BEYOND GLYCEMIC CONTROL:
ENHANCING GLUCOSE METABOLISM AND ENERGY HOMEOSTASIS THROUGH DUAL AGONISM OF INCRETINS
Meet Mr. Murray

Background
- 52-year-old black male
- Oil rig technician for over 25 years
- Diagnosed with T2D 10 years ago
- Has always struggled to achieve good glycemic control and has had progressive increase in body weight over the past 15 years
- Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself

Social History/Lifestyle
- Married and has 4 grown children that have left the house; non-smoker and rare ETOH
- “No time for healthy eating or exercise due to demands at work…. Often away from home and healthy diet is difficult”
- Excellent health insurance through employer

Not an actual patient or profile; “Mr. Murray” will be used throughout the presentation.
Mr. Murray’s Clinical History

Medical History
- T2D, obesity, hypertension, dyslipidemia, sleep apnea, NAFLD, and OA of knees (no known ASCVD)

Physical Exam and Labs
- BP 132/75 mmHg
- Weight 115 kg, BMI 36 kg/m²
- Normal retinal and thyroid exam
- A1c 8.6% (6 months ago 8.4%)
- Lipids: TC 182 mg/dL, LDL-C 108 mg/dL, TG 181 mg/dL, HDL-C 38 mg/dL
- Mildly elevated AST and ALT levels
- eGFR: 92 mL/min/1.73 m²
- UACR: <30 mg/g

Current Medications T2D
- metformin 1000 mg BID, glimepiride 4 mg QD, sitagliptin 100 mg QD

Other Meds/Treatments
- losartan 100 mg QD, amlodipine 5 mg QD, chlorthalidone 50 mg QD,
  atorvastatin 10 mg QD, nightly CPAP
Unmet needs in T2D

Dr. Donna Ryan
Goals of diabetes care

• Improve cardiometabolic health
• Prevent complications
• Improve health-related quality of life
Where do we stand in optimal diabetes care?

“After more than a decade of progress from 1999 to the early 2010s, glycemic and blood-pressure control declined in adult NHANES participants with diabetes, while lipid control leveled off”

Twin epidemics of T2D and obesity

T2D: 9.8% →→→→14.3%

Diagnosed, undiagnosed, and total diabetes

16
14
12
10
8
6
4
2
0

Year

UNDIAGNOSED

DIAGNOSED

TOTAL

Prevalence, %


Obesity (BMI > 30): 30.5% →→→→42.4%

Obesity³

Severe obesity³

Survey years

0 20 40 60

Percent

https://www.cdc.gov/nchs/products/databriefs/db360.htm#fig4
The obesity and diabetes syndemic

Physical environment
- Food
- Physical activity
- Safety
- Alcohol

Social environment
- Disadvantage
- Sociocultural barriers
- Income inequality

Obesity
- Sleep disorders
- Inability to be active
- Stigma and impaired mental health

Promotes 2 core defects
- Insulin resistance
- β-cell decompensation

Medication-induced weight gain
- Neuropathy and decreased activity
- Hypoglycemia and stimulation of food intake
- Stigma and impaired mental health

T2D
Moderate weight loss has benefits—greater weight loss is associated with greater benefits

- Measures of glycemia\(^1\)
- Triglycerides and HDL cholesterol\(^1\)
- Systolic and diastolic blood pressure\(^1\)
- Progression from prediabetes to diabetes\(^1\)
- Hepatic steatosis (measured by MRS)\(^2\)
- Measures of feeling and function
  - Symptoms of urinary stress incontinence\(^1\)
  - Measures of sexual function\(^3\)
  - Quality of life measures (IWQOL)\(^4\)
- NASH activity score (measured by biopsy)\(^1\)
- Apnea-hypopnea index\(^1\)
- Reduction in CV events, mortality, remission of T2D\(^5,6\)

