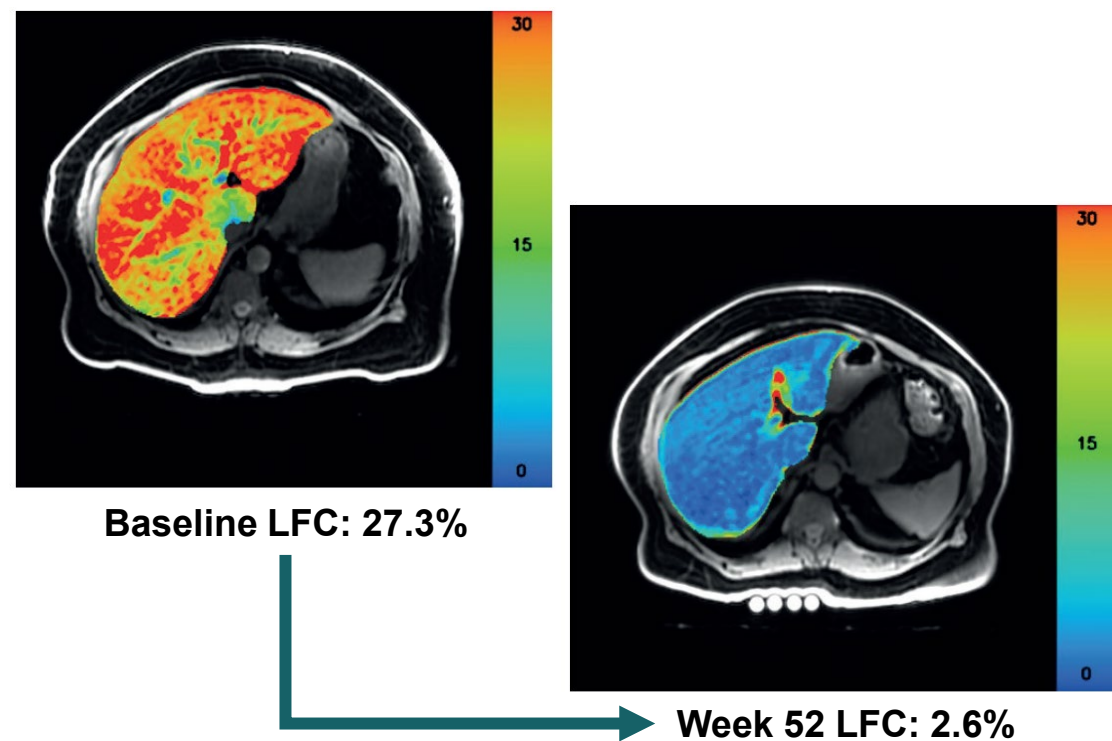


# SURPASS-3 Sub-study in Liver Fat Content

## Relative Changes in Liver Fat Content from Baseline to Week 52

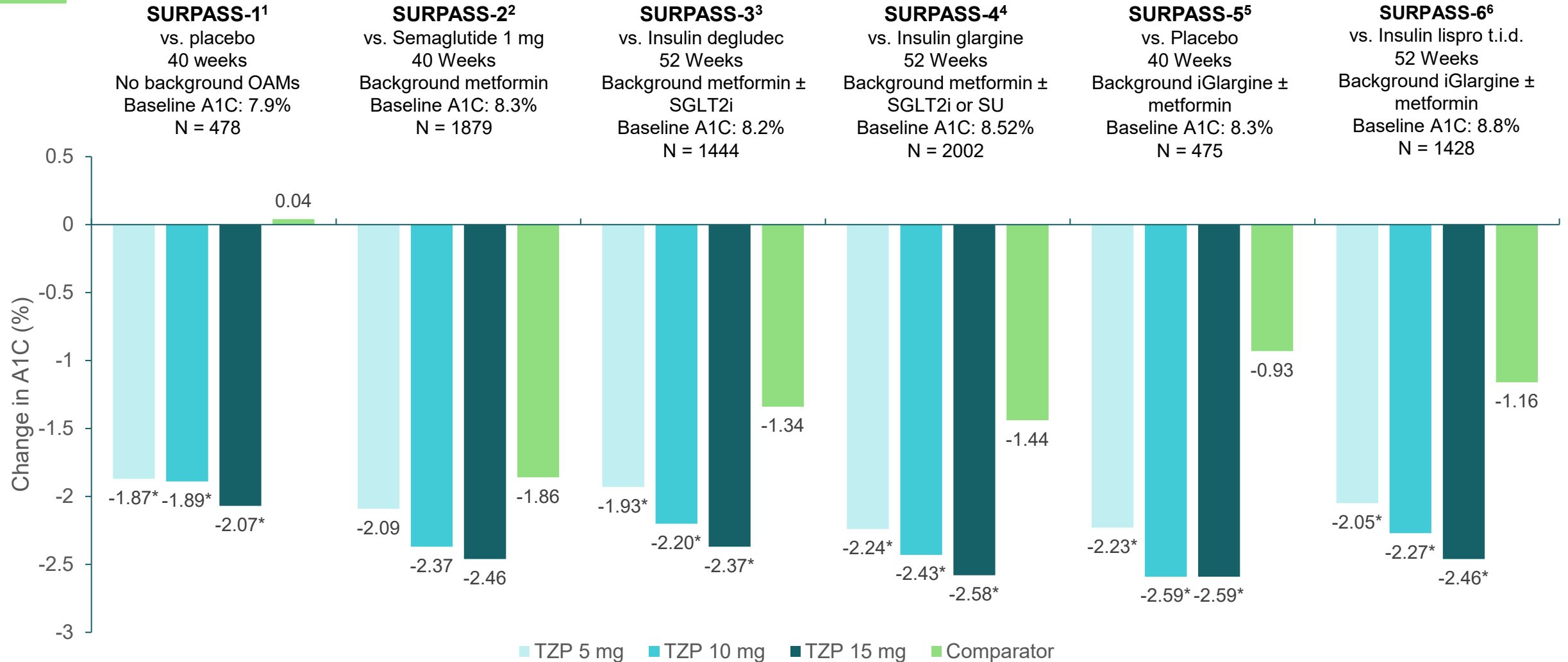


## Example of Change in Liver Fat Content: Individual Patient Randomized to TZP 5 mg





# SURPASS Program: Summary of A1C Lowering\*



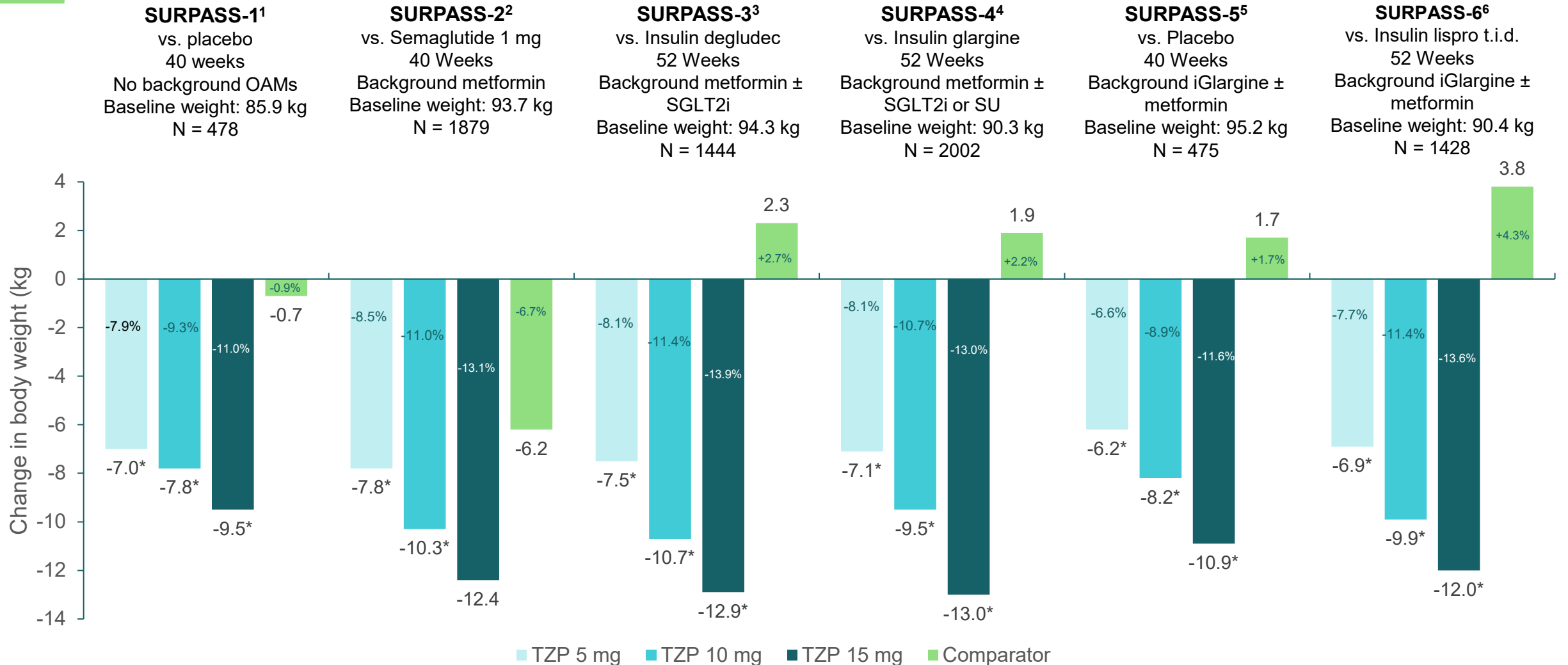
\*All Statistically significant vs. comparator

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. Frias 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



\*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. Frias 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 $\geq 1$ 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)
<b>TEAEs with <math>\geq 5\%</math> frequency</b>				
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 (0.6)
