



# TIME **2** DECIDE

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CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES



# Presenter Disclosure

Name	Credentials and Affiliations
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## Relationships With Financial Sponsors

<b>SPEAKERS BUREAU/HONORARIA:</b>	
<b>GRANTS/RESEARCH SUPPORT:</b>	
<b>CONSULTING FEES:</b>	
<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 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 activity has been approved by the College of Family Physicians of Canada and the [insert chapter name] Chapter for up to 3 Mainpro+ credits.

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



[www.theMedEdPledge.com](http://www.theMedEdPledge.com)



# Program Agenda for 1.5-hour Events

10 minutes	Introduction, disclosure slides, SPC, learning objectives, pre-test polling questions
5 minutes	Meet our Patient - Andrée
10 minutes	Type 2 Diabetes: Treatment Goals and Unmet Needs – didactic presentation
30 minutes	A New Class of Antihyperglycemic Medication: GLP-1 / GIP Dual Receptor Agonists
25 minutes	What if Scenarios
5 minutes	Post-Test Polling Questions
5 minutes	Conclusion and Closing remarks

# Faculty

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# Program Learning Objectives

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

Explain the key goals of therapy for patients with T2D beyond reduction of A1C

Identify treatment gaps among patients with type 2 diabetes (T2D) with the existing classes of antihyperglycemic therapy in Canada

Incorporate new treatment options in the decision-making process for optimal holistic management of people with T2D

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# Getting to Goal

Attaining A1C Targets in Type 2 Diabetes

## Pre-Test Question #1

**According to Diabetes Canada's clinical practice guidelines, what is the target A1C for people with type 2 diabetes at low risk of hypoglycemia?**

- A.  $\leq 5.7\%$
- B.  $\leq 6.0\%$
- C.  $\leq 6.5\%$
- D.  $\leq 7.0\%$
- E.  $\leq 7.5\%$

## Pre-Test Question #2

**Tirzepatide works through dual agonism of the glucagon-like peptide-1 (GLP-1) receptor and which other receptor?**

- A. Angiotensin II receptor
- B. Dipeptyl peptidase (DPP) 4 receptor
- C. Glucose-dependent insulinotropic polypeptide (GIP) receptor
- D. Sodium-glucose co-transport-2 (SGLT2) receptor
- E. None of the above

## Pre-Test Question #3

From a mean baseline A1C of 8.3% in the SURPASS-2 study, the mean A1C reduction for semaglutide 1 mg was 1.9% at 40 weeks (efficacy estimand). What was the mean A1C reduction for tirzepatide 15 mg at 40 weeks?

- A. 1.3%
- B. 2.0%
- C. 2.5%
- D. 3.2%

# Consider This Patient, Andrée

## History

- 52-year-old female
- 10-year history of type 2 diabetes
- Long history and ongoing struggles with her weight
- Has consulted with a dietitian twice and has found implementing dietary recommendations challenging

## Physical examination

- Height: 160 cm
- Weight: 72 kg
- Body mass index: 28.1 kg/m<sup>2</sup>
- Waist circumference: 92 cm
- BP: 124/76 mmHg

## Investigations

- A1C: 8.3%
- eGFR and UACR in normal range
- Lipids at target

## Medications

- Metformin 1 g b.i.d.
- Gliclazide MR 60 mg q.d.
- Perindopril 8 mg q.d.
- Atorvastatin 20 mg q.d.



Andrée decided to stop the gliclazide on her own after reading about SUs and hypoglycemia



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# Type 2 Diabetes: Treatment Goals and Unmet Needs

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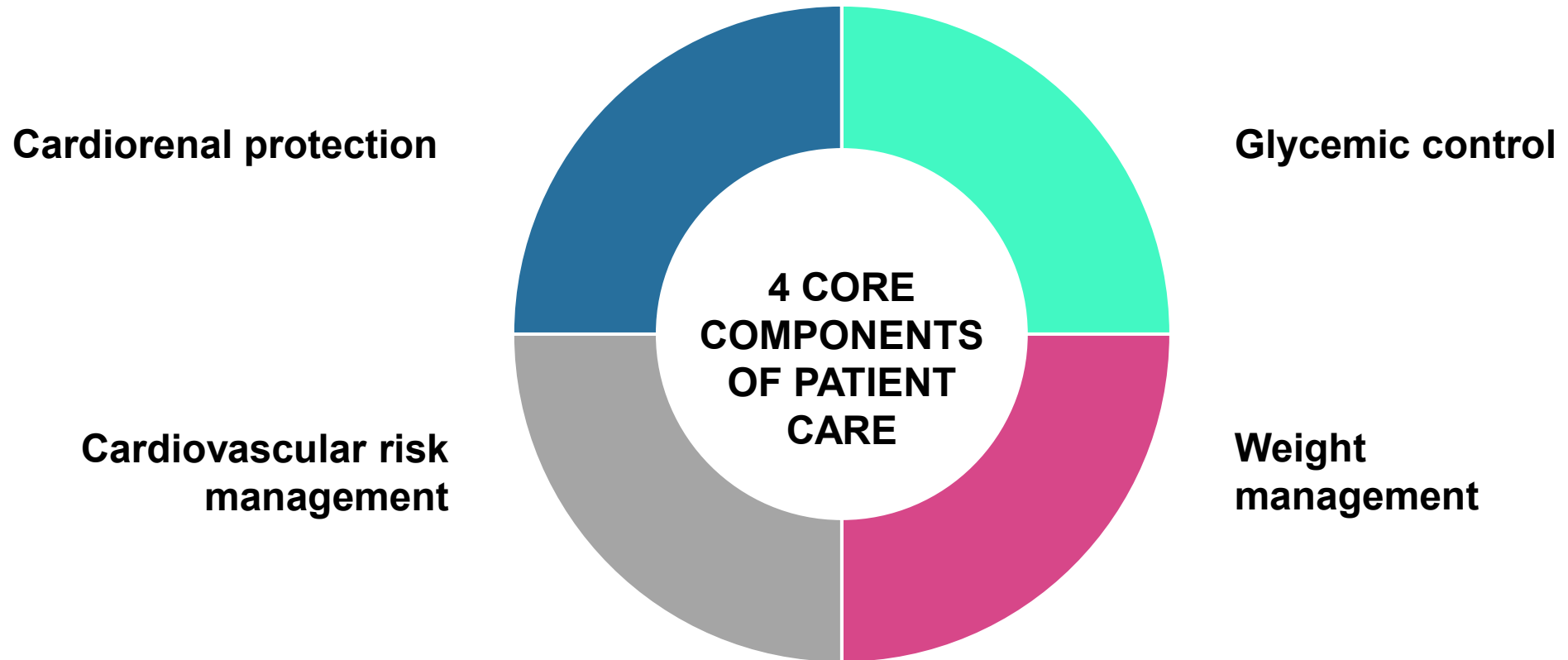
## Opinion Question

**What approach might you choose to help this patient achieve glycemic control?**

- A. Add the sulfonylurea back
- B. Add a DPP4 inhibitor
- C. Add a GLP-1 receptor agonist
- D. Add an SGLT2 inhibitor
- E. Add a GLP-1 / GIP dual receptor agonist
- F. Something else

# Comprehensive Treatment Goals for People with Type 2 Diabetes: 4 Key Components

A 2022 Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) Lists 4 Key Components of Care for People with T2D



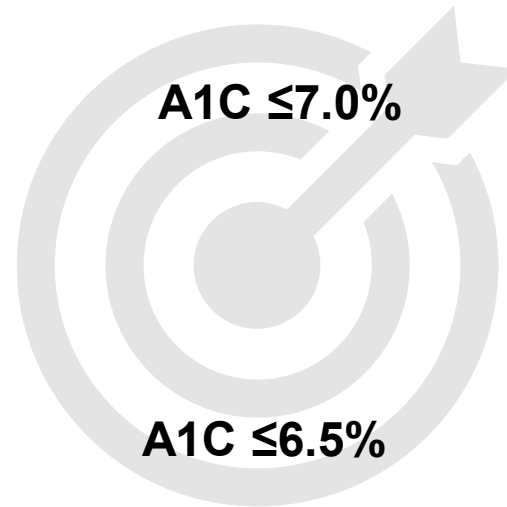
# Within the Comprehensive Treatment Paradigm, Don't Forget the Importance of Glycemic Control and Individualization of Glycemic Targets!

Recommendations from Diabetes Canada  
Clinical Practice Guidelines (2018)<sup>1</sup>

## Who?



## What target?



## Why?

To reduce the risk of micro- and macrovascular complications<sup>2</sup>

To reduce the risk of microvascular complications<sup>2</sup>

A1C, glycated hemoglobin; T2D, type 2 diabetes

\*Based on class of antihyperglycemic medication(s) used and person's characteristics

Adapted from 1. Imran SL, et al. Targets for Glycemic Control. Can J Diabetes. 2018;42(suppl.):S42-S46; and 2. Holman RR, et al. N Engl J Med. 2008;359(15):1577-89 (UKPDS 10-year follow-up).

# Are There Patients Who Might Benefit from an Even Lower A1C?

A1C	Targets
≤6.5*	Selected adults with type 2 diabetes with potential for remission to normoglycemia
≤6.5*	Adults with type 2 diabetes to reduce the risk of chronic kidney disease and retinopathy if at low risk of hypoglycemia <sup>†</sup>
≤7.0*	<b>MOST ADULTS WITH TYPE 1 OR TYPE 2 DIABETES</b>
7.1 ↓ 8.5	<p>7.1-8.0%: Functionally dependent 7.1-8.5%:</p> <ul style="list-style-type: none"> <li>• Recurrent severe hypoglycemia and/or hypoglycemia unawareness</li> <li>• Limited life expectancy</li> <li>• Frail elderly and/or with dementia<sup>‡</sup></li> </ul> <p>Avoid higher A1C to minimize risk of symptomatic hyperglycemia and acute and chronic complications</p>

A1C, glycated hemoglobin


\*Target 6.0 to <6.5 for adults with type 2 diabetes with potential for remission to prediabetes; <sup>†</sup>Based on class of antihyperglycemic medication(s) used and person's characteristics; <sup>‡</sup>See the guideline chapter "Diabetes in Older People".

Adapted from Mackay D, et al. Remission of Type 2 Diabetes: Diabetes Canada Clinical Practice Guidelines Expert Working Group. Can J Diabetes. 2022;46:753-61.

# Avoid Therapeutic Inertia! Adjust Therapy if Patients Can be Better Optimized for Treatment


Can J Diabetes 42 (2018) S47-S53

Contents lists available at [ScienceDirect](#)


 **ELSEVIER**

Canadian Journal of Diabetes  
journal homepage:  
[www.canadianjournalofdiabetes.com](http://www.canadianjournalofdiabetes.com)

**DIABETES CANADA**




2018 Clinical Practice Guidelines  
**Monitoring Glycemic Control**  
Diabetes Canada Clinical Practice Guidelines Expert Committee  
Lori D. Berard RN, CDE, Rick Siemens BSc Pharm, CDE, Vincent Woo MD, FRCPC




“For most individuals with diabetes, A1C should be measured **approximately every 3 months\*** to ensure that glycemic goals are being met or maintained”<sup>1</sup>

Contents lists available at [ScienceDirect](#)


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Canadian Journal of Diabetes  
journal homepage:  
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**DIABETES CANADA**



Special Article  
**Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update**  
Diabetes Canada Clinical Practice Guidelines Expert Committee



If A1C NOT at target **and/or change in clinical status<sup>†</sup>** – Adjust or advance therapy<sup>2</sup>

**\*Testing at 6-month intervals may be considered in situations where glycemic targets are consistently achieved.**

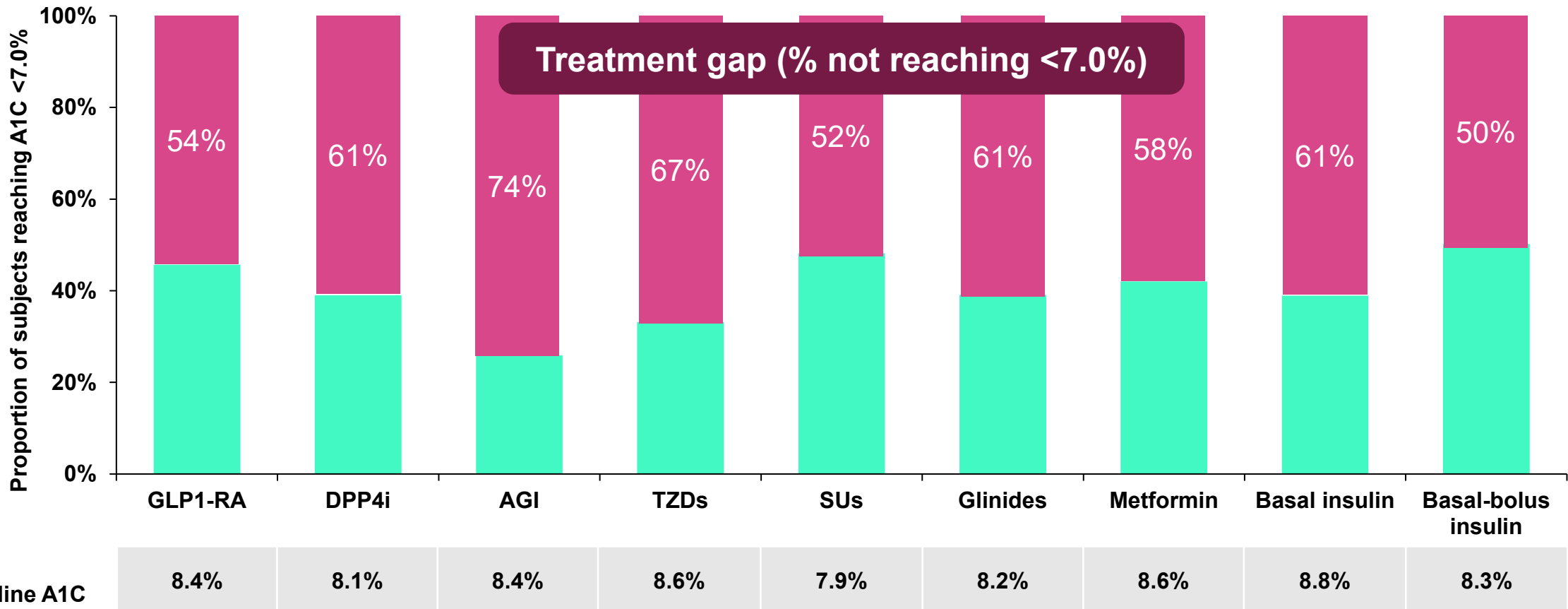
<sup>†</sup>Factors to consider include: atherosclerotic cardiovascular disease, chronic kidney disease, heart failure, age over 60 with concomitant cardiovascular risk factors, clinical considerations (body weight, hypoglycemia)

A1C, glycated hemoglobin; HCP, healthcare provider.

Adapted from 1. Berard LD, et al. Monitoring Glycemic Control. Can J Diabetes. 2018;42(suppl.):S47-S53; 2. Lipscombe L, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. Can J Diabetes. 2020;44:575-91.

# Why Do We Need Another Class of Antihyperglycemic Medication? Unmet Needs for Glycemic Control

Proportion of People with T2D Reaching A1C <7.0% by Antihyperglycemic Class: Meta-analysis\*1



\*Meta-analysis included studies where the antihyperglycemics were used as monotherapy or were added on to background therapy with other agents  
 A1C, glycated hemoglobin; AGI, alpha-glucosidase inhibitor; DPP4i, Dipeptidyl peptidase 4 inhibitors; GLP1-RA, glucagon-like peptide-1 receptor agonist; SU, sulfonylurea; T2D, type 2 diabetes; TZD, thiazolidinedione  
 Adapted from 1. Esposito K, et al. Diabetes Obes Metab. 2012;14:228-33; and 2. Imran SA, et al. Targets for Glycemic Control. Can J Diabetes. 2018;42:S42-S46.

# Weight Loss Goals for People with T2D

“

A modest **weight loss of 5% to 10%** of initial body weight **can improve insulin sensitivity, glycemic control and blood pressure.** Greater amounts of weight loss may be needed to improve obstructive sleep apnea and dyslipidemia.

-- Diabetes Canada Guidelines (2018)<sup>1</sup>

A 5-10% reduction in body weight may also improve:  
osteoarthritis, metabolic dysfunction-associated steatotic liver disease,  
polycystic ovary syndrome, gastroesophageal reflux disease and quality of life<sup>2,3</sup>

# Ideal Patient Counseling on Weight Loss: Non-judgmental, Respectful and Empathetic

## Acknowledge . . .

- . . . that societal bias has told them that weight and diabetes are their fault (e.g., “just move more and eat less”)
- . . . how exercise is critical for overall health... but is not normally an effective tool for weight loss
- . . . that changing eating habits can be difficult, restrictive and challenging, especially over the long term

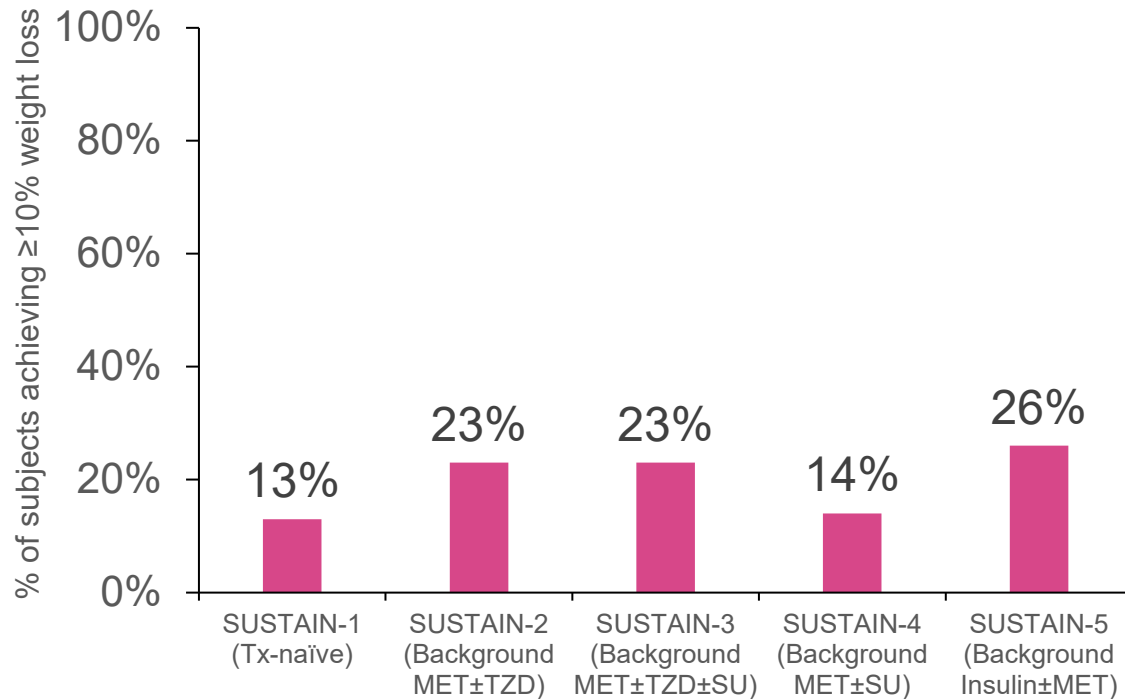
## Reassure . . .

- . . . that diabetes and weight are NOT totally their fault, but rather due to complex interplay between genetics, biology and their environment
- . . . that you will help them develop a strategy that is individualized and sustainable

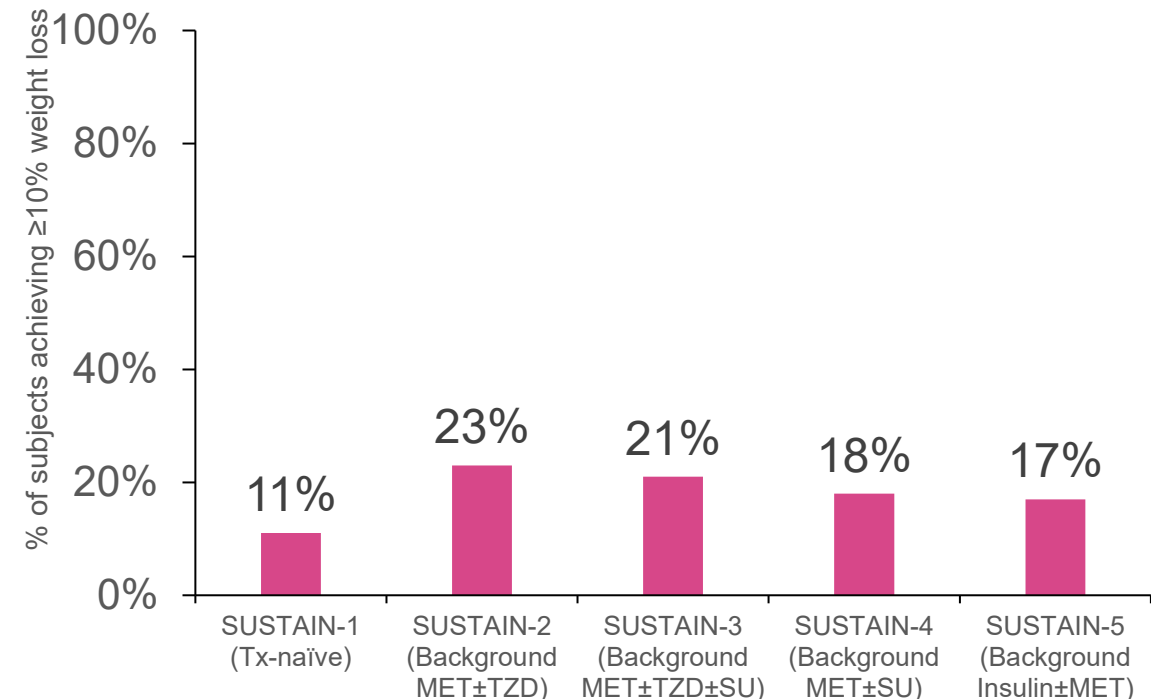
# Why Do We Need Another Class of Antihyperglycemic Medication? Unmet Needs for Body Weight

**% of People with T2D and Obesity Achieving  $\geq 10\%$  Reduction in Body Weight with Semaglutide 1.0 mg / week (GLP1-RA) in the SUSTAIN Clinical Trial Program, by Baseline BMI**

## Baseline BMI 30 to $<35$ kg/m<sup>2</sup>



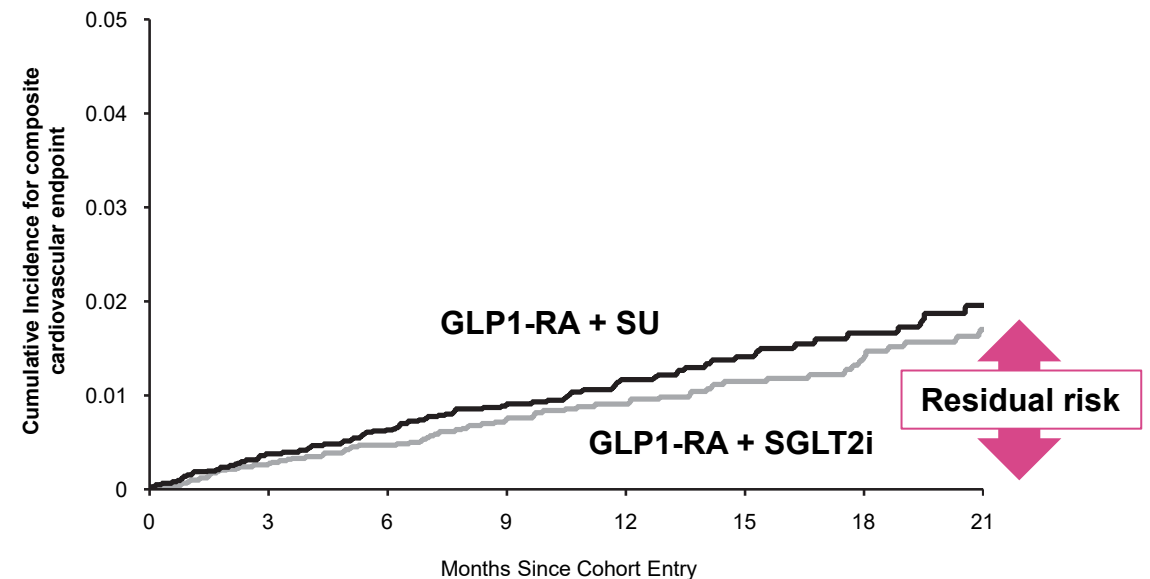
## Baseline BMI $\geq 35$ kg/m<sup>2</sup>



# Why Do We Need Another Class of Antihyperglycemic Medication? Unmet Needs for CV Protection

- Cardiovascular disease is the most common cause of death for people with T2D<sup>1</sup>
- This remains true despite recent advances in cardiorenal protection (e.g., SGLT2i, GLP1-RA)<sup>2</sup>
- Additional interventions to further lower CV risk are necessary

**Cumulative Risk of Composite CV Endpoint\* Among Patients taking BOTH SGLT2i and GLP1-RA (US Claims Data)<sup>2</sup>**



Event rate for group on both SGLT2i and GLP1-RA: 107 per 1000 person-years

\*Myocardial infarction hospitalizations, stroke hospitalizations, and all-cause mortality.

CI, confidence interval; CV, cardiovascular; GLP1-RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; SGLT2i, sodium glucose co-transporter 2 inhibitor; SD, standard deviation; SU, sulfonylurea; T2D, type 2 diabetes

Adapted from 1. Sharma A, et al. Diabetes Care. 2017;40(12):1763-70; 2. Dave CV, et al. Circulation. 2021;143(8):770-9.

# Why Do We Need Another Class of Antihyperglycemic Therapies? Summary

**Despite many advances in antihyperglycemic therapy, significant treatment gaps remain for individuals with T2D**

**People with T2D often:**

Do not achieve A1C targets

Do not achieve meaningful, sustainable weight loss

Remain at high risk for CV events

Remain at risk for hypoglycemia

# Other Aspects of Current Unmet Needs: Polypharmacy and Suboptimal Adherence



Polypharmacy may be necessary to achieve A1C lowering in addition to micro- and macrovascular protection<sup>1</sup>



**However**, adherence generally decreases with the number of medications and number of daily doses<sup>2,3</sup>



Evaluate adherence at each diabetes visit, stressing the rationale for treatment, treatment goals and the role of each medication<sup>4</sup>

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# A New Class of Antihyperglycemic Medication: GLP-1 / GIP Dual Receptor Agonists

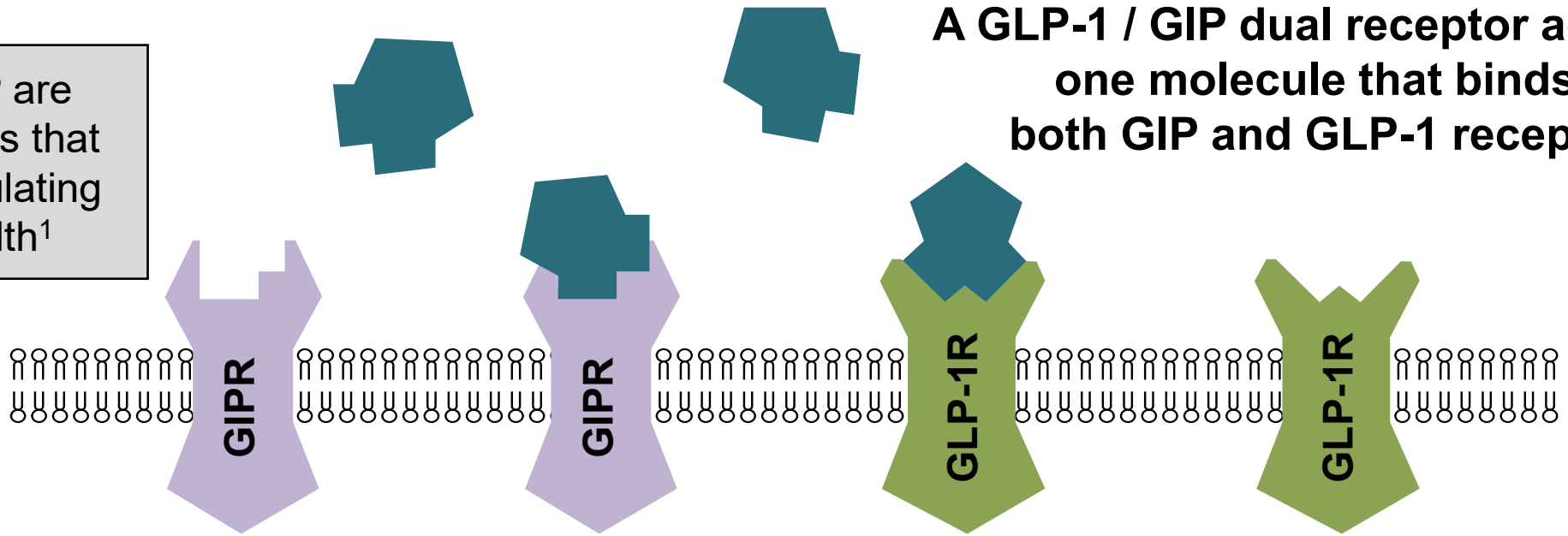
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Where Do These Agents Fit In?

# What is GLP-1 / GIP Dual Receptor Agonism?

## New Method of Modulating the Incretin Pathway

GLP-1 and GIP are incretin hormones that play roles in regulating metabolic health<sup>1</sup>