Emergence of new classes of T2D therapeutics

- GLP-1 RAs (2005)
  - Favorable weight loss profiles (liraglutide and semaglutide)
  - CV risk reduction (liraglutide, dulaglutide, semaglutide)
- SGLT2 inhibitors (2015)
  - Favorable weight loss and blood pressure profile
  - CV risk reduction, nephropathy reduction
- Dual GIP/GLP-1R agonist (2022)
  - Novel, once-weekly GIP and GLP-1 dual receptor agonist—new class
  - Enhanced glycemic control and weight loss benefits

Treatment for T2D to minimize weight gain/promote weight loss

Used with permission from: Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clin Diabetes. 2022;40:10-38. doi:10.2337/cd22-as01
Meeting the challenge of weight-centric diabetes management

- Be selective in choosing patients for intensive efforts in weight management, just as in the ADA approach to individualizing glycemic targets.
- Prescribe wisely; choose medications with favorable weight profiles whenever possible.
- Remember to use motivational interviewing and shared decision-making techniques.

How to talk to your patients about weight management

Individualizing and achieving glycemic targets with shared decision making optimizes T2D outcomes
Patient communication is key to weight management success

**Patients prefer** the terms “excess body weight,” “BMI,” “above ideal body weight,” and “maintaining a healthy weight”

**They dislike** the terms “excess fat,” “obese,” and “obesity”

Seek the patient’s permission to discuss weight

- “As we get your glucose under control, do you have additional goals concerning your weight?”
- “What kind of help from me would you like regarding your weight?”

Mr. Murray

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- Oil rig technician for over 25 years
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Delineating the incretin effect and the roles of GLP-1 and GIP

Potential benefits of agonism of multiple receptors: mechanism of action of unimolecular dual agonists

Dr. Michael Nauck
The incretin effect in healthy subjects

[Graphs showing the effects of oral glucose and isoglycaemic i.v. glucose on plasma glucose, insulin, GIP, glucose infusion rate, C-peptide, and GLP-1 over time.]

The incretin effect in type 2 diabetes

GIP and GLP-1 administered as single agents or in combination in T2D patients

GLP-1 stimulates insulin secretion and reduces plasma glucose, but GIP has no effect

The traditional view

A reduced incretin effect in T2D indicates an inability of GIP to stimulate insulin secretion
Is GIP the obesity hormone?

- Overnutrition → GIP expression → Insulin release → Storage of fat → Intestinal glucose absorption
The traditional view

GIP receptor stimulation promotes obesity
Recent findings on GIP receptor agonism and body weight in animal studies

GIP receptor stimulation leads to reduced food intake and weight loss
GIP add GLP-1 receptor expression in hypothalamic neurons (eg, arcuate nucleus)


ARC, arcuate; DMH, dorsomedial hypothalamic; Gip, glucose-dependent insulino tropic polypeptide; Gipr, GIP receptor; Glp1r, glucagon-like peptide-1 receptor
GIP reduces food intake and body weight by interacting with CNS-GIPR

Acyl, acylated (free fatty acid residue attached); mGIPR ko, mouse GIP receptor knockout
GIP, GLP-1, and their combination reduce food intake and body weight in mice

The combination of GIP and GLP-1 is particularly effective in reducing food intake and body weight.

Intracerebroventricular injection

Effects of exogenous GIP, GLP-1, and their combination on food intake in human subjects

The reduction in energy intake with GLP-1 is confirmed. GIP alone was without effect. The combination with GLP-1 showed a reduced effect.

Bariatric surgery creates a novel pancreatic-intestinal hormonal milieu

<table>
<thead>
<tr>
<th>Gut/Pancreas Peptide Hormone</th>
<th>Secretion After Gastric Bypass</th>
<th>Effect on appetite</th>
<th>Body Weight Energy Expenditure</th>
<th>Effects on Plasma Glucose</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLP-1</td>
<td>↑↑↑↑</td>
<td>↓</td>
<td>≈</td>
<td>↓</td>
</tr>
<tr>
<td>Glucagon</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>GIP</td>
<td>↑ / ≈</td>
<td>(↓/↑)</td>
<td>≈</td>
<td>(↓/↑)</td>
</tr>
<tr>
<td>PYY</td>
<td>↑↑↑↑</td>
<td>↓</td>
<td>≈</td>
<td>↓</td>
</tr>
</tbody>
</table>

Bariatric surgery creates a gut hormonal milieu associated with weight loss and T2D remission

GIP and GLP-1 (plus additional hormones) together may participate in these effects
The influence of GIP and GLP-1 on postprandial glucose tested by use of specific receptor antagonists in human subjects

Glucose control (intensified regimen) improved insulin and β-cell response to GLP-1 and GIP in patients with T2D

Mean blood glucose before (navy circles) and during (green circles) 4 weeks of insulin treatment. The patients measured blood glucose seven times per day three times per week. Data are mean ± SEM

Tirzepatide: a single molecule stimulating GIP and GLP-1 receptors

Native human incretin hormones

- Amino acid unique to GLP-1
- Amino acid unique to GIP
- Amino acid common to GLP-1 and GIP
- Amino acid not common to either GLP-1 or GIP
- AIB: Amino iso-butyric acid (non-natural amino acid)

Amino acid number (relative to native GLP-1)

GLP-1 (7-36) Amide

GIP (1-42) Amide

LY3298176 Tirzepatide

Amino acid number (relative to native GIP)

Albumin

C-20 Free fatty di-acid

Slide courtesy of M Nauck

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Clinical implications of dual agonist efficacy data: glucose

Dr. Juan Pablo Frias
Advanced engineering: dual GIP/GLP-1 receptor agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, engineered to bind to both GIP and GLP-1 receptors
- 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Mean half-life of ~5 days (116.7 h), enabling once-weekly dosing
- Plasma concentrations in people with renal and hepatic impairment do not differ from healthy people

Single agent possessing activity at 2 pharmacologic targets


GIP, glucose-dependent insulinoctropic polypeptide; GLP-1, glucagon-like peptide-1
The SURPASS program: clinical trials across the spectrum of T2D

- **Monotherapy**
  - **SURPASS-1** vs placebo\(^1\)
    - Drug-naïve or washout from any OAM

- **2-Drug Combination**
  - **SURPASS-2** vs semaglutide\(^2\)
    - Add-on to metformin

- **2-3 Drug Combinations**
  - **SURPASS-3** vs insulin degludec\(^3\)
    - Add-on to metformin with or without SGLT-2i

- **2-4 Drug Combinations**
  - **SURPASS-4** vs insulin glargine\(^4\)
    - Add-on to \(\geq 1\) and \(\leq 3\) OAMs (metformin, SGLT-2i, or SU)

- **Combination With Insulin**
  - **SURPASS-5** vs placebo\(^5\)
    - Both with insulin glargine with or without metformin

  - **SURPASS-6** vs insulin lispro (TID)\(^6\)
    - Both with insulin glargine with or without metformin (ongoing)

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**SURPASS-CVOT** vs dulaglutide\(^7\)
- **ongoing**

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OAM = oral antihyperglycemic medication; SU = sulfonylurea; TID = three times daily
SURPASS trial design: tirzepatide 5, 10, and 15 mg versus active comparator or placebo

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.
Tirzepatide at all doses significantly reduced A1c versus placebo or active comparators

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Duration</th>
<th>Baseline A1c (%)</th>
<th>Add-on to</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURPASS-1</td>
<td>40 weeks</td>
<td>7.9%</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>(N=478)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-2</td>
<td>40 weeks</td>
<td>8.3%</td>
<td>MET</td>
</tr>
<tr>
<td>(N=1,878)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-3</td>
<td>52 weeks</td>
<td>8.2%</td>
<td>MET ± SGLT-2i</td>
</tr>
<tr>
<td>(N=1,437)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-4</td>
<td>52 weeks</td>
<td>8.5%</td>
<td>1-3 OAMs (MET/SU/SGLT-2i)</td>
</tr>
<tr>
<td>(N=1,995)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-5</td>
<td>40 weeks</td>
<td>8.3%</td>
<td>Basal insulin ± MET</td>
</tr>
<tr>
<td>(N=475)</td>
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</tbody>
</table>

Mean Change in A1c, % (SE)

TZP 5 mg  TZP 10 mg  TZP 15 mg  Placebo  Semaglutide  Degludec  Glargine

Treatment regimen estimates:
Tirzepatide significantly reduced A1c and more patients achieved A1c targets compared with semaglutide 1 mg

Data are LSM (SE); mITT (efficacy analysis set) ANOVA analysis (week 0) and MMRM analysis (week 40). Arrows indicate when the maintenance dose of tirzepatide 5 mg, 10 mg and 15 mg and semaglutide 1 mg are achieved. *p<0.001 vs. semaglutide 1 mg

Tirzepatide improved self-monitored pre- and postprandial glucose compared with semaglutide 1 mg

Tirzepatide improved time in range versus insulin degludec after 52 weeks of treatment

All tirzepatide doses (5, 10, and 15 mg) had greater time in range (70-180 mg/dL) and less time below range (<70 mg/dL) compared with insulin degludec at week 52

Mr. Murray

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Clinical implications of dual agonist efficacy data: weight and lipids

Dr. Ildiko Lingvay
Tirzepatide decreased weight (kg and %) more than comparators in SURPASS trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Baseline Weight (kg)</th>
<th>Add-on Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURPASS-1</td>
<td>40 weeks</td>
<td>85.9</td>
<td>Monotherapy</td>
</tr>
<tr>
<td>SURPASS-2</td>
<td>40 weeks</td>
<td>93.7</td>
<td>MET</td>
</tr>
<tr>
<td>SURPASS-3</td>
<td>52 weeks</td>
<td>94.3</td>
<td>MET ± SGLT-2i</td>
</tr>
<tr>
<td>SURPASS-4</td>
<td>52 weeks</td>
<td>90.3</td>
<td>1-3 OAMs (MET/SU/SGLT-2i)</td>
</tr>
<tr>
<td>SURPASS-5</td>
<td>40 weeks</td>
<td>95.2</td>
<td>Basal insulin ± MET</td>
</tr>
</tbody>
</table>

### Mean Change in Weight (kg) [SE]

<table>
<thead>
<tr>
<th>Study</th>
<th>Week</th>
<th>Change (kg)</th>
<th>% Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURPASS-1</td>
<td></td>
<td>-6.3**</td>
<td>-7.9%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-7.0**</td>
<td>-9.3%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-7.8**</td>
<td>-11.0%</td>
</tr>
<tr>
<td>SURPASS-2</td>
<td></td>
<td>-7.5</td>
<td>-8.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-9.3**</td>
<td>-11.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-11.2**</td>
<td>-13.1%</td>
</tr>
<tr>
<td>SURPASS-3</td>
<td></td>
<td>-5.7</td>
<td>-6.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>-7.0**</td>
<td>-8.1%</td>
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<td>-11.4%</td>
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<td></td>
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<td>-8.1%</td>
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<tr>
<td></td>
<td></td>
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<td>-10.7%</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>-9.8**</td>
<td>-11.6%</td>
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### Color Changes

- **TZP 5 mg**
- **TZP 10 mg**
- **TZP 15 mg**
- **Placebo**
- **Semaglutide**
- **Degludec**
- **Glargine**

---


Treatment regimen estimated superiority vs placebo or active comparator: *p < 0.05; **p < 0.001"
Tirzepatide sustained the trajectory of weight change (kg and %) over 40 and 52 w better than comparators (SURPASS 2 and 3)

**SURPASS-2**
Overall mean baseline weight = 93.8 kg

**SURPASS-3**
Overall mean baseline weight = 94.5 kg

Efficacy estimand
All doses of tirzepatide resulted in greater mean weight change (kg and %) over 2 years (SURPASS 4)

**SURPASS-4**

Overall mean baseline weight = 90.3 kg

Mean Change in Weight (kg) [SE] (% change)

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Week 0</th>
<th>Week 8</th>
<th>Week 16</th>
<th>Week 24</th>
<th>Week 32</th>
<th>Week 40</th>
<th>Week 52</th>
<th>Week 58</th>
<th>Week 64</th>
<th>Week 88</th>
<th>Week 104</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin glargine</td>
<td>978</td>
<td>880</td>
<td>891</td>
<td>600</td>
<td>97</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZP 5 mg</td>
<td>326</td>
<td>283</td>
<td>285</td>
<td>196</td>
<td>38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TZP 10 mg</td>
<td>321</td>
<td>289</td>
<td>288</td>
<td>193</td>
<td>32</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>TZP 15 mg</td>
<td>334</td>
<td>291</td>
<td>291</td>
<td>194</td>
<td>35</td>
<td></td>
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Efficacy estimand

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More participants achieved 10% weight loss with all disease of tirzepatide vs comparators

SURPASS-1\(^1\) (N=478)
SURPASS-2\(^2\) (N=1,878)
SURPASS-3\(^3\) (N=1,437)
SURPASS-4\(^4\) (N=1,995)
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40 weeks
Basal insulin ± MET

% of Patients Achieving Body Weight Loss ≥ 10%

- TZP 5 mg
- TZP 10 mg
- TZP 15 mg
- Placebo
- Semaglutide
- Degludec
- Glargine


Treatment-regimen estimand
Superiority vs placebo or active comparator: *p < 0.05; **p < 0.001
All doses of tirzepatide generally improved lipid profiles better than semaglutide at 40 weeks (SURPASS-2)

<table>
<thead>
<tr>
<th></th>
<th>Triglycerides</th>
<th>Total Cholesterol</th>
<th>HDL Cholesterol</th>
<th>LDL Cholesterol</th>
<th>VLDL Cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mg/dL</td>
<td>166 167 164 165</td>
<td>172 171 169 171</td>
<td>43 43 43 43</td>
<td>88 88 86 88</td>
<td>33 33 32 33</td>
</tr>
</tbody>
</table>

Mean % Change from Baseline [SE]

Efficacy estimand
Change from Baseline: *p < 0.05; **p < 0.001

Up to 60% of participants on tirzepatide achieved composite endpoint compared to 22% on once-weekly semaglutide 1 mg (SURPASS-2)

Prespecified composite endpoint
- A1c ≤6.5%, and
- Weight loss ≥10%, and
- No Level 2 (<54 mg/dL [3.0 mmol]) or Level 3 (severe) hypoglycemia
### Mr. Murray

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Back to Mr. Murray

• You discuss all options with the patient. You agree to target 15% weight loss and better glycemic control.

• He attends a group discussion of bariatric surgery but says, “I want to try something less aggressive, first.”

• He also agrees to follow your lead on changing his medications and adding medications to promote weight loss.
Clinical implications of dual agonist data: safety, tolerability, and CV effects
Dr. Juan Pablo Frias
Tirzepatide safety and tolerability

- Side effect profile similar to that of selective GLP-1 receptor agonists
- Most common adverse events were gastrointestinal in nature and occurred primarily during dose escalation period

<table>
<thead>
<tr>
<th>Preferred Term, %</th>
<th>TZP 5 mg (N=470)</th>
<th>TZP 10 mg (N=469)</th>
<th>TZP 15 mg (N=470)</th>
<th>Sema 1 mg (N=469)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any GI TEAE</td>
<td>40.0</td>
<td>46.1</td>
<td>44.9</td>
<td>41.2</td>
</tr>
<tr>
<td>Nausea</td>
<td>17.4</td>
<td>19.2</td>
<td>22.1</td>
<td>17.9</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>13.2</td>
<td>16.4</td>
<td>13.8</td>
<td>11.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.7</td>
<td>8.5</td>
<td>9.8</td>
<td>8.3</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7.2</td>
<td>6.2</td>
<td>9.1</td>
<td>6.6</td>
</tr>
<tr>
<td>Constipation</td>
<td>6.8</td>
<td>4.5</td>
<td>4.5</td>
<td>5.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3.0</td>
<td>4.5</td>
<td>5.1</td>
<td>5.1</td>
</tr>
</tbody>
</table>

Incidence of nausea over time through 40 weeks (SURPASS-2)

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

# Low incidence of hypoglycemia in SURPASS trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Monotherapy</th>
<th>Metformin</th>
<th>Metformin ± SGLT-2i</th>
<th>Metformin ± SU ± SGLT-2i</th>
<th>Basal Insulin ± Metformin</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SURPASS-1</strong></td>
<td>TZP 5 mg (N=121)</td>
<td>TZP 5 mg (N=470)</td>
<td>TZP 5 mg (N=356)</td>
<td>TZP 5 mg (N=329)</td>
<td>TZP 5 mg (N=116)</td>
</tr>
<tr>
<td></td>
<td>TZP 10 mg (N=119)</td>
<td>TZP 10 mg (N=469)</td>
<td>TZP 10 mg (N=360)</td>
<td>TZP 10 mg (N=328)</td>
<td>TZP 10 mg (N=119)</td>
</tr>
<tr>
<td></td>
<td>TZP 15 mg (N=120)</td>
<td>TZP 15 mg (N=470)</td>
<td>TZP 15 mg (N=359)</td>
<td>TZP 15 mg (N=338)</td>
<td>TZP 15 mg (N=120)</td>
</tr>
<tr>
<td></td>
<td>Placebo (N=115)</td>
<td>Semaglutide (N=469)</td>
<td>Degludec (N=358)</td>
<td>Glargine (N=1,000)</td>
<td>Placebo (N=120)</td>
</tr>
</tbody>
</table>

- **Hypoglycemia**
  - **SURPASS-1**: 0, 0, 0, 1.4, 0.88
  - **SURPASS-2**: 0.9, 0.2, 1.7, 7.3
  - **SURPASS-3**: 0.21, 0.21, 0.28
  - **SURPASS-4**: 8.8, 6.1, 8.0, 19.1
  - **SURPASS-5**: 15.5, 19.3, 14.2, 12.5

- **Severe hypoglycemia**
  - **SURPASS-1**: 0, 0, 0, 0
  - **SURPASS-2**: 0.9, 0, 0.21, 0
  - **SURPASS-3**: 0, 0, 0
  - **SURPASS-4**: 0.30, 0, 0.89
  - **SURPASS-5**: 0, 1.68, 0.83

References:
### Other adverse events of special interest

<table>
<thead>
<tr>
<th>Parameters</th>
<th>SURPASS-1</th>
<th>SURPASS-2</th>
<th>SURPASS-3</th>
<th>SURPASS-4</th>
<th>SURPASS-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatitis</td>
<td>0</td>
<td>2 (TZP 10 mg)</td>
<td>0</td>
<td>3 (TZP 5mg)</td>
<td>0</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>1 (TZP 5 mg)</td>
<td>4 (TZP 5 mg)</td>
<td>2 (TZP 5mg)</td>
<td>3 (TZP 5mg)</td>
<td>1 (TZP 5 mg)</td>
</tr>
<tr>
<td>Medullary Thyroid Carcinoma</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>N/A*</td>
</tr>
<tr>
<td>Diabetic Retinopathy</td>
<td>0</td>
<td>2 (TZP 10 mg)</td>
<td>2 (TZP 5mg)</td>
<td>2 (TZP 5mg)</td>
<td>N/A*</td>
</tr>
</tbody>
</table>

Pooled tirzepatide vs pooled comparator effect on time to first MACE-4

HR: 0.80  
95% CI: (0.57, 1.11)  
$P$ value: 0.183

SURPASS-CVOT is estimated to complete in 2024

Planned follow-up period

- GPGB (30 weeks)
- SURPASS-1, -2 and -5 (44 weeks)
- SURPASS-3 and J-mono (56 weeks)
- SURPASS-4 (56–108 weeks)

Cumulative number of events: number of patients at risk


MACE-4, CV death, MI, stroke, and hospitalized unstable angina. $P$ values were based on the Wald chi-square test.

Mr. Murray

- 52-year-old black man
- Oil rig technician for over 25 years
- Diagnosed with T2D 10 years ago
- Has struggled to achieve glycemic control and has had progressive increase in body weight over the past 15 years
- Several family members have recently suffered significant complications of T2D and obesity, and he is motivated to take better care of himself

Medical History

- T2D, obesity, hypertension, dyslipidemia, sleep apnea, NAFLD, and OA of knees (no known ASCVD)

Social History/ Lifestyle

- Married and has 4 grown children that have left the house; non-smoker and rare ETOH
- “No time for healthy eating or exercise due to demands at work…. Often away from home and healthy diet is difficult”
- Excellent health insurance through employer

Physical Exam & Labs

- BP 132/75 mmHg
- Weight 115 kg, BMI 36 kg/m²
- Normal retinal and thyroid exam
- A1c 8.6% (6 months ago 8.4%)
- Lipids: TC 182 mg/dL, LDL-C 108 mg/dL, TG 181 mg/dL, HDL-C 38 mg/dL
- eGFR: 92 mL/min/1.73 m²
- UACR: <30 mg/g

Current Medications

- T2D - metformin 1000 mg BID, glimepiride 4 mg QD, sitagliptin 100 mg QD

Other Meds/ Treatments

- Losartan 100 mg QD, amlodipine 5 mg QD, chlorthalidone 50 mg QD, atorvastatin 10 mg QD, nightly CPAP
Reflection: What do you consider the most important goal(s) and action(s) for the management of Mr. Murray?

1. Better glycemic and lipid control. We need to add a thiazolidinedione and intensify lipid-lowering therapy.

2. Better glycemic, lipid, and weight control. We need to stop the glimepiride and add tirzepatide. Intensify lipid-lowering therapy and consider adding a SGLT2i.

3. Better glycemic, lipid, and weight control. We need to intensify lipid-lowering therapy and refer for bariatric surgery.

4. Better glycemic, lipid, and weight control. We need to stop the glimepiride and add a GLP-1 RA with a good CV risk and weight loss profile and consider adding an SGLT2i.
Tirzepatide: key prescribing information and instructions for use

Indicated as an adjunct to diet and exercise to improve glycemic control in adults with T2D

- Single-dose prefilled pen
- 2.5 mg, 5 mg, 7.5 mg, 10 mg, 12.5 mg, and 15 mg per 0.5 mL
- The recommended starting dosage is 2.5 mg SC once weekly
- After 4 weeks, increase to 5 mg SC once weekly
- If additional glycemic control is needed, increase the dosage in 2.5-mg increments after at least 4 weeks on the current dose
- The maximum dosage is 15 mg SC once weekly
- Administer once weekly at any time of day, with or without meals
- Inject SC in the abdomen, thigh, or upper arm; rotate injection sites with each dose

Tirzepatide: key prescribing information and instructions for use

Contraindications

- Personal or family history of MTC or patients with MEN2
- Known serious hypersensitivity to tirzepatide or any of the excipients

Limitations of Use

- Has not been studied in patients with a history of pancreatitis
- Is not indicated for use in patients with type 1 diabetes

Warnings and Precautions

- Pancreatitis
- Hypoglycemia with concomitant use of insulin secretagogues or insulin
- Hypersensitivity reactions
- Acute kidney injury
- Severe gastrointestinal disease
- Diabetic retinopathy complications in patient with a history of diabetic retinopathy
- Acute gallbladder disease

Take home messages
Dr. Juan Pablo Frias
Dr Donna Ryan
Dr Michael Nauck
Dr. Ildiko Lingvay
Dr. David D’Alessio