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 (0.2)
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



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



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



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



Studied across  
spectrum of people  
living with T2D<sup>1-5</sup>

Superior A1C and  
body weight  
reduction compared  
to placebo,  
semaglutide 1mg,  
insulin degludec,  
insulin glargine  
U100<sup>1-4</sup>

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

Awaiting results of  
SURPASS-CVOT  
(estimated  
completion date  
2024)<sup>6</sup>

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.













# Discussion

How might dual GIP/GLP-1 receptor agonist therapy fit into the comprehensive management of T2D?

# 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

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

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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.

# 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

# 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 insulintropic polypeptide (GIP)
- B. Glucagon-like peptide-1 (GLP-1)
- C. GIP and GLP-1 are thought to have roughly equivalent impact

# 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

# Thank you for your participation!



Please complete the **evaluation form** and **access the program website** on your phone.

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**

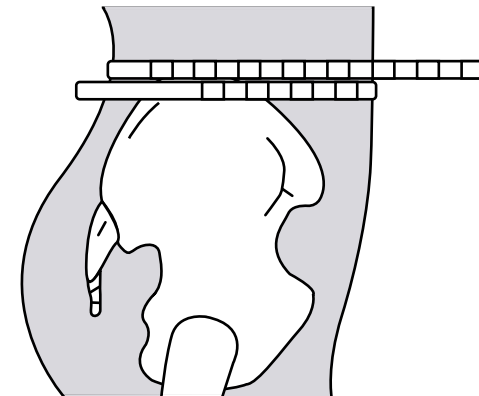


# Hyperlinks



# 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



[Click here to return to the program](#)



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