Demystifying the Evolving Science and Potential Role of Incretins in T2D
Demystifying the Evolving Science and Potential Role of Incretins in T2D: Unmet Needs

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Associate Professor of Medicine
Head, 1st Medical Department
Landstrasse Clinic
Vienna, Austria
The Global Burden of Diabetes is Projected to Grow to 700 Million People by 2045

- **North America and Caribbean**
  - 2019: 48 million
  - 2045: 63 million

- **Middle East and North Africa**
  - 2019: 55 million
  - 2045: 108 million

- **Africa**
  - 2019: 19 million
  - 2045: 47 million

- **Europe**
  - 2019: 59 million
  - 2045: 68 million

- **Southeast Asia**
  - 2019: 68 million
  - 2045: 153 million

- **Western Pacific**
  - 2019: 163 million
  - 2045: 212 million

Adapted with permission from the International Diabetes Foundation.
http://www.diabetesatlas.org

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**Diabetes Is Associated with Many Complications that Contribute to Mortality and Substantial Health Care Costs**

<table>
<thead>
<tr>
<th>Complications of Diabetes&lt;sup&gt;1&lt;/sup&gt;</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Deaths Worldwide in 2016&lt;sup&gt;2&lt;/sup&gt;</strong></td>
<td>1.6 million</td>
</tr>
<tr>
<td><strong>Annual Cost&lt;sup&gt;1&lt;/sup&gt;</strong></td>
<td>USD 827 billion</td>
</tr>
<tr>
<td><strong>Projected Global GDP Loss&lt;sup&gt;1&lt;/sup&gt;</strong> (2011–2030)</td>
<td>USD 1.7 trillion</td>
</tr>
<tr>
<td><strong>Health Expenditure&lt;sup&gt;3,a&lt;/sup&gt;</strong> 8%–19% of the total health expenditure</td>
<td></td>
</tr>
<tr>
<td><strong>Projected Rise in Total Healthcare Expenditure&lt;sup&gt;3,a&lt;/sup&gt;</strong> (2019–2045)</td>
<td>11%</td>
</tr>
</tbody>
</table>

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<sup>1</sup>Based on ages 20–79 years.

<sup>2</sup>USD = United States dollar; GDP = gross domestic product.


Complex Pathophysiology of Obesity and T2D

**Genetics** (polygenic diseases)
- Adipokines (e.g., leptin and adiponectin)
- Pro-inflammatory cytokines
- NEFA

**Epigenetics** (fetal/neonatal programming)
- Excess visceral (ectopic) fat
- Adiposopathy

**Environment** (unhealthy diet, sedentary lifestyle, and pollutants)
- Ghrelin
- GLP-1
- GIP
- Cholecystokinin
- Oxyntomodulin
- Microbiota changes
- Gut barrier dysfunction

- β-cell burden, dysfunction, or apoptosis

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"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%


Obesity (BMI > 30): 30.5% →→→→ 42.4%

https://www.cdc.gov/nchs/products/databriefs/db360.htm#fig4
Type 2 Diabetes – Remission due to Weight Loss

- Weight loss
  - Liver fat ↓
  - Pancreas fat ↓

Predictors for Remission
- Age
- Duration of T2D
- Baseline HbA1c
- No of diabetes medication
- Use of insulin

FIGURE 3: USE OF GLUCOSE-LOWERING MEDICATIONS IN THE MANAGEMENT OF TYPE 2 DIABETES

- Healthy lifestyle behaviours: diabetes self-management education and support (DSME); social determinants of health (SDOH)

Goal: Cardiovascular Risk Reduction in High-Risk Patients with Type 2 Diabetes: Is addition to comprehensive CV risk management?*

- Indicators of high risk
  - Moderate or severe kidney disease
  - Congestive heart failure
  - Prior stroke
  - Peripheral artery disease

- HF: Current onset of HF
  - With or without additional CV risk factors

- GFR < 60 ml/min per 1.73 m² or HF
  - HF with moderate or severe kidney disease

- GFR 45-59 ml/min per 1.73 m² or HF
  - Previous HF event
  - HF with moderate or severe kidney disease