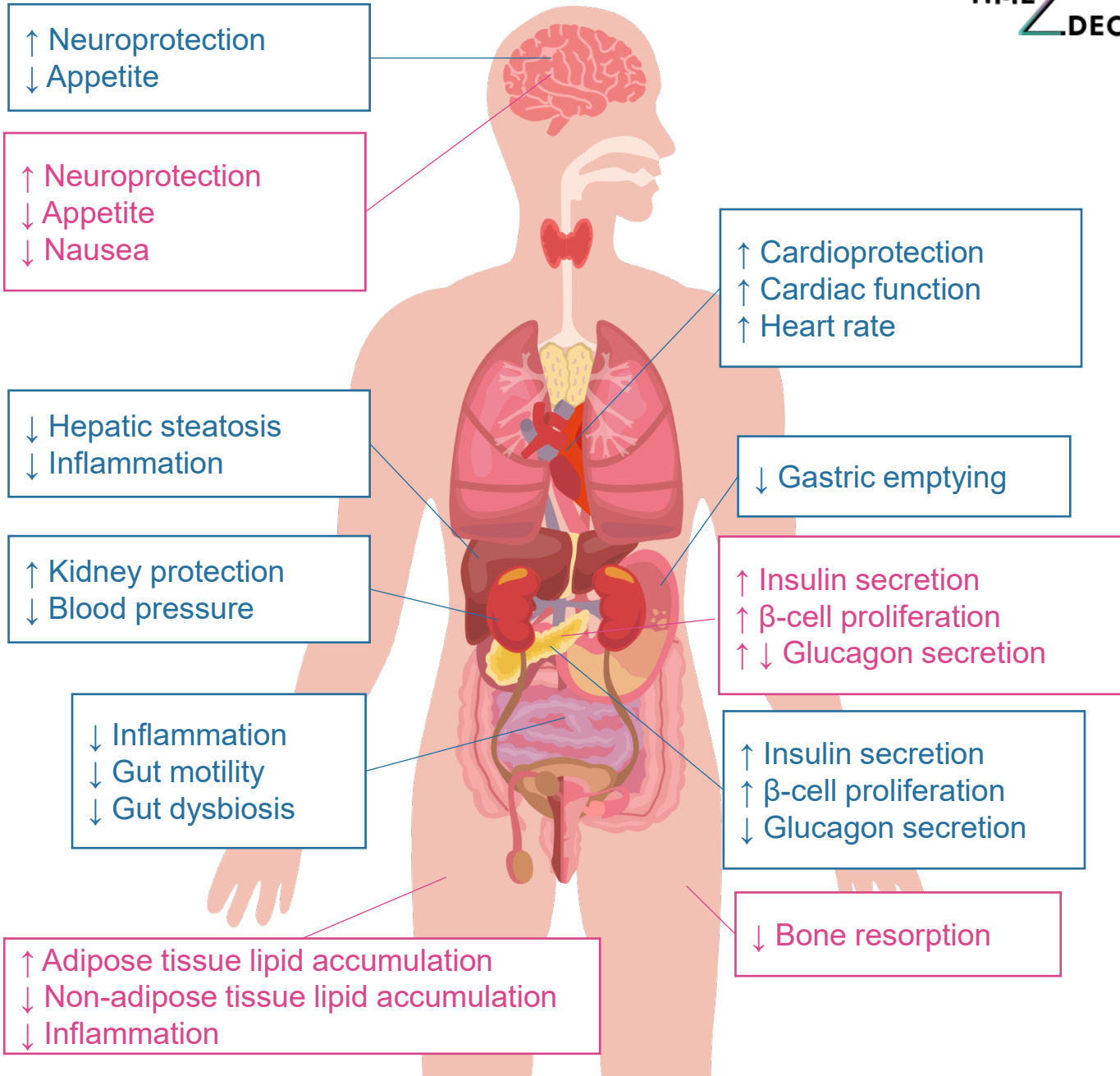


**A GLP-1 / GIP dual receptor agonist is one molecule that binds to both GIP and GLP-1 receptors<sup>2</sup>**

**Tirzepatide is the first GLP-1 / GIP dual receptor agonist to be approved in Canada<sup>3</sup>**

GIP, glucose-dependent insulinotropic polypeptide; GIPR, glucose-dependent insulinotropic polypeptide receptor; GLP-1, glucagon-like peptide-1; GLP-1R, glucagon-like peptide-1 receptor  
 1. Drucker DJ, et al. Diabetologia. 2023;66(10):1765-79; 2. Skow MA, et al. Diabetes Obes Metab. 2016;18(9):847-54; 3. Eli Lilly Canada Inc. Pirmounjaro™ Product Monograph. July 10, 2024.

# GIP & GLP-1: Gut Hormones with Potential for Therapeutic Synergy



## GLP-1

The actions of GLP-1 receptor agonism have been established based on extensive basic science, clinical trial and real-world evidence.

## GIP

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

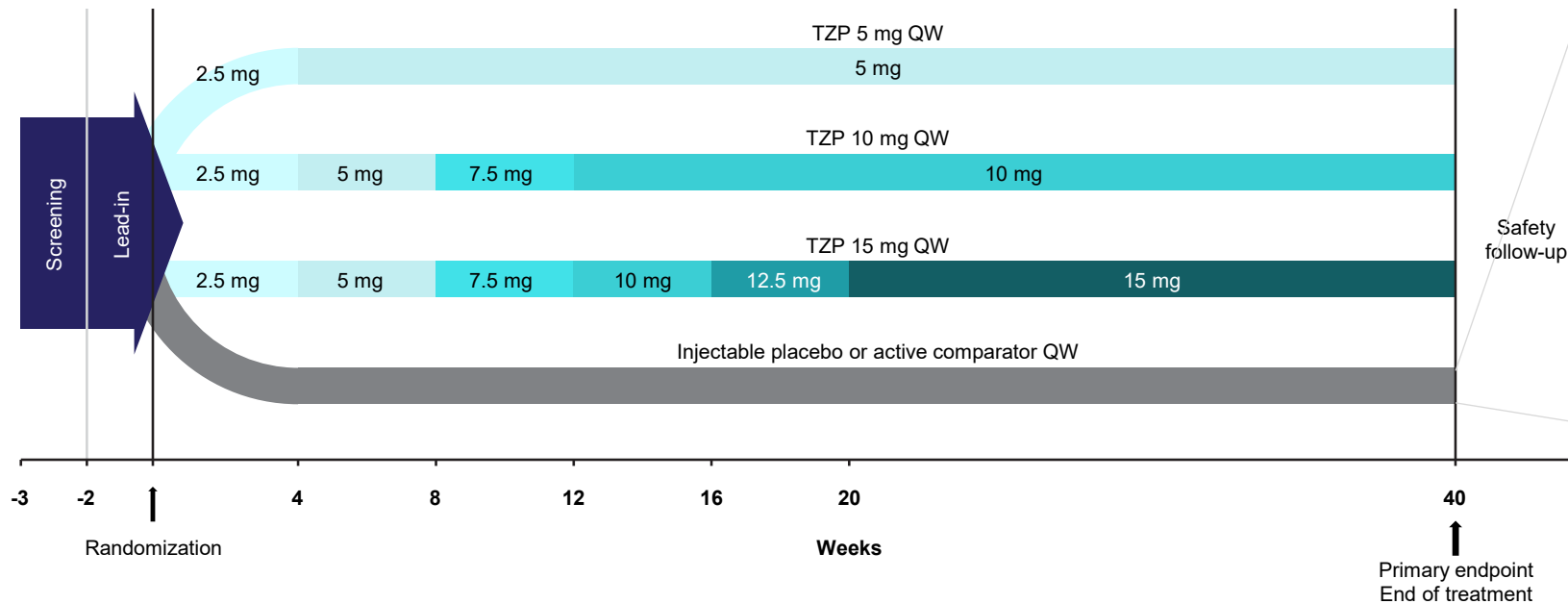
# A New Option for Type 2 Diabetes: Tirzepatide

**Indication:** Tirzepatide injection is indicated 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 mellitus

- As **monotherapy** when metformin is inappropriate due to contraindication or intolerance
- **In combination with:**
  - Metformin, or
  - Metformin and a sulfonylurea, or
  - Metformin and a sodium-glucose cotransporter 2 inhibitor (SGLT2i), or
  - Basal insulin with or without metformin

# A New Approach: GLP-1/GIP Dual Receptor Agonist Tirzepatide—The SURPASS Clinical Trial Program

Six Similarly Designed Trials (SURPASS–1 to SURPASS–6), with Different Populations and Control Arm Comparators



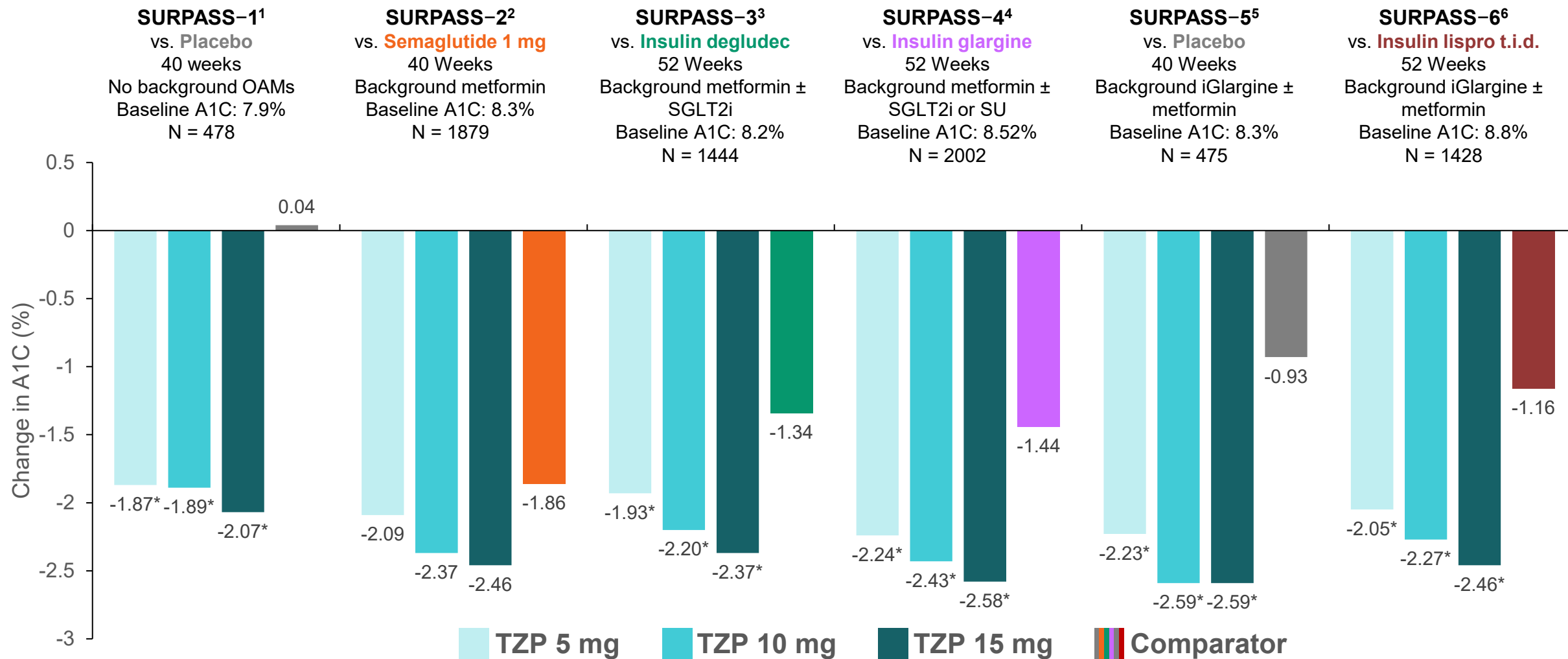
**SURPASS Study Comparators**

- SURPASS–1: Placebo
- SURPASS–2: Semaglutide (1.0 mg QW)
- SURPASS–3: Insulin degludec
- SURPASS–4: Insulin glargine
- SURPASS–5: Placebo
- SURPASS–6: Insulin lispro

**Primary objective for each study: Mean change in A1C from baseline at 40 or 52 weeks.**

A1C, glycated hemoglobin; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; 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; 6. Rosenstock J, et al. JAMA. 2023;330(17):1631-40.

# SURPASS 1-6: Summary of Glycemic Results (Absolute A1C Changes from Baseline)



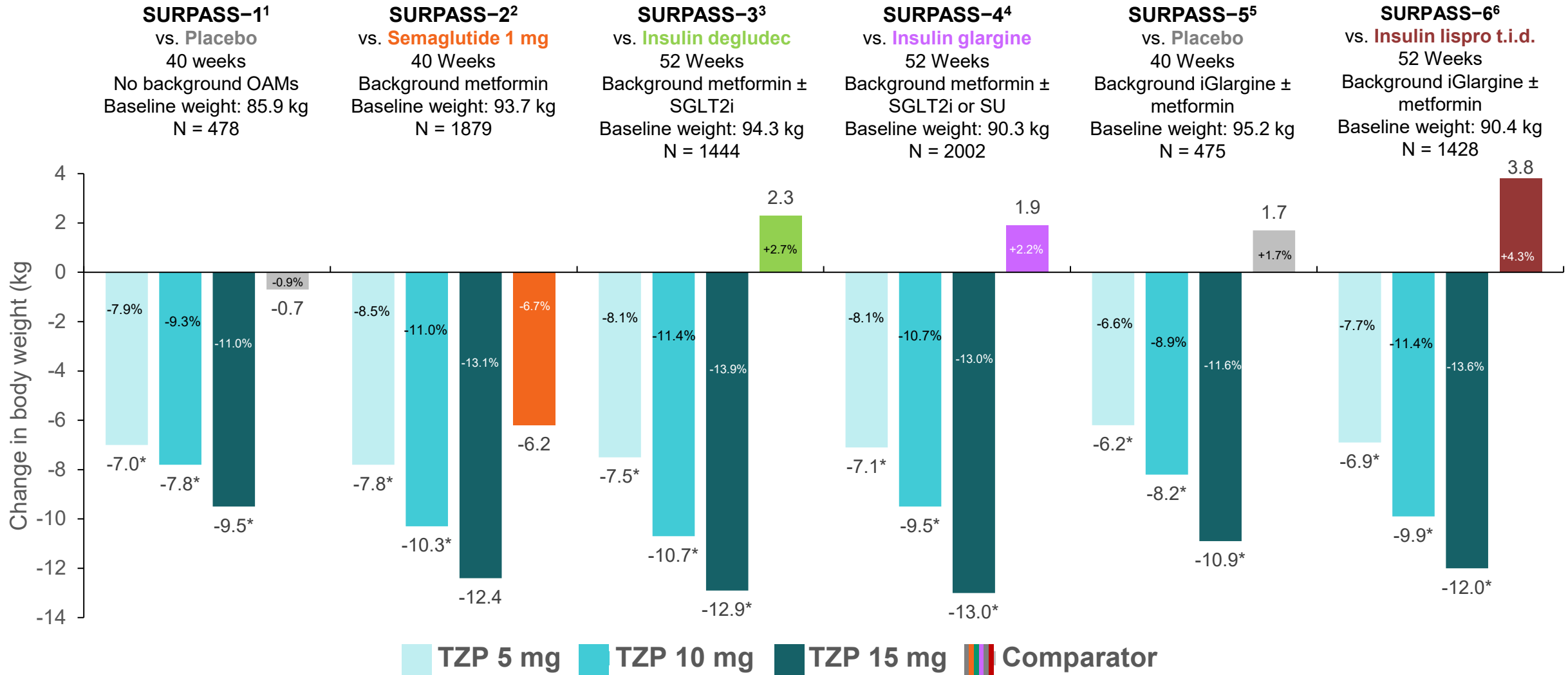
\*All Statistically significant vs. comparator; results are for efficacy estimand

A1C: glycated hemoglobin; OAM: Oral antihyperglycemic medication; SGLT2i: sodium-glucose cotransporter-2 inhibitor; SU: sulfonylureas; t.i.d., three times a day; 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. JAMA. 2023;330(17):1631-40.

# SURPASS 1-6: Summary of Weight Results (Absolute Weight Change from Baseline)



\*Statistically significant vs. comparator; results are for efficacy estimand

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. JAMA. 2023;330(17):1631-40.

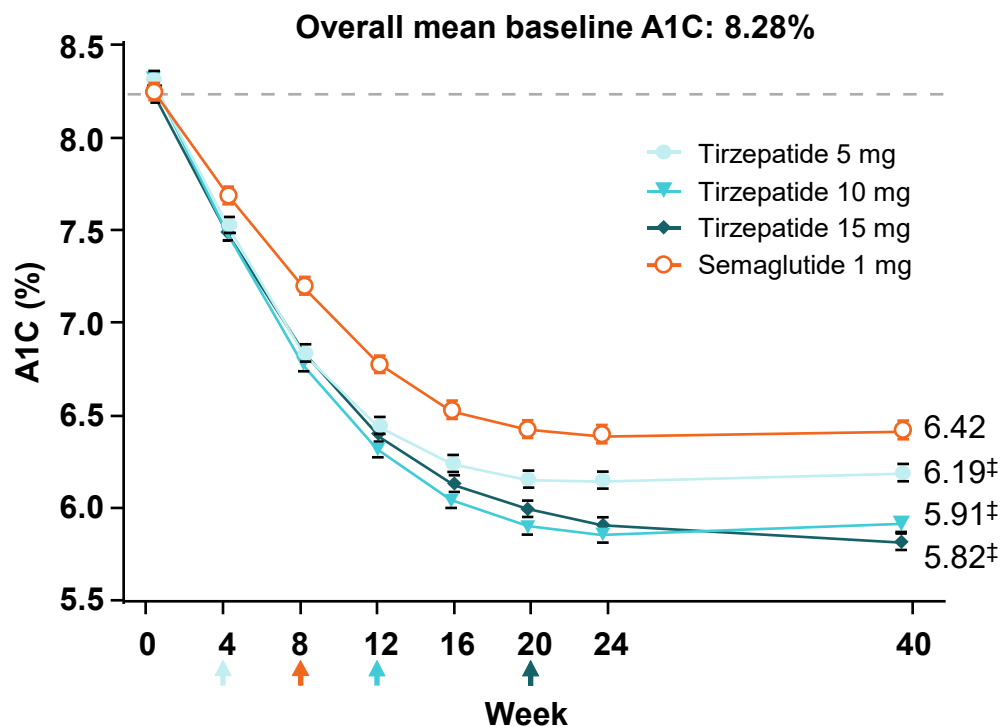
# Most Applicable SURPASS Study for Andrée



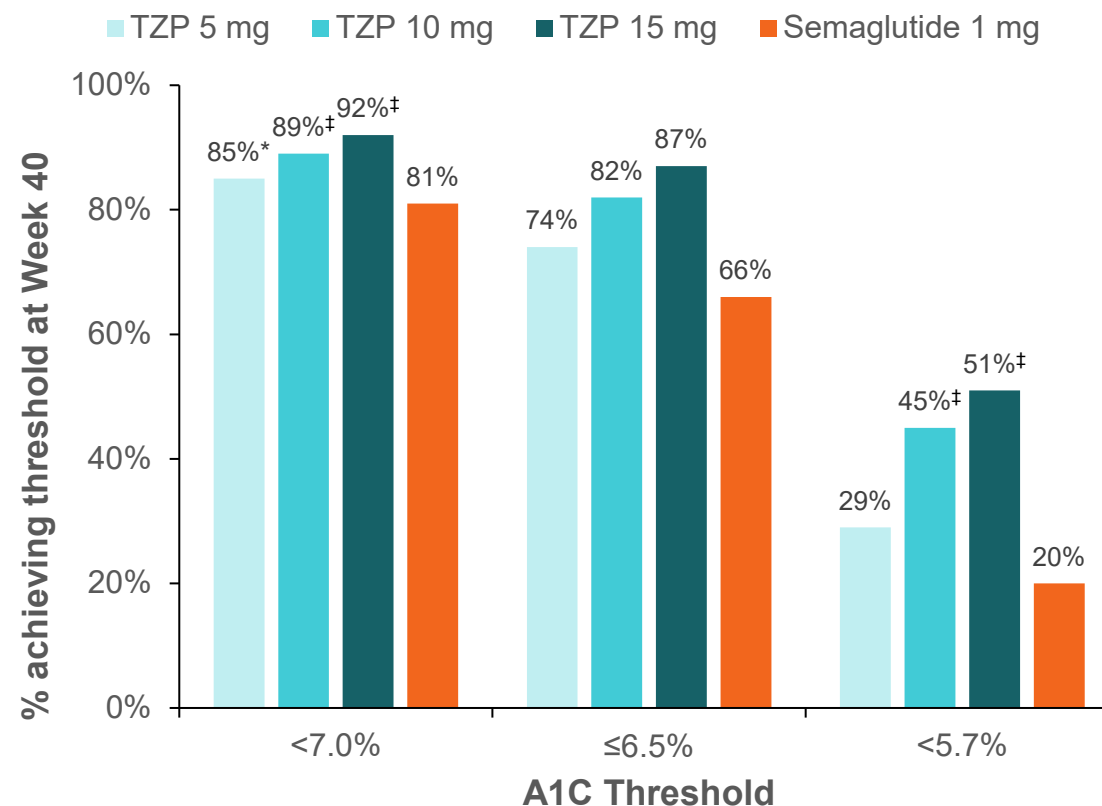
## SURPASS-2: Tirzepatide vs. Semaglutide 1 mg (GLP1-RA) – All Patients on Background Metformin

Andrée's  
A1C: 8.3%

### A1C Reductions from Baseline



### % Reaching A1C Thresholds



\*p<0.05; †p<0.01; ‡p<0.001 vs. semaglutide; results are for efficacy estimand; arrows on the x-axes indicate where maintenance doses were achieved  
A1C, glycated hemoglobin; GLP1-RA, glucagon-like peptide-1 receptor agonist; TZP, tirzepatide  
Frías JP, et al. N Engl J Med. 2021;385(6):503-15.

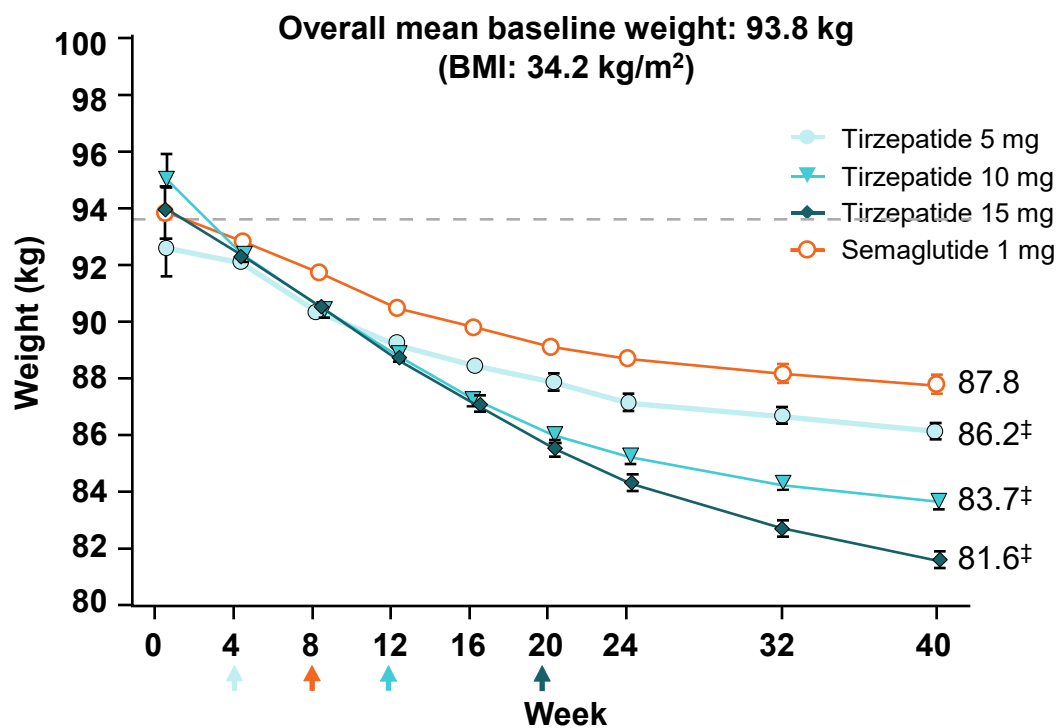
# Tirzepatide Therapy Is Also Associated with Clinically Significant Weight Reduction



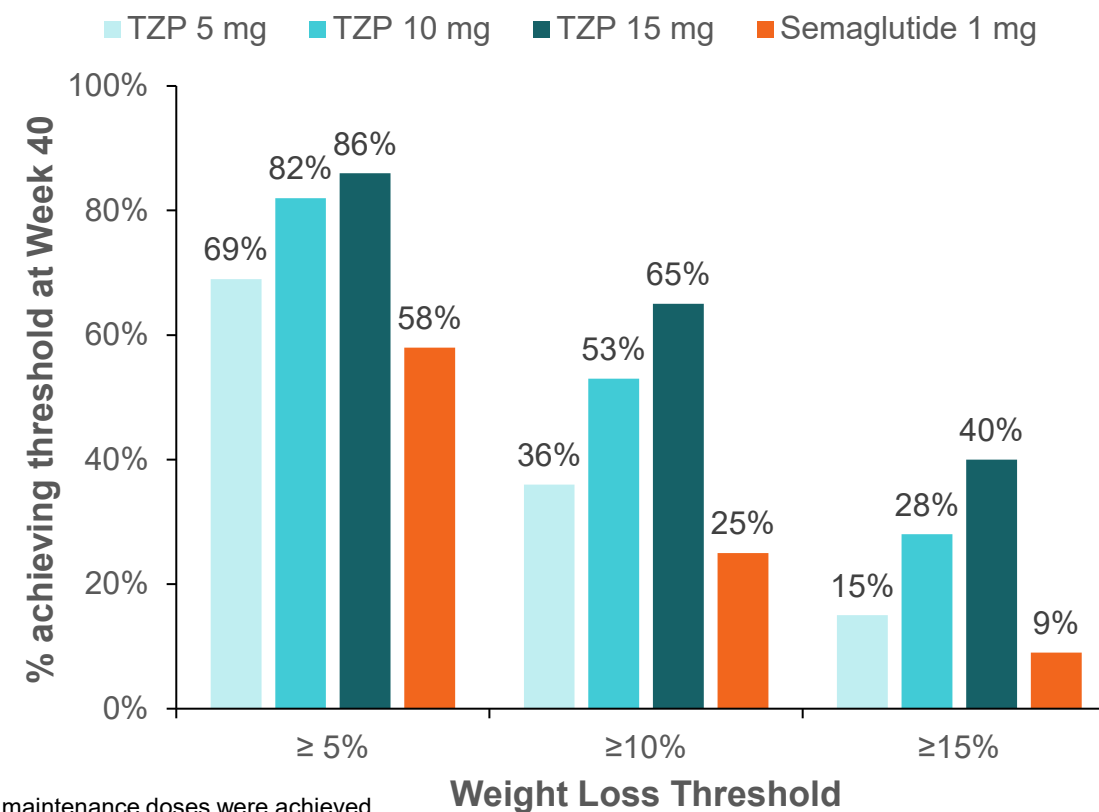
Andrée:  
Weight: 72 kg  
BMI: 28 kg/m<sup>2</sup>

## SURPASS-2: Tirzepatide vs. Semaglutide 1 mg (GLP1-RA) – All Patients on Background Metformin

### Body Weight Changes from Baseline



### % Reaching Weight Loss Thresholds



\*p<0.05; †p<0.01; ‡p<0.001 vs. semaglutide; results are for efficacy estimand; Arrows on the x-axes indicate where maintenance doses were achieved  
 BMI, body mass index; GLP1-RA, glucagon-like peptide-1 receptor agonist; TZP, tirzepatide  
 Frías JP, et al. N Engl J Med. 2021;385(6):503-15.

# GI Side Effects Were the Most Common Adverse Effects of Tirzepatide Therapy

## Example of the SURPASS-2 Study vs. Semaglutide 1 mg

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)
<b>TEAEs with ≥5% 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

GI, gastrointestinal; 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.

# What About Cardiorenal Protection?

## The Ongoing SURPASS–CVOT<sup>1,2</sup> Will Provide Answers

- **Subjects** (N = 12,500):
  - T2D
  - Confirmed CVD
  - A1C  $\geq 7.0\%$  to  $\leq 10.5\%$
  - BMI  $\geq 25$  kg/m<sup>2</sup>
  - No major CV event within the last 60 days or planned revascularization
- **Interventions:** Dulaglutide (GLP1-RA with proven CV protection<sup>3</sup>) or tirzepatide
- **Primary outcome:** Time to first occurrence of CV death, MI or stroke
- **Expected completion:** October 2024

# Back To Andrée: Polling Question Revisited



## Recall Andrée's profile:

- 52-year-old woman with 10-year history of type 2 diabetes

## Physical examination

- Height: 160 cm; Weight: 72 kg; BMI: 28 kg/m<sup>2</sup>
- Waist circumference: 92 cm
- BP: 124/76 mmHg

## Investigations

- A1C: 8.3%
- eGFR and UACR in normal range
- LDL-C at target

## Medications

- Metformin 1 g b.i.d.; perindopril 8 mg q.d.; atorvastatin 20 mg q.d.

## NOW what approach might you choose to help Andrée achieve glycemic control?

- A. Add the sulfonylurea back
- B. Add a DPP4 inhibitor
- C. Add a GLP-1 receptor agonist
- D. Add an SGLT2 inhibitor
- E. Add a GLP-1 / GIP dual receptor agonist
- F. Something else

# Discussion

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Why did you pick the strategy you picked?

Do you think tirzepatide would be a good option for Andrée?

If yes, what challenges might you encounter in getting her on this therapy?



TIME **2** DECIDE

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CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES

# Tirzepatide Dosing and Titration

- **Recommended starting dose:** 2.5 mg injected subcutaneously once weekly
  - This dosage is for treatment initiation and is not intended for long-term use
- **Titration:**
  - After 4 weeks, increase to 5 mg once weekly
  - If additional glycemic control is needed, increase in 2.5 mg increments after no less than 4 weeks on the current dose
- **Maximum dose:** 15 mg once weekly
- **Renal or hepatic Insufficiency:** No dose adjustment is required in patients with renal impairment or hepatic insufficiency
- **Geriatrics** ( $\geq 65$  years): No dose adjustment required
- **Pediatrics** ( $< 18$  years): The safety and effectiveness of tirzepatide have not been studied in this group
  - Tirzepatide is not indicated for pediatric use

# Tirzepatide Current Availability (Dec. 2023): Single-Dose Vials

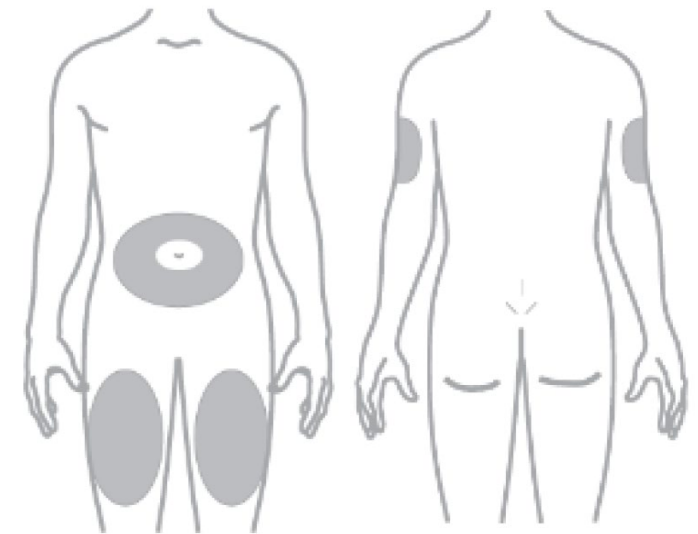
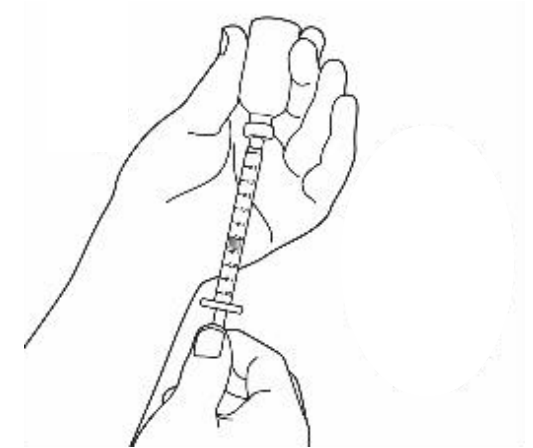


Route of Administration	Dosage Form	Dosage strength / Volume	Additional information
Subcutaneous injection	Sterile solution	2.5 mg / 0.5 mL	Do not split doses (risk of contamination due to lack of preservative)
		5 mg / 0.5 mL	
		7.5 mg / 0.5 mL	
		10 mg / 0.5 mL	
		12.5 mg / 0.5 mL	
		15 mg / 0.5 mL	

**Each of the tirzepatide dosage strengths is 0.5 mL in volume.**

# Tirzepatide Administration

- Instruct patients using the single-dose vial to use a syringe equipped with a needle appropriate for subcutaneous injection (e.g., tuberculin or insulin syringe with a 28- to 31-gauge needle more than 2.1 mm in length that is capable of measuring a 0.5 mL dose volume)
- Administer once weekly, any time of day, with or without meals
- Tirzepatide is to be injected subcutaneously in the abdomen, in the thigh, or in the upper arm
  - Rotate injection sites with each dose
- When using tirzepatide with insulin, administer as separate injections and never mix
  - Acceptable to inject tirzepatide and insulin in the same body region, but not adjacent to each other
- Tirzepatide should not be administered intramuscularly or intravenously



# Tirzepatide: Gastrointestinal Adverse Reactions

- The most frequently reported adverse reactions in clinical trials were gastrointestinal, including nausea, diarrhea and vomiting
- In general, these reactions were mild or moderate in severity
- Gastrointestinal adverse reactions (4.2%) were the most common reasons for treatment discontinuation

# Clinical Pearls for Managing GI Side Effects During Tirzepatide Therapy

- There is currently no published guidance on mitigating GI AEs with tirzepatide
- For now, it is reasonable to suggest following the guidance established for GLP1-RAs<sup>2</sup>



Up-titrate slowly to maximally tolerated dose



Eat small meals more frequently



Avoid fatty, spicy, and high-fibre foods



Stay hydrated



Set realistic expectations



Learn to be aware of satiety cues

# Tirzepatide Serious Warnings and Precautions: Thyroid C-Cell Tumors

- Tirzepatide causes dose-dependent and treatment-duration-dependent thyroid C-cell tumors (adenomas and carcinomas) at clinically relevant exposures in male and female rats
- It is unknown whether tirzepatide causes thyroid C-cell tumors, including medullary thyroid carcinoma (MTC) in humans
- The human relevance of tirzepatide-induced rodent thyroid C-cell tumors has not been determined
- Tirzepatide is contraindicated in patients with a personal or family history of MTC and in patients with Multiple Endocrine Neoplasia syndrome type 2 (MEN 2)
- It is unknown whether monitoring with serum calcitonin or thyroid ultrasound will mitigate human risk of thyroid C-cell tumors
- Patients should be counseled regarding the risk and symptoms of thyroid tumors

# Tirzepatide: Other Warnings and Precautions

Safety consideration	Guidance
Reproductive Health	<ul style="list-style-type: none"> <li>• TZP is contraindicated during pregnancy</li> <li>• Women of childbearing potential are recommended to use contraception when treated with TZP.</li> <li>• Advise patients using oral hormonal contraceptives to switch to a non-oral contraceptive method, or add a barrier method of contraception for 4 weeks after initiation and for 4 weeks after each dose escalation</li> </ul>
Perioperative Considerations: Aspiration during general anesthesia or deep sedation	<ul style="list-style-type: none"> <li>• Pulmonary aspiration has been reported in patients receiving long-acting GLP-1 receptor agonists undergoing general anesthesia or deep sedation</li> <li>• Consider the benefits and risks, and advise patients of these, prior to such procedures</li> </ul>
Psychiatric: suicidal ideation and behavior	<ul style="list-style-type: none"> <li>• Monitor patients treated with TZP for the emergence or worsening of depression, suicidal thoughts or behaviours, and/or any unusual changes in mood or behaviour</li> <li>• Consider the benefits and risks to individual patients prior to initiating or continuing therapy in patients with suicidal thoughts or behaviours, or history of suicidal attempts</li> </ul>

# Tirzepatide: Other Safety Considerations of Clinical Importance

Safety consideration	Observations from clinical trials	Guidance
Pancreatitis	Acute pancreatitis was more common in TZP (0.23 patients per 100 years of exposure) vs. comparators (0.11 patients per 100 years of exposure)	TZP has not been evaluated in patients with a prior history of pancreatitis and should be used with caution in these patients
Cholelithiasis	Acute gallbladder disease (i.e., acute cholecystitis, biliary colic, and cholecystectomy) was more common among TZP-treated patients (0.6%) than placebo-treated patients (0%)	If cholelithiasis is suspected, gallbladder diagnostic studies and appropriate clinical follow-up are indicated.

# Getting to Goal: Summary of Key Learnings


- There are unmet needs for the management of T2D: Many patients would benefit from additional A1C reduction, weight reduction and further cardiorenal protection
- Tirzepatide is the first GLP-1 / GIP dual receptor agonist therapy approved for use in Canada
- In clinical trials, tirzepatide has demonstrated more robust/superior A1C and body weight reductions compared to placebo, to GLP-1 receptor agonist, as well as to basal insulin and to bolus insulin
- The SURPASS–CVOT trial is underway, investigating the possibility of cardiovascular protection with tirzepatide (vs. active comparator dulaglutide)

## Optional “What-if...” Scenarios

**What if this was a recent diagnosis, the A1C was even higher (e.g., 9.8%) and the patient was already taking metformin?**

**What if the patient had an A1C of 8.3%, but a BMI of 21 kg/m<sup>2</sup> and weight loss was not desirable?**

**What if the patient had an A1C of 8.3%, a BMI of 27 kg/m<sup>2</sup> and also had atherosclerotic cardiovascular disease?**



What if this was a recent diagnosis, the A1C was even higher (e.g., 9.8%\*) and the patient was already taking metformin?

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**Andrée's new profile:**

52-year-old woman with 10-year history recent diagnosis of type 2 diabetes

**Physical examination**

Height: 160 cm; Weight: 72 kg;  
BMI: 28 kg/m<sup>2</sup>  
Waist circumference: 92 cm  
BP: 124/76 mmHg

**Investigations**

A1C: ~~8.3%~~ 9.8%  
eGFR and UACR in normal range  
LDL-C at target

**Medications**

Metformin 1 g b.i.d.; perindopril 8 mg q.d.;  
atorvastatin 20 mg q.d.

\*Assume the patient is non-catabolic and non-ketotic;  
A1C, glycated hemoglobin; b.i.d., twice daily; BMI, body mass index; BP, blood pressure; eGFR, estimated glomerular filtration rate; LDL-C, low-density lipoprotein-cholesterol;;  
q.d., once daily; UACR, urine albumin-to-creatinine ratio.

## “What-if” Opinion Question

**What approach might you choose to help this patient achieve glycemic control?**

- A. Add a DPP4 inhibitor
- B. Add a GLP-1 receptor agonist
- C. Add an SGLT2 inhibitor
- D. Add a GLP-1 / GIP dual receptor agonist
- E. Add insulin
- F. Something else

# Discussion

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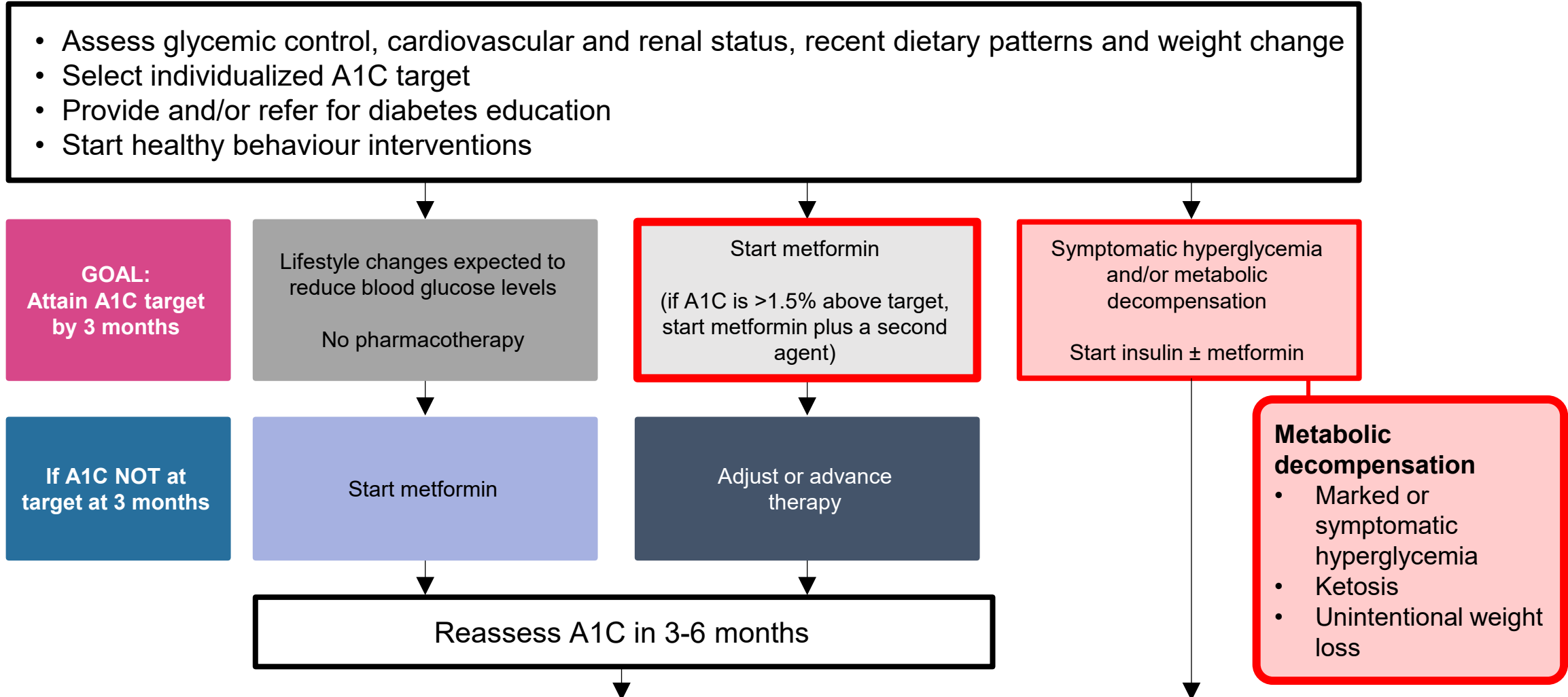
Why did you pick the strategy you picked?



TIME **2** DECIDE

CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES

# Diabetes Canada Guidance for Initial Glycemic Management (2020)



# Differing A1C-Lowering Potencies of Antihyperglycemic Therapies Available in Canada

## Very high Potency

- Tirzepatide
- Semaglutide
- Insulin
- Combination GLP1-RA / insulin

## High Potency

- GLP1-RAs not listed in the very high group
- Metformin
- SGLT2 inhibitors
- Sulfonylureas
- Thiazolidinediones

## Intermediate Potency

- DPP4 inhibitors

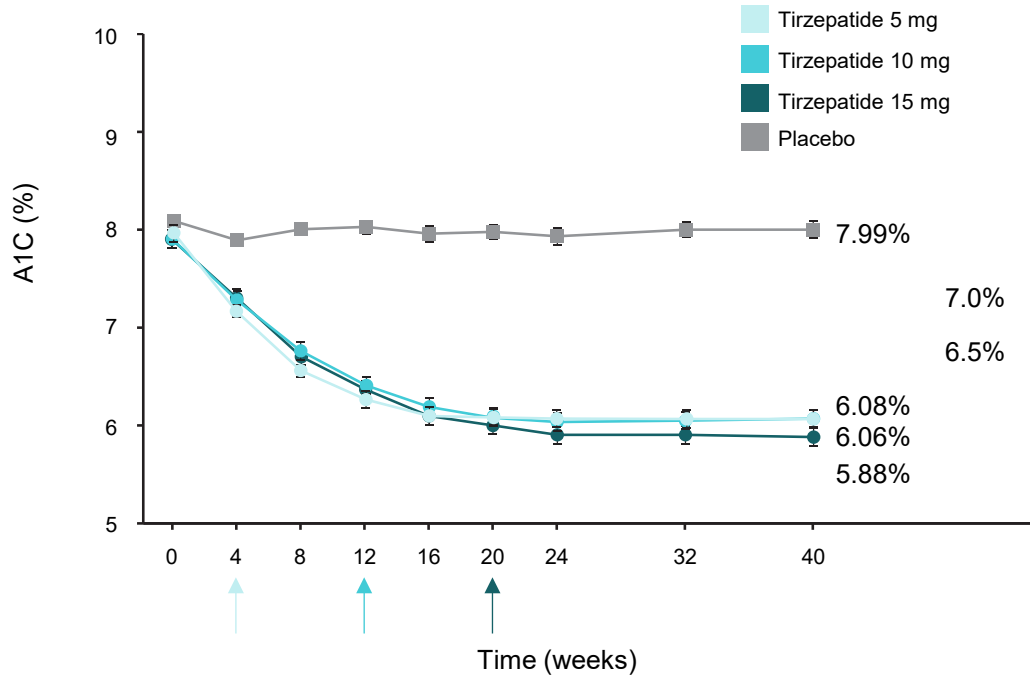
# Would Tirzepatide Be an Option?

## SURPASS-1: A1C reduction with TZP + Metformin

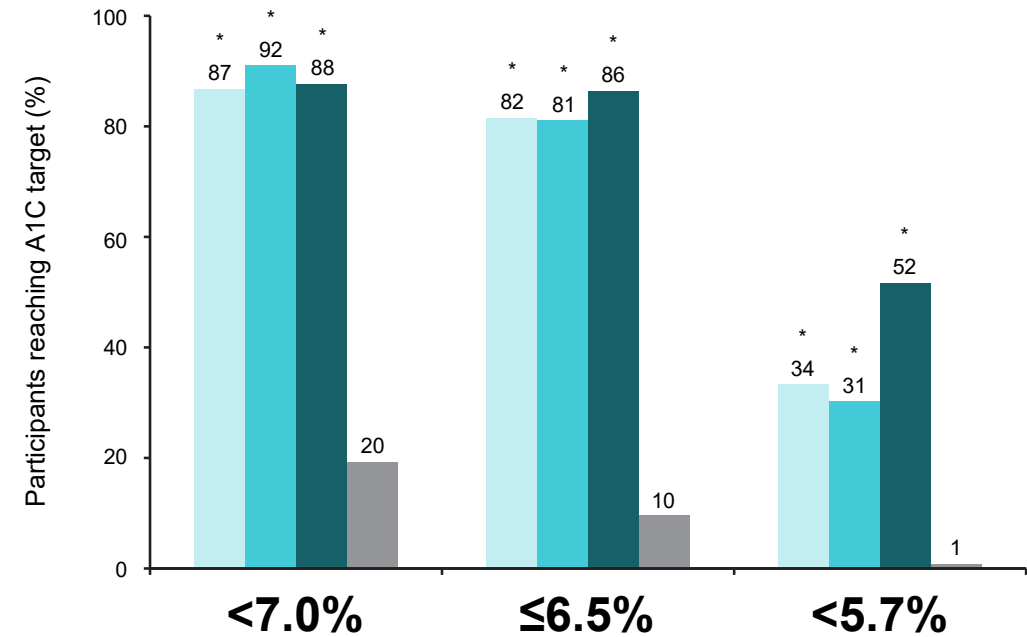
Return to What-if menu

Patients on Background Metformin, Mean Baseline A1C = 7.95%

### A1C Changes to Week 40




### % Reaching A1C Thresholds



\*p<0.0001 versus placebo at 40 weeks; results are for efficacy estimand  
 arrows on the x-axis indicate where maintenance doses were achieved  
 A1C, glycated hemoglobin; T2D, type 2 diabetes; TZP, tirzepatide  
 Adapted from Rosenstock J, et al. Lancet 2021;398(10295):143-55.

**Note:** There are no current phase 3 data available for TzP in individuals with a recent diagnosis of T2D



What if the patient had an A1C of 8.3%, but a BMI of 21 kg/m<sup>2</sup> and weight loss was not desirable?

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**Andrée's new profile:**

52-year-old woman with 10-year history of type 2 diabetes

**Physical examination**

Height: 160 cm; Weight: 72 kg;

BMI: ~~28 kg/m<sup>2</sup>~~ 21 kg/m<sup>2</sup>

Waist circumference: 92 cm

BP: 124/76 mmHg

**Investigations**

A1C: 8.3%

eGFR and UACR in normal range

LDL-C at target

**Medications**

Metformin 1 g b.i.d.; perindopril 8 mg q.d.; atorvastatin 20 mg q.d.

## “What-if” Opinion Question

**What approach might you choose to help this patient achieve glycemic control?**

- A. Add a DPP4 inhibitor
- B. Add an s.c. GLP-1 receptor agonist
- C. Add an oral GLP-1 receptor agonist
- D. Add an SGLT2 inhibitor
- E. Add a GLP-1 / GIP dual receptor agonist
- F. Something else

# Discussion

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Why did you pick the strategy you picked?

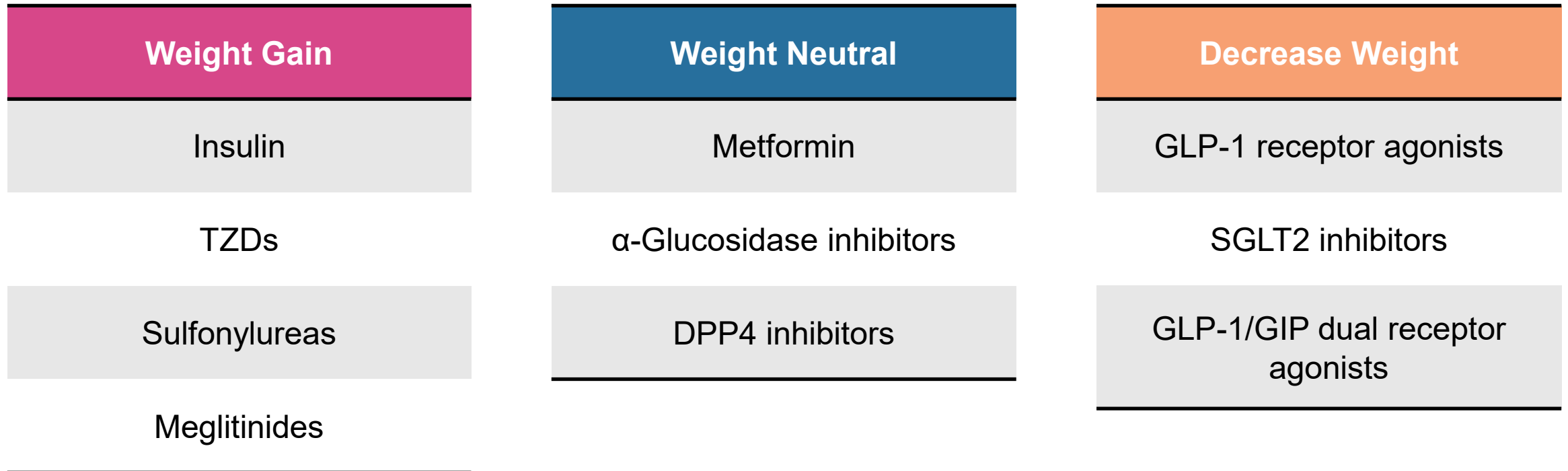



TIME **2** DECIDE

CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES

# Weight Effects of Current Antihyperglycemic Therapies

 [Return to What-if menu](#)





What if the patient had an A1C of 8.3%, a BMI of 27 kg/m<sup>2</sup> and also had atherosclerotic cardiovascular disease?

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### Andrée's new profile:

52-year-old woman with 10-year history of type 2 diabetes and 5-year history of atherosclerotic CVD

### Physical examination

Height: 160 cm; Weight: 72 kg;

BMI: ~~28 kg/m<sup>2</sup>~~ 27 kg/m<sup>2</sup>

Waist circumference: 92 cm

BP: 124/76 mmHg

### Investigations

A1C: 8.3%

eGFR and UACR in normal range

LDL-C at target

### Medications

Metformin 1 g b.i.d.; perindopril 8 mg q.d.; atorvastatin 20 mg q.d.; EC-ASA 81 mg q.d.; metoprolol 100 mg b.i.d.

## “What-if” Opinion Question

**What approach might you choose to help this patient achieve glycemic control?**

- A. Add a GLP-1 receptor agonist
- B. Add an SGLT2 inhibitor
- C. Add an GLP-1 receptor agonist AND an SGLT2 inhibitor
- D. Add a GLP-1 / GIP dual receptor agonist
- E. Add a GLP-1 / GIP dual receptor agonist AND an SGLT2 inhibitor
- F. Something else

# Discussion

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Why did you pick the strategy you picked?



TIME **2** DECIDE

CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES

# Diabetes Canada Guidance for Individuals with T2D and ASCVD

ASCVD, CKD or HF or age > 60 with 2 CV risk factors

ADD or SUBSTITUTE AHA with demonstrated cardiorenal benefits

		Established CV or renal disease			Risk factors
		ASCVD	CKD	HF	> 60 years with CV risk factors
Lower risks observed in outcome trials	MACE	GLP1-RA or SGLT2i*	SGLT2i* or GLP1-RA		GLP1-RA
	HHF	SGLT2i*	SGLT2i*	SGLT2i* (and lower CV mortality)	SGLT2i*
	Progression of nephropathy	SGLT2i*	SGLT2i*		SGLT2i*
		Grade A evidence	Grade B evidence	Grade C or D evidence	*Initiate only if eGFR >30mL/min/1.73m <sup>2</sup>

AHA: antihyperglycemic agent; ASCVD: atherosclerotic cardiovascular diseases; CKD: chronic kidney disease; CV: cardiovascular; eGFR, estimated glomerular filtration rate; 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. Adapted from Lipscombe L, et al. Pharmacologic Glycemic Management of Type 2 Diabetes in Adults: 2020 Update. Can J Diabetes. 2020;44:575-91.

# What About Cardiorenal Protection?

## The Ongoing SURPASS–CVOT<sup>1,2</sup> Will Provide Answers

- **Subjects** (N = 12,500):
  - T2D
  - Confirmed CVD
  - A1C  $\geq 7.0\%$  to  $\leq 10.5\%$
  - BMI  $\geq 25$  kg/m<sup>2</sup>
  - No major CV event within the last 60 days or planned revascularization
- **Interventions:** Dulaglutide (GLP1-RA with proven CV protection<sup>3</sup>) or tirzepatide
- **Primary outcome:** Time to first occurrence of CV death, MI or stroke
- **Expected completion:** October 2024

## Post-Test Question #1

**According to Diabetes Canada's clinical practice guidelines, what is the target A1C for people with type 2 diabetes at low risk of hypoglycemia?**

A.  $\leq 5.7\%$

B.  $\leq 6.0\%$

C.  $\leq 6.5\%$

D.  $\leq 7.0\%$

E.  $\leq 7.5\%$

## Post-Program Knowledge Question #2

**Tirzepatide works through dual agonism of the glucagon-like peptide-1 (GLP-1) receptor and which other receptor?**

- A. Angiotensin II receptor
- B. Glucose-dependent insulinotropic polypeptide (GIP) receptor**
- C. Dipeptyl peptidase (DPP) 4 receptor
- D. Sodium-glucose co-transport-2 (SGLT2) receptor
- E. None of the above

## Post-Program Knowledge Question #3

From a mean baseline A1C of 8.3% in the SURPASS-2 study, the mean A1C reduction for semaglutide 1 mg was 1.9% at 40 weeks (efficacy estimand). What was the mean A1C reduction for tirzepatide 15 mg at 40 weeks?

- A. 1.3%
- B. 2.0%
- C. 2.5%
- D. 3.2%

# Thank you for your participation!

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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.



## TIME 2 DECIDE

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CASE-BASED APPROACHES TO OPTIMAL  
A1C REDUCTION IN **T**YPE **2** **D**IABETES