- GFR < 45 ml/min per 1.73 m² or HF

PREVENTIVE

- SGLT2i with primary evidence of reducing CV events

- GLP-1 RA with proven CV benefit

IF HbA1c above target

- For patients on a GLP-1 RA consider adding SGLT2i with proven CV benefit or a risk ratio

IF additional cardiovascular risk reduction or glycemic lowering needed

SGLT2i with proven CV benefit in this population

BENEFIT

- SGLT2i with proven HF benefit

- GLP-1 RA with proven CV benefit

IF HbA1c above target, for patients on SGLT2i, consider incorporating a GLP-1 RA or vice versa

*In people with HbA1c established CVD or multiple risks for CVD, the decision to use a GLP-1 RA or SGLT2i with proven benefit should be independent of background use of metformin. A strong recommendation is reserved to people with CVD and a weaker recommendation to those with indicators of high CV risk. However, a higher absolute risk reduction and lower numbers needed to treat are seen at higher levels of baseline risk and should be factored into the shared decision-making process. The low risk threshold for use may be better balanced and similarly effective. If the SGLT2i clinical outcomes results demonstrate their efficacy in reducing the risk of composite MACE, CV death, all-cause mortality, MI, MI and revascularisation in individuals with T2D with established/high risk of CVD, if for GLP-1 RA, CV events demonstrate their efficacy in reducing composite MACE, CV death, all-cause mortality, MI, stroke and revascularisation in individuals with T2D with established/high risk of CVD.
ADA/EASD Consensus Report 2022

Achievement and Maintenance of Weight Management Goals

**Glycaemic Management:** Choose approaches that provide the efficacy to achieve goals:
- Metformin OR Agent(s) including COMBINATION therapy that provide adequate EFFICACY to achieve and maintain treatment goals
- Consider avoidance of hypoglycaemia a priority in high-risk individuals

In general, higher efficacy approaches have greater likelihood of achieving glycaemic goals
- Efficacy for glucose lowering:
  - Very High: Dulaglutide (high dose), Semaglutide, Tirzepatide, Insulin
  - Combination Oral, Combination Injectable (GLP-1 RA/Insulin)
  - High: GLP-1 RA (not listed above), Metformin, SGLT2i, Sulfonylurea, TZD
  - Intermediate: DPP-4i

**Achievement and Maintenance of Weight Management Goals:**
- Set individualised weight management goals
- General lifestyle advice: medical nutrition therapy/exercising patterns/physical activity
- Intensive evidence-based structured weight management programme
- Consider medication for weight loss
- Consider metabolic surgery

When choosing glucose-lowering therapies:
- Consider regimen with high-to-very-high dual glucose and weight efficacy

**Efficacy for weight loss:**
- Very High: Semaglutide, Tirzepatide
- High: Dulaglutide, Liraglutide
- Intermediate: GLP-1RA (not listed above), SGLT2i
- Neutral: DPP-4i, Metformin

Clinical Inertia Is a Multifactorial Problem

### Patient-related
- Denial of disease
- Lack of awareness of progressive nature of disease, leading to feeling of “failure”
- Lack of awareness of implications of poor glycemic control
- Fear of side effects (hypoglycemia, weight gain)
- Concerns about ability to manage more complicated treatment regimens
- Too many medicines
- Treatment costs
- Poor communication with physician
- Lack of support
- Lack of trust in physician

### Physician-related
- Time constraints
- Lack of support, eg, from nursing staff
- Concerns about costs of treatment/testing, etc
- Reactive rather than proactive care
- Underestimation of patients’ needs
- Difficulties navigating guidelines and algorithms
- Lack of information of understanding of new treatment options and potential benefits
- Lack of information on side effects/fear of causing harm (eg, hypoglycemia)
- Lack of clear guidance on individualizing treatment
- Concerns about patients’ ability to manage more complicated treatment regimens
- Concerns about patient adherence

### Health Care System-related
- No clinical guidelines
- No disease registry
- No visit planning
- No active outreach to patients
- No decision support
- No team approach to care
- Poor communication between physician and staff

Social Determinants of Health

Available at: https://www.medisked.com/solutions/social-determinants-of-health-sdoh/
GIP/GLP-1 Receptor Agonists Mode of Action

Thomas Forst, MD
Johannes Gutenberg University Mainz
Chief Medical Officer, Chairman of the Executive Board, Clinical Research Services
Mannheim, Germany
The Incretin Effect Is Reduced in People With T2D

In healthy people, insulin secretion is enhanced after oral vs IV administration of glucose (incretin effect)

The incretin effect is diminished in people with T2D

IV = intravenous; T2D = type 2 diabetes.

Nauck MA, Meier JJ. Diabetes Obes Metab. 2018;20(suppl 1):S5-S21.
GLP-1 Receptor Agonists

GLP-1 is secreted from L cells after ingestion of food

Increase in satiety
Decrease in hunger

Alpha cells:
Decrease in postprandial glucagon release

Beta cells:
Increase in glucose-dependent insulin release

Liver:
Decreased glucagon
Reduced endogenous glucose release

Stomach:
Reduced mortality


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Incretin Agonism in the Postprandial Regulation of Metabolism and Energy Homeostasis

Gcg-RA  GLP-1-RA  GIP-RA

Gcg-R  GLP-1-R  GIP-R

Courtesy of Professor Thomas Forst
Incretin Signaling in Alpha- and Beta-cell Regulation

**Intestine**

<table>
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<tr>
<th>Source</th>
<th>Intestinal Hormone</th>
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<tbody>
<tr>
<td>L Cells</td>
<td>Glucagon-like peptide 1 (GLP-1)</td>
</tr>
<tr>
<td>L Cells</td>
<td>Oxyntomodulin</td>
</tr>
<tr>
<td>L Cells</td>
<td>Peptide YY (PYY)</td>
</tr>
<tr>
<td>K Cells</td>
<td>Glucose-dependent insulinotropic hormone (GIP)</td>
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</table>

**Langerhans Islet**

<table>
<thead>
<tr>
<th>Source</th>
<th>Hormone</th>
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<tbody>
<tr>
<td>Alpha Cells</td>
<td>Glucagon</td>
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<tr>
<td>Beta Cells</td>
<td>Insulin</td>
</tr>
</tbody>
</table>

**Glucose level**

- Glucose↑
- Glucose↓
The Gut-Pancreas Axis: Incretin Signaling to the Pancreas in Response to Nutrient Load

- Nutrient load in the gut stimulates release of the incretin hormones GIP and GLP-1
- GIP and GLP-1 signal to pancreatic islet cells to enhance glucose-dependent insulin secretion
- This “incretin effect” is a major contributor to regulation of PPG clearance in healthy people

GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1; PPG = postprandial glucose.

# Additive and Complementary Effects of GLP-1 and GIP

<table>
<thead>
<tr>
<th>GLP-1</th>
<th>GIP</th>
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<tbody>
<tr>
<td>Islet of Langerhans</td>
<td>• Insulin ↑</td>
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<tr>
<td></td>
<td>• Glucagon ↓ (postprandial)</td>
</tr>
<tr>
<td></td>
<td>• Insulin ↑</td>
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<tr>
<td></td>
<td>• Glucagon ↑ (in case of low glucose)</td>
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</table>

The in vivo relation of plasma glucagon (dark blue curves, squares) and serum C-peptide (light blue curves, circles) to selected PG values between 3 and 12 mmol/L in the presence of stimulated GIP concentrations (broken lines, filled symbols) or basal levels (full lines, open symbols). Data are means ± SEM. *Significant differences (P < 0.05) according to paired t tests.

GIP=glucose-dependent insulinotropic polypeptide; PG=plasma glucagon; SEM=standard error of the mean.

## Additive and Complementary Effects of GLP-1 and GIP

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<td>• Glucagon ↑ <em>(in case of low glucose)</em></td>
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<tr>
<td>Central Nervous System</td>
<td>• Satiety ↑</td>
<td>• Satiety ↑</td>
</tr>
<tr>
<td></td>
<td>• Nausea/Vomiting ↑</td>
<td>• Anti Emetic</td>
</tr>
</tbody>
</table>

Central Effects of GLP-1 and GIP on Satiety

GLP-1

- ↓ Food Intake
- ↑ Satiety
- ↓ Body Weight
- ↑ Nausea

GIP*

- ↓ Food Intake
- ↓ Body Weight
- ↓ Nausea

*Data from preclinical studies
## Additive and Complementary Effects of GLP-1 and GIP

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<td>• Anti Emetic</td>
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</table>

Effects of GIP in Adipose Tissue

Adipose tissue perfusion

Effects of GIP on Adipose Tissue Perfusion, Lipoproteinlipase, Triglyceride Uptake, Lipid Buffering Capacity
Effects of GIP in Adipose Tissue

Adipose Tissue Perfusion

Glucose Uptake (Insulin Sensitivity)

Lipoproteinlipase Activity

Cytokine, Adipokine Activity


Used with permission:


Dual Agonists in the Postprandial Regulation of Metabolism and Energy Homeostasis

Courtesy of Professor Thomas Forst
Tirzepatide is a dual GIPR/GLP-1R agonist

- Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIPR and GLP-1R
- Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
- Tirzepatide has a mean half-life of approximately 5 days (116.7 hours), enabling once-weekly dosing
Tirzepatide Is a Potent GIPR and GLP-1R Single-Molecule Dual Agonist

In vitro, tirzepatide has a potency for the GIPR similar to native GIP*.

Potency for the GLP-1R is slightly weaker than native GLP-1*.

*In overexpressed HEK cells.

cAMP = cyclic adenosine monophosphate; HEK = human endometrial adenocarcinoma; TZP = tirzepatide.

Tirzepatide Mechanism of Action: Effects on Endocrine Function and Insulin Resistance in Patients with T2D: Study Design

Key Inclusion Criteria
- T2D for at least 6 months
- Aged 20 to 74 years
- BMI 25-45 kg/m²
- HbA1c value 7%-9% if on metformin ± another agent

Randomization schedule
- 3:3:2 (placebo)

Change from Baseline in Insulin Secretion Rate

First Phase ISR (0-8 min)
- Placebo: 67, Baseline: 298%
- Semaglutide 1.0mg: 39, Baseline: 466%
- Tirzepatide 15mg: 42, Baseline: 20%

Second Phase ISR (20-120 min)
- Placebo: 159, Baseline: 6%
- Semaglutide 1.0mg: 135, Baseline: 223%
- Tirzepatide 15mg: 132, Baseline: 302%

Total ISR (0-120 min)
- Placebo: 154, Baseline: 6%
- Semaglutide 1.0mg: 127, Baseline: 217%
- Tirzepatide 15mg: 126, Baseline: 294%

Left: Data are group averages. Right: Data are estimates (with standard errors). *p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide for ANCOVA on change from baseline. ANOVA (baseline). PD analysis set. Heise T, et al. Lancet Endocrinol Diab. 2022;10:418-429.
Change from Baseline in Whole-Body Insulin Sensitivity

**Glucose Infusion Rate**

- Placebo
- Semaglutide 1.0mg
- Tirzepatide 15mg

**Whole-body Insulin Sensitivity, M-value**

- % Change from Baseline to Week 28

Left: Data are group averages. Dashed lines represent baseline values; solid lines represent Week 28 values.
Right: estimates. *p<0.001 vs placebo, #p=0.003 tirzepatide vs semaglutide for ANCOVA on change from baseline. ANOVA (baseline). PD analysis set.
Triple Agonists in the Postprandial Regulation of Metabolism and Energy Homeostasis

Courtesy of Professor Thomas Forst
Conclusions

• Dual GIP and GLP-1 agonism has shown several additive and complementary metabolic and pleiotropic effects

• Tirzepatide is a non-balanced GIP/GLP-1 receptor agonist with strong metabolic effects on glucose and lipid metabolism

• In patients with T2D tirzepatide has shown to improve
  • Insulin sensitivity
  • Alpha- and beta-cell response
  • Prandial glucose and lipid control
Clinical Implications of a Dual Agonist’s Efficacy and Safety Data

Stefano Del Prato, MD
Professor of Endocrinology, Chief – Section of Diabetes and Metabolic Diseases, Department of Clinical and Experimental Medicine University of Pisa
Pisa, Italy
Tirzepatide: Dual GIP/GLP-1 Receptor Agonist

• Tirzepatide is a multi-functional peptide based on the native GIP peptide sequence, modified to bind to both GIP and GLP-1 receptors
• Tirzepatide is a 39 amino acid linear peptide and includes a C20 fatty diacid moiety
• In vitro, it has higher potency to native GIP and is less potent to native GLP-1
• Tirzepatide has a mean half-life of ~5 days (116.7 h), enabling once-weekly dosing

GIP=glucose-dependent insulinotropic polypeptide; GLP-1 RAs=glucagon-like peptide-1 receptor agonists
The SURPASS Program: Studies of Tirzepatide in Patients with T2D

Initiation: Dec 2018

- SURPASS 1: monotherapy
- SURPASS 2: vs semaglutide
- SURPASS 3: vs degludec
- SURPASS 4: vs glargine (established CV disease)
- SURPASS 5: add-on to basal insulin
- SURPASS Japan: monotherapy
- SURPASS Japan: OAM combination
- SURPASS Asia Pacific: vs glargine (China)

Global submissions

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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 HbA1c from baseline at 40 or 52 weeks.

HbA1c = glycated hemoglobin; QW = once weekly; TZP = tirzepatide.
### Meta-analysis Results for Tirzepatide vs Placebo and vs GLP1-RAs for Changes in HbA1c

#### TZP vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>Placebo</th>
<th>N</th>
<th>Mean</th>
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<tbody>
<tr>
<td>Tirzepatide 5 mg vs placebo</td>
<td>47</td>
<td>-17.47</td>
<td>10.93</td>
<td>41</td>
<td>1.10</td>
<td>10.93</td>
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<td>Frias et al (2018) [23]</td>
<td>121</td>
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<td>11.33</td>
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<td>0.40</td>
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<td>9.89</td>
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<td>-17.71</td>
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<tr>
<td>Heterogeneity: $I^2 = 83%$, $P = 0.01$</td>
<td>-1.3%</td>
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<tr>
<td>Tirzepatide 10 mg vs placebo</td>
<td>43</td>
<td>-21.84</td>
<td>11.50</td>
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<tr>
<td>Tirzepatide 15 mg vs placebo</td>
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<td>-22.35</td>
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#### TZP vs GLP1-RAs

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<th>Treatment</th>
<th>N</th>
<th>Mean</th>
<th>SD</th>
<th>GLP-1 RA</th>
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<tr>
<td>Tirzepatide 15 mg vs GLP-1 RA</td>
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<tr>
<td>Heterogeneity: $I^2 = 89%$, $P &lt; 0.01$</td>
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Meta-analysis Results for Tirzepatide vs Placebo and vs GLP1-RAs for Changes in Body Weight

TZP vs Placebo

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MD</th>
<th>95% CI</th>
<th>Weight Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzepatide 5 mg vs placebo</td>
<td>-6.31</td>
<td>(-8.25 to -4.38)</td>
<td>-6.3kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-5 [19]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>285</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 70%$, $t^2 = 2.11$, $p = 0.04$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzepatide 10 mg vs placebo</td>
<td>-8.43</td>
<td>(-10.09 to -6.77)</td>
<td>-8.4kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-5 [19]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>281</td>
<td>274</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 58%$, $t^2 = 1.33$, $p = 0.09$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzepatide 15 mg vs placebo</td>
<td>-9.36</td>
<td>(-12.53 to -6.20)</td>
<td>-9.4kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-5 [19]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>320</td>
<td>294</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 91%$, $t^2 = 9.50$, $p &lt; 0.01$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

TZP vs GLP1-RAs

<table>
<thead>
<tr>
<th>Treatment</th>
<th>MD</th>
<th>95% CI</th>
<th>Weight Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tzepatide 5 mg vs GLP-1 RA</td>
<td>-1.68</td>
<td>(-2.52 to -0.84)</td>
<td>-1.7kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-2 [28]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>509</td>
<td>508</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 0%$, $t^2 = 0$, $p = 0.67$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzepatide 10 mg vs GLP-1 RA</td>
<td>-4.78</td>
<td>(-6.57 to -3.00)</td>
<td>-4.8kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-2 [28]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>503</td>
<td>508</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 59%$, $t^2 = 1.07$, $p = 0.12$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tzepatide 15 mg vs GLP-1 RA</td>
<td>-7.16</td>
<td>(-9.46 to -4.86)</td>
<td>-7.2kg</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SURPASS-2 [28]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Random-effects model</td>
<td>499</td>
<td>508</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 72%$, $t^2 = 2.08$, $p = 0.06$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Efficacy of Tirzepatide 5, 10, and 15 mg vs Semaglutide 2 mg in Patients with T2D: An Adjusted Indirect Treatment Comparison

SURPASS 4 — Blood Pressure and Lipids at 52 Weeks and Over Time

Systolic Blood Pressure

Triglycerides

Non-HDL

mITT population (efficacy analysis set). Data are LSM (SE) at 52 weeks and up to 104 weeks from MMRM analysis using log transformation. *p<0.001 vs. insulin glargine. Arrows indicate time of primary endpoint.

Tirzepatide Reduces UACR and Stabilizes eGFR in Patients Using and not Using SGLT2 Inhibitors

**UACR**

<table>
<thead>
<tr>
<th>SGLT2-i use at baseline</th>
<th>N</th>
<th>UACR change (95% CI)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TZP</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>498</td>
<td>-7.9 (-19.7, 5.7)</td>
<td>55.2 (34.5, 79.0)</td>
</tr>
<tr>
<td>No</td>
<td>1488</td>
<td>-10.4 (-19.6, -0.0)</td>
<td>26.6 (13.5, 41.2)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SGLT2-i use at baseline</th>
<th>No. of patients</th>
<th>eGFR slope (mL/min/1.73m²/year)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TZP</td>
</tr>
<tr>
<td>Yes</td>
<td>498</td>
<td>-1.2 (0.4)</td>
</tr>
<tr>
<td>No</td>
<td>1488</td>
<td>-1.5 (0.3)</td>
</tr>
</tbody>
</table>

Mean percent changes in log-transformed UACR and changes in eGFR from baseline to end of treatment. Slope data are mean decline (SE) per year and differences between TZP and iGLAR are with 95% CI. CI=confidence interval; eGFR=estimated glomerular filtration rate; iGLAR=insulin glargine; N=number of participants in specified population; TZP=tirzepatide; SE=standard error; SGLT-2=sodium-glucose co-transporter 2 inhibitor; UACR=urine albumin-creatinine ratio.

SURPASS 4 — Time to First Occurrence of Positively Adjudicated MACE-4

<table>
<thead>
<tr>
<th></th>
<th>Patients (n)</th>
<th>Events (n)</th>
<th>HR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled</td>
<td>995</td>
<td>47</td>
<td>0.74 (0.51–1.08)</td>
</tr>
<tr>
<td>Tirzepatide</td>
<td>1000</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glargine</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Cumulative probability (%)

Number at risk

Time from first dose to first occurrence of MACE-4 (week)

**Tirzepatide Cardiovascular Event Risk Assessment: a Pre-specified Meta-analysis**

<table>
<thead>
<tr>
<th>Event</th>
<th>All tirzepatide</th>
<th>All comparator</th>
<th>Hazard ratio with 95% CI</th>
<th>Hazard ratio (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite MACE-4</td>
<td>72 (1.35)</td>
<td>70 (1.61)</td>
<td></td>
<td>0.80 (0.57, 1.11)</td>
<td>0.183</td>
</tr>
<tr>
<td>Death due to cardiovascular cause</td>
<td>25 (0.46)</td>
<td>22 (0.43)</td>
<td></td>
<td>0.90 (0.50, 1.61)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30 (0.56)</td>
<td>30 (0.71)</td>
<td></td>
<td>0.76 (0.45, 1.28)</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>15 (0.27)</td>
<td>15 (0.35)</td>
<td></td>
<td>0.81 (0.39, 1.68)</td>
<td></td>
</tr>
<tr>
<td>Hospitalization for unstable angina</td>
<td>5 (0.09)</td>
<td>9 (0.20)</td>
<td></td>
<td>0.46 (0.15, 1.41)</td>
<td></td>
</tr>
<tr>
<td>Composite MACE-3</td>
<td>67 (1.25)</td>
<td>62 (1.42)</td>
<td></td>
<td>0.83 (0.58, 1.18)</td>
<td>0.306</td>
</tr>
<tr>
<td>Composite MACE-3 or hospitalization for heart failure</td>
<td>74 (1.39)</td>
<td>71 (1.71)</td>
<td></td>
<td>0.78 (0.56, 1.08)</td>
<td>0.137</td>
</tr>
<tr>
<td>Hospitalization for heart failure</td>
<td>10 (0.19)</td>
<td>9 (0.29)</td>
<td></td>
<td>0.67 (0.26, 1.70)</td>
<td></td>
</tr>
<tr>
<td>All-cause death</td>
<td>41 (0.76)</td>
<td>39 (0.86)</td>
<td></td>
<td>0.80 (0.51, 1.25)</td>
<td></td>
</tr>
</tbody>
</table>

The SURPASS Program: Studies of Tirzepatide in Patients with T2D

Initiation: Dec 2018

2019

- SURPASS 1: monotherapy
- SURPASS 3: vs degludec
- SURPASS 4: vs glargine (established CV disease)
- SURPASS Japan: monotherapy
- SURPASS Japan: OAM combination
- SURPASS Asia Pacific: vs glargine (China)

2020

- SURPASS 2: vs semaglutide
- SURPASS 5: add-on to basal insulin
- SURPASS CV Outcomes Trial (event driven)

2021

Global submissions

2022

SURMOUNT
2539 adults with obesity (104.8 kg; 38.0 kg/m²; 94.5% with BMI >30)
Randomized (1:1:1:1) to tirzepatide 5, 10, 15 mg or placebo
72 wk treatment
Tirzepatide Once Weekly for the Treatment of Obesity

Overall Percent Change in Body Weight from Baseline (treatment-regimen estimand)

- Percent Change in Body Weight:
  - Tirzepatide, 5 mg: -15.0
  - Tirzepatide, 10 mg: -19.5
  - Tirzepatide, 15 mg: -20.9
  - Placebo: -3.1

Participants Who Met Weight-Reduction Targets (treatment-regimen estimand)

- Percentage of Participants:
  - Body Weight Reduction Target (%):
    - ≥5: 85.1 ± 1.8
    - ≥10: 88.9 ± 1.8
    - ≥15: 90.9 ± 1.8
    - ≥20: 78.5 ± 2.2
    - ≥25: 66.6 ± 2.6

# Tirzepatide Once Weekly for the Treatment of Obesity

## End Points

<table>
<thead>
<tr>
<th></th>
<th>Pooled Tirzepatide Groups</th>
<th>Placebo (N=643)</th>
<th>Estimated Treatment Difference from Placebo (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Key secondary end points</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline to week 20 in body weight — kg</td>
<td>-12.8 (-13.1 to -12.5)</td>
<td>-2.7 (-3.2 to -2.2)</td>
<td>-10.1 (-10.7 to -9.6)</td>
</tr>
<tr>
<td>Change in measure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SF-36 physical function score</td>
<td>3.6 (3.2 to 4.0)</td>
<td>1.7 (0.8 to 2.6)</td>
<td>1.9 (1.0 to 2.9)</td>
</tr>
<tr>
<td>Systolic blood pressure — mm Hg</td>
<td>-7.2 (-7.8 to -6.7)</td>
<td>-1.0 (-2.3 to -0.3)</td>
<td>-6.2 (-7.7 to -4.8)</td>
</tr>
<tr>
<td>Percentage change in level</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides — mg/dl</td>
<td>-24.8 (-26.3 to -23.1)</td>
<td>-5.6 (-10.0 to -1.2)</td>
<td>-20.3 (-24.3 to -16.1)</td>
</tr>
<tr>
<td>Non-HDL cholesterol — mg/dl</td>
<td>-9.7 (-10.7 to -8.6)</td>
<td>-2.3 (-4.9 to -0.2)</td>
<td>-7.5 (-10.1 to -4.9)</td>
</tr>
<tr>
<td>HDL cholesterol — mg/dl</td>
<td>8.0 (6.9 to 9.1)</td>
<td>-0.7 (-2.9 to 1.5)</td>
<td>8.8 (6.1 to 11.5)</td>
</tr>
<tr>
<td>Fasting insulin — mIU/liter</td>
<td>-42.9 (-44.9 to -40.9)</td>
<td>-6.6 (-15.3 to 2.2)</td>
<td>-38.9 (-44.8 to -32.4)</td>
</tr>
</tbody>
</table>

# Tirzepatide Once Weekly for the Treatment of Obesity

<table>
<thead>
<tr>
<th>Variable</th>
<th>Tirzepatide, 5 mg (N = 630)</th>
<th>Tirzepatide, 10 mg (N = 636)</th>
<th>Tirzepatide, 15 mg (N = 630)</th>
<th>Placebo (N = 643)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events leading to discontinuation of trial drug or placebo</td>
<td>27 (4.3%)</td>
<td>45 (7.1%)</td>
<td>39 (6.2%)</td>
<td>17 (2.6%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (1.0%)</td>
<td>7 (1.1%)</td>
<td>12 (1.9%)</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (0.3%)</td>
<td>5 (0.8%)</td>
<td>3 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0</td>
<td>2 (0.3%)</td>
<td>3 (0.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>4 (0.6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cholecystitis</td>
<td>4 (0.6%)</td>
<td>3 (0.5%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>1 (0.2%)</td>
<td>4 (0.6%)</td>
<td>1 (0.2%)</td>
<td>0</td>
</tr>
<tr>
<td>Chronic cholecystitis</td>
<td>1 (0.2%)</td>
<td>1 (0.2%)</td>
<td>3 (0.5%)</td>
<td>3 (0.5%)</td>
</tr>
</tbody>
</table>

TZP Effects on Glycemic Control and Body Weight

% with HbA1c ≤ 5.7%: 45%

% with BW loss ≥ 20%: 37%

## Association between T2D Remission and Percent Total Weight Loss after Bariatric Surgery

<table>
<thead>
<tr>
<th>Weight loss</th>
<th>N</th>
<th>HR</th>
<th>p</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-5%</td>
<td>115</td>
<td>Reference</td>
<td>0.23</td>
<td>(0.88 - 1.68)</td>
</tr>
<tr>
<td>5-10%</td>
<td>356</td>
<td>1.22</td>
<td>0.00</td>
<td>(1.47 - 2.64)</td>
</tr>
<tr>
<td>10-15%</td>
<td>684</td>
<td>1.97</td>
<td>0.00</td>
<td>(1.74 - 3.11)</td>
</tr>
<tr>
<td>15-20%</td>
<td>1157</td>
<td>2.33</td>
<td>0.00</td>
<td>(2.11 - 3.75)</td>
</tr>
<tr>
<td>20-25%</td>
<td>1366</td>
<td>2.81</td>
<td>0.00</td>
<td>(2.16 - 3.83)</td>
</tr>
<tr>
<td>25-30%</td>
<td>1136</td>
<td>2.88</td>
<td>0.00</td>
<td>(2.19 - 3.88)</td>
</tr>
<tr>
<td>&gt;30%</td>
<td>1114</td>
<td>2.92</td>
<td>0.00</td>
<td></td>
</tr>
</tbody>
</table>

Treatment with Tirzepatide: a Perspective

A first opportunity for diabetes remission?

Novel Form of Combination Therapy

Tirzepatide

Superior CV benefit?

Superior and sustained glucose and BW lowering

Ask Me Anything: Incretins Edition

Final Q